Efficacy and safety of concurrent chemoradiotherapy following neoadjuvant chemoimmunotherapy in patients with stage III NSCLC who experienced neoadjuvant failure: A real-world study

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Received October 4, 2025; Accepted February 26, 2026

DOI: 10.3892/ol.2026.15555

Abstract. Neoadjuvant chemoimmunotherapy followed by surgery markedly improves outcomes in patients with stage III unresectable non-small cell lung cancer (NSCLC). However, the efficacy and safety of continuing concurrent chemoradiotherapy (cCRT) followed by immunotherapy consolidation in patients who experience failure of neoadjuvant treatment remain unclear. The present real-world study included patients who received cCRT and consolidation immunotherapy after failure of neoadjuvant chemoimmunotherapy at The Second Affiliated Hospital of Nanchang University, Nanchang, China, between May 2018 and August 2024. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were treatment-related adverse events and overall survival (OS). PFS time among patients who experienced neoadjuvant treatment failure was compared with that of patients with unresectable stage III NSCLC treated with the PACIFIC regimen at the same center. A total of 67 patients were included. The median PFS time was 26.0 months (95% CI, 17.8-39.0), with 1-, 2- and 3-year OS rates of 92.5, 79.1 and 77.6%, respectively. The incidence of immune-related adverse events was 34.33% and radiation-related adverse events occurred in 63.2% of patients. Grade ≥3 immunotherapy-related pneumonitis occurred in 5.97% of cases and radiation-related pneumonitis occurred in 4.48%. Comparison with 30 patients previously treated with the PACIFIC regimen showed no significant difference in PFS (HR, 1.155; 95% CI, 0.657-2.032; P=0.615). Notably, treatment-related adverse events were frequent, with bone marrow suppression observed in 86.57% of cases. In conclusion, induction immunotherapy combined with chemotherapy followed by cCRT and immunotherapy consolidation appears effective and safe for patients with stage III NSCLC who have failed neoadjuvant chemoimmunotherapy.

Introduction

Stage III non-small cell lung cancer (NSCLC), a subgroup characterized by substantial heterogeneity, accounts for 20-25% of all NSCLC cases (1-4). Patients are typically categorized as having resectable, unresectable or partially resectable disease after neoadjuvant treatment (5). A multidisciplinary team (MDT) approach is recommended for treatment decision-making (6). Neoadjuvant chemoimmunotherapy has emerged as a promising strategy for patients with initially unresectable, locally advanced NSCLC. Previous studies have demonstrated that neoadjuvant chemoimmunotherapy improves the pathological response rate in patients undergoing surgery for stage III NSCLC (7-9). Furthermore, the CheckMate 816 and NeoTORCH trials demonstrated that neoadjuvant chemoimmunotherapy notably improved clinical outcomes in surgically treated patients (10,11). However, 10-33% of patients did not proceed to surgical intervention after neoadjuvant therapy (7-9). For patients who do not undergo surgery following neoadjuvant chemoimmunotherapy, the efficacy and safety of consolidation immune checkpoint inhibitors (ICIs) after concurrent chemoradiotherapy (cCRT) remain uncertain.

Immunotherapy and radiotherapy may exhibit synergistic antitumor effects but can also increase toxicity (12,13). The toxicities and adverse effects associated with cCRT after chemoimmunotherapy remain a concern. The PACIFIC regimen, which combines cCRT with durvalumab consolidation, markedly improves prognosis and has become the standard treatment strategy for patients with unresectable stage III NSCLC (14-16). However, the PACIFIC-2 trial found that administering durvalumab during cCRT did not confer

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Key words: stage III, neoadjuvant chemoimmunotherapy, PACIFIC, concurrent chemoradiotherapy

significant survival benefits compared with a placebo, and the CheckMate-73L trial reported that adding nivolumab did not improve progression-free survival (PFS) (17,18). These findings may be related to premature T-cell exhaustion and cumulative toxicity (19,20). Nevertheless, the 5-year follow-up results of the KEYNOTE-799 trial indicated that pembrolizumab combined with cCRT provides durable antitumor activity in patients with unresectable, locally advanced stage III NSCLC and maintains a manageable safety profile (21). In addition, real-world studies have also demonstrated similar inconsistencies, suggesting that optimization strategies for induction immunotherapy require further investigation (22,23). Therefore, for patients who experience failure of neoadjuvant chemoimmunotherapy, the efficacy and safety of radical cCRT following combined immunochemotherapy remain controversial.

In the present study, a retrospective analysis was conducted to evaluate the efficacy and safety of cCRT followed by immunotherapy consolidation in patients with stage III NSCLC who experienced failure of neoadjuvant chemoimmunotherapy.

Patients and methods

Patients and study design. The present retrospective study included patients who received first-line immunotherapy at The Second Affiliated Hospital of Nanchang University, Nanchang, China, between May 2018 and August 2024. The inclusion criteria were as follows: i) Age ≥18 years; ii) histologically confirmed stage III NSCLC; and iii) receipt of cCRT. The exclusion criteria were as follows: i) Presence of other active malignancy; ii) prior surgical resection for lung cancer; iii) incomplete radiotherapy course; iv) loss to follow-up during first-line immunotherapy; and v) receipt of consolidation ICIs only. To contextualize the efficacy of the study intervention, a retrospective comparator cohort of 30 patients was identified. These patients had initially unresectable stage III NSCLC and were treated strictly according to the standard PACIFIC regimen at the same institution between March 2017 and December 2023. Key differences from the primary cohort were: i) Patients received definitive cCRT without any prior induction immunotherapy; and ii) consolidation immunotherapy utilized programmed death-ligand 1 (PD-L1) inhibitors. The same inclusion/exclusion criteria otherwise applied. According to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (24), neoadjuvant failure was defined as disease progression after neoadjuvant treatment or, following MDT discussion, the tumor failure to shrink sufficiently to allow surgical resection. This study was approved by the Institutional Review Board of the Second Affiliated Hospital of Nanchang University.

Treatment strategy. All patients in this study received two to four cycles of induction immunotherapy with PD-1 inhibitors in combination with chemotherapy. All patients received the same baseline dose of chemotherapy. For patients with non-squamous cell carcinoma, pemetrexed combined with carboplatin is the common treatment regimen. The dose of pemetrexed is 500 mg/m^2, and the carboplatin dosage is administered at an area under the curve (AUC) of 5, once/3 weeks. For patients with squamous cell carcinoma, the treatment regimen usually involves paclitaxel or albumin-bound paclitaxel combined with carboplatin. The administration regimen of paclitaxel was 175 mg/m^2, administered once every three weeks. Albumin-bound paclitaxel also follows a 21-day cycle. During each cycle, three doses are administered on the first day, the eighth day, and the fifteenth day, with each dose being 100 mg/m^2. The administration scheme and dosage of carboplatin are the same as those for non-squamous cell carcinoma patients. Patients who were unable to undergo or declined surgery subsequently received cCRT. Radiotherapy was administered using intensity-modulated radiation therapy. Most patients received a total dose of 60 Gy in 30 fractions, whereas 3 patients underwent an escalated regimen of 70 Gy delivered as 40 Gy in 20 fractions plus 30 Gy in 10 fractions. In the PACIFIC cohort, 2 patients used the same escalating dose regimen, while the remaining patients received irradiation with a total dose of 60 Gy. The concurrent chemotherapy regimen was as follows: For non-squamous carcinoma, pemetrexed combined with a platinum agent every 3 weeks; and for squamous carcinoma, paclitaxel + platinum agent administered weekly. For patients with non-epithelial carcinoma, the administration regimen was the same as that of induction chemotherapy. Patients with squamous cell carcinoma received weekly administration regimen of paclitaxel + carboplatin. The paclitaxel dose was 50 mg/m^2 and carboplatin at an AUC of 2. All patients received consolidation immunotherapy for up to 2 years or until the occurrence of intolerable adverse events or disease progression.

Data collection. Baseline demographic and treatment data were extracted from electronic medical records, including sex, age, Eastern Cooperative Oncology Group (ECOG) performance status (25), smoking history, cancer stage, pathological subtype of NSCLC, PD-L1 expression level, radiotherapy dose and volume, and the types and grades of treatment-related toxicity. Tumor staging was performed according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM classification system (26). Adverse events were graded based on the Common Terminology Criteria for Adverse Events version 5.0 (27), and treatment efficacy was evaluated using RECIST version 1.1.

Statistical analysis. Kaplan-Meier curves were used to analyze survival outcomes for the neoadjuvant immunotherapy and consolidation immunotherapy groups. The primary endpoint was PFS, and the secondary endpoints were treatment-related adverse events and overall survival (OS). PFS was defined as the time from treatment initiation to tumor progression or death from any cause, and OS was defined as the time from treatment initiation to death from any cause or the last follow-up. The log-rank test was used to compare survival differences between groups. Missing data were treated as separate categorical variables in the analysis. As this was a single-arm, retrospective real-world study, no prospective hypothesis-driven sample size calculation was performed.

In the univariate analysis, the Cox proportional hazards regression model was used to identify factors significantly associated with survival, including sex, age, ECOG performance status, smoking history, cancer stage, pathological subtype of NSCLC, PD-L1 expression level, and the types and grades of treatment-related toxicities. All variables were

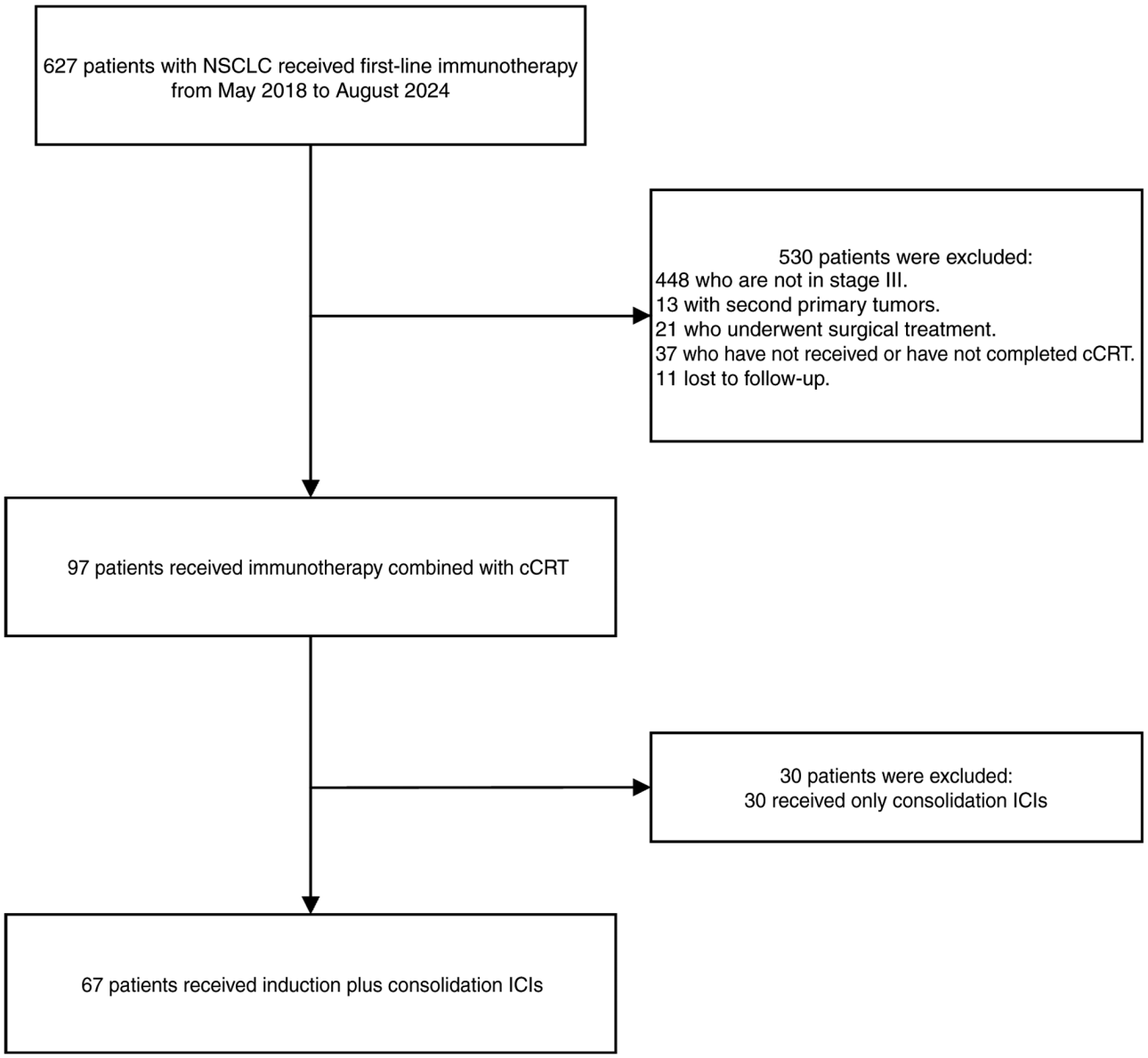

Figure 1. Flowchart of patient selection. NSCLC, non-small cell lung cancer; cCRT, concurrent chemoradiotherapy; ICIs, immune checkpoint inhibitors.

analyzed as either continuous or categorical, as appropriate. Variables with a P-value <0.20 in the univariate analysis were included in the multivariate regression model. Results are expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using R software version 4.4.0 (R Foundation for Statistical Computing), and two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 67 patients with unresectable stage III NSCLC who experienced neoadjuvant immunotherapy failure were included in the present study (Fig. 1). Baseline demographic and clinical characteristics are summarized in Table I. The median age was 65 years [interquartile range (IQR), 58-69 years]. There were 3 women (4.48%) and 64 men (95.52%). Most had an ECOS PS of 1, and more patients had a score of 2 than 0. Squamous cell carcinoma accounted for 73.13% of cases, and non-squamous cell carcinoma for 26.87%. According to the eighth edition of the AJCC staging system, 11 patients (16.42%) had stage IIIA, 47 (70.15%) had stage IIIB and nine (13.43%) had stage IIIC disease. PD-L1 expression ≥1% was detected in 44.78% of patients. The treatment regimen primarily consisted of platinum-based doublet chemotherapy combined with ICIs as induction therapy, followed by concurrent or sequential chemoradiotherapy and subsequent consolidation immunotherapy. In the PACIFIC regimen cohort, the median age was 63 years (IQR, 57-70 years), with 24 males (80.00%) and 6 women (20.00%). The majority of patients had an ECOG performance status of 0 or 1. In terms of histology, squamous cell carcinoma accounted for 53.33% (16/30) and non-squamous cell carcinoma for 46.67% (14/30) of cases. Disease staging according to the AJCC staging 8th edition was as follows: 6 patients (20.00%) with stage IIIA, 19 patients (63.33%) with stage IIIB and five patients (16.67%) with IIIC. PD-L1 expression was ≥1% in 36.67% of patients. All patients

Table I. Baseline characteristics of patients (n=97).

Variable	Induction + consolidation ICIs (n=67)	Consolidation ICIs (n=30)
Median age (Q_1-Q_3), years	65.00 (58.00-69.00)	63.00 (57.00-70.00)
Sex, n (%)		
Male	64 (95.52)	24 (80.00)
Female	3 (4.48)	6 (20.00)
ECOG PS, n (%)		
0	4 (5.97)	2 (6.67)
1	56 (83.58)	20 (66.67)
2	7 (10.45)	8 (26.67)
Smoking history, n (%)		
No	9 (13.43)	6 (20.00)
Yes	58 (86.57)	24 (80.00)
T stage, n (%)		
T1	6 (8.96)	2 (6.67)
T2	19 (28.36)	9 (30.00)
T3	24 (35.82)	10 (33.33)
T4	18 (26.87)	9 (30.00)
N stage, n (%)		
N0	2 (2.99)	0 (0.00)
N1	3 (4.48)	2 (6.67)
N2	41 (61.19)	20 (66.67)
N3	21 (31.34)	8 (26.67)
Overall stage, n (%)		
IIIA	11 (16.42)	6 (20.00)
IIIB	47 (70.15)	19 (63.33%)
IIIC	9 (13.43)	5 (16.67%)
Pathological type, n (%)		
Non-squamous cell carcinoma	18 (26.87)	14 (46.47)
Squamous cell carcinoma	49 (73.13)	16 (53.33)
PD-L1 expression, n (%)		
NA	17 (25.37)	19 (63.33)
<1	20 (29.85)	0 (0.00)
1-50	11 (16.42)	8 (26.67)
>50	19 (28.36)	3 (10.00)
Median PTV dose (range), Gy	60 (60-70)	60 (60-70)
Median PTV (Q_1-Q_3)	206.28 (114.28-327.07)	49.09 (34.54-76.42)

Missing data (e.g., 'N/A') were included in the analysis where applicable. ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; PTV, planning target volume; Gy, gray.

received platinum-based doublet chemotherapy concurrent with radiotherapy, followed by consolidation immunotherapy with a PD-L1 inhibitor.

Survival outcomes. At a median follow-up of 19.4 months, 38 patients (56.72%) had disease progression, and 20 patients (29.85%) had died at the data cutoff (data not shown). The PACIFIC regimen remains the standard treatment for patients with unresectable stage III NSCLC. To evaluate the efficacy of consolidation immunotherapy following cCRT after failure of neoadjuvant chemoimmunotherapy, PFS was compared between patients in this study and previously treated patients at The Second Affiliated Hospital of Nanchang University who received the PACIFIC regimen. The median PFS time was 26.0 months (95% CI, 17.8-39.0) in the induction plus consolidation ICI group (Fig. 2A), compared with 22.1 months (95% CI, 11.7-not reached) in the consolidation ICI-only group. No statistically significant difference was observed between the two groups (HR, 1.155; 95% CI, 0.657-2.032; log-rank P=0.615; Fig. 2B). The 1-, 2- and 3-year OS rates were 92.5, 79.1 and 77.6%, respectively. The median OS time was not reached (Fig. 2C).

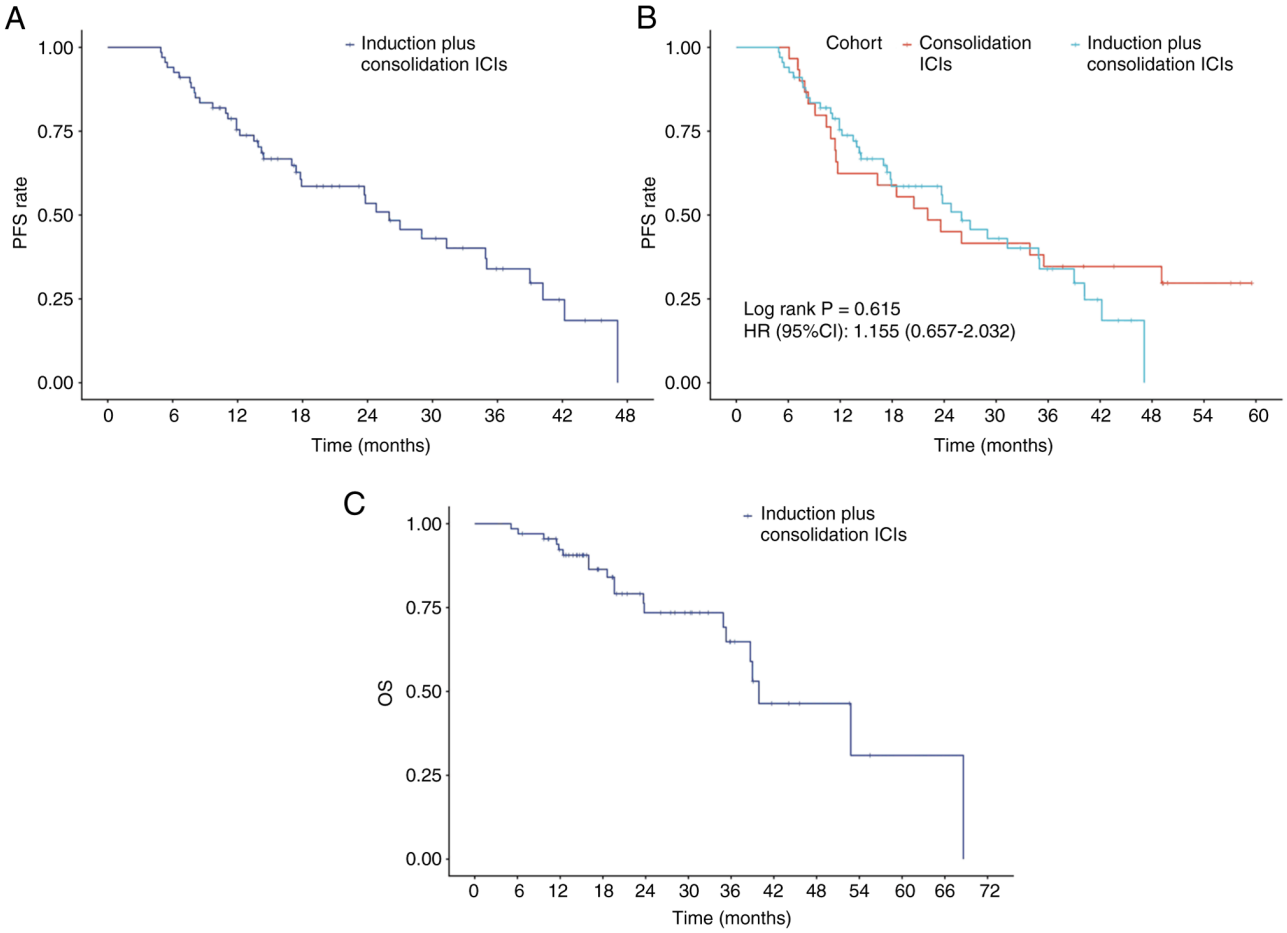

Figure 2. Kaplan-Meier curves of PFS. (A) PFS in the induction + consolidation ICIs cohort. (B) Comparison of PFS between the Induction plus consolidation ICIs and the Consolidation ICIs. (C) OS in the Induction plus consolidation ICIs cohort. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitors.

Safety profiles. Treatment-related adverse events are summarized in Table II. The overall incidence of bone marrow suppression was 86.57%, including the reduction of white blood cells, granulocytes, as well as the decrease in red blood cells and platelets. Leukopenia occurred in 50 patients (74.63%). Granulocytopenia was reported in 67.17% of patients, thrombocytopenia in 40.3% and erythropenia in 68.66%. Immune-related adverse events (irAEs) were observed in 23 patients (34.33%), and radiation-related adverse events (rrAEs) in 43 patients (64.18%). IrAEs included Pruritus (itching), Immune-related pneumonitis, Hepatic dysfunction, Hypothyroidism, Cognitive impairment, Colitis and Fatigue. RrAE include Radiation esophagitis, Radiation pneumonitis and Radiodermatitis. Grade ≥3 pneumonitis associated with immunotherapy and radiotherapy occurred in 4 cases (5.97%) and three cases (4.48%), respectively. No unexpected safety signals were detected.

Prognostic factors. In the multivariate analysis, grade ≥3 granulocytopenia was identified as a significant prognostic factor, with an HR of 3.78 (95% CI, 1.23-11.62; P=0.020). Grade ≥3 erythropenia was also significantly associated with poorer PFS, with an HR of 5.70 (95% CI, 1.58-20.59; P=0.008), indicating a strong relationship between severe hematological toxicity and unfavorable PFS. Conversely, grade 1-2 thrombocytopenia was significantly associated with improved PFS, with an HR of 0.20 (95% CI, 0.06-0.67; P=0.009). Other factors analyzed were not significant predictors of PFS in the multivariate model (Table III).

Discussion

The present study evaluated the efficacy and safety of consolidation immunotherapy following cCRT in patients with unresectable stage III NSCLC who experienced treatment failure after neoadjuvant chemoimmunotherapy. The median PFS time was 26.0 months. When compared with 30 patients treated according to the PACIFIC regimen, no significant difference in PFS time was observed (HR, 1.155; 95% CI, 0.657-2.032; P=0.615). Additionally, the overall safety profile was manageable. To the best of our knowledge, this study represents the first real-world analysis of clinical outcomes and safety in patients with unresectable stage III NSCLC who experienced failure of neoadjuvant chemoimmunotherapy.

Patients who successfully undergo conversion therapy can achieve significantly improved prognoses after surgery (28-30). The present results indicated that there was no significant difference in prognosis between patients who experienced failure of conversion therapy and those who received standard treatment. However, multiple studies have

Table II. Treatment-related adverse events (n=67).

Adverse event	Grade <3, n (%)	Grade ≥3, n (%)
Any	64 (95.52)	38 (56.72)
Leukopenia	34 (50.75)	16 (23.88)
Granulocytopenia	30 (44.78)	15 (22.39)
Thrombocytopenia	20 (29.85)	7 (10.45)
Erythropenia	36 (53.73)	10 (14.93)
Erythema	4 (5.97)	1 (1.49)
Pruritus (itching)	1 (1.49)	0 (0.0)
Immune-related pneumonitis	5 (7.46)	4 (5.97)
Hepatic dysfunction	1 (1.49)	2 (2.99)
Hypothyroidism	2 (2.99)	2 (2.99)
Cognitive impairment	0 (0.0)	2 (2.99)
Colitis	0 (0.0)	1 (1.49)
Fatigue	1 (1.49)	0 (0.0)
Radiation esophagitis	29 (43.28)	5 (7.46)
Radiation pneumonitis	8 (11.94)	3 (4.48)
Radiodermatitis	2 (2.99)	0 (0.0)

reported differing findings regarding the optimal timing of immunotherapy intervention. According to research by Yang *et al* (22), induction combined with consolidation therapy using ICIs significantly reduced the risk of distant metastasis compared with consolidation immunotherapy alone, with trends toward a greater benefit observed in patients <65 years and those with N3 disease (22). Another study reported that, among patients with unresectable stage III disease, neoadjuvant chemoradiotherapy combined with immunotherapy achieved better outcomes than consolidation immunotherapy with fewer treatment cycles (23). The phase II clinical trial KEYNOTE-799 further demonstrated the potential benefits of early immunotherapy intervention (21). In Cohort A, which included both patients with squamous and non-squamous disease, the median PFS time was 29.0 months (95% CI, 16.6-48.5), while the median OS time was 35.6 months (95% CI, 26.1-44.2). By contrast, Cohort B, which included only patients with non-squamous disease, had a median PFS time of 45.3 months (95% CI, 17.9-not reached) and a median OS time of 56.7 months (95% CI, 41.1-not reached) (21). The discrepancy between the present findings and those of the aforementioned studies may be attributed to the distinct characteristics of the present study population. Whereas the previous studies included all patients with stage III NSCLC, the present study focused on patients who experienced failure of neoadjuvant chemoimmunotherapy, a group likely to have a higher tumor burden and more aggressive disease biology. Furthermore, patients in the present study received two to four cycles of combined chemoimmunotherapy before cCRT, whereas in the KEYNOTE-799 trial (21), cCRT combined with immunotherapy was initiated after a single cycle of chemoimmunotherapy. This earlier initiation may have led to T cell exhaustion, potentially influencing both treatment efficacy and safety outcomes. Radiotherapy induces the expression of chronic type I interferons and interferon-stimulated genes, upregulates PD-L1 and indoleamine 2,3-dioxygenase, an essential enzyme involved in tumor proliferation and immune suppression, on the tumor surface, enhances the activity of immunosuppressive cells, and ultimately leads to lymphocyte depletion and exhaustion of immune effector cells (31). This process may represent a key potential mechanism underlying the poor clinical response observed in some patients during the subsequent immune maintenance phase. Furthermore, the KEYNOTE-799 study (21) demonstrated that enhanced immune activation resulted in longer survival outcomes among patients with non-squamous cell carcinoma. However, in the present cohort, a higher proportion of patients had squamous cell carcinoma (73.13%), which may partially explain the shorter median PFS time compared with that reported in the KEYNOTE-799 trial (21). Several other studies support this interpretation, indicating that histological subtype is an important modulatory factor influencing the therapeutic efficacy of treatment in stage III NSCLC (32,33).

A high proportion of the patients included in the present study exhibited squamous cell carcinoma and were male. This population distribution is closely associated with the epidemiological characteristics of lung cancer in China and with the specific inclusion criteria of the present study. First, smoking is the principal risk factor for lung cancer in China, and squamous cell carcinoma is strongly correlated with tobacco exposure (34). Second, previous research has reported a high prevalence of stage III squamous cell carcinoma (35). While earlier large-scale Chinese studies have documented a clear male predominance in squamous cell carcinoma (36), emerging evidence reveals a significant rise in female incidence and a shifting epidemiological landscape (37). The present cohort composition, with its predominance of male patients, mirrors the historical distribution pattern of this disease in China. Given that male patients continue to constitute a major proportion of the squamous cell carcinoma population, the present results maintain clinical relevance for this subgroup. Nevertheless, this population imbalance may limit the generalizability of the study findings. Future prospective, multicenter studies should aim to recruit a more balanced patient population to validate and extend these results.

Regarding treatment-related adverse events, although the overall incidence was 95.52%, the incidence of chemotherapy-related bone marrow suppression reached 86.57%. While some studies have suggested that combining chemotherapy with immunotherapy may increase the risk of bone marrow suppression (38-40), additional clinical data are required to confirm this association. The incidence of adverse events related to immunotherapy and radiotherapy in the present study was higher than that reported in the PACIFIC trial (41), but comparable to the findings of the KEYNOTE-799 trial (21). This difference may be attributed to the synergistic interaction between radiotherapy and immunotherapy, which can result in additive tissue damage. Nevertheless, the overall safety profile remained manageable. Notably, univariate analysis revealed a positive trend between irAEs and rrAEs and prolonged PFS time, although this did not reach statistical significance. This finding provides further support for a synergistic effect between radiotherapy and immunotherapy.

Table III. Univariate and multivariate analyses of prognostic factors for progression-free survival.

Variables	P-value	HR (95% CI)	P-value	HR (95% CI)
Age	0.462	0.98 (0.94-1.03)		
Sex				
Female		1.00 (Reference)		
Male	0.745	1.27 (0.30-5.36)		
ECOG PS				
0		1.00 (Reference)		
1	0.755	1.26 (0.30-5.29)		
2	0.471	1.88 (0.34-10.50)		
Smoking status				
Never		1.00 (Reference)		
Smoker	0.357	1.64 (0.57-4.71)		
Stage at diagnosis				
IIIA		1.00 (Reference)		
IIIB	0.239	1.88 (0.66-5.42)		
IIIC	0.405	1.72 (0.48-6.12)		
Histology				
NSCC		1.00 (Reference)		
SCC	0.506	1.28 (0.61-2.69)		
PD-L1 expression				
Negative		1.00 (Reference)		
1-49%	0.494	1.35 (0.57-3.20)		
≥50%	0.365	0.54 (0.15-2.03)		
N/A	0.696	0.84 (0.35-2.02)		
Leukopenia				
No		1.00 (Reference)		
Grade 1-2	0.614	0.81 (0.36-1.83)		
Grade ≥3	0.245	1.69 (0.70-4.11)		
Granulocytopenia				
No		1.00 (Reference)		1.00 (Reference)
Grade 1-2	0.875	0.94 (0.43-2.07)	0.629	1.23 (0.52-2.91)
Grade ≥3	0.103	1.99 (0.87-4.53)	0.020[a]	3.78 (1.23-11.62)
Thrombocytopenia				
No		1.00 (Reference)		1.00 (Reference)
Grade 1-2	0.172	0.58 (0.27-1.27)	0.009[a]	0.20 (0.06-0.67)
Grade ≥3	0.399	1.52 (0.57-4.02)	0.332	0.51 (0.13-1.97)
Erythropenia				
No		1.00 (Reference)		1.00 (Reference)
Grade 1-2	0.184	1.74 (0.77-3.93)	0.460	1.39 (0.58-3.34)
Grade ≥3	0.058	2.69 (0.97-7.47)	0.008[a]	5.70 (1.58-20.59)
irAE				
No		1.00 (Reference)		
Grade 1-2	0.377	0.67 (0.27-1.64)		
Grade ≥3	0.460	0.71 (0.29-1.75)		
rrAE				
No		1.00 (Reference)		1.00 (Reference)
Grade 1-2	0.721	0.88 (0.43-1.79)	0.495	0.76 (0.35-1.66)
Grade ≥3	0.169	0.52 (0.20-1.32)	0.545	0.72 (0.25-2.06)

[a]P<0.05. HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; NSCC, non-SCC; irAE, immune-related adverse event; rrAE, radiation-related adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1.

Based on clinical data and relevant literature, factors with a P-value <0.20 in the univariate analysis may also influence prognosis (42). Therefore, variables with a P-value <0.20 were included in the multivariate regression model. The multivariate analysis demonstrated a strong association between grade ≥3 granulocytopenia and erythropenia and poorer PFS. Severe bone marrow suppression may affect clinical outcomes by altering drug dosage, shortening treatment duration and increasing susceptibility to infection. Furthermore, a reduction in granulocytes can weaken innate immunity, whereas anemia exacerbates hypoxia within the tumor microenvironment and impairs the efficacy of antitumor therapy (43,44). These findings suggest that severe treatment-related toxicities may adversely affect therapeutic effectiveness and highlight the need to develop alternative treatment strategies for patients experiencing severe adverse events to improve prognosis. Notably, grade 1-2 thrombocytopenia was significantly associated with prolonged PFS in the present study, possibly reflecting the role of platelets in modulating the tumor microenvironment and promoting tumor cell survival and proliferation (45).

The present study has several limitations. As a single-center retrospective analysis, it is inherently subject to bias. First, differences exist between the patient cohorts. The study population consisted of patients with stage III disease who did not undergo surgery after neoadjuvant chemoimmunotherapy, whereas the PACIFIC cohort included patients with initially unresectable stage III disease who received definitive cCRT followed by consolidation immunotherapy. Second, temporal variations in clinical practice may have introduced era bias. The treatment periods of the two cohorts spanned several years, during which advances occurred in radiotherapy techniques, supportive care and the management of immune-related adverse events. Additionally, the KEYNOTE-799 study (21) demonstrated survival differences between squamous and non-squamous cell carcinoma. Due to the limited sample size, subgroup analysis to evaluate prognostic differences among histological subtypes was not feasible in the present study. Future large-scale, prospective, multicenter studies are warranted to validate these findings and to better identify prognostic factors and therapeutic targets for this high-risk population.

In conclusion, the present study evaluated the prognosis and safety of patients with unresectable stage III NSCLC who experienced failure of neoadjuvant chemoimmunotherapy. The results indicate that their prognosis was comparable to that of patients receiving standard treatment, with a manageable safety profile. Therefore, neoadjuvant chemoimmunotherapy may represent a promising therapeutic approach for newly diagnosed, unresectable stage III NSCLC, offering efficacy and safety comparable to standard treatment regardless of conversion therapy outcome.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZZ conceived and designed the study. LP, FZ, RL and ZZ performed the data analysis. LP, FZ and RL drafted the manuscript. LP, FZ, RL, JH, CL, ZC and ZZ reviewed the manuscript. RL, LP, JH, CL and ZC interpreted data. ZZ supervised the entire study. All authors have read and approved the final version of the manuscript. RL and LP confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Review Committee of the Second Affiliated Hospital of Nanchang University [Nanchang, China; (2025). no. 111]. As this research involved retrospective data analysis and all patient information was anonymized, the committee waived the requirement for written informed consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Patient consent for publication

This article contains no personally identifiable information, and all data are presented in aggregated form. Therefore, individual patient consent for publication was not required.

Competing interests

The authors declare that they have no competing interests.

References

1. Feng R, Su Q, Huang X, Basnet T, Xu X and Ye W: Cancer situation in China: What does the china cancer map indicate from the first national death survey to the latest cancer registration? Cancer Commun (Lond) 43: 75-86, 2023.
2. Wei W, Zeng H, Zheng R, Zhang S, An L, Chen R, Wang S, Sun K, Matsuda T, Bray F and He J: Cancer registration in China and its role in cancer prevention and control. Lancet Oncol 21: e342-e349, 2020.
3. Zeng H, Ran X, An L, Zheng R, Zhang S, Ji JS, Zhang Y, Chen W, Wei W and He J; HBCR Working Group: Disparities in stage at diagnosis for five common cancers in China: A multicentre, hospital-based, observational study. Lancet Public Health 6: e877-e887, 2021.
4. Chen Z, Fillmore CM, Hammerman PS, Kim CF and Wong KK: Non-small-cell lung cancers: A heterogeneous set of diseases. Nat Rev Cancer 14: 535-546, 2014.
5. Remon J, Soria JC and Peters S; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org: Early and locally advanced non-small-cell lung cancer: An update of the ESMO clinical practice guidelines focusing on diagnosis, staging, systemic and local therapy. Ann Oncol 32: 1637-1642, 2021.
6. Park K, Vansteenkiste J, Lee KH, Pentheroudakis G, Zhou C, Prabhash K, Seto T, Voon PJ, Tan DSW, Yang JCH, *et al*: Pan-asian adapted ESMO clinical practice guidelines for the management of patients with locally-advanced unresectable non-small-cell lung cancer: A KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. Ann Oncol 31: 191-201, 2020.

7. Ricciuti B, Fusco F, Cooper A, Garbo E, Pecci F, Aldea M, Wang X, Mayoral Penalva M, Ginsberg M, Sholl LM, *et al*: Neoadjuvant PD-1 and PD-L1 blockade with chemotherapy for borderline resectable and unresectable stage III non-small cell lung cancer. JAMA Oncol 11: 735-741, 2025.
8. Sun C, Wang X, Xu Y, Shao G, Chen X, Liu Y, Zhang P, Lin X, Ma X, Qiu S, *et al*: Efficiency and safety of neoadjuvant PD-1 inhibitor (sintilimab) combined with chemotherapy in potentially resectable stage IIIA/IIIB non-small cell lung cancer: Neo-pre-IC, a single-arm phase 2 trial. EClinicalMedicine 68: 102422, 2024.
9. Yu X, Huang C, Du L, Wang C, Yang Y, Yu X, Lin S, Yang C, Zhao H, Cai S, *et al*: Efficacy and safety of perioperative sintilimab plus platinum-based chemotherapy for potentially resectable stage IIIB non-small cell lung cancer (periSCOPE): An open-label, single-arm, phase II trial. EClinicalMedicine 79: 102997, 2024.
10. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick SR, Brahmer JR, Swanson SJ, *et al*: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 386: 1973-1985, 2022.
11. Lu S, Zhang W, Wu L, Wang W, Zhang P; Neotorch Investigators; Fang W, Xing W, Chen Q, Yang L, *et al*: Perioperative toripalimab plus chemotherapy for patients with resectable non-small cell lung cancer: The neotorch randomized clinical trial. JAMA 331: 201-211, 2024.
12. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, Stratford IJ, Poon E, Morrow M, Stewart R, *et al*: Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 74: 5458-5468, 2014.
13. Wei J, Montalvo-Ortiz W, Yu L, Krasco A, Ebstein S, Cortez C, Lowy I, Murphy AJ, Sleeman MA and Skokos D: Sequence of αPD-1 relative to local tumor irradiation determines the induction of abscopal antitumor immune responses. Sci Immunol 6: eabg0117, 2021.
14. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, *et al*: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 377: 1919-1929, 2017.
15. Zhou Q, Chen M, Jiang O, Pan Y, Hu D, Lin Q, Wu G, Cui J, Chang J, Cheng Y, *et al*: Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): Interim results of a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 23: 209-219, 2022.
16. Wu YL, Wang L, Sendur MAN, Kim YC, Zhu Z, Cheng Y, Li P, Qin Y, Macpherson E, Dennis PA and Lu S: PACIFIC-5: Phase III study of durvalumab after either concurrent or sequential chemoradiotherapy (CRT) in patients with stage III NSCLC. Ann Oncol 30: ix113-ix114, 2019.
17. Bradley JD, Sugawara S, Lee KHH, Ostoros G, Demirkazik A, Zemanova M, Sriuranpong V, Gelatti A, Menezes J, Zurawski B, *et al*: LBA1 durvalumab in combination with chemoradiotherapy for patients with unresectable stage III NSCLC: Final results from PACIFIC-2. ESMO open 9: 102986, 2024.
18. Peters S, Tan DSW, Gerber DE, Urbanic J, Ramalingam SS, Yu J, Xing L, Rittmeyer A, Ciuleanu TE, Menezes JE, *et al*: 65O CheckMate 73L: Phase III study comparing nivolumab (N) + concurrent chemoradiotherapy (CCRT) followed by N ± ipilimumab (I) v CCRT followed by durvalumab (D) for previously untreated, locally advanced stage (stg) III NSCLC. ESMO 24: 100808, 2024.
19. Kumar V, Bauer C and Stewart JH IV: Cancer cell-specific cGAS/STING signaling pathway in the era of advancing cancer cell biology. Eur J Cell Biol 102: 151338, 2023.
20. Boukhaled GM, Harding S and Brooks DG: Opposing roles of type I interferons in cancer immunity. Annu Rev Pathol 16: 167-198, 2021.
21. Reck M, Lee KH, Frost N, Breder V, Kowalski DM, Levchenko E, Reguart N, Martinez-Marti A, Houghton B, Paoli JB, *et al*: 1860: Pembrolizumab (pembro) plus concurrent chemoradiation therapy (cCRT) in unresectable locally advanced non-small cell lung cancer (NSCLC): final analysis of KEYNOTE-799. J Thoracic Oncol 20: S124-S125, 2025.
22. Yang Y, Wang J, Zhang T, Zhou Z, Wang Y, Jiang Y, Liu W, Xiao Z, Deng L, Feng Q, *et al*: Efficacy and safety of definitive chemoradiotherapy with or without induction immune checkpoint inhibitors in patients with stage III non-small cell lung cancer. Front Immunol 14: 1281888, 2023.
23. Guan S, Wang Y, Liu Q, Yan M, Ren K, Wang J, Bi N and Zhao L: Induction chemoimmunotherapy may achieve non-inferior outcomes to consolidation immunotherapy in patients with unresectable stage III NSCLC: A real-world multicenter retrospective study. Front Immunol 16: 1591134, 2025.
24. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
25. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649-655, 1982.
26. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR (eds.), *et al*: AJCC Cancer Staging Manual. 8th edition. Springer-Verlag, New York, NY, USA, pp 431-467, 2017.
27. U.S. Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE) Version 5, 2017.
28. Guan S, Sun J, Wang Y, Han S, Chen C, Yue D, Huang Y, Ren K, Wang J, Wang J and Zhao L: Chemoradiotherapy versus surgery after neoadjuvant chemoimmunotherapy in patients with stage III NSCLC: A real-world multicenter retrospective study. Cancer Immunol Immunother 73: 120, 2024.
29. Deng H, Liu J, Cai X, Chen J, Rocco G, Petersen RH, Brunelli A, Ng CSH, D'Amico TA, Liang W and He J: Radical minimally invasive surgery after immuno-chemotherapy in initially-unresectable stage IIIB non-small cell lung cancer. Ann Surg 275: e600-e602, 2022.
30. Wang M, Wang X, Yang R, Geng M, Zhang S, Yang Z, Huang Q, Wang S, Xu S, Jiang K and Liao Y: Conversion surgery for initially unresectable stage III nonsmall cell lung cancer after induction treatment of immunochemotherapy: A multicenter study. Clin Lung Cancer 26: e131-e140.e1, 2025.
31. Wang X, Wang Y, Zhang Y, Shi H, Liu K, Wang F, Wang Y, Chen H, Shi Y and Wang R: Immune modulatory roles of radioimmunotherapy: Biological principles and clinical prospects. Front Immunol 15: 1357101, 2024.
32. Toriyama K, Yomota M, Asai M, Hashimoto K, Mirokuji K, Kawai S, Watanabe K, Narita K and Hosomi Y: Real-world prognostic data on unresectable stage III non-small-cell lung cancer treated with concurrent chemoradiation therapy by histological type. Intern Med 63: 2757-2765, 2024.
33. Johnson ML, Cho BC, Luft A, Alatorre-Alexander J, Geater SL, Laktionov K, Kim SW, Ursol G, Hussein M, Lim FL, *et al*: Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non-small-cell lung cancer: The phase III POSEIDON study. J Clin Oncol 41: 1213-1227, 2023.
34. Leiter A, Veluswamy RR and Wisnivesky JP: The global burden of lung cancer: Current status and future trends. Nat Rev Clin Oncol 20: 624-639, 2023.
35. Yu J, Xing L, Cheng G, Chen L, Dong L, Fu X, Guo Y, Han Z, Jiang D, Li J, Lin Y, *et al*: P21.10 real-world treatment patterns in Chinese stage III NSCLC patients-a prospective, non-interventional study (MOOREA trial). J Thoracic Oncol 16: S367-S368, 2021.
36. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J: Cancer statistics in China, 2015. CA Cancer J Clin 66: 115-132, 2016.
37. Wang J, Cao H, He N, Liu X, Fu F, Deng C, Li Y, Zhang Y and Chen H: Evolving trends in surgically managed lung cancer: A 16-year hospital-based epidemiological analysis. Lung Cancer 208: 108754, 2025.
38. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, *et al*: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378: 2078-2092, 2018.
39. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, *et al*: Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med 381: 2020-2031, 2019.
40. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, *et al*: Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 378: 2288-2301, 2018.

41. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, Vansteenkiste JF, Garassino MC, Hui R, Quantin X, *et al*: Five-year survival outcomes from the PACIFIC Trial: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. J Clin Onco 40: 1301-1311, 2022.
42. Heinze G and Dunkler D: Five myths about variable selection. Transpl Int 30: 6-10, 2017.
43. Tang Z, Hu J, Li XC, Wang W, Zhang HY, Guo YY, Shuai X, Chu Q, Xie C, Lin D and Zhong B: A subset of neutrophils activates anti-tumor immunity and inhibits non-small-cell lung cancer progression. Dev Cell 60: 379-395.e8, 2025.
44. Zhang Y, Guo F and Wang Y: Hypoxic tumor microenvironment: Destroyer of natural killer cell function. Chin J Cancer Res 36: 138-150, 2024.
45. Goubran HA, Stakiw J, Radosevic M and Burnouf T: Platelet-cancer interactions. Semin Thromb Hemost 40: 296-305, 2014.