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Immunotherapy in Non-Small Cell Lung Cancer: A Comprehensive Literature Synthesis

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Abstract:
This study aims to assess the therapeutic impact of immune checkpoint inhibitors (ICIs) targeting PD-1, PD-L1 and CTLA-4 in non-small cell lung cancer (NSCLC), with particular emphasis on PD-L1–guided treatment strategies and implementation challenges in low- and middle-income countries (LMICs). A structured case-study–based literature synthesis was conducted, including landmark randomized clinical trials, meta-analyses and international guidelines published between 2015 and 2025, retrieved from PubMed, Scopus and Web of Science, focusing on clinical efficacy, immune-related adverse events and biomarker-driven decision-making. The results indicate that ICIs significantly improve overall survival in NSCLC, extending median survival from approximately 8 months with conventional chemotherapy to nearly 24 months in selected patients; therapeutic benefit varies according to PD-L1 expression, favoring monotherapy for PD-L1 ≥50% and chemo-immunotherapy combinations for lower expression levels, while immune-related toxicities and biomarker heterogeneity remain major limitations. From a policy and public-health perspective, LMICs such as Algeria require standardized PD-L1 testing, reinforced multidisciplinary expertise for toxicity management, and adaptive health policies incorporating cost-containment strategies and digital oncology tools to optimize equitable access and maximize the clinical impact of immunotherapy in NSCLC.
Keywords: immunotherapy; non-small cell lung cancer; PD-L1; immune checkpoint inhibitors; immune-related adverse events.

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1. Introduction

Non-small cell lung cancer (NSCLC) represents ~85% of lung cancers and remains a leading cause of cancer mortality worldwide. Although platinum-based doublet chemotherapy historically offered limited survival benefit in advanced disease, the therapeutic landscape has been reshaped by immune checkpoint inhibitors (ICIs) and the progressive integration of biomarker-guided strategies. Long-term follow-up data confirm durable benefit with anti-PD-1 therapy in PD-L1-high metastatic NSCLC, with 5-year outcomes supporting pembrolizumab monotherapy as a reference option in selected patients (Reck et al., 2021). In parallel, immunotherapy has expanded beyond metastatic settings: consolidation durvalumab after concurrent chemoradiotherapy in unresectable stage III NSCLC demonstrated sustained overall survival benefit at 5 years (Spigel et al., 2022), and perioperative/neoadjuvant regimens have shown clinically meaningful improvements in event-free survival and pathologic response, notably with nivolumab plus chemotherapy in resectable disease (Forde et al., 2022). These advances underscore the need to link **biological mechanisms, clinical evidence across PD-L1 strata,** and **implementation constraints**—particularly in low- and middle-income countries (LMICs), where access, testing standardization, and toxicity management capacity can determine real-world impact.

2. Evolution of NSCLC Immunotherapy

2.1 Historical Perspective on NSCLC Treatment

In the early 2000s, systemic therapy for advanced NSCLC was largely dominated by platinum-based chemotherapy doublets, with modest survival outcomes and significant toxicity. As molecular oncology matured, targeted therapies improved outcomes in oncogene-addicted subgroups, but their scope remained limited to specific alterations. The modern immunotherapy era emerged from the recognition that tumors exploit immune checkpoints to suppress antitumor T-cell responses, enabling durable clinical responses with ICIs across broader patient populations. Over the last five years, the field has accelerated through **treatment intensification strategies** (chemo-IO and dual-IO regimens) with sustained long-term follow-up, including 3-year updates and subsequent longer analyses of nivolumab–ipilimumab–based approaches

(Bordenave, S et al., 2024), and **stage migration of immunotherapy** into curative-intent settings, such as adjuvant atezolizumab after resection and chemotherapy (IMpower010) (Felip et al., 2021) and perioperative pembrolizumab strategies supported by maturing survival analyses (Spicer et al., 2024). Collectively, these milestones position immunotherapy not as an "add-on," but as a central pillar of NSCLC care across stages, with PD-L1 testing and multidisciplinary capacity increasingly critical to treatment selection and safety.

2.2 Mechanisms of Immune Checkpoint Inhibition

ICIs restore antitumor immunity by blocking inhibitory pathways that restrain T-cell activation and effector function. The PD-1/PD-L1 axis primarily downregulates T-cell signaling in peripheral tissues and within the tumor microenvironment; interruption of this interaction can reinvigorate exhausted T cells and enhance cytotoxic activity against tumor cells (Liu et al., 2024). By contrast, CTLA-4 mainly acts earlier in the immune response, competing with CD28 co-stimulation and limiting T-cell priming, providing a rationale for combinatorial regimens that may increase breadth and depth of response but at the cost of higher immune-related toxicities. In clinical practice, PD-L1 immunohistochemistry (IHC) remains a pragmatic biomarker to guide first-line choices; however, assay-related variability and threshold-dependent interpretation can influence eligibility and outcomes. Recent comparative analyses report strong concordance between commonly used assays (e.g., SP263 vs 22C3) in NSCLC-relevant contexts, supporting harmonization efforts (Zhou et al., 2023). Because ICIs can induce immune-related adverse events affecting multiple organs, implementation requires standardized toxicity recognition pathways and guideline-based management; updated international guidance remains foundational for safe scale-up (Schneider et al., 2021).

Research question:

To what extent do PD-1/PD-L1 and CTLA-4 immune checkpoint inhibitors improve clinical outcomes across PD-L1 expression strata in NSCLC, and what implementation barriers (PD-L1 testing standardization, toxicity management capacity, and access constraints) most critically shape their real-world impact in LMIC settings such as Algeria?

3. Literature Review Methodology

3.1 Search Strategy

A structured literature review was conducted to identify relevant studies addressing the role of immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC). Searches were performed in **PubMed, Scopus**, and **Web of Science**, covering publications from **January 2015 to March 2025**, with particular emphasis on updated evidence from **2021–2025**. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords, including *"non-small cell lung cancer," "immunotherapy," "PD-1," "PD-L1," "CTLA-4," "immune checkpoint inhibitors," "immune-related adverse events,"* and *"precision oncology."*

Eligible studies included randomized controlled trials (RCTs), meta-analyses, pooled analyses, and international clinical guidelines published in English. Priority was given to landmark phase II–III trials and high-impact journals. Additional references were identified through manual citation tracking to ensure comprehensive coverage of both clinical efficacy and implementation perspectives, including global health considerations relevant to low- and middle-income countries (LMICs).

3.2 Theoretical Analysis and Data Synthesis

Data extraction focused on study design, patient population, line of treatment, PD-L1 expression assessment, therapeutic strategy (single-agent immunotherapy, chemo-immunotherapy, or dual immunotherapy), and key clinical outcomes. Primary endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and safety profiles.

A **narrative and comparative synthesis** approach was adopted to integrate evidence from pivotal RCTs (e.g., *KEYNOTE-024, KEYNOTE-189, CheckMate-057, CheckMate-227*) and contemporary meta-analyses. Studies were analyzed within a conceptual framework linking immune checkpoint biology, biomarker-driven decision-making, and real-world feasibility. Particular attention was paid to challenges related to PD-L1 assay variability, toxicity management, and disparities in access to immunotherapy across healthcare systems.

3.3 Efficacy According to PD-L1 Expression Levels

To evaluate treatment effectiveness, studies were stratified according to tumor PD-L1 expression levels (≥50%, 1–49%, and <1%), as assessed by immunohistochemistry. In patients with **high PD-L1 expression (≥50%),** single-agent anti–PD-1 therapy demonstrated substantial clinical benefit, with durable responses and significantly prolonged OS compared to chemotherapy.

For tumors with **intermediate PD-L1 expression (1–49%)**, combination strategies integrating immunotherapy with platinum-based chemotherapy consistently improved survival outcomes over chemotherapy alone. In contrast, patients with **low or negative PD-L1 expression (<1%)** derived limited benefit from immunotherapy monotherapy, with better outcomes observed using chemo-immunotherapy or selected dual immunotherapy regimens. This stratified synthesis highlights the central role of PD-L1 as a predictive biomarker while underscoring its limitations and the need for complementary markers.

3.4 Immune-Related Adverse Events (irAEs)

Immune checkpoint inhibition is associated with a distinct spectrum of immune-related adverse events (irAEs) resulting from nonspecific immune activation. The reviewed studies consistently reported dermatologic, gastrointestinal, hepatic, pulmonary, and endocrine toxicities, typically emerging within the first **3 to 6 months** of treatment. While most irAEs are low-grade and manageable, severe grade 3–4 events occur in a minority of patients and may require systemic corticosteroids or immunosuppressive therapy.

The analysis also considered atypical clinical patterns, such as pseudo-progression, which can complicate radiologic assessment, and infectious complications, including reactivation of latent infections. These safety considerations are particularly relevant in LMIC contexts, where diagnostic resources and specialized multidisciplinary management may be limited. The synthesis emphasizes the importance of early recognition protocols, clinician training, and standardized management guidelines to ensure safe and effective immunotherapy deployment.

5. Development Hypotheses (Non-tested)

Based on the theoretical framework of immune checkpoint inhibition, biomarker-driven oncology, and health-system constraints in LMICs, the

present literature review is guided by the following non-tested developmental hypotheses:

- **H1**: PD-L1 expression level is a key determinant of immunotherapy efficacy in NSCLC and should guide first-line therapeutic strategies.
- **H2**: Chemo-immunotherapy combinations provide superior survival benefit compared to immunotherapy alone in patients with low or intermediate PD-L1 expression.
- **H3**: Variability in PD-L1 assessment significantly impacts treatment allocation and clinical outcomes, particularly in resource-limited settings.
- **H4**: Immune-related adverse events constitute a major barrier to immunotherapy implementation in LMICs due to limited multidisciplinary expertise.
- **H5**: Health-system constraints (cost, infrastructure, geographic access) substantially limit the real-world effectiveness of ICIs in LMICs such as Algeria.

These hypotheses structure the interpretation of the results and highlight the originality of this synthesis at the intersection of molecular oncology and health policy.

6. Results

6.1 Descriptive Statistical Framework and Study Variables

To structure the synthesis of evidence, variables were classified into **dependent, independent**, and **control variables**, as summarized in Table 1.

Table 1. Descriptive Framework of Variables Used in the Literature Synthesis

Variable Type	Variable	Description
Dependent variables	Overall survival (OS)	Median and long-term survival outcomes reported in RCTs
	Progression-free survival (PFS)	Time to disease progression or death
	Objective response rate (ORR)	Proportion of patients achieving partial or complete response
	Incidence of irAEs	Frequency and severity of immune-related adverse events

Variable Type	Variable	Description
Independent variables	PD-L1 expression level	Stratified as ≥50%, 1–49%, <1%
	Treatment strategy	IO monotherapy, CT-IO, IO-IO
	Type of immune checkpoint	PD-1, PD-L1, CTLA-4
Control variables	Line of treatment	First-line vs later lines
	Disease stage	Resectable, locally advanced, metastatic
	Patient characteristics	Performance status, disease burden
	Healthcare setting	High-income vs LMIC context

6.2 Summary of Clinical Efficacy Across PD-L1 Subgroups

The synthesis of randomized trials demonstrates a clear gradient of efficacy according to PD-L1 expression. In patients with **PD-L1 ≥50%**, single-agent anti-PD-1 therapy consistently yields the highest ORR (≈40–45%) and median OS approaching 24 months. In the **PD-L1 1–49% subgroup**, chemo-immunotherapy combinations significantly improve OS and PFS compared with chemotherapy alone. For **PD-L1 <1% tumors**, immunotherapy monotherapy shows limited benefit, while CT-IO strategies outperform IO-IO regimens in most analyses, except in selected high-TMB populations.

6.3 Safety Outcomes and Immune-Related Adverse Events

Across trials, irAEs were reported in all immunotherapy regimens, with dermatologic, gastrointestinal, endocrine, hepatic, and pulmonary toxicities predominating. Grade 3–4 irAEs occurred in less than 10% of patients but required prompt immunosuppressive management. Pseudo-progression and infectious complications were infrequent but clinically significant, particularly in LMIC settings where diagnostic and monitoring resources are limited.

7. Discussion

Immunotherapy has profoundly altered the prognosis of NSCLC, transforming a historically lethal disease into one with durable responses in a substantial proportion of patients. The results synthesized in this review support **PD-L1 expression as a central—but imperfect—biomarker** guiding

treatment stratification. High PD-L1 tumors derive marked benefit from immunotherapy monotherapy, whereas intermediate and low expressors benefit most from combination approaches.

However, **biomarker variability** remains a critical limitation. Differences between PD-L1 assays and intratumoral heterogeneity may lead to misclassification and suboptimal treatment selection, an issue magnified in LMICs where access to standardized platforms is inconsistent. Strengthening pathology infrastructure and harmonizing testing protocols are therefore essential steps toward equitable precision oncology.

The burden of **immune-related toxicities** represents another major challenge. While manageable in well-resourced centers, irAEs require multidisciplinary expertise that is often scarce in LMICs. Tailored protocols, training programs, and early-warning systems are needed to safely scale immunotherapy in such contexts.

Finally, **access barriers**—including high drug costs, centralized oncology services, and rural–urban disparities—limit the real-world effectiveness of ICIs in countries like Algeria. International experiences suggest that regional collaboration, negotiated pricing, and digital health solutions (tele-oncology, e-MDTs) may partially mitigate these constraints.

Table 2. Summary of Development Hypotheses and Supporting Evidence (Originality Table)

Hypothesis	Supporting Evidence from Literature	Contribution of This Study
H1: PD-L1 predicts efficacy	KEYNOTE-024, KEYNOTE-189	Integrated across molecular and policy dimensions
H2: CT-IO superior in low PD-L1	CheckMate-227, KEYNOTE-189	Stratified synthesis by PD-L1 thresholds
H3: PD-L1 variability impacts outcomes	Blueprint IHC Project	Contextualized for LMIC implementation
H4: irAEs limit adoption in LMICs	ESMO guidelines, real-world studies	Highlighted as structural health-system issue
H5: Access constraints reduce impact	Global oncology reports	Algeria-focused translational perspective

7. Conclusion

Immunotherapy has profoundly transformed the therapeutic landscape of non-small cell lung cancer (NSCLC), shifting treatment paradigms from uniformly limited survival outcomes toward durable, biomarker-guided clinical benefit. The integration of immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 has enabled significant improvements in overall and progression-free survival, particularly when treatment selection is guided by tumor PD-L1 expression. This evolution confirms immunotherapy as a cornerstone of precision oncology in NSCLC across multiple disease stages.

However, the clinical promise of immunotherapy is tempered by persistent challenges that limit its real-world effectiveness, especially in low- and middle-income countries (LMICs). Variability in PD-L1 immunohistochemical assessment, disparities in assay availability, and intratumoral heterogeneity undermine consistent patient stratification. In parallel, immune-related adverse events necessitate specialized multidisciplinary expertise and structured monitoring pathways, which remain insufficiently developed in resource-constrained healthcare systems. Economic barriers, centralized oncology services, and geographic inequities further restrict access to these high-cost therapies, perpetuating survival disparities.

Addressing these limitations requires a coordinated and context-adapted strategy. Standardization of PD-L1 testing, reinforcement of pathology and oncology training programs, and the implementation of harmonized toxicity-management protocols are essential prerequisites for safe and effective immunotherapy deployment. Moreover, regional collaboration, negotiated pricing models, and the integration of digital health solutions—such as electronic multidisciplinary tumor boards (e-MDTMs) and tele-oncology platforms—offer pragmatic avenues to expand access and optimize decision-making. In this context, Algeria has the potential to emerge as a regional reference for precision oncology in North Africa by aligning molecular diagnostics, clinical expertise, and health policy innovation. Such an integrated approach is critical to ensuring equitable access to life-saving immunotherapies and maximizing their public-health impact in NSCLC.

8. References

Bordenave, S., Reck, M., Ciuleanu, T. E., Schenker, M., Juan-Vidal, O., & FELIP, E. (2024). Five-year outcomes with first-line nivolumab plus ipilimumab with 2 cycles of chemotherapy versus 4 cycles of chemotherapy alone in patients with metastatic non-small cell lung cancer in the randomized CheckMate 9LA trial. DOI: 10.1016/j.ejca.2024.114296. Epub 2024 Aug 25.

Felip, E., Altorki, N., Zhou, C., Csőszi, T., Vynnychenko, I., Goloborodko, O., ... & Wakelee, H. (2021). Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. The Lancet, 398(10308), 1344-1357. DOI: 10.1016/S0140-6736(21)02098-5

Forde, P. M., Spicer, J., Lu, S., Provencio, M., Mitsudomi, T., Awad, M. M., ... & Girard, N. (2022). Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. New England Journal of Medicine, 386(21), 1973-1985. DOI: full/10.1056/nejmoa2202170

Liu, R., Li, HF., Li, S. (2024). PD-1-mediated inhibition of T cell activation: Mechanisms and strategies for cancer combination immunotherapy. Cell Insight ; Volume 3, Issue 2, April 2024, 100146. https://doi.org/10.1016/j.cellin.2024.100146

Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A., ... & Brahmer, J. R. (2021). Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non–small-cell lung cancer with PD-L1 tumor proportion score≥ 50%. Journal of Clinical Oncology, 39(21), 2339-2349. DOI: 10.1200/JCO.21.00174

Schneider, B. J., Naidoo, J., Santomasso, B. D., Lacchetti, C., Adkins, S., Anadkat, M., ... & Bollin, K. (2021). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. Journal of Clinical Oncology, 39(36), 4073-4126. DOI: 10.1200/jco.21.01440

Spicer, J. D., Garassino, M. C., Wakelee, H., Liberman, M., Kato, T., Tsuboi, M., ... & Liu, G. (2024). Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung

cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 404(10459), 1240-1252. DOI: 10.1016/S0140-6736(24)01756-2

Spigel, D. R., Faivre-Finn, C., Gray, J. E., Vicente, D., Planchard, D., Paz-Ares, L., ... & Antonia, S. J. (2022). Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. Journal of Clinical Oncology, 40(12), 1301-1311. DOI: 10.1200/JCO.21.01308

Zhou, C., Srivastava, M. K., Xu, H., Felip, E., Wakelee, H., Altorki, N., ... & Novello, S. (2023). Comparison of SP263 and 22C3 immunohistochemistry PD-L1 assays for clinical efficacy of adjuvant atezolizumab in non-small cell lung cancer: results from the randomized phase III IMpower010 trial. Journal for Immunotherapy of Cancer, 11(10), e007047. DOI: 10.1136/jitc-2023-007047