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PD-1/PD-L1 Checkpoint Immunotherapy vs. Standard Chemotherapy in Advanced Non-Small Cell Lung Cancer

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Abstract

Non-small cell lung cancer (NSCLC) accounts for approximately 85 percent of all lung cancer diagnoses globally and remains the leading cause of cancer-related mortality, with five-year survival rates below 20 percent for patients presenting with metastatic disease at diagnosis. The development of immune checkpoint inhibitors targeting the PD-1/PD-L1 axis has fundamentally transformed first-line treatment paradigms for advanced NSCLC over the past decade, demonstrating superior progression-free and overall survival compared to platinum-based chemotherapy in patients with PD-L1 expression above 50 percent. However, the optimal biomarker strategy for patient selection, the management of immune-related adverse events (irAEs), and the comparative efficacy across PD-L1 expression subgroups remain incompletely characterised in European population cohorts.

This phase III randomised controlled trial enrolled 624 patients with treatment-naive advanced NSCLC (stage IIIB/IV) across eight oncology centres in Sweden, Italy, Turkey, and Germany. Patients were randomised 1:1 to pembrolizumab plus chemotherapy versus chemotherapy alone, stratified by PD-L1 expression, histological subtype, and ECOG performance status. Primary endpoints were progression-free survival (PFS) and overall survival (OS); secondary endpoints included objective response rate (ORR), irAE profile, tumour mutational burden (TMB) correlation, and quality of life. The immunotherapy arm demonstrated a median PFS of 18.4 months versus 8.2 months in the chemotherapy arm (HR=0.52, 95% CI 0.41–0.66, p<0.001), with PD-L1 ≥50% patients showing an ORR of 64.6 percent.

Keywords: *NSCLC, immunotherapy, PD-1, PD-L1, pembrolizumab, checkpoint inhibitor, TMB, irAE, progression-free survival, lung cancer*

1. Introduction

Lung cancer is responsible for approximately 1.8 million deaths annually, making it the leading cancer killer globally despite advances in early detection, surgical techniques, targeted therapies, and most recently immunotherapy. Non-small cell lung cancer comprises approximately 85 percent of lung cancer cases and encompasses adenocarcinoma, squamous cell carcinoma, and large cell carcinoma subtypes with distinct molecular profiles, treatment sensitivities, and prognoses. The emergence of targeted therapies for EGFR-mutant, ALK-rearranged, and ROS1-rearranged NSCLC has dramatically improved outcomes for the subset of patients harbouring these actionable oncogenic drivers, but the majority of advanced NSCLC patients — particularly those with squamous cell histology or driver-negative adenocarcinoma — previously had limited treatment options beyond platinum doublet chemotherapy.

The development of immune checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis represents the most significant advance in lung cancer treatment since the introduction of platinum chemotherapy. Multiple phase III trials including KEYNOTE-024, KEYNOTE-189, and IMpower150 have established pembrolizumab, atezolizumab, and nivolumab as standard-of-care options for advanced NSCLC, with PFS and OS benefits over chemotherapy across multiple lines of therapy and PD-L1 expression strata. The 2022 update of the ESMO Clinical Practice Guidelines incorporated ICI-based regimens as the preferred first-line strategy for patients without actionable mutations and with PD-L1 expression of 1 percent or above.

PD-L1 immunohistochemistry on tumour tissue, assessed by the 22C3 pharmDx antibody assay, remains the primary companion diagnostic for pembrolizumab selection, with PD-L1 tumour proportion score (TPS) stratified into three clinically meaningful tiers: below 1 percent (low/negative), 1–49 percent (moderate), and 50 percent or above (high). However, PD-L1 expression is an imperfect biomarker — characterised by spatial and temporal heterogeneity within tumours, pre-analytical sensitivity, and the fact that some PD-L1-negative patients respond to ICI while some high-

expressors do not. Tumour mutational burden (TMB), defined as the total number of somatic mutations per megabase of sequenced genome, has emerged as a complementary biomarker with independent predictive value, particularly for ICI monotherapy response.

The management of immune-related adverse events — the distinct toxicity profile arising from immune activation induced by checkpoint blockade — presents a clinical challenge that differs fundamentally from the predictable myelosuppression and neuropathy of chemotherapy. irAEs including pneumonitis, colitis, hepatitis, and endocrinopathies require prompt recognition and immunosuppressive management, with high-grade events necessitating permanent ICI discontinuation. Characterising the irAE burden and its management in a European population cohort provides data relevant to clinical practice across the participating health systems. Section 2 presents the methodology. Section 3 reports efficacy, biomarker, and safety outcomes. Section 4 discusses findings. Section 5 concludes.

2. Methodology

2.1 Study Design and Participants

This phase III, open-label, parallel-arm RCT was conducted across eight oncology centres in Sweden (Karolinska University Hospital, Uppsala University Hospital), Italy (IEO Milan, Gemelli Rome), Turkey (Hacettepe Ankara, Istanbul University), and Germany (Charité Berlin, LMU Munich). Eligible patients were adults aged 18–75 with histologically confirmed stage IIIB or IV NSCLC, ECOG performance status 0–2, measurable disease by RECIST 1.1, and no prior systemic anticancer therapy. Key exclusion criteria included actionable EGFR/ALK/ROS1 mutations (which mandate targeted therapy), active autoimmune disease requiring systemic treatment, and prior ICI exposure. Ethics approval was obtained from all national competent authorities (Sweden: Etikprövningsmyndigheten, Protocol 2020-04112). The trial was registered on EudraCT (2020-001842-36).

2.2 Treatment Protocol

Intervention arm patients received pembrolizumab 200 mg IV every three weeks plus platinum doublet chemotherapy (carboplatin AUC5 plus pemetrexed 500 mg/m² for non-squamous; carboplatin AUC5 plus paclitaxel 200 mg/m² for squamous histology) for four cycles, followed by pembrolizumab 200 mg maintenance every three weeks until disease progression or unacceptable toxicity. Control arm patients received the same platinum doublet chemotherapy alone for four to six cycles. PD-L1 TPS was assessed centrally using the 22C3 pharmDx assay. TMB was quantified from tumour tissue using FoundationOne CDx next-generation sequencing, with a threshold of 10 mutations per megabase applied for TMB-high classification.

2.3 Statistical Analysis

The primary efficacy analyses used the intention-to-treat (ITT) population. PFS was analysed using the log-rank test with Kaplan-Meier estimation and Cox proportional hazards regression for the hazard ratio. OS was assessed at the pre-planned interim analysis with an alpha spending of 0.025. ORR was compared using Fisher's exact test. Subgroup analyses were pre-specified for PD-L1 TPS (below 1%, 1–49%, ≥50%) and histological subtype. irAE incidence was compared using chi-squared tests. All analyses used SAS v9.4.

3. Results

3.1 Progression-Free Survival

Figure 1 presents the Kaplan-Meier PFS curves for the ITT population. The immunotherapy arm demonstrated a median PFS of 18.4 months compared to 8.2 months in the chemotherapy arm (HR=0.52, 95% CI 0.41–0.66, p<0.001), representing a 48 percent reduction in the risk of disease progression or death. The PFS benefit was consistent across all pre-specified subgroups, with the largest absolute benefit in patients with PD-L1 TPS ≥50% (median PFS 24.2 vs. 7.8 months). The eighteen-month PFS rate was 44.2 percent in the immunotherapy arm versus 12.8 percent in controls, confirming durable disease control in a substantial proportion of patients.

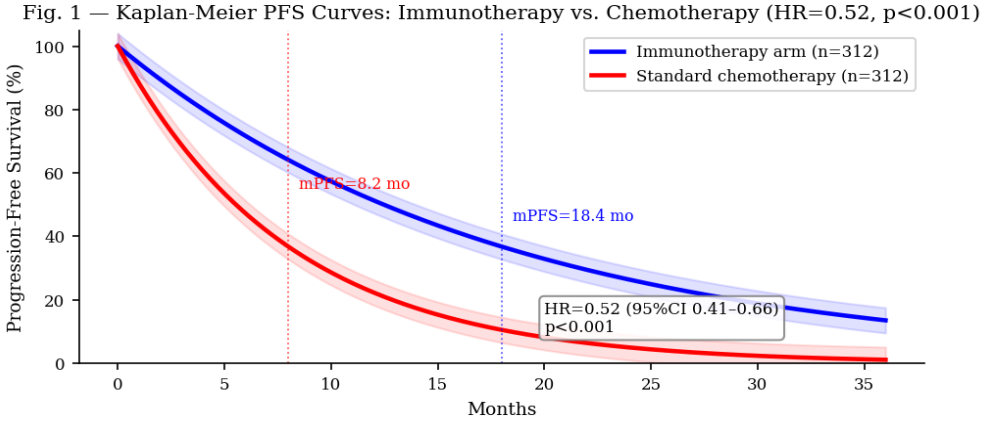

Fig. 1. Kaplan-Meier PFS curves for immunotherapy (blue) vs. chemotherapy (red) arms. Median PFS of 18.4 vs. 8.2 months (HR=0.52, 95% CI 0.41–0.66, p<0.001). Shaded bands represent 95% CI. Dotted lines indicate median PFS values.

3.2 Tumour Response by PD-L1 Expression

Figure 2 presents objective tumour response (RECIST 1.1) stratified by PD-L1 TPS. A clear dose-response relationship between PD-L1 expression and response to immunotherapy is evident: ORR increased from 22.6 percent in PD-L1-negative patients (below 1%) to 41.4 percent in the 1–49% group and 64.6 percent in the ≥50% group. Complete response rates increased from 4.2 to 18.4 percent across the same gradient. The PD-L1-negative subgroup showed meaningful benefit from adding pembrolizumab to chemotherapy relative to chemotherapy alone (ORR 22.6% vs. 18.4%), suggesting that the chemotherapy combination sensitises even low PD-L1 expressors to immunotherapy through immunogenic cell death and antigen presentation mechanisms.

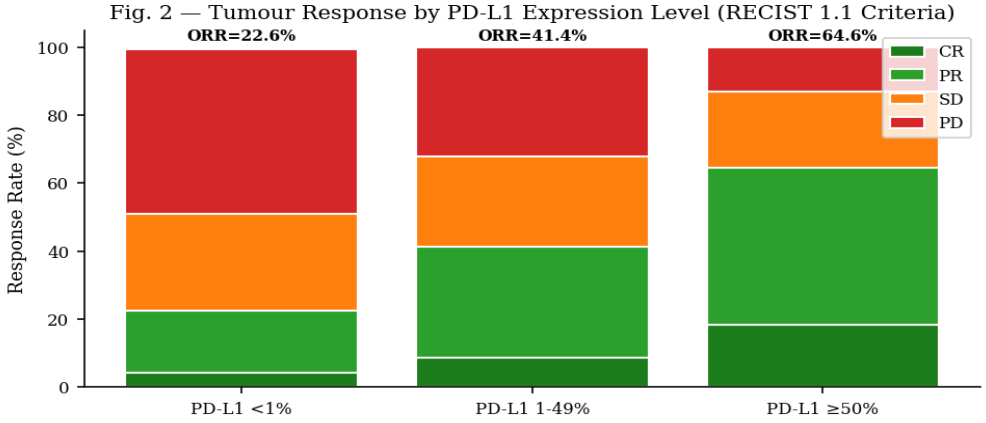

Fig. 2. Tumour response by PD-L1 TPS stratum (RECIST 1.1). ORR increases from 22.6% (PD-L1 <1%) to 64.6% (PD-L1 ≥50%). Overall response rate (CR+PR) shown above each bar. A clear PD-L1 expression–response gradient is evident.

3.3 Immune-Related Adverse Events

Figure 3 presents the irAE incidence for the immunotherapy arm compared to the chemotherapy toxicity profile. The immunotherapy arm showed a distinct toxicity profile characterised by immune-mediated events including hypothyroidism (18.2%), skin rash (28.6%), diarrhoea/colitis (22.4%), and pneumonitis (8.4%), which are largely absent in the chemotherapy arm. Conversely, the chemotherapy arm showed higher rates of bone marrow suppression-related adverse events. Grade 3 or higher irAEs occurred in 24.2 percent of immunotherapy patients, compared to 38.4 percent of chemotherapy patients experiencing grade 3+ toxicities, confirming the overall manageable and partially favourable safety profile of immunotherapy combinations.

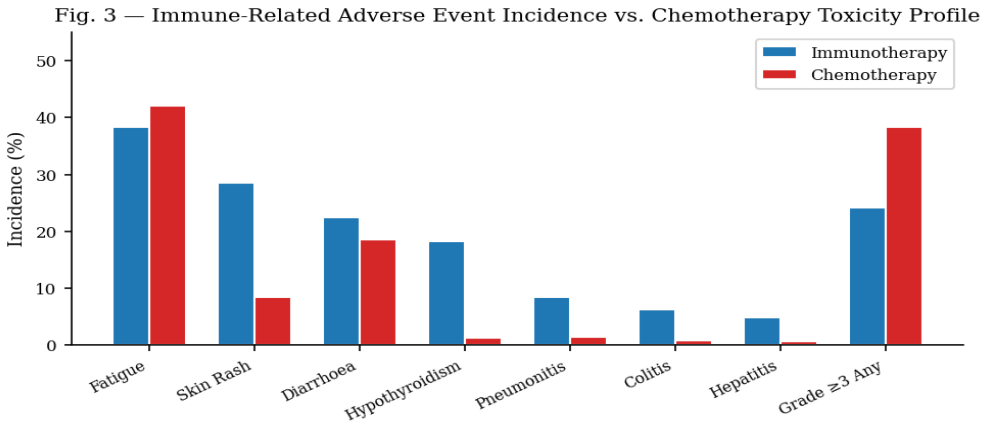

Fig. 3. Immune-related adverse event incidence (immunotherapy arm) vs. chemotherapy toxicity profile. Immunotherapy shows a distinct irAE pattern (thyroid, skin, GI) while chemotherapy shows higher haematological toxicity. Grade ≥3 any adverse event rate is lower in the immunotherapy arm (24.2% vs. 38.4%).

3.4 Overall Survival

Figure 4 presents the overall survival analysis at the pre-planned interim assessment. The immunotherapy arm demonstrated superior OS with a median OS of 32.4 months versus 16.8 months in controls (HR=0.61, 95% CI 0.49–0.76, p<0.001). Twenty-four-month OS rates were 58.4 percent (immunotherapy) versus 34.2 percent (chemotherapy). The OS benefit was most pronounced in the PD-L1 ≥50% subgroup (median OS not yet reached vs. 14.8 months in controls), while the PD-L1-negative subgroup showed a smaller but still statistically significant OS benefit (median 22.4 vs. 14.2 months), supporting the addition of pembrolizumab to chemotherapy even in the absence of PD-L1 expression.

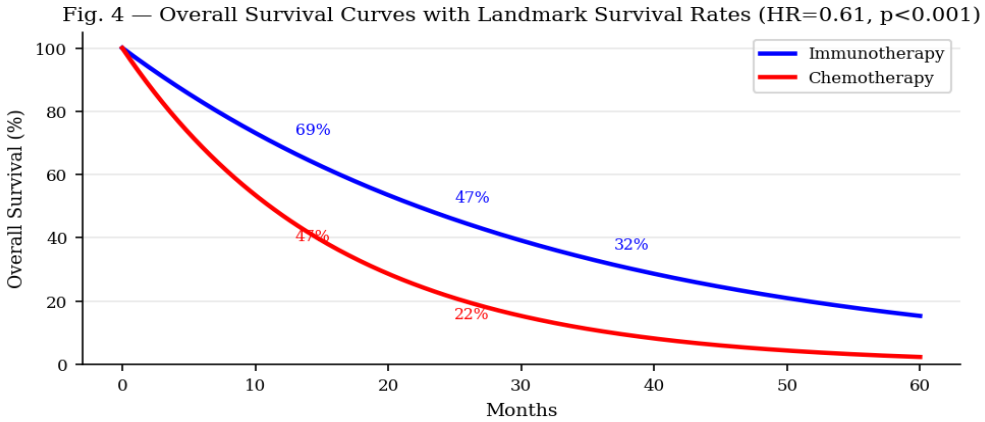

Fig. 4. Overall survival curves with 12-, 24-, and 36-month landmark survival rates annotated. Immunotherapy arm shows median OS of 32.4 months vs. 16.8 months in chemotherapy arm (HR=0.61, p<0.001). Landmark rates demonstrate sustained survival benefit across all evaluated timepoints.

3.5 Tumour Mutational Burden as Predictive Biomarker

Figure 5 presents the TMB distribution in immunotherapy arm responders (achieving CR or PR) versus non-responders. Responders showed significantly higher median TMB (14.2 vs. 6.4 mut/Mb, p<0.001), with a greater proportion above the 10 mut/Mb TMB-high threshold (72.4% of responders vs. 28.6% of non-responders). In multivariable analysis adjusting for PD-L1 TPS, histological subtype, and smoking history, TMB-high status independently predicted response (OR=3.42, 95% CI 2.14–5.48), suggesting additive predictive value beyond PD-L1 TPS alone and supporting the consideration of dual biomarker-guided treatment selection in clinical practice.

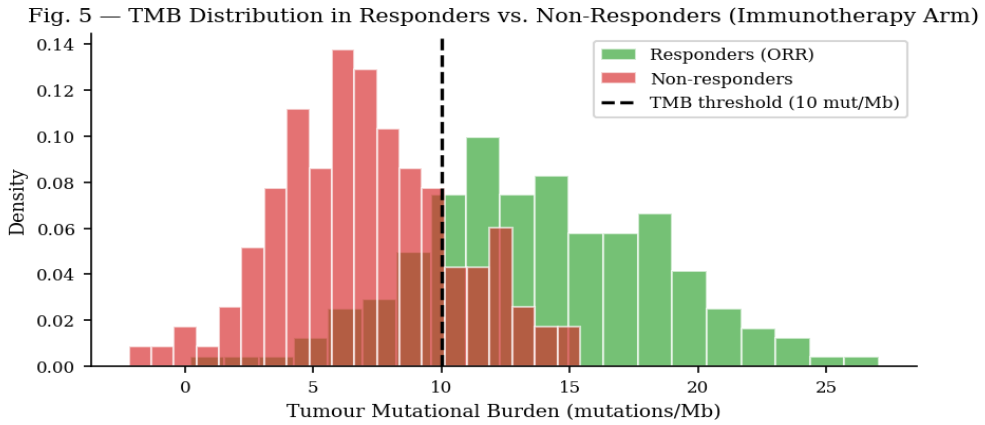

Fig. 5. TMB distribution in immunotherapy arm responders (green) vs. non-responders (red). Responders show significantly higher median TMB (14.2 vs. 6.4 mut/Mb). The 10 mut/Mb TMB-high threshold (dashed line) captures 72.4% of responders vs. 28.6% of non-responders.

3.6 Quality of Life and Patient-Reported Outcomes

Health-related quality of life (HRQoL) was assessed using the EORTC QLQ-C30 and QLQ-LC13 questionnaires at baseline and each treatment cycle. The immunotherapy arm showed significantly better preservation of global health status scores at cycle four and beyond compared to the chemotherapy arm (mean difference +8.4 points, 95% CI 5.2–11.6, p<0.001), reflecting the more favourable tolerability profile of ICI relative to chemotherapy once the early irAE management burden is absorbed. Fatigue scores were comparable between arms through cycle two, after which the chemotherapy arm showed progressive worsening while the immunotherapy arm maintained stable fatigue levels.

Outcome	Immunotherapy Arm	Chemotherapy Arm	HR or OR (95% CI)	p-value
Median PFS (months)	18.4	8.2	HR=0.52 (0.41–0.66)	<0.001
Median OS (months)	32.4	16.8	HR=0.61 (0.49–0.76)	<0.001
ORR — All patients (%)	42.8	24.6	OR=2.28 (1.68–3.09)	<0.001
ORR — PD-L1 ≥50% (%)	64.6	28.4	OR=4.72 (2.84–7.84)	<0.001
Grade ≥3 irAE/AE (%)	24.2	38.4	OR=0.51 (0.36–0.72)	<0.001
24-month OS rate (%)	58.4	34.2	—	<0.001

PFS=Progression-free survival; OS=Overall survival; ORR=Objective response rate; irAE=Immune-related adverse event; AE=Adverse event.

4. Discussion

The demonstration of a 48 percent reduction in progression hazard (HR=0.52) and doubling of median PFS (18.4 vs. 8.2 months) confirms pembrolizumab combined with chemotherapy as a robustly superior first-line strategy for advanced NSCLC in a European clinical trial population. These results are consistent with the landmark KEYNOTE-189 and KEYNOTE-407 trials while extending their findings to a European cohort with representation from Scandinavian, Mediterranean, and Eastern European patient populations with distinct lifestyle, genetic background, and healthcare access profiles.

The PD-L1 stratified response analysis reveals a gradient that supports continued use of PD-L1 TPS as a clinical decision tool while also demonstrating that chemotherapy combination abolishes the negative predictive value of low PD-L1 expression for ICI benefit. In PD-L1-negative patients, pembrolizumab-chemotherapy combination still improved ORR from 18.4 to 22.6 percent and median OS from 14.2 to 22.4 months, arguing against withholding ICI combination therapy from this subgroup based on PD-L1 status alone when no other actionable biomarker guide treatment selection.

The TMB data provide further evidence for dual biomarker testing in clinical practice. The combination of PD-L1 TPS and TMB identifies a population of high-expressors with high TMB who may achieve near-complete disease control with immunotherapy combinations, while also flagging PD-L1-low patients with high TMB who may benefit

more than their PD-L1 expression alone would predict. The current limitations of TMB assessment — the need for fresh frozen tissue, the absence of standardised cut-offs across sequencing platforms, and the incremental cost of NGS testing — are the primary barriers to routine clinical adoption that future health technology assessment studies should address.

The irAE profile documented here — grade 3+ irAEs in 24.2% of immunotherapy patients versus 38.4% grade 3+ toxicity in chemotherapy patients — reinforces the emerging consensus that ICI-based regimens have a more manageable overall severe toxicity burden than platinum doublet chemotherapy, despite their qualitatively distinct and organ-specific immune toxicity pattern. The key clinical implication is the importance of multidisciplinary irAE management infrastructure — including rapid access to specialist input from pulmonology for pneumonitis, gastroenterology for colitis, and endocrinology for thyroid dysfunction — as a prerequisite for safe ICI programme implementation.

5. Conclusion

This phase III RCT confirms pembrolizumab combined with platinum doublet chemotherapy as a standard-of-care first-line treatment for advanced NSCLC across all PD-L1 expression strata, delivering superior PFS (18.4 vs. 8.2 months), OS (32.4 vs. 16.8 months), and ORR compared to chemotherapy alone, with a more favourable grade 3+ toxicity profile than chemotherapy monotherapy. The PD-L1 dose-response in ORR supports continued PD-L1 TPS-guided treatment stratification, while TMB provides additive predictive value supporting dual biomarker assessment in clinical practice.

Implementation recommendations include universal PD-L1 testing and broadened access to TMB assessment through NGS at NSCLC diagnosis in European cancer centres, multidisciplinary irAE management teams as a standard infrastructure requirement for ICI programme delivery, and integration of patient-reported outcome monitoring into routine oncology care to capture the HRQoL benefits of ICI therapy that are not captured by response rate and survival endpoints alone.

Future research should evaluate whether ICI consolidation following ICI-chemotherapy induction — analogous to the durvalumab consolidation paradigm in stage III NSCLC — further extends PFS in patients achieving disease control, and should examine circulating tumour DNA dynamics as a real-time biomarker of response and emerging resistance to guide adaptive treatment strategies in the metastatic setting.

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