British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(2): 50722
https://doi.org/10.31083/BJHM50722

Article

Efficacy and Safety of Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer With Lymph Node Metastasis

Liangliang Xue[1], Ru Ma[2], Ge Wang[3], Wenhai Li[1], Kai Ma[1,*]

[1]Department of Thoracic Surgery, Xi'an International Medical Center Hospital, 710000 Xi'an, Shaanxi, China
[2]Department of General Medicine, Xi'an International Medical Center Hospital, 710000 Xi'an, Shaanxi, China
[3]Department of Nephrology, The Second Affiliated Hospital of Xi'an Jiaotong University, 710006 Xi'an, Shaanxi, China
*Correspondence: mkmkmk0208@163.com (Kai Ma)
Academic Editor: John Alcolado
Submitted: 24 April 2025 Revised: 15 September 2025 Accepted: 22 September 2025 Published: 5 February 2026

Abstract

Aims/Background: Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of all lung cancers, and lymph node metastasis is a key determinant of patient prognosis, often leading to poorer clinical outcomes. Although immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape of advanced NSCLC, their specific efficacy in patients with lymph node metastases remains unclear. This study aimed to evaluate the efficacy and safety of ICI monotherapy versus chemotherapy in previously treated, unresectable NSCLC patients with lymph node metastasis. **Methods**: A retrospective analysis was performed on patients with unresectable, previously treated NSCLC with lymph node metastasis who received treatment at Xi'an International Medical Center Hospital between April 2019 and October 2022. Following 1:1 propensity score matching (PSM), 112 patients were included in the final analysis, comprising 56 in the ICI group (treated with pembrolizumab) and 56 in the chemotherapy group (treated with docetaxel). The primary endpoint was objective response rate (ORR), while secondary endpoints included disease control rate (DCR), overall survival (OS), and safety. **Results**: The ICI group demonstrated a significantly higher ORR compared with the chemotherapy group (50.0% vs. 26.8%, $p = 0.012$). No significant difference in DCR was observed between the groups ($p = 0.057$). Kaplan-Meier analysis revealed significantly longer OS in the ICI group ($p = 0.009$). Multivariate analysis indicated a high risk of death in the chemotherapy group compared to the ICI group (hazard ratio [HR] = 1.796; 95% confidence interval [CI]: 1.112–2.900; $p = 0.017$). In terms of safety, leukopenia occurred more frequently in the chemotherapy group ($p = 0.039$), while immune-related adverse events (irAEs), including hypothyroidism ($p = 0.027$) and rash ($p = 0.008$), were more common in the ICI group. **Conclusion**: In previously treated patients with unresectable NSCLC and lymph node metastasis, real-world evidence from this study suggests that pembrolizumab monotherapy offers superior efficacy and survival benefits compared with docetaxel chemotherapy. Moreover, the two therapies display distinct safety profiles, with ICI therapy associated with fewer severe hematologic toxicities.

Keywords: immune checkpoint inhibitors; pembrolizumab; non-small cell lung cancer; lymph node metastasis; survival

1. Introduction

Lung cancer remains the leading cause of cancer-related deaths globally, with non-small cell lung cancer (NSCLC) representing the majority of cases, accounting for approximately 80–85% of all lung cancer diagnoses [1,2]. Prognosis and treatment strategies for NSCLC are largely determined by disease stage at diagnosis, with lymph node metastasis serving as a critical prognostic factor [3]. As the predominant route of NSCLC dissemination, lymphatic spread complicates both diagnosis and therapeutic decision-making, often resulting in poorer clinical outcomes.

The advent of immune checkpoint inhibitors (ICIs), particularly those targeting the Programmed Cell Death Protein 1/Programmed Cell Death Ligand 1 (PD-1/PD-L1) pathway, has fundamentally transformed the therapeutic landscape for advanced NSCLC [4,5]. Landmark clinical trials have established the superiority of ICI monotherapy over conventional chemotherapy, especially in selected populations such as patients with high PD-L1 expression, where significant survival benefits have been demonstrated [6].

However, the specific efficacy of ICIs in patients with lymph node metastases remains unclear. Although pivotal trials have included individuals with metastatic disease, outcomes stratified by the extent of nodal involvement (N1–N3) have not been consistently reported. This constitutes a significant knowledge gap, as the tumour immune microenvironment within lymph nodes may differ immunologically and potentially influence responsiveness to immunotherapy [7,8].

Given that NSCLC patients with lymph node metastasis represent a complex and prognostically heterogeneous subgroup, it is clinically relevant to determine whether ICI monotherapy provides sustained benefit in this population. The current lack of targeted evidence has created uncertainty regarding the optimal application of ICI use in these patients.

Therefore, this study aimed to address this clinical question by directly comparing the efficacy and safety of ICI monotherapy with standard chemotherapy in a real-world cohort of previously treated, unresectable NSCLC patients with lymph node metastasis following failure of platinum-based therapy. By evaluating objective response rate (ORR), disease control rate (DCR), and survival outcomes, this study aimed to clarify the therapeutic value of ICIs and support evidence-based treatment decisions for this challenging patient subgroup.

2. Methods

2.1 Study Population

This study retrospectively analysed data from a cohort of patients diagnosed with non-small cell lung cancer (NSCLC) with lymph node metastasis at Xi'an International Medical Center Hospital between April 2019 and October 2022. The study protocol was approved by the Ethics Committee of Xi'an International Medical Center Hospital (Approval No. 2024034) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients or their legal guardians.

Patient selection followed a structured process. Initially, 155 patients who met the preliminary diagnostic criteria were identified from hospital records, including 70 patients who received ICI and 85 patients treated with chemotherapy. Propensity score matching (PSM) was subsequently performed in a 1:1 ratio, yielding a final analysis cohort of 112 patients, with 56 assigned to each group (ICI and chemotherapy).

Patients were eligible for the study if they met the following criteria: age $\geq$18 years; histologically confirmed NSCLC with lymph node metastasis [3]; disease progression or intolerance after at least one platinum-based chemotherapy regimen; unresectable disease scheduled for immunotherapy or chemotherapy; actual survival of more than 3 months; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 [9]; and at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 [10].

Exclusion criteria included: prior surgical treatment for NSCLC; concurrent malignancies or severe interstitial lung disease; presence of autoimmune diseases or requirement for corticosteroid or immunosuppressive therapy; and any other contraindications to immunotherapy or chemotherapy.

2.2 Treatment Regimens and Data Collection

The final matched cohort was divided into two treatment groups. The ICI group (n = 56) received pembrolizumab monotherapy (JS20180031, MSD Ireland, Berlin, Germany) at a fixed dose of 200 mg administered intravenously every 21 days. The chemotherapy group (n = 56) received docetaxel monotherapy (H20020543, Hengrui Co., Ltd., Nanjing, China) at 75 mg/m^2, administered every 21 days.

Clinical variables, including age, gender, histological subtype, ECOG performance status, PD-L1 expression level, smoking history, tumour-node-metastasis (TNM) staging (N classification), epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutation status, and the number of prior systemic therapy lines, were retrospectively retrieved from the electronic medical records of the hospital.

2.3 Study Endpoints and Assessments

The primary efficacy endpoint was the objective response rate (ORR). Secondary endpoints included the disease control rate (DCR) and survival outcomes.

Efficacy assessment: tumour response was radiologically evaluated every two treatment cycles (approximately every 6 weeks) according to RECIST version 1.1 [10]. Tumour responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). ORR was defined as the proportion of patients achieving CR or PR:

$$\text{ORR } (\%) = [(\text{CR} + \text{PR})/ \text{ total number }] \times 100.$$

DCR was defined as the proportion of patients achieving CR, PR, or SD:

$$\text{DCR } (\%) = [(\text{CR} + \text{PR} + \text{SD})/ \text{ total number }] \times 100.$$

Survival follow-up: from treatment initiation, patient survival status was evaluated every three months through outpatient visits or telephone interviews. Follow-up continued until death or the last recorded contact.

Safety assessment: adverse events (AEs) were monitored from treatment initiation until 30 days after the final dose. Collected safety data included common AEs (e.g., anaemia, leukopenia, thrombocytopenia, nausea, vomiting, and elevated transaminases) as well as immune-related adverse events (irAEs). All AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) [11].

2.4 Statistical Analysis

Statistical analyses were performed using SPSS software (version 26.0, IBM Corp., New York, NY, USA), while graphical presentations were generated with GraphPad Prism (version 6.0, GraphPad Prism Software Inc., San Diego, CA, USA). A two-sided p-value < 0.05 was considered statistically significant.

To minimise selection bias and balance baseline characteristics, 1:1 nearest-neighbour propensity score matching (PSM) was applied. Matching variables included age, gender, histological subtype, ECOG performance status, PD-L1 expression level, smoking history, number of prior

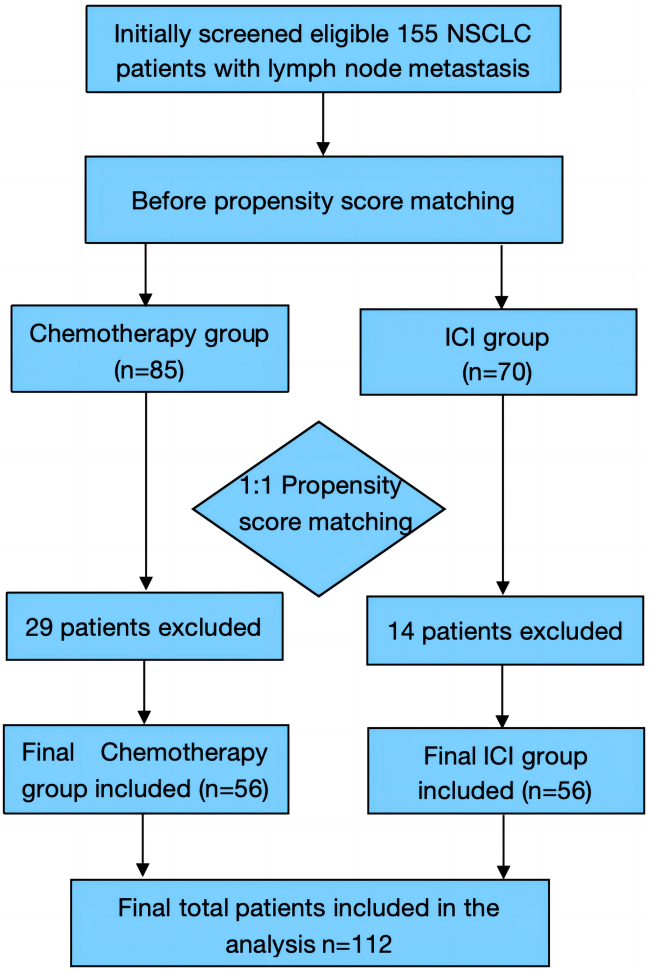

Fig. 1. Patient selection flowchart. NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor.

systemic therapies, N stage status, EGFR mutation status, and ALK rearrangement status. The calliper width was set at 0.05. In addition to *p*-values, standardized mean differences (SMDs) were calculated to assess the balance of baseline covariates between groups. An SMD < 0.2 was considered to indicate negligible imbalance.

Categorical variables are presented as counts (n) and proportions (%). Group comparisons were selected based on the minimum expected frequency (T) in contingency tables: the chi-square test was applied if T $\geq$5; the chi-square corrected test if 1 $\leq$ T $<$ 5; and Fisher's exact test if T $<$1. The chi-square test was employed to compare ORR and DCR between groups. Survival outcomes were estimated using the Kaplan-Meier method and compared with the log-rank test. Independent prognostic factors for overall survival (OS) were identified using univariate and multivariate Cox proportional hazards regression analyses. Variables of clinical significance, including treatment group, age, ECOG performance status, and PD-L1 expression, were entered into the multivariate model to assess their independent effects on survival, irrespective of their significance in univariate testing. For subgroup analyses of objective response rate (ORR), treatment efficacy was assessed by calculating odds ratios (ORs) with 95% confidence intervals (CIs) derived from logistic regression models for each predefined subgroup.

3. Results

3.1 Patient Demographics and Disease Characteristics

A total of 155 patients with unresectable NSCLC and lymph node metastasis were initially identified, including 85 patients in the chemotherapy group and 70 in the ICI group. Following 1:1 PSM, a final matched cohort of 112 patients was established, with 56 participants in each treatment group (Fig. 1). Detailed demographic and clinical characteristics of patients before and after PSM are presented in Table 1. Before matching, ECOG performance status differed significantly between the two groups (p = 0.017). However, other baseline variables, including age, gender, histological subtype, PD-L1 expression, smoking history, number of prior therapies, TNM stage, and driver gene status (EGFR/ALK), were comparable between groups (all $p > 0.05$). After PSM, the imbalance in baseline characteristics was substantially reduced, as reflected by decreased SMD values across most covariates. No sta-

Table 1. Demographic and disease characteristics before and after propensity score matching (PSM).

Variable	Before PSM					After PSM				
	Chemotherapy (n = 85)	ICI group (n = 70)	SMD	Chi-square value	*p*-value	Chemotherapy (n = 56)	ICI group (n = 56)	SMD	Chi-square value	*p*-value
Age, years, n (%)			0.144	1.673	0.196			0.152	1.328	0.249
<65	56 (65.9%)	39 (55.7%)				36 (64.3%)	30 (53.6%)			
≥65	29 (34.1%)	31 (44.3%)				20 (35.7%)	26 (46.4%)			
Gender, n (%)			0.207	3.314	0.069			0.050	0.146	0.703
Female	44 (51.8%)	26 (37.1%)				23 (41.1%)	25 (44.6%)			
Male	41 (48.2%)	44 (62.9%)				33 (58.9%)	31 (55.4%)			
Histological type, n (%)			0.197	3.168	0.075			0.025	0.036	0.850
Non-squamous carcinoma	58 (68.2%)	38 (54.3%)				31 (55.4%)	30 (53.6%)			
Squamous carcinoma	27 (31.8%)	32 (45.7%)				25 (44.6%)	26 (46.4%)			
ECOG score, n (%)			0.253	5.689	0.017			0.000	0.000	1.000
0	20 (23.5%)	29 (41.4%)				16 (28.6%)	16 (28.6%)			
1	65 (76.5%)	41 (58.6%)				40 (71.4%)	40 (71.4%)			
PD-L1 expression, %, n (%)			0.073	0.405	0.525			0.000	0.000	1.000
1–49%	42 (49.4%)	31 (44.3%)				27 (48.2%)	27 (48.2%)			
≥50%	43 (50.6%)	39 (55.7%)				29 (51.8%)	29 (51.8%)			
Smoking history, n (%)			0.116	1.611	0.447			0.110	0.995	0.608
Never smoked	29 (34.1%)	18 (25.7%)				19 (33.9%)	17 (30.4%)			
Former smoker	26 (30.6%)	27 (38.6%)				17 (30.4%)	22 (39.3%)			
Current smoker	30 (35.3%)	25 (35.7%)				20 (35.7%)	17 (30.4%)			

Table 1. Continued.

Variable	Before PSM					After PSM				
	Chemotherapy (n = 85)	ICI group (n = 70)	SMD	Chi-square value	*p*-value	Chemotherapy (n = 56)	ICI group (n = 56)	SMD	Chi-square value	*p*-value
Previous systemic treatments, n (%)			0.063	0.309	0.578			0.051	0.145	0.704
1	46 (54.1%)	41 (58.6%)				30 (53.6%)	32 (57.1%)			
≥2	39 (45.9%)	29 (41.4%)				26 (46.4%)	24 (42.9%)			
N stage, n (%)			0.012	0.033	0.984			0.152	3.021	0.221
N1	13 (15.3%)	11 (15.7%)				9 (16.1%)	9 (16.1%)			
N2	59 (69.4%)	49 (70.0%)				37 (66.1%)	43 (76.8%)			
N3	13 (15.3%)	10 (14.3%)				10 (17.9%)	4 (7.1%)			
EGFR mutation, n (%)			0.067	0.591	0.442			0.126	1.465	0.226
No	72 (84.7%)	56 (80.0%)				48 (85.7%)	43 (76.8%)			
Yes	13 (15.3%)	14 (20.0%)				8 (14.3%)	13 (23.2%)			
ALK rearrangement, n (%)			0.031	0.425	0.792*			0.126	-	0.495**
No	82 (96.5%)	66 (94.3%)				56 (100.0%)	54 (96.4%)			
Yes	3 (3.5%)	4 (5.7%)				0 (0.0%)	2 (3.6%)			

Notes: PSM, propensity score matching; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; EGFR, epidermal growth factor receptor; SMD, standardised mean difference; ALK, anaplastic lymphoma kinase; PD-L1, Programmed Cell Death Ligand 1. **p*-values were calculated using chi-square corrected test; ***p*-values were calculated using Fisher's exact test.

Table 2. Comparison of therapeutic efficacy between the ICI and chemotherapy groups.

Variable	ICI group (n = 56)	Chemotherapy group (n = 56)	Chi-square value	*p*-value
Complete response	14	8	-	-
Partial response	14	7	-	-
Stable disease	17	21	-	-
Progressive disease	11	20	-	-
Objective response rate, n (%)	28 (50.0%)	15 (26.8%)	6.38	0.012
Disease control rate, n (%)	45 (80.4%)	36 (64.3%)	3.61	0.057

Notes: ICI, immune checkpoint inhibitor.

tistically significant differences were observed between the ICI and chemotherapy groups (all $p > 0.05$).

3.2 Treatment Efficacy

Treatment outcomes, including ORR and DCR, are summarised in Table 2. The ORR was significantly higher in the ICI group compared with the chemotherapy group ($p = 0.012$). Conversely, the DCR did not differ significantly between the two groups ($p = 0.057$).

3.3 Subgroup Analysis of ORR Between the Two Groups

As shown in Fig. 2, subgroup analysis demonstrated that ICI therapy was associated with higher ORR compared with chemotherapy across several patient subgroups. Notably, patients with PD-L1 expression $\geq$50%, ECOG performance status of 1, N2-stage disease, and age $\geq$65 years exhibited significantly greater benefit from ICI treatment. Additionally, a trend favouring ICI over chemotherapy was observed among patients with PD-L1 expression of 1–49%, age <65 years, and ECOG performance status of 0, although these differences did not reach statistical significance.

3.4 Survival Analysis

Patients were followed for a median duration of 24 months. Overall survival (OS) was estimated using the Kaplan-Meier method, and survival curves for the ICI and chemotherapy groups are presented in Fig. 3. During the 24-month follow-up period, patients in the ICI group consistently demonstrated a higher survival probability compared with those in the chemotherapy group. The 1-year survival rates were 76.8% for the ICI group and 44.6% for the chemotherapy group. At the 24-month cutoff, the 2-year survival rate of 48.2% for the ICI group versus 28.6% for the chemotherapy group.

The median OS was 22 months in the ICI group compared with 11.5 months in the chemotherapy group. Survival distributions differed significantly between the two groups, as determined by the log-rank test ($p = 0.009$). These findings indicate that ICI monotherapy significantly prolongs overall survival compared with chemotherapy.

3.5 Cox Regression Analysis

Table 3 presents the results of the univariate and multivariate Cox proportional hazards analyses for OS. In the univariate analysis, the treatment group emerged as the only significant predictor of OS. Compared with the ICI group, patients receiving chemotherapy had a significantly increased risk of death (hazard ratio [HR] = 1.836; 95% CI: 1.144–2.948; $p = 0.012$). No other baseline characteristics were identified as significant predictors in the univariate analysis (all $p > 0.05$).

For a robust multivariate analysis, treatment group and other clinically relevant variables (age, ECOG performance status, and PD-L1 expression) were included to adjust for potential confounders. After adjustment, the treatment group remained an independent and significant prognostic factor for OS. Chemotherapy was associated with a significantly higher risk of mortality relative to ICI therapy (adjusted hazard ratio [aHR] = 1.796; 95% CI: 1.112–2.900; $p = 0.017$).

3.6 Safety and Tolerability

Adverse events (AEs) observed in this study are summarised in Table 4. Clear differences in safety profiles were noted between the two groups, with the most prominent disparities observed in hematologic toxicity. The incidence of leukopenia was significantly higher in the chemotherapy group ($p = 0.039$). Similarly, anaemia (any grade) was significantly more frequent in the chemotherapy group compared to the ICI group ($p = 0.013$). irAEs were predominantly observed in the ICI group. Compared with the chemotherapy group, patients receiving ICI therapy experienced significantly higher rates of hypothyroidism ($p = 0.027$) and rash/pruritus ($p = 0.008$), both at any grade level.

4. Discussion

In this retrospective study, we analysed pretreated patients with NSCLC and lymph node metastasis. Pembrolizumab monotherapy demonstrated significantly superior efficacy over docetaxel chemotherapy, with significant improvements in ORR and OS. Although not statistically significant, a trend toward a higher DCR was observed in the ICI group. Furthermore, the safety profile of the ICI treatment was more favourable, showing fewer severe hematologic toxicities.

Table 3. Factors associated with overall survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	aHR (95% CI)[1]	*p*-value
Treatment group (Chemo vs. ICI)	1.836 (1.144–2.948)	0.012	1.796 (1.112–2.900)	0.017
Age (≥65 vs. <65)	1.085 (0.676–1.742)	0.736	1.022 (0.625–1.671)	0.930
Gender (Male vs. Female)	1.108 (0.693–1.771)	0.668	-	-
Histology (Squamous vs. Non-squamous)	0.878 (0.551–1.400)	0.585	-	-
ECOG score (1 vs. 0)	1.307 (0.790–2.163)	0.297	1.308 (0.782–2.188)	0.307
PD-L1 expression (≥50% vs. 1–49%)	1.280 (0.802–2.040)	0.300	1.245 (0.778–1.995)	0.361
Smoking history	-	0.763	-	-
Past smoker vs. Never smoked	0.932 (0.516–1.684)	0.816	-	-
Current smoker vs. Never smoked	1.147 (0.657–2.000)	0.630	-	-
Previous systemic treatments (≥2 vs. 1)	1.296 (0.805–2.087)	0.285	-	-
N stage	-	0.055	-	-
N2 vs. N1	1.009 (0.452–2.247)	0.983	-	-
N3 vs. N1	1.869 (0.955–3.650)	0.068	-	-
EGFR mutation (Yes vs. No)	0.951 (0.521–1.735)	0.869	-	-
ALK rearrangement (Yes vs. No)	1.738 (0.241–12.517)	0.583	-	-

Notes: HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor. [1]Multivariate model was adjusted for treatment group, age, ECOG score, and PD-L1 expression.

Table 4. Comparison of treatment-related adverse events between the ICI and chemotherapy groups.

Adverse event	Severity	ICI group (n = 56)	Chemotherapy group (n = 56)	Chi-square value	*p*-value*
		n (%)	n (%)		
Leukopenia	All grades	3 (5.4%)	10 (17.9%)	4.264	0.039
	Grade ≥3	1 (1.8%)	5 (8.9%)	1.585	0.208*
Anaemia	All grades	7 (12.5%)	18 (32.1%)	6.231	0.013
	Grade ≥3	1 (1.8%)	4 (7.1%)	0.837	0.360*
Thrombocytopenia	All grades	4 (7.1%)	10 (17.9%)	2.939	0.086
	Grade ≥3	0 (0.0)	2 (3.6%)	0.509	0.476*
Nausea	All grades	12 (21.4%)	15 (26.8%)	0.439	0.508
	Grade ≥3	0 (0.0)	1 (1.8%)	-	1.000**
Hypothyroidism	All grades	6 (10.7%)	0 (0.0)	4.403	0.027**
	Grade ≥3	0 (0.0)	0 (0.0)	-	-
Rash/Pruritus	All grades	11 (19.6%)	2 (3.6%)	7.049	0.008
	Grade ≥3	1 (1.8%)	0 (0.0)	-	1.000**
Pneumonitis	All grades	1 (1.8%)	0 (0.0)	-	1.000**
	Grade ≥3	0 (0.0)	0 (0.0)	-	-

Notes: ICI, immune checkpoint inhibitor. **p*-values were calculated using the chi-square corrected test; ***p*-values were calculated using Fisher's exact test.

Our findings on the efficacy of ICI monotherapy are consistent with results from landmark clinical trials that established the utility of ICIs in second-line therapy for advanced NSCLC [6]. For instance, Zhao *et al.* [6] demonstrated that pembrolizumab, an anti-Programmed Cell Death Protein 1 (anti-PD-1) monoclonal antibody, demonstrated significant antitumour efficacy and favourable safety in patients with advanced NSCLC expressing PD-L1 in at least 50% of tumour cells. Interestingly, the ORR observed in our study (50.0% in the ICI group vs. 26.8% in the chemotherapy group) was higher than that reported in multiple large randomised controlled trials [4,12,13]. This discrepancy may be attributed to the single-center, retrospective design, which could introduce selection bias. Although PSM helped balance known baseline variables, residual confounding from unmeasured variables cannot be fully excluded.

Notably, the benefits of ICI therapy were markedly pronounced in specific subgroups. Compared to chemotherapy, ICI treatment significantly improved

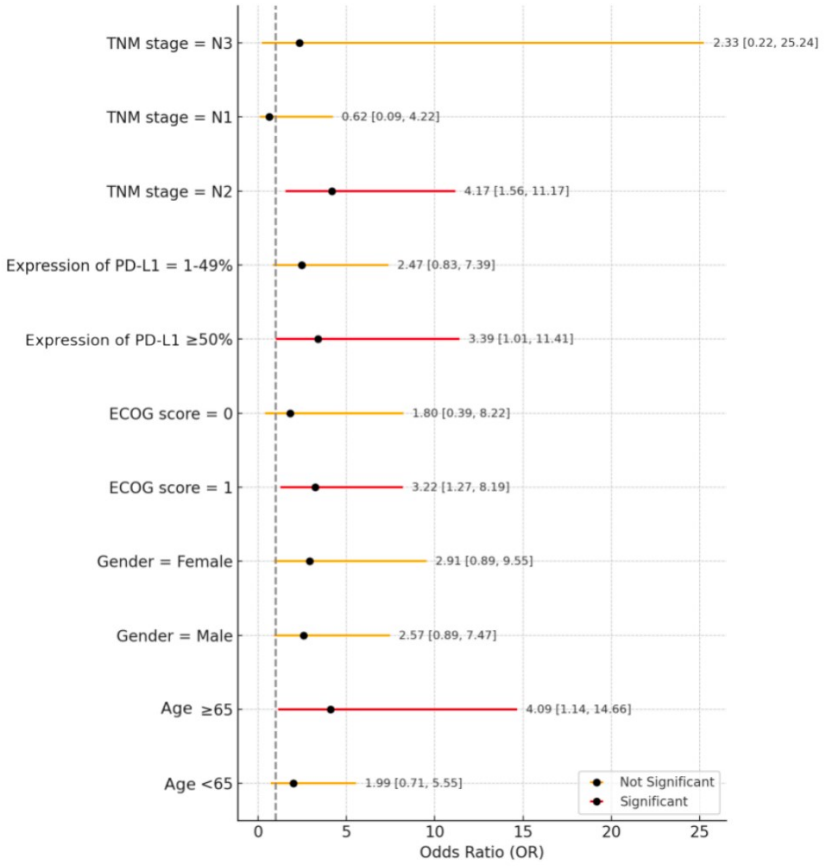

Fig. 2. Forest plot of objective response rate (ORR) by subgroup (ICI vs. Chemotherapy). TNM, tumour-node-metastasis; PD-L1, Programmed Cell Death Ligand 1.

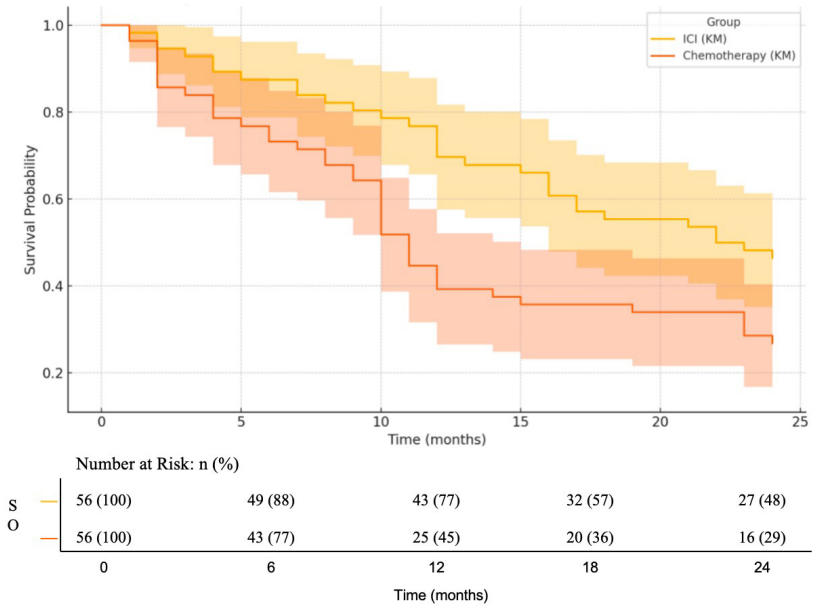

Fig. 3. Kaplan-Meier (KM) analysis of overall survival with integrated number at risk.

ORR in patients with PD-L1 expression ≥50%, ECOG performance status of 1, N2-stage disease, and age ≥65 years. The survival advantage in the PD-L1-high subgroup aligns with the established mechanism of ICIs and extensive prior evidence, further supporting PD-L1 expression as a predictive biomarker for immunotherapy response

[12,14]. Similarly, our study demonstrated that elderly patients (≥65 years) and those with an ECOG performance status of 1 derived significant benefit from ICI therapy. These findings offer valuable real-world evidence to guide treatment decision-making in these large, often underrepresented patient populations. One possible explanation is that the favourable tolerability profile of ICIs allows such patients, who may not be in optimal physical condition, to complete therapy more effectively and achieve clinical benefit [4,15]. Nevertheless, caution is warranted when interpreting results from other subgroups. The limited sample sizes in subgroup analyses reduce statistical power, making it premature to infer a lack of efficacy in those populations. These exploratory findings require validation through larger, prospective studies.

In terms of safety, our study revealed distinct toxicity profiles between the chemotherapy and ICI groups. These results are consistent with previous key clinical trials [4,13,16] and underscore the fundamentally different mechanisms of action of the two treatment strategies. In the chemotherapy group, adverse events were dominated by bone marrow suppression, particularly leukopenia, consistent with the classical toxicity pattern of cytotoxic agents. Chemotherapy exerts antitumour effects by targeting rapidly dividing cells but also inevitably damages proliferating normal cells, such as hematopoietic stem cells, resulting in predictable hematologic toxicities. In contrast, the ICI group exhibited a lower overall incidence of severe adverse events, highlighting their advantage in reducing conventional cytotoxicity. However, immune-related adverse events (irAEs), including hypothyroidism and rash, were unique to the ICI group, consistent with previous study [14]. Unlike chemotherapy, ICI toxicities stem not from direct cytotoxic damage but from immune system hyperactivation, which may induce autoimmunity and injury to healthy tissues. These distinct toxicity profiles require different clinical management strategies. For chemotherapy, supportive care and organ function recovery are critical, whereas ICI management relies on immunosuppression, requiring a careful balance between controlling irAEs and maintaining antitumour immunity. Future research should prioritise early detection systems and refined grading strategies to optimise irAE management.

This study has several limitations. First, as a single-center retrospective analysis, its generalizability is restricted, and selection bias may exist. Second, although data collection was comprehensive, rare irAEs such as colitis and hepatitis may have been underreported. Third, while PSM reduced baseline imbalances between groups, it cannot substitute for randomisation. Finally, the relatively small sample size may have constrained the statistical power of subgroup analyses. Future multicenter, prospective studies with larger cohorts are necessary to validate these findings.

5. Conclusion

In summary, this real-world study provides evidence that pembrolizumab monotherapy offers superior tumour response rates and survival benefits compared with docetaxel monotherapy in patients with unresectable NSCLC with lymph node metastasis following failure of prior platinum-based chemotherapy. Moreover, pembrolizumab demonstrated a distinct safety profile, with a notably lower incidence of severe hematologic toxicities. These findings support the role of ICI monotherapy as a viable and potentially advantageous treatment option for this challenging and clinically significant patient population.

Key Points

- In previously treated NSCLC patients with lymph node metastasis, pembrolizumab monotherapy significantly improved the objective response rate (ORR) compared to docetaxel chemotherapy.
- The safety profile of pembrolizumab differed markedly from that of docetaxel, showing a significantly lower incidence of severe hematologic toxicity.
- Subgroup analyses revealed that the therapeutic advantage of ICIs was particularly evident in specific populations, including patients aged ≥65 years, those with an ECOG performance status of 1, PD-L1 expression ≥50%, and N2-stage disease.
- Multivariate Cox regression analysis identified treatment modality (ICI vs. chemotherapy) as an independent prognostic factor for overall survival, with the efficacy benefit of ICI remaining independent of baseline characteristics, including age, ECOG score, and PD-L1 expression.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

LX, GW and WL designed the study. All authors conducted the study. RM and KM collected and analysed the data. LX drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors participated fully in the work, took public responsibility for appropriate portions of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Xi'an International Medical Center Hospital (approval

number: 2024034) and was performed in accordance with the principles of the Declaration of Helsinki. Informed consent has been obtained from all participants involved in the study.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Zhou J, Xu Y, Liu J, Feng L, Yu J, Chen D. Global burden of lung cancer in 2022 and projections to 2050: Incidence and mortality estimates from GLOBOCAN. Cancer Epidemiology. 2024; 93: 102693. https://doi.org/10.1016/j.canep.2024.102693.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021; 71: 209–249. https://doi.org/10.3322/caac.21660.

[3] Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, *et al.* The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology. 2016; 11: 39–51. https://doi.org/10.1016/j.jtho.2015.09.009.

[4] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, *et al.* Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. The New England Journal of Medicine. 2015; 373: 1627–1639. https://doi.org/10.1056/NEJMoa1507643.

[5] Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature. 2018; 553: 446–454. https://doi.org/10.1038/nature25183.

[6] Zhao B, Zhao H, Zhao J. Efficacy of PD-1/PD-L1 blockade monotherapy in clinical trials. Therapeutic Advances in Medical Oncology. 2020; 12: 1758835920937612. https://doi.org/10.1177/1758835920937612.

[7] Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, *et al.* Understanding the tumor immune microenvironment (TIME) for effective therapy. Nature Medicine. 2018; 24: 541–550. https://doi.org/10.1038/s41591-018-0014-x.

[8] Fridman WH, Zitvogel L, Sautès-Fridman C, Kroemer G. The immune contexture in cancer prognosis and treatment. Nature Reviews. Clinical Oncology. 2017; 14: 717–734. https://doi.org/10.1038/nrclinonc.2017.101.

[9] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology. 1982; 5: 649–656.

[10] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer. 2009; 45: 228–247. https://doi.org/10.1016/j.ejca.2008.10.026.

[11] Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, *et al.* CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Seminars in Radiation Oncology. 2003; 13: 176–181. https://doi.org/10.1016/S1053-4296(03)00031-6.

[12] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, *et al.* Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017; 389: 255–265. https://doi.org/10.1016/S0140-6736(16)32517-X.

[13] Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, *et al.* Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. The New England Journal of Medicine. 2018; 378: 2288–2301. https://doi.org/10.1056/NEJMoa1716948.

[14] Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, *et al.* Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. The New England Journal of Medicine. 2015; 373: 123–135. https://doi.org/10.1056/NEJMoa1504627.

[15] Nosaki K, Saka H, Hosomi Y, Baas P, de Castro G, Jr, Reck M, *et al.* Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1-positive advanced non-small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies. Lung Cancer. 2019; 135: 188–195. https://doi.org/10.1016/j.lungcan.2019.07.004.

[16] Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, *et al.* Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. The Lancet. Oncology. 2015; 16: 257–265. https://doi.org/10.1016/S1470-2045(15)70054-9.