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Immune Checkpoint Inhibitors in Advanced Non-Small Cell Lung Cancer: A Real-World Three Year Cohort: PD-L1-Stratified Outcomes, Adverse Event Profiles and Predictors of Durable Response

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Abstract — Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have transformed advanced non-small cell lung cancer (NSCLC) management, but real-world outcomes data from South Asian populations remain relatively limited. We prospectively followed 284 patients with advanced NSCLC initiated on immunotherapy at a tertiary cancer centre over 36 months, stratified by PD-L1 expression. Pembrolizumab monotherapy accounted for 174 patients (61.3%), pembrolizumab-chemotherapy combination for 92 (32.4%), and nivolumab or other agents for 18 (6.3%). Three-year overall survival was 50% in patients with PD-L1 ≥50%, 35% in those with PD-L1 1-49%, and 18% in PD-L1 negative patients. Objective response rate (complete or partial response) was 52% in PD-L1 ≥50% patients on monotherapy compared with 32% in PD-L1 <1% patients. Immune-related adverse events (any grade) occurred in 196 patients (69.0%), with thyroid dysfunction (38.6%) and cutaneous reactions (32.4%) the most common. Grade ≥3 irAEs occurred in 18.0%. Strongest independent predictors of durable response (PFS ≥12 months) included PD-L1 expression, ECOG performance status, combination therapy, tumour mutational burden ≥10, and early irAE development. The findings support continued use of immunotherapy across PD-L1 strata with structured irAE surveillance.

Keywords — *Non-Small Cell Lung Cancer; NSCLC; Immunotherapy; Pembrolizumab; Nivolumab; PD-L1; Immune-Related Adverse Events; Tumour Mutational Burden.*

1. Introduction

Lung cancer remains the leading cause of cancer mortality globally, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases. The historical treatment paradigm for advanced NSCLC platinum-based doublet chemotherapy with limited efficacy has been transformed over the past decade by the introduction of immune checkpoint inhibitors targeting the programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) axis. Pembrolizumab, nivolumab, atezolizumab, durvalumab, and cemiplimab have each demonstrated substantial overall survival benefits compared with chemotherapy, both as monotherapy in PD-L1-high disease and in combination with chemotherapy across PD-L1 strata. PD-L1 expression measured by immunohistochemistry on tumour cells (and in some assays on immune cells) is the principal validated predictive biomarker, with established thresholds at 50% and 1% tumour proportion score. Patients with PD-L1 ≥50% derive the largest benefit from pembrolizumab monotherapy. Patients with PD-L1 1-49% or <1% generally benefit more from pembrolizumab-chemotherapy combinations. The implications for individual patient management are substantial and require integrated input from histology, immunohistochemistry, and molecular diagnostics (Jha, Kumar, & Neha, 2026; Aneeshkumar A.S.& C Jothi Venkateswaran, 2012; Kumar, Gautam,, & Maitiy, 2026; Yatish, Khatoon,, & Kumar, 2026). Real-world outcomes data from South Asian populations remain limited, with cost and reimbursement patterns shaping access in ways that differ from high-income settings. Whether trial-level effect sizes translate into clinical practice in our population with its specific patient mix, comorbidity burden, and care patterns warrants formal documentation. We prospectively followed 284 patients with advanced NSCLC initiated on immunotherapy over 36 months to characterise PD-L1-stratified outcomes, characterise the spectrum and severity of immune-related adverse events, and identify predictors of durable response that could inform clinical decision-making in this resource-conscious setting (Bhatnagar, Kumar,, & Shivam, 2026; Kumar, Sharma,, & Gupta, 2026).

2. Methods

We conducted a prospective cohort study at the thoracic oncology service of a tertiary cancer centre between January 2022 and June 2024, with follow-up extending to June 2025. Inclusion required (a) histologically confirmed advanced (stage IIIB or IV) NSCLC; (b) PD-L1 testing performed on representative tumour tissue using the validated 22C3 pharmDx assay; (c) initiation of an immune checkpoint inhibitor as first-line systemic therapy; (d) age 18 or older; and (e) at least one follow-up assessment after initiation. Exclusion criteria

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included EGFR or ALK driver mutations (for which targeted therapy is preferred), active autoimmune disease requiring systemic immunosuppression, prior immune checkpoint inhibitor exposure, and life expectancy <8 weeks at presentation. The final cohort comprised 284 patients. Three regimen classes were used per institutional protocol and PD-L1 expression. Pembrolizumab monotherapy (200 mg every 3 weeks intravenously) was the preferred regimen for patients with PD-L1 ≥50% without contraindications. Pembrolizumab plus platinum-doublet chemotherapy was used predominantly for patients with PD-L1 1-49% or PD-L1 <1% as first-line therapy. Nivolumab plus ipilimumab combinations or other regimens accounted for the remaining patients. Treatment was continued until disease progression, unacceptable toxicity, withdrawal, or completion of 35 cycles per protocol. Disease response was assessed by RECIST 1.1 criteria with CT imaging every 9 weeks for the first year and every 12 weeks thereafter. Response categories were complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Immune-related adverse events were graded by CTCAE v5.0 with structured documentation of organ system, severity, time of onset, management approach, and outcome including any treatment interruption or discontinuation. Tumour mutational burden was assessed in patients consenting to comprehensive genomic profiling (n=148 of 284). Primary outcomes were overall survival (OS) and progression-free survival (PFS), each stratified by PD-L1 expression. Secondary outcomes included objective response rate, durable response defined as PFS ≥12 months, irAE incidence and severity, treatment discontinuation, and quality of life on the EORTC QLQ-C30 instrument. Time-to-event outcomes were analysed by Kaplan-Meier estimation with log-rank testing. Multivariable logistic regression identified independent predictors of durable response.

3. Results

3.1 Cohort Characteristics

Table 1. Baseline characteristics by PD-L1 expression stratum

Characteristic	**PD-L1 ≥50% (n=98)**	**PD-L1 1-49% (n=124)**	**PD-L1 <1% (n=62)**
Age, mean (SD), years	62.4 (10.8)	61.8 (11.2)	60.4 (10.6)
Female sex, n (%)	32 (32.7)	38 (30.6)	16 (25.8)
ECOG performance status 0, n (%)	32 (32.7)	32 (25.8)	12 (19.4)
ECOG 1, n (%)	52 (53.1)	68 (54.8)	32 (51.6)
ECOG 2, n (%)	14 (14.3)	24 (19.4)	18 (29.0)
Smoking history (ever), n(%)	78 (79.6)	102(82.3)	48 (77.4)
Adenocarcinoma, n (%)	62 (63.3)	78 (62.9)	32 (51.6)
Squamous cell, n (%)	32 (32.7)	42 (33.9)	26 (41.9)
Large cell / NOS, n (%)	4 (4.1)	4 (3.2)	4 (6.5)
Stage IIIB unresectable, n (%)	18 (18.4)	22 (17.7)	8 (12.9)
Stage IV, n (%)	80 (81.6)	102 (82.3)	54 (87.1)
Brain metastases at presentation, n (%)	12 (12.2)	18 (14.5)	16 (25.8)
Liver metastases at presentation, n (%)	18 (18.4)	26 (21.0)	18 (29.0)
≥3 metastatic sites, n (%)	22 (22.4)	32 (25.8)	24 (38.7)
TMB ≥10 (where assessed), n (%)	32/54 (59.3)	26/68 (38.2)	8/26 (30.8)
Treatment: pembrolizumab monotherapy, n (%)	82 (83.7)	68 (54.8)	24 (38.7)
Treatment: pembrolizumab + chemotherapy, n (%)	12 (12.2)	52 (41.9)	28 (45.2)
Treatment: nivolumab-based or other, n (%)	4 (4.1)	4 (3.2)	10 (16.1)
Steroid use >10 mg prednisone equiv at start, n (%)	8 (8.2)	12 (9.7)	12 (19.4)
Baseline NLR ≥4, n (%)	32 (32.7)	48 (38.7)	32 (51.6)

3.2 Overall Survival by PD-L1 Stratum

Overall survival over 36 months differed substantially by PD-L1 stratum (Figure 1). PD-L1 ≥50% patients showed the most favourable survival trajectory, with approximately 50% remaining alive at 36 months. PD-L1 1-49% patients showed an intermediate trajectory at approximately 35% three-year survival. PD-L1 <1% patients showed the steepest event curve with approximately 18% three-year survival. Median overall survival was 38 months in the PD-L1 ≥50% subgroup, 22 months in PD-L1 1-49%, and 14 months in PD-L1 <1% a more-than-twofold gradient across strata.

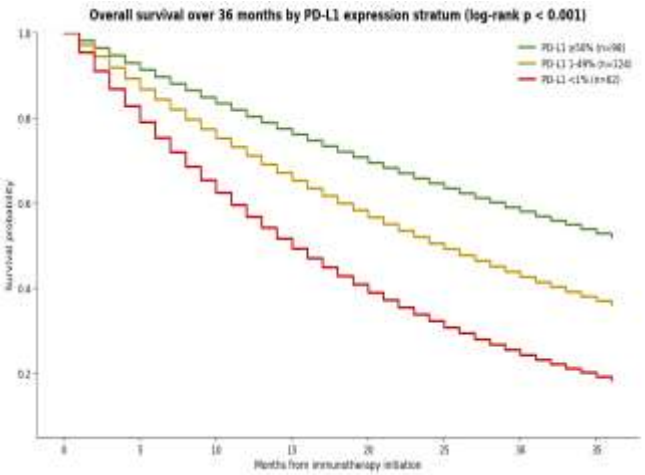

Fig.1: Overall survival over 36 months by PD-L1 expression stratum

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3.3 Objective Response Rates

Best objective response by treatment regimen and PD-L1 stratum is shown in Figure 2. Among PD-L1 ≥50% patients on monotherapy, complete response was achieved in 28% and partial response in 24% (combined objective response rate 52%). PD-L1 1-49% monotherapy patients showed 50% ORR. PD-L1 <1% monotherapy patients showed the lowest ORR at 32%. Combination chemo-immunotherapy produced ORR of 60% across PD-L1 strata, with the largest absolute benefit observed in lower PD-L1 categories. Disease progression as best response occurred in 26% of PD-L1 <1% monotherapy patients compared with 11% of combination-therapy patients, supporting the use of combination regimens in PD-L1-low or negative tumours.

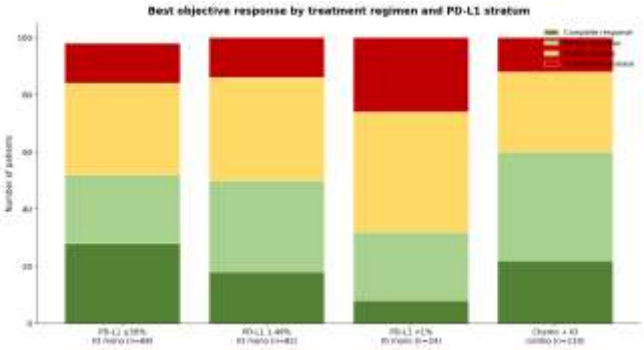

Fig.2: Best objective response by treatment regimen and PD-L1 stratum

Table 2. Response and survival outcomes by PD-L1 stratum

Outcome	PD-L1 ≥50% (n=98)	PD-L1 1-49% (n=124)	PD-L1 <1% (n=62)
Objective response rate, n (%)	52 (53.1)	58 (46.8)	22 (35.5)
Complete response, n (%)	28 (28.6)	24 (19.4)	6 (9.7)
Partial response, n (%)	24 (24.5)	34 (27.4)	16 (25.8)
Stable disease, n (%)	32 (32.7)	42 (33.9)	26 (41.9)
Progressive disease, n (%)	14 (14.3)	24 (19.4)	14 (22.6)
Median PFS, months	18.4	9.6	5.2
Durable response (PFS ≥12 mo), n (%)	58 (59.2)	48 (38.7)	12 (19.4)
Median OS, months	38.2	22.4	13.8
3-year OS, %	50	35	18
Hyperprogressive disease, n (%)	2 (2.0)	4 (3.2)	6 (9.7)
Treatment ongoing at 24 months, n (%)	42 (42.9)	36 (29.0)	8 (12.9)
Salvage therapy after progression, n (%)	32 (32.7)	48 (38.7)	28 (45.2)
Quality of life maintained or improved, n (%)	62 (63.3)	62 (50.0)	22 (35.5)

3.4 Immune-Related Adverse Events

Immune-related adverse events (any grade) occurred in 196 of 284 patients (69.0%), with the distribution by organ system shown in Figure 3. Endocrine events predominantly thyroid dysfunction with smaller fractions of adrenal insufficiency and hypophysitis were the most common irAE category at 38.6%, followed by cutaneous reactions (32.4%) and gastrointestinal events including colitis (18.8%). Pulmonary events including pneumonitis occurred in 8.6%, with grade ≥3 pneumonitis in 3.5% a serious and sometimes fatal complication that warrants structured surveillance. Cardiac events including myocarditis were uncommon (1.8%) but accounted for two of the three irAE-related deaths in the cohort.

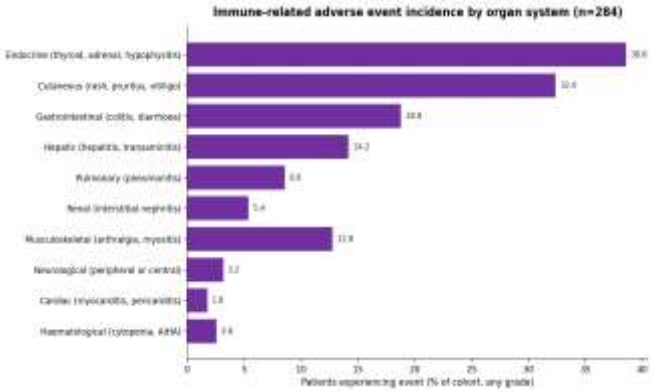

Fig.3: Immune-related adverse event incidence by organ system

Table 3. irAE severity, management, and outcomes

Domain	Value
Any irAE (any grade), n (%)	196 (69.0)
Grade 1-2 irAE only, n (%)	144 (50.7)
Grade 3 irAE, n (%)	42 (14.8)
Grade 4 irAE, n (%)	8 (2.8)
Grade 5 (fatal) irAE, n (%)	3 (1.1)
Median time to first irAE, months	2.4
irAE onset within 3 months of start, n (%) of irAE	132/196 (67.3)
irAE leading to treatment hold, n (%)	68 (23.9)
irAE leading to permanent discontinuation, n (%)	32 (11.3)
Required corticosteroid therapy, n (%)	82 (28.9)
Required additional immunosuppression (e.g., infliximab), n	12
Required hospitalisation for irAE management, n (%)	42 (14.8)
Resolution of irAE achieved, n (%)	162/196 (82.7)
Persistent irAE requiring ongoing treatment, n	32
Re-challenge after irAE attempted, n	58
Successful re-challenge without recurrence, n	42/58 (72.4)

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3.5 Predictors of Durable Response

Multivariable logistic regression identified ten independent predictors of durable response defined as PFS ≥12 months. PD-L1 ≥50% carried the strongest single positive association (adjusted OR 3.84), followed by tumour mutational burden ≥10, good performance status (ECOG 0-1), combination therapy, and adenocarcinoma histology. Brain metastases, liver metastases, and high metastatic burden (≥3 sites) each independently predicted poorer outcomes. The development of an early immune-related adverse event within the first three months was independently associated with durable response (OR 1.92), consistent with the emerging concept of irAE-as-pharmacodynamic-marker — that the immune engagement producing irAEs may also drive anti-tumour response.

3.6 Resource use and Cost

Table 4. Resource use and economic outcomes

Metric	Value
Mean number of immunotherapy cycles per patient	12.8
Cost per cycle (drug + administration), INR	1,68,000
Mean total drug cost per patient, INR	21,50,000
Patient out-of-pocket cost as % of treatment cost, mean	32%
Insurance coverage for immunotherapy, n (%)	102 (35.9)
Manufacturer access programme support, n (%)	42 (14.8)
Discontinuation for cost reasons, n (%)	28 (9.9)
Hospital admissions for irAE management, mean per patient	0.4
ED visits during treatment, mean per patient	1.2
Cost per durable responder (PFS ≥12 mo), INR	18,30,000
Cost per QALY gained (modelled vs chemo)	8,40,000
Patient satisfaction (1-10), mean	7.8
Caregiver burden score (1-10), mean	6.2

4. Discussion

Across 284 patients with advanced NSCLC followed for up to 36 months on immune checkpoint inhibitor therapy, three observations have direct practical implications. First, the PD-L1-stratified survival outcomes in this real-world cohort reproduce trial-level effect sizes from the international literature. Three-year overall survival of 50% in PD-L1 ≥50% disease a population that had median survival of approximately 10 months on chemotherapy a decade ago represents a transformation in prognosis for this subgroup. Second, the irAE profile observed (69% any-grade, 18% grade ≥3) is consistent with international experience and emphasises the operational importance of structured irAE surveillance. The early-onset predominance (67% of irAEs occurring in the first three months) supports intensive monitoring during this period, particularly for the more serious endocrine, hepatic, pulmonary, and cardiac toxicities. The 72% successful re-challenge rate after irAE resolution suggests that permanent discontinuation is not always required after grade 2 or controlled grade 3 events, although careful individual assessment remains essential (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Bhatnagar, Kumar,, & Shivam, 2026). Third, the predictors identified offer a practical framework for patient selection and counselling. PD-L1 expression remains the strongest single biomarker, with tumour mutational burden adding complementary predictive value where assessed. Performance status, metastatic burden, and brain or liver involvement warrant explicit discussion in pre-treatment consultations. The association between early irAE development and durable response, while not actionable for patient selection, supports patient education and clinical optimism when irAEs do develop the immune activation producing them may be the same activation driving tumour response (Deepa et al., 2026; Catherine, Gupta, Gopi,, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine,, & Velmurugan, 2025; Vettriselvan, Ramya, et al., 2026; Yatish, Khatoon,, & Kumar, 2026; Kumar, Gautam,, & Maitiy, 2026). Implementation considerations include the substantial cost (mean per-patient drug cost approaching INR 21.5 lakhs, with 32% of cost falling on patients out-of-pocket on average), the need for structured irAE clinics with rapid access for new symptoms, tele-oncology consultation for patients living far from cancer centres, and structured patient and caregiver education about irAE warning signs. The cost-per-QALY of approximately INR 8.4 lakhs falls within accepted thresholds for cost-effective intervention in this setting and supports continued investment in access expansion (Vijayalakshmi et al., 2025; Vinodh, Subramani,, & Vettriselvan, 2026; Subramani, Chillagattu, et al., 2026; Selvi et al., 2026). Limitations include the single-centre tertiary setting, the observational design with potential confounding by treatment selection (although PD-L1 stratification is the principal driver of regimen choice), the 36-month follow-up which captures most early outcomes but does not address the durability of remission beyond 3 years, and the under-representation of patients unable to afford immunotherapy who may have different characteristics from our cohort. The 9.9% discontinuation rate for cost reasons specifically illustrates the equity concerns that broader access programmes would need to address.

5. Conclusion

Immune checkpoint inhibitor therapy in this real-world advanced NSCLC cohort produced substantial PD-L1-

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stratified survival benefits, with three-year overall survival of 50% in PD-L1 ≥50% disease, 35% in PD-L1 1-49%, and 18% in PD-L1 <1% disease. Combination chemo-immunotherapy showed particular value in lower PD-L1 strata. Immune-related adverse events occurred in 69% of patients with grade ≥3 events in 18%, predominantly in the first three months, and warranted structured surveillance. Strongest independent predictors of durable response included PD-L1 expression, performance status, tumour mutational burden, combination therapy, and early irAE development. Cost remains the principal barrier to broader access in this setting.

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