ImmunoTargets and Therapy

Dovepress
Taylor & Francis Group

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REVIEW

The Role of PD-L1 in Lung Cancer: From Biology to Clinical Application

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Abstract: Lung cancer remains the primary cause of cancer-related mortality worldwide and is mainly classified into non-small cell lung cancer, which accounts for approximately 85% of cases, and small cell lung cancer, representing about 15%. In recent years, major therapeutic progress has been achieved through the development of immunotherapies, particularly immune checkpoint inhibitors targeting the PD-1/PD-L1 axis. These treatments aim to restore antitumor immune responses by blocking the interaction between PD-1, expressed on T lymphocytes, and its ligand PD-L1, which can be overexpressed by tumor cells. Under physiological conditions, PD-L1 plays an essential role in maintaining immune tolerance; however, its dysregulated expression in cancer contributes to immune evasion. The level of PD-L1 expression assessed by immunohistochemistry has emerged as a key predictive biomarker for patient response to immunotherapy. Nevertheless, PD-L1 expression is heterogeneous and influenced by multiple biological, clinical and technical factors. In this review, we aim to summarize the biological role of PD-L1 in lung cancer, discuss its expression patterns and regulatory mechanisms, describe current assessment methods, and highlight its clinical relevance in guiding immunotherapy strategies.

Keywords: PD-L1, lung cancer, immune checkpoint inhibitors, immunotherapy, immunohistochemistry, predictive biomarker

Introduction

Lung cancer represents the most frequently diagnosed carcinoma and remains the principal cause of cancer-related mortality worldwide. It is broadly classified into two major histological categories: non-small cell lung cancer (NSCLC), which accounts for approximately 85% of all cases and mainly includes adenocarcinoma and squamous cell carcinoma, and small cell lung cancer (SCLC), representing nearly 15% of cases.[1] In Morocco, lung cancer ranks as the second most commonly diagnosed malignancy in both sexes (13.9%), following breast cancer, and constitutes the leading cancer type among men, with an estimated prevalence of 25.6%.[2,3]

Despite significant progress in conventional treatment modalities, including surgery, chemotherapy, radiotherapy, and targeted therapies, immunotherapy has emerged as a major therapeutic breakthrough in lung cancer. In particular, immune checkpoint inhibitors (ICIs) targeting the PD-1 (programmed cell death protein 1)/PD-L1 (programmed death-ligand 1) axis have become a cornerstone in current treatment strategies. Their clinical success is mainly attributed to their favorable safety profile, the durability of antitumor responses associated with immune memory, and their demonstrated clinically meaningful but modest efficacy in selected patient populations.[4]

Nevertheless, despite the demonstrated clinical benefit of immune checkpoint inhibitors targeting PD-1 and PD-L1, only a subset of patients with solid malignancies derives a significant therapeutic response. This limitation underscores the increasing need to identify reliable predictive biomarkers, such as PD-L1 expression evaluated by immunohistochemistry (IHC), in order to optimize patient selection and guide therapeutic decision-making. However, the predictive value of PD-L1 remains imperfect and subject to biological and technical variability, including intratumoral heterogeneity and assay-dependent differences.[5]

https://doi.org/10.2147/ITT.S591588
Received: 25 December 2025
Accepted: 26 February 2026
Published: 19 March 2026

This review aims to provide an overview of the role of PD-L1 in lung cancer by discussing its biological features, its expression patterns in lung tumors, the methods used for its evaluation in clinical practice, and its relevance in the context of immunotherapy.

Methods

This narrative review was conducted based on a structured literature search of the PubMed, Scopus and Web of Science databases up to January 2026. Relevant articles were identified using combinations of keywords, including "PD-L1", "lung cancer", "non-small cell lung cancer", "small cell lung cancer", and "immune checkpoint inhibitors". Studies published within the last five years were prioritized to reflect current knowledge and clinical practice. Older studies were only included when they were considered essential for providing context. The review included original research articles, clinical trials and review articles that addressed the biology, expression, assessment methods and clinical relevance of PD-L1 in lung cancer. Preclinical studies only, case reports and articles not directly related to lung cancer were excluded. Studies were selected based on their relevance to the scope and objectives of this review.

Characteristics and Role of PD-1/PD-L1

The innate and adaptive immune systems play a fundamental role in the recognition and elimination of malignant cells. Nevertheless, tumor cells are able to evade immune control by exploiting the PD-1/PD-L1 immune checkpoint pathway, leading to the inhibition of T-cell activation and antitumor immune responses.[6]

PD-1, also known as CD279, is an immunoinhibitory receptor that specifically interacts with its ligands PD-L1 and PD-L2 and belongs to the CD28/CTLA-4 immunoglobulin superfamily. Structurally, it consists of an extracellular IgV-like domain, a single hydrophobic type I transmembrane domain, and an intracellular tail containing two phosphorylation motifs, namely an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). PD-1 is expressed on multiple immune cell populations, including activated T lymphocytes, natural killer cells, B lymphocytes, macrophages, dendritic cells, particularly under inflammatory conditions, and monocytes. Its expression is especially pronounced on tumor-specific T cells.[7,8] The PD-1 protein is encoded by the PDCD1 gene, whose transcription is regulated by several transcription factors involved in immune activation. Through its regulatory function, PD-1 contributes to immune homeostasis by promoting immunological tolerance and limiting excessive or inappropriate immune activation. In the tumor setting, however, increased PD-1 expression thereby promotes tumor immune evasion.[9]

PD-L1, also referred to as B7-H1 or CD274, is a type I transmembrane glycoprotein belonging to the B7 family.[10,11] The protein is encoded by the CD274 gene, and its expression is primarily regulated by interferon-γ (IFN-γ)–dependent signaling pathways.[12] Structurally, PD-L1 is organized into three main domains. The extracellular region contains variable immunoglobulin-like segments, including proximal and distal domains, followed by a transmembrane region and an intracellular tail. The cytoplasmic domain harbors three conserved amino acid motifs, RMLD-VEKC, DTSSK, and QFEET, which are involved in the regulation of STAT3 phosphorylation.[9] PD-L1 serves as a functional ligand for PD-1, a receptor expressed on the surface of numerous hematopoietic cells, such as T lymphocytes, neutrophils, and antigen-presenting cells, including B lymphocytes, macrophages, and dendritic cells. Beyond the immune compartment, PD-L1 expression has also been documented in several non-hematopoietic tissues, including the heart, pancreas, placenta, vascular endothelium, skeletal muscle, liver, lungs, eyes, and skin. Notably, PD-L1 is frequently upregulated in a wide range of tumors, including melanoma,[13] renal cell carcinoma,[14] breast cancer,[15] head and neck squamous cell carcinoma,[16] and gastric cancer,[17] where it functions as an adaptive immune-resistance mechanism that enables malignant cells to evade immune-mediated destruction.[9,10]

PD-1/PD-L1 Signaling

Under physiological conditions, optimal T-cell activation requires the integration of two distinct signals. The first signal is initiated by engagement of the T-cell receptor (TCR) upon recognition of antigenic peptides presented by antigen-presenting cells or tumor cells through the major histocompatibility complex (MHC). The second signal involves costimulatory interactions, notably the binding of CD28 on T lymphocytes to its ligands CD80 and CD86 expressed on antigen-presenting cells.[10] In parallel, the PD-1/PD-L1 signaling axis acts as a negative regulatory pathway

contributing to immune tolerance. In the tumor microenvironment, however, cancer cells exploit this inhibitory pathway to evade immune surveillance mechanisms.[7]

The interaction between PD-1 expressed on T cells and its ligand PD-L1 present on tumor cells or antigen-presenting cells triggers the phosphorylation of tyrosine residues located within the ITSM and ITIM motifs of the PD-1 intracellular domain. This process is mediated by the Src family kinase Lck. Phosphorylation of the ITSM motif leads to the recruitment of the phosphatase SHP2, which subsequently attenuates TCR signaling by reducing the phosphorylation of the ζ-chain–associated protein ZAP-70 through Lck-dependent mechanisms.[6,7] As a consequence, downstream signaling cascades involved in T-cell activation are inhibited, including the PI3K-AKT pathway, RAS signaling, extracellular signal-regulated kinase (ERK), VAV, and phospholipase C-γ (PLCγ) pathways.

SHP2 activation further modulates downstream pathways, including PI3K-AKT and RAS/ERK signaling, reinforcing T-cell inhibition.[18,19]

Moreover, engagement of PD-1 by its ligand not only suppresses T-cell activation through the inhibition of TCR-mediated signaling, but also attenuates the CD28 costimulatory pathway by promoting its dephosphorylation via SHP2.[7]

This inhibitory signaling cascade provides the biological rationale for therapeutic blockade of the PD-1/PD-L1 axis in cancer treatment.

Collectively, these alterations result in functional T-cell inhibition[9] (Figure 1).

In lung cancer, the persistent activation of this pathway within the tumor microenvironment contributes to immune evasion and forms the basis of the rationale for immune checkpoint blockade therapy.

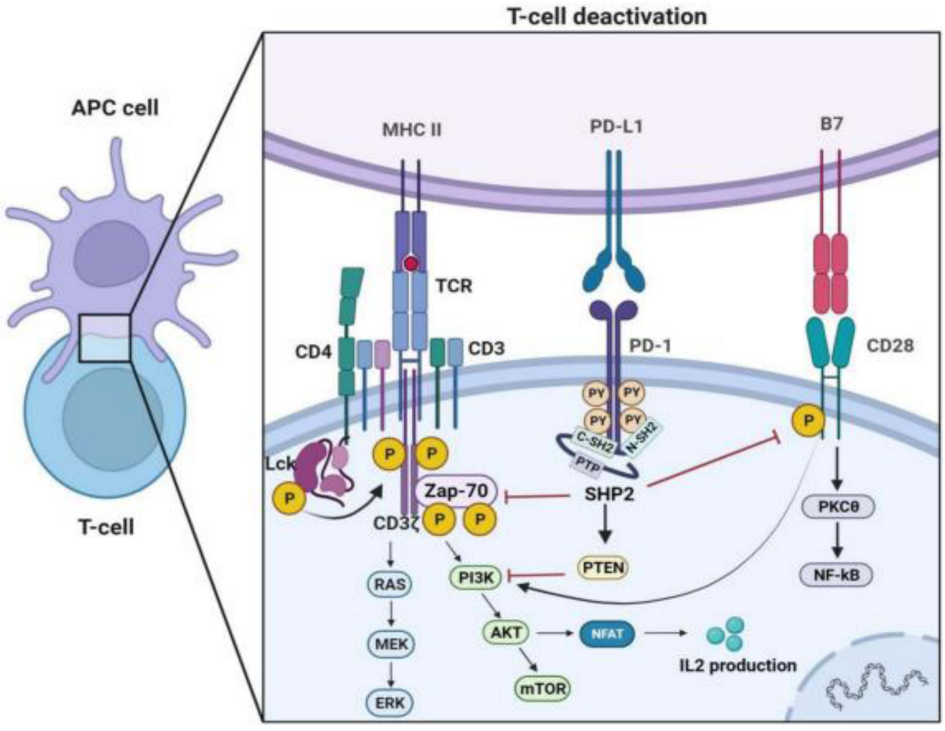

Figure 1 The immune regulatory mechanism of the PD-1/PD-L1 axis.[7] T-cell activation relies mainly on two signals: (1) the TCR, when it recognizes the antigen presented by antigen-presenting cells (APCs) or tumor cells via MHC, which activates the intracellular signaling pathways RAS-MEK-ERK and PI3K-AKT-mTOR, promoting IL-2 production; (2) the co-stimulatory signal, corresponding to the binding of CD28 to its CD80/CD86 ligands on APCs, activating the PKCθ and NF-κB pathways. However, the interaction between PD-1 and its ligand PD-L1 recruits the phosphatase SHP2 and activates PTEN, inhibiting these signaling pathways and leading to T-cell deactivation. This schematic representation has been included to provide a concise, mechanistic framework to support clinical discussions about immune checkpoint inhibition in lung cancer. Reproduced from,[7] with permission.

Abbreviations: APC, Antigen Presenting Cell; TCR, T-cell Receptor; CD, Cluster of Differentiation; Lck, Lymphocyte-specific protein tyrosine kinase; ZAP-70, Zeta-chain-associated protein kinase 70; SHP2, Src homology region 2 domain-containing phosphatase 2; PI3K, Phosphatidylinositol 3-kinase; AKT, Protein kinase B; PTEN, Phosphatase and tensin homolog; mTOR, Mammalian Target Of Rapamycin; RAS, Rat sarcoma oncogene family; MEK, MAPK/ERK kinase; ERK, Extracellular signal-regulated kinase; PKCθ, Protein Kinase C theta; NFAT, Nuclear Factor of Activated T-cells; IL-2, Interleukin-2; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells.

https://doi.org/10.2147/ITT.S591588

PD-L1 Status in Lung Cancer

Numerous studies have demonstrated that PD-L1 expression is frequently observed in lung cancer.[7] The prevalence of PD-L1 expression has been estimated at approximately 55% in non-small cell lung cancer (NSCLC)[20,21] and around 26% in small cell lung cancer (SCLC).[22] Moreover, elevated PD-L1 expression in tumor tissues has been associated with unfavorable prognostic outcomes in patients with lung cancer, including reduced overall survival (OS). However, reported prevalence rates and prognostic associations vary considerably across studies, partly due to differences in detection assays, scoring systems, and tumor heterogeneity.[23,24]

Clinical studies indicate that PD-L1 expression plays a predictive role in response to immune checkpoint inhibitors, particularly in patients with high PD-L1 levels.[25] However, its prognostic value remains less clear and inconsistent across studies. Variability in assays, cutoff definitions, and tumor heterogeneity may partly explain these discrepancies.[26] These findings suggest that PD-L1 should be interpreted primarily as a context-dependent predictive biomarker rather than a universal prognostic factor.

Importantly, PD-L1 expression is not a fixed characteristic of lung tumors. There is growing evidence that its expression can change over time and in response to treatment, reflecting the dynamic interactions within the tumor immune microenvironment.[26] This variability in time and space may contribute to inconsistent predictive results across studies and underscores the limitations of relying on a single biopsy for treatment decisions.

Despite its central role in patient selection, PD-L1 remains a controversial biomarker. While it demonstrates predictive value in certain patients, its prognostic significance is inconsistent across studies. Additionally, differences in antibody clones, scoring systems, and cutoff thresholds may introduce assay-related bias and affect patient classification. Furthermore, PD-L1 expression is not static and can change over time or in response to treatment, complicating its interpretation in routine practice.

The expression of PD-L1 in lung cancer is influenced by a variety of biological, clinical and technical factors, including mechanisms related to the immune microenvironment. An overview of these contributing factors is presented in Table 1.

Table 1 Factors Influencing PD-L1 Status in Lung Cancer

Factors Influencing PD-L1 Status	PD-L1 Status in Lung Cancer		
	NSCLC	SCLC	
Smoking status	Smokers show high expression of PD-L1	The association between PD-L1 status and smoking status remains unclear. A 2020 meta-analysis found no significant association, while another 2024 study reported that all patients with PD-L1-positive expression were smokers, without statistical significance.	[21, 27, 28]
Histological subtype	PD-L1 is more highly expressed in squamous cell carcinoma than in adenocarcinoma.	-	[20, 29]
Clinical stage	High PD-L1 expression in advanced stages (III or IV)	A study reported more frequent expression of PD-L1 in early stages of SCLC.	[29–31]
Genetic mutations	Studies have reported lower PD-L1 expression in NSCLC patients with EGFR mutations compared to those with other mutations (KRAS, ALK, MET, ROS1, and RET).	The association between PD-L1 status and genetic mutations is not yet fully understood, requiring further research to better understand this relationship.	[30]
Immune microenvironment (IFN-γ signaling)	The release of IFN-γ by activated immune cells is a key factor in the upregulation of PD-L1 on tumor cells, which reflects adaptive immune resistance.	IFN-γ, secreted by activated cytotoxic T lymphocytes, induces the expression of PD-L1 and PD-L2 proteins on SCLC cells	[32, 33]

(*Continued*)

Table 1 (Continued).

Factors Influencing PD-L1 Status	PD-L1 Status in Lung Cancer		
	NSCLC	**SCLC**	
Tumor-infiltrating lymphocytes (TILs)	The presence of immune cells infiltrating tumors is not systematically associated with PD-L1 expression in tumors.	The expression of PD-L1 in SCLC tumors is not consistently correlated with tumor-infiltrating lymphocytes. While some studies report no association between PD-L1 expression on tumor cells and TIL density, others describe correlations between PD-L1 expression and PD-L1-positive immune cells or specific TIL subsets	[31, 34–36]
Inflammation	The inflammatory and immune-activated tumor microenvironment, characterized by the release of cytokines such as IFN-γ, contributes to PD-L1 upregulation.	Chronic inflammatory signalling, primarily driven by IFN-γ and other pro-inflammatory cytokines, plays a role in PD-L1 upregulation and immune evasion in small cell lung cancer (SCLC).	[32, 33]
Patient treatment history	The expression of PD-L1 on tumor cells may increase during radiotherapy or chemoradiotherapy, reflecting treatment-induced modulation.	There are limited data on the modulation of PD-L1 expression induced by treatment in SCLC, and no robust longitudinal studies are available.	[32]
Temporal heterogeneity	The expression of PD-L1 may change during the progression of the disease, including between the initial diagnosis and the relapse. This reflects the temporal heterogeneity of the disease.	Research on the changes in PD-L1 expression over time in SCLC is currently limited	[37]
Spatial heterogeneity	The expression of PD-L1 may differ between primary tumors and metastatic sites. A meta-analysis reported spatial heterogeneity in PD-L1 expression, with differences observed between primary lung tumors and brain metastases.	There is currently limited clinical evidence for spatial discordance between primary and metastatic sites in SCLC, and this requires further investigation.	[38]
Technical factors	The assessment of PD-L1 is influenced by technical factors, including the choice of IHC assay, antibody clone, scoring system and pathologist interpretation. Differences between assays limit interchangeability and may affect how patients are classified.		[39]

Abbreviations: EGFR, Epidermal Growth Factor Receptor; KRAS, Kirsten Rat Sarcoma viral oncogene homolog; ALK, Anaplastic Lymphoma Kinase; MET, Mesenchymal-Epithelial Transition factor; ROS1, c-ros oncogene 1; RET, Rearranged during Transfection.

Techniques for Evaluating PD-L1 as a Predictive Marker for Immunotherapy

PD-L1 expression can be assessed using several techniques. These include enzyme-linked immunosorbent assay (ELISA), which enables qualitative or quantitative measurement of PD-L1 levels in plasma; Western blotting for the detection of PD-L1 in tissue homogenates; and molecular analyses such as next-generation sequencing (NGS) for the identification of genetic alterations, as well as the evaluation of messenger RNA and microRNA expression. However, IHC remains the current standard in clinical practice and for companion diagnostic purposes.[40,41]

Professional associations, including the College of American Pathologists (CAP), the Association for Molecular Pathology (AMP), the International Association for the Study of Lung Cancer (IASLC), the Pulmonary Pathology Society and the LUNGevity Foundation, have jointly published evidence-based guidelines to inform the use of biomarkers in the treatment of non-small cell lung cancer with immune checkpoint inhibitors. The guidelines recommend PD-L1 assessment by IHC as the current standard approach for selecting patients, while acknowledging that additional biomarkers, such as tumor mutational burden (TMB) and microsatellite instability (MSI), may offer supplementary clinical insights in certain contexts.[42]

A schematic overview of the main steps involved in PD-L1 IHC is shown in Figure 2.

https://doi.org/10.2147/ITT.S591588

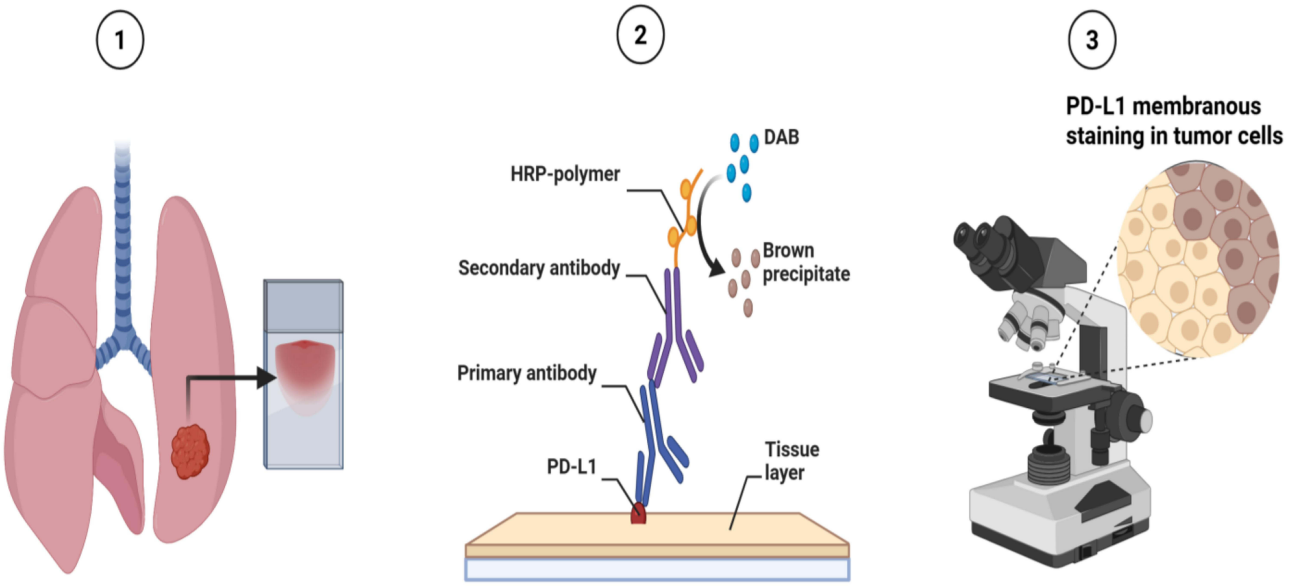

Figure 2 Evaluation of PD-L1 expression by IHC.[43] (**1**) Tumor sampling and tissue processing. (**2**) PD-L1 detection using specific antibodies (clone 22C3, Dako Autostainer Link 48 platform). (**3**) Microscopic evaluation of stained slides for PD-L1 expression assessment. Adapted from,[43] with permission, and created with BioRender.
Abbreviations: PD-L1, Programmed death-ligand 1; DAB, Diaminobenzidine; HRP, Horseradish peroxidase.

Compared to other methods, IHC offers numerous advantages, including high availability in laboratories, greater cost-effectiveness, and rapid execution, making it a valuable tool for identifying genetic alterations, analyzing biomarkers for targeted therapies, and utilizing small tumor samples.[40] However, despite its advantages, IHC has certain limitations related to commercial IHC tests, their sensitivity, methodology, sampling, and tissue preparation, in addition to the lack of harmonization and standardization of IHC tests. Inter-assay variability, differences between antibody clones, and lack of universal cut-offs remain major challenges affecting reproducibility and clinical interpretation. This assay-dependent variability can introduce bias into the reported prevalence of PD-L1 and may influence treatment eligibility and clinical decision-making.

Pathologists study PD-L1 expression by IHC on formalin-fixed, FFPE histological samples. They use one of the antibodies validated by the FDA (Food and Drug Administration), namely 22C3, 28–8, SP263, and SP142, on different platforms. Two main scoring systems are used, depending on the antibodies and the treatment being considered. The tumor proportion score (TPS), which is most commonly used in NSCLC, represents the percentage of tumor cells with complete or partial PD-L1 membrane expression relative to all tumor cells present in the sample, and the immune cell score (IC), which represents the proportion of the tumor area occupied by PD-L1-expressing immune cells[44] (Table 2).

Although these assays target the same molecule, they differ in their scoring systems and threshold definitions. This may affect patient stratification in clinical practice. Therefore, when interpreting PD-L1 results, it is important to consider the specific assay used.

Beyond these commonly used scoring systems, the literature has reported additional approaches for PD-L1 assessment. The combined positive score (CPS), which takes into account both PD-L1-positive tumor cells and immune cells, has been employed in certain clinical studies. Furthermore, the evaluation of PD-L1 staining intensity has been investigated, primarily in a research context, to provide a more accurate reflection of tumor heterogeneity.[47,48] Recently, automated, deep-learning-based approaches have been proposed to make PD-L1 assessment easier, mainly by automating tumor proportion score assessment and improving reproducibility. These approaches aim to reduce inter-observer variability and improve standardization.[49]

Inter- and intra-tumor heterogeneity, sample details such as type, age, status (naive or treated samples), cancer type (primary or metastatic), as well as pre-analytical factors such as time of collection and fixation conditions are factors that can influence PD-L1 expression and interpretation.[50] This has paved the way for the interpretation of IHC images using artificial intelligence.

Table 2 The Main Anti-PD-L1 Antibodies Used in IHC in Lung Cancer

Antibody Clone (Species)	Platform	Score	Type of Diagnosis	Therapeutic Indication	Threshold	Ref.
22C3 (Mouse)	Dako	TPS	Companion	Pembrolizumab	If TPS: • <1%: no expression • 1–49: weak expression • ≥50: strong expression	[19]
28–8 (Rabbit)	Dako	(TPS)	Supplementary	Nivolumab	If TPS: • <1%: negative expression • 1–5%: weak expression • 5–10%: intermediate expression • >10%: high expression	[40]
SP263 (Rabbit)	Ventana	(TPS)	Supplementary	Durvalumab	If TPS: • ≥25: positive expression	[44]
SP142 (Rabbit)	Ventana	(TC and IC)	Supplementary	Atezolizumab	TC (% of tumor cells expressing PD-L1): • TC0: < 1% • TC1: 1–5% • TC2: 5–50% • TC3: ≥ 50% IC (% of immune cells expressing PD-L1): • IC0: < 1% • IC1: 1–5% • IC2: 5–10% • IC3: ≥ 10% ✓ Positivity if: TC1/2/3 and/or IC1/2/3	[45,46]

Abbreviations: TPS, tumor proportion score; TC, tumor cells; IC, immune cells.

In addition to PD-L1, several other biomarkers are actively being investigated as potential predictors of response to immune checkpoint inhibitor–based immunotherapy in lung cancer. These include TMB,[51] the presence of TILs,[52] and MSI.[53] According to international recommendations, particularly those of the European Society for Medical Oncology (ESMO), these biomarkers provide additional information to the PD-L1 assessment, and their clinical relevance depends on the type of tumor and the context.[54]

Although PD-L1 is the most widely used biomarker in clinical practice, it is not an absolute predictor. Conflicting results have been reported across clinical trials, and its accuracy may be influenced by assay variability, threshold selection, and spatial and temporal heterogeneity. Tumor mutational burden (TMB) has also been associated with an improved response to immune checkpoint inhibitors, particularly in patients with a high mutational load. However, differences in sequencing platforms, cutoff definitions, and intratumoral heterogeneity limit the standardization of TMB. Microsatellite instability (MSI-H/dMMR) is a strong predictive biomarker in certain tumor types. However, its prevalence in lung cancer is relatively low, which limits its applicability. Similarly, tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, reflect the immune contexture of the tumor microenvironment. They have been associated with better clinical outcomes. However, variability in assessment methods remains a challenge.

Given these limitations, recent studies have explored combinatorial approaches that integrate PD-L1 with TMB or immune contexture markers, such as CD8+ TILs. Clinical trials suggest that combined biomarker models may provide improved predictive accuracy compared to single-parameter assessment. This highlights the potential value of multidimensional strategies in refining patient selection for immunotherapy.[5]

Beyond single- or dual-biomarker models, recent studies have explored multi-omic approaches that integrate genomic, transcriptomic, and immune-related data in order to better predict responses to immunotherapy. Gene expression signatures reflecting interferon-γ activity or T-cell-inflamed tumor profiles, for example, have shown complementary value to PD-L1 and TMB. Additionally, artificial intelligence–based models are being developed to combine multiple biological and clinical parameters into integrated predictive tools. While these strategies are still being clinically validated, they may improve patient stratification compared to single-biomarker approaches.[55]

PD-1/PD-L1 and Immunotherapy in Lung Cancer

Immunotherapy has become a standard therapeutic approach for patients with advanced or metastatic lung cancer. This strategy is based on blocking the PD-1/PD-L1 axis to enhance antitumor immunity.[56] These agents may be administered as monotherapy or in combination with conventional treatments such as radiotherapy, chemotherapy, or other ICIs, with the objective of limiting tumor growth and dissemination while improving symptom control in advanced disease.[44,57]

Despite the clinical benefits reported in the literature, only a limited proportion of patients, generally between 15% and 30% in most solid tumors achieve an objective response to ICI-based immunotherapy. This observation underscores the need to identify reliable predictive biomarkers capable of distinguishing patients who are more likely to benefit from these treatments.[58]

In lung cancer, particularly in NSCLC, research efforts have largely focused on the immunohistochemical assessment of PD-L1 expression as a predictive biomarker of response to immune checkpoint inhibition.[59] Numerous clinical studies have validated the clinical relevance of PD-L1 by demonstrating associations between its expression levels and therapeutic response in patients with NSCLC treated with ICIs.[60,61] However, evidence also indicates that PD-L1 expression alone is not a fully reliable predictor of response to anti-PD-1/anti-PD-L1 therapies in all SCLC cases.[62,63]

Worldwide, health authorities have approved several ICIs for the treatment of advanced or metastatic NSCLC and extensive-stage SCLC. These therapies act by targeting PD-1 or PD-L1 (Table 3).

Although these agents target the same immune checkpoint pathway, Table 3 illustrates the differences in their molecular structures (IgG subclass), target specificity (PD-1 versus PD-L1) and approved applications in NSCLC and SCLC. These distinctions contribute to variations in clinical application and safety profiles.

PD-1 Inhibitors

Nivolumab (Opdivo)

Nivolumab (Opdivo) is a fully humanized, genetically modified monoclonal antibody that belongs to the anti-PD-1 ICIs category. These antibodies block the PD-1 receptor in order to reactivate anti-tumor activity mediated by cytotoxic T cells.[68]

Table 3 ICIs Approved by the FDA for the Treatment of NSCLC and SCLC (2025)

ICI (Trade Name)	Target	Definition and Mechanism	Type of Cancer	Ref.
Nivolumab (Opdivo)	PD-1	A human IgG4 monoclonal antibody developed by Bristol-Myers Squibb that inhibits T cell inactivation by blocking the PD-1 receptor on T cells.	NSCLC	[64]
Pembrolizumab (Keytruda)	PD-1	A human IgG4-Kappa monoclonal antibody that inhibits the PD pathway by blocking PD-1 present on the surface of T cells.	NSCLC	[65]
Cemiplimab (Libtayo)	PD-1	A human IgG4 monoclonal antibody that targets the PD-1 receptor	NSCLC	[66]
Durvalumab (Imfinzi)	PD-L1	A human IgG1 monoclonal antibody that inhibits the interaction between PD-1 (on T cells) and PD-L1 (on tumor cells) by blocking PD-L1.	NSCLC SCLC	[67]
Atezolizumab (Tecentriq)	PD-L1	A humanized IgG1 monoclonal antibody that acts as an inhibitor of the PD-L1 ligand.	NSCLC SCLC	[12]

Abbreviations: IgG, Immunoglobuline G.

As a second-line treatment for advanced NSCLC, nivolumab has been approved by the FDA for the treatment of patients with metastatic squamous NSCLC that has progressed during or after platinum-based chemotherapy, as well as patients with advanced metastatic non-squamous NSCLC who have progressed during or after platinum-based chemotherapy, following the results of the CheckMate-017[69] and CheckMate-057[70] studies, respectively, which showed a significant improvement in OS, with a median OS of 9.2 months versus 6.0 months in squamous NSCLC and 12.2 months versus 9.4 months in non-squamous NSCLC, compared to docetaxel.

It was subsequently approved in combination with chemotherapy as a neoadjuvant treatment for patients with resectable NSCLC based on the CheckMate-816 study.[71] In 2024, approval was extended to perioperative treatment, combining nivolumab with neoadjuvant chemotherapy, followed by nivolumab as adjuvant therapy, for patients with resectable NSCLC without EGFR/ALK mutations. This approval was made possible by the CHECKMATE-77T study.[72]

Nivolumab was studied in the CheckMate-9LA trial. This trial demonstrated a significant improvement in OS, with a median OS of 14.1 months for the combination of nivolumab plus ipilimumab with two cycles of chemotherapy versus 10.7 months with chemotherapy alone, in patients with metastatic NSCLC.[73] These findings led to regulatory authorization of this combination (nivolumab + ipilimumab + chemotherapy) as a first-line treatment for metastatic NSCLC without EGFR/ALK genetic alterations.

Pembrolizumab (Keytruda)

Pembrolizumab (Keytruda) is a humanized IgG4κ monoclonal antibody that targets the PD-1 receptor on T cells in order to reactivate their antitumor activity. It is one of the anti-PD-1 ICIs that have shown efficacy in the treatment of NSCLC, particularly as first-line monotherapy or in combination.[68]

Pembrolizumab has been evaluated in two major studies as monotherapy. In the KEYNOTE-024 trial, pembrolizumab significantly improved overall survival, with an estimated 6-month overall survival rate of 80.2% compared with 72.4% with platinum-based chemotherapy in patients with advanced NSCLC and PD-L1 expression ≥50%.[61] These results prompted the FDA to recommend pembrolizumab for the first-line treatment of metastatic NSCLC without EGFR mutations or ALK rearrangements, as monotherapy, with PD-L1 expression ≥50%. Subsequently, the FDA extended this indication to patients with metastatic or locally advanced NSCLC without EGFR/ALK genetic alterations and with low PD-L1 expression ≥1% in the KEYNOTE-042 study.[74]

In combination with chemotherapy, pembrolizumab has been studied in two pivotal trials. The KEYNOTE-189 study showed longer OS and progression-free survival (PFS) in patients with metastatic non-squamous NSCLC without EGFR/ALK mutations who were treated with pembrolizumab in combination with chemotherapy compared to chemotherapy alone.[75] These findings supported the clinical adoption of the combination for the first-line treatment of metastatic non-squamous NSCLC without EGFR or ALK mutations. At the same time, based on the results of the KEYNOTE-407 study, which reported a significant improvement in OS and PFS in patients with metastatic squamous NSCLC treated with pembrolizumab in combination with chemotherapy compared to chemotherapy alone,[76] the FDA has authorized the use of this combination for the first-line treatment of metastatic squamous NSCLC.

Pembrolizumab has been approved for use as a perioperative treatment for resectable stage II to III NSCLC. The KEYNOTE-671 study showed that this treatment, administered in combination with chemotherapy before surgery and then alone after surgery, resulted in better disease control and improved patient survival.[77]

Cemiplimab (Libtayo)

Cemiplimab (Libtayo) is a human monoclonal antibody that belongs to the PD-1 inhibitor family, designed to enhance the cytotoxic activity of T cells and thereby strengthen the antitumor immune response.[68] It was approved by the FDA in February 2021, based on the Phase 3 EMPOWER-Lung1 study,[78] as a first-line monotherapy treatment for patients with locally advanced or metastatic NSCLC with PD-L1 status ≥50% and no EGFR, ALK, or ROS1 genetic alterations.[78,79] In the EMPOWER-Lung 1 trial, cemiplimab monotherapy significantly improved OS, with median OS not reached compared with 14.2 months with platinum-based chemotherapy, in patients with advanced NSCLC and PD-L1 expression ≥50%.[78]

https://doi.org/10.2147/ITT.S591588

In November 2022, the results of the EMPOWER-Lung3 study led to regulatory authorization of Cemiplimab in combination with platinum-based chemotherapy as a first-line treatment for adult patients with advanced NSCLC without EGFR, ALK, or ROS1, regardless of PD-L1 status and disease histology.[80]

Other studies are currently being evaluated, such as the EMPOWER-Lung 4 trial, which is evaluating the combination of cemiplimab with ipilimumab as a second-line treatment in patients with advanced NSCLC with PD-L1 expression <50%.[81]

Collectively, PD-1 inhibitors have demonstrated consistent survival benefits across multiple treatment settings in NSCLC, although efficacy remains influenced by PD-L1 expression levels and tumor biology.

PD-L1 Inhibitors

Durvalumab (Imfinzi)

Durvalumab (Imfinzi) is a human IgG1 monoclonal antibody that binds to the PD-L1 ligand expressed on tumor cells. It belongs to the class of ICIs.[12] It was evaluated in a phase 3 study called PACIFIC as a consolidation treatment after chemoradiotherapy in patients with unresectable stage III NSCLC. It demonstrated a significant improvement in PFS compared to placebo, with a longer median time to death or distant metastasis (23.2 months versus 14.6 months).[82] These results led to the approval of Durvalumab as a consolidation treatment after chemoradiotherapy for patients with unresectable stage III NSCLC whose disease has not progressed after concomitant chemoradiotherapy.

As the PACIFIC study did not include a PD-L1 threshold, an exploratory analysis was conducted to evaluate the efficacy of durvalumab based on PD-L1 status. This analysis demonstrated the efficacy of durvalumab in all patients except those with PD-L1 status below 1%.[83] Based on these results, the European Medicines Agency (EMA) approved the use of durvalumab for the treatment of locally advanced, unresectable NSCLC in patients whose tumors express PD-L1 ≥1% and whose disease has not progressed after chemoradiotherapy.

The Phase III POSEIDON study[84] demonstrated improved OS and PFS in patients with metastatic NSCLC without EGFR/ALK mutations, thanks to the combination of durvalumab with tremelimumab and chemotherapy.[84] These data resulted in the clinical implementation of the combination of durvalumab + tremelimumab + chemotherapy as first-line treatment for metastatic NSCLC without EGFR/ALK mutations by the FDA in 2022 and by the EMA.

Based on the CASPIAN study, which showed a significant improvement in OS in patients with extensive-stage SCLC thanks to the combination of durvalumab with etoposide, platinum, or cisplatin-based chemotherapy,[85] the EMA[86] and the FDA (in 2020) approved durvalumab in combination with etoposide, platinum, or cisplatin-based chemotherapy for the first-line treatment of advanced SCLC.

Atezolizumab (Tecentriq)

Atezolizumab (Tecentriq) is a humanized IgG1 monoclonal antibody belonging to the family of ICIs that block the PD-L1 ligand.[68] It is used for the treatment of NSCLC either as monotherapy or in combination with chemotherapy.

Based on the IMpower150 study, which showed a significant improvement in PFS and OS in patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status, Using the combination of atezolizumab with bevacizumab and chemotherapy,[87] the FDA has authorized the use of atezolizumab in combination with bevacizumab and chemotherapy for the first-line treatment of patients with metastatic non-squamous NSCLC without EGFR or ALK genomic alterations.

In 2020, the FDA approved the use of atezolizumab monotherapy for the first-line treatment of patients with metastatic NSCLC with high PD-L1 expression (tumor cells ≥50% or immune cells ≥10%) and no EGFR or ALK genetic alterations. This approval is based on the IMpower110 study, in which atezolizumab resulted in significantly longer OS than platinum-based chemotherapy, with a median OS of 20.2 months versus 13.1 months, in patients with metastatic NSCLC with high PD-L1 expression, regardless of histological type and without EGFR/ALK mutations.[88]

In 2021, atezolizumab was approved by the FDA as adjuvant therapy after resection and platinum-based chemotherapy in patients with stage II–IIIA NSCLC with PD-L1 expression ≥1%. This approval is based on the IMpower010 study.[89]

Based on the results of the IMpower133 study,[90] the FDA approved the use of atezolizumab in combination with carboplatin and etoposide chemotherapy for the first-line treatment of patients with advanced SCLC.

PD-L1 inhibitors have expanded treatment options in both NSCLC and SCLC, particularly in consolidation and combination strategies.

Although pivotal clinical trials have consistently demonstrated the survival benefits of PD-1/PD-L1 inhibitors in NSCLC and, to a lesser extent, SCLC, several methodological considerations should be acknowledged. Most randomized studies have enrolled patients who were carefully selected on the basis of their good performance status and limited comorbidities. This may restrict the generalizability of the outcomes to broader real-world populations. Furthermore, differences in study design, inclusion criteria and PD-L1 assessment methods make indirect cross-trial comparisons between agents complicated. Despite these advances, a substantial proportion of patients do not achieve long-lasting responses, reflecting resistance mechanisms and tumor heterogeneity. These factors emphasize the need for ongoing evaluation of immunotherapy outcomes beyond the controlled environment of clinical trials.

Limitations of ICIs in Lung Cancer

Although ICIs targeting the PD-1/PD-L1 axis have improved outcomes for patients with lung cancer, they only benefit a subset of patients. Primary resistance is frequently observed, and acquired resistance may develop following an initial response. This reflects tumor heterogeneity and the dynamic interactions within the tumor immune microenvironment. Furthermore, adaptive immune mechanisms may facilitate immune evasion during treatment. Mechanisms such as loss of antigen presentation, alterations in interferon signaling, and T-cell exhaustion have been implicated in resistance to ICIs. The use of ICIs is still limited by immune-related adverse events, which can affect multiple systems and organs, sometimes requiring treatment to be interrupted. It is important to note that selecting patients remains challenging, as PD-L1 expression alone is not a reliable predictive biomarker due to its dynamic and heterogeneous nature. Together, these limitations highlight the need to improve biomarkers and refine therapeutic strategies to optimise the efficacy of immunotherapy in lung cancer.[91,92]

Notably, PD-L1 expression has limited negative predictive value. Clinical evidence suggests that some patients with low or negative PD-L1 expression may benefit from immune checkpoint inhibitors, while not all patients with high expression respond.[30]

Recent studies have identified additional molecular and epigenetic biomarkers in NSCLC, including DNA methylation of ABCG1 and integrative transcriptomic signatures. These biomarkers have been associated with patient survival and immune-related pathways, further emphasizing the biological heterogeneity of lung cancer and the need for multiparametric biomarker strategies.[93,94]

Comparative Efficacy of ICIs in Lung Cancer

Clinical evidence suggests that the efficacy of ICIs for treating lung cancer depends on the type of lung cancer and how it is being treated. In non-small cell lung cancer, ICIs have consistently improved clinical outcomes, particularly in the first line of treatment and in specific patient groups. Durable responses have been observed in some cases. By contrast, the benefit of ICIs in small-cell lung cancer is generally more limited, primarily being observed when these agents are combined with chemotherapy rather than used as monotherapy. These differences are thought to reflect the underlying biological disparities between NSCLC and SCLC, including variations in the tumor immune microenvironment and the reliability of biomarkers. Overall, the current evidence base supports the idea that the efficacy of ICIs depends on the context rather than allowing direct comparisons between individual agents. Differences in trial design, patient selection criteria, and PD-L1 assessment methodologies further complicate cross-trial comparisons.[4]

A comparative overview of regulatory-approved ICIs in lung cancer, including treatment strategy, efficacy, toxicity, and biomarker dependence, is presented in Table 4.

Figure 3 provides an integrative overview of the biological regulation of PD-L1, its assessment methods, clinical applications, and current limitations in lung cancer.

Table 4 Comparative Overview of FDA-Approved PD-1/PD-L1 Inhibitors in Lung Cancer

Immune Checkpoint Inhibitor	Line of Treatment	Therapeutic Strategy	Efficacy	Toxicity	Biomarker Dependence
Nivolumab	• Second-line metastatic NSCLC • Neoadjuvant/perioperative resectable NSCLC • First-line metastatic NSCLC	• Monotherapy • Combination with chemotherapy +/- ipilimumab	• Significant OS benefit in advanced NSCLC • Improved outcomes in perioperative and combination settings	Immune-related adverse events	• Not strictly PD-L1 dependent
Pembrolizumab	• First-line metastatic NSCLC • Perioperative resectable NSCLC	• Monotherapy • Combination with chemotherapy • Perioperative combination	• Significant OS and PFS benefit in metastatic NSCLC • Improved disease control in perioperative setting	Immune-related adverse events; higher in combination therapy	• PD-L1 dependent in monotherapy • Not strictly required in combination settings
Cemiplimab	• First-line advanced/metastatic NSCLC	• Monotherapy • Combination with chemotherapy	• Significant overall survival benefit in PD-L1 ≥50% • Extended benefit in combination therapy	Immune-related adverse events	• PD-L1 dependent in monotherapy
Durvalumab	• Consolidation in Stage III unresectable NSCLC • First-line metastatic NSCLC • First-line extensive-stage SCLC	• Monotherapy (consolidation) • Combination with chemotherapy ±tremelimumab	• Improved PFS and OS depending on disease stage and treatment setting	Immune-related adverse events; pneumonitis	• Not strictly PD-L1 dependent; EMA restriction ≥1% in stage III setting
Atezolizumab	• First-line metastatic NSCLC • Adjuvant resected NSCLC • First-line extensive-stage SCLC	• Monotherapy • Combination with chemotherapy ± bevacizumab • Adjuvant therapy	• Improved OS and PFS in metastatic NSCLC • Benefit in adjuvant setting • OS improvement in extensive-stage SCLC	Immune-related adverse events; higher in combination therapy	• PD-L1 dependent in monotherapy and adjuvant settings • Not strictly required in combination regimens

https://doi.org/10.2147/ITT.S591588

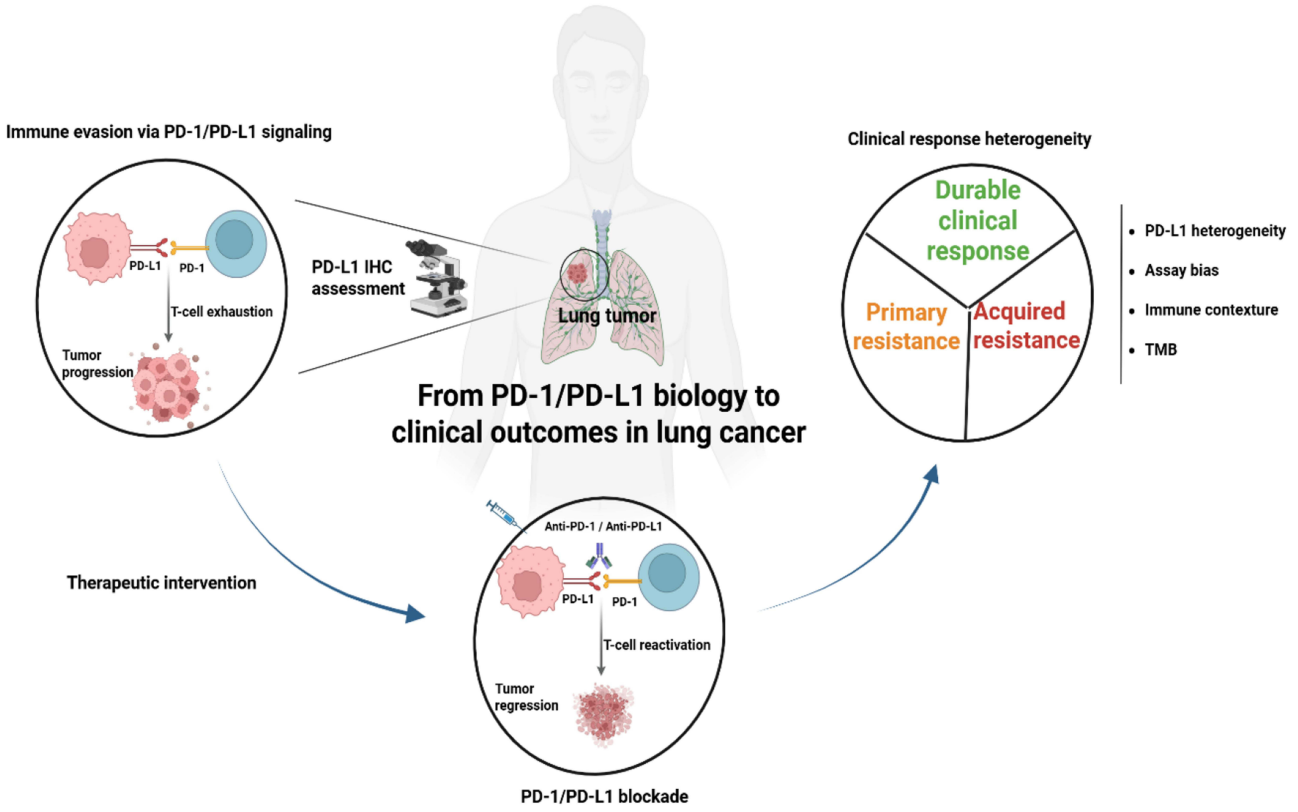

Figure 3 The PD-1/PD-L1 pathway in lung cancer: biological basis, therapeutic targeting, and clinical response variability (Created with BioRender). This figure summarizes the biological regulation of PD-L1 in the tumor microenvironment, how it is assessed by immunohistochemistry (TPS, IC, and CPS), and its role as a predictive biomarker for PD-1/PD-L1 immune checkpoint inhibitors in NSCLC and SCLC. It also illustrates major limitations, including heterogeneity, assay variability, and resistance mechanisms, highlighting the need for improved combinatorial biomarker strategies. Created with BioRender.

Conclusion

The PD-1/PD-L1 pathway plays a pivotal role in immune evasion in lung cancer, hindering the activity of cytotoxic T cells within the tumor microenvironment. Targeting this pathway with ICIs has transformed the treatment of both NSCLC and SCLC, improving survival rates in certain cases.

Currently, PD-L1 expression, as assessed by IHC, is the main predictive biomarker used to guide immunotherapy decisions, particularly for selecting anti-PD-1/PD-L1 monotherapy. However, due to its dynamic regulation, intratumoral heterogeneity, and variability across assays, PD-L1 expression alone remains an imperfect predictor of response. Therefore, clinically, PD-L1 testing should be interpreted within the broader biological and therapeutic context. Future research should focus on improving patient selection through the integration of complementary biomarkers, including molecular and epigenetic factors, as well as characteristics of the tumor immune microenvironment, in order to optimize the overall benefit of immunotherapy in lung cancer.

Data Sharing Statement

Data sharing is not applicable to this review article. However, data are available from the corresponding author upon reasonable request.

Acknowledgments

The authors would like to express their sincere thanks to the Laboratory of Cellular and Molecular Pathology at the Faculty of Medicine and Pharmacy at Hassan II University in Casablanca, as well as to the Laboratory of Pathological anatomy and cytology at the CHU Ibn Rochd in Casablanca, for their technical support and contributions to this work.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research did not receive any funding from a specific grant or other funding agency.

Disclosure

The authors report no potential conflicts of interest in this work.

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