Am J Cancer Res 2025;15(2):573-586
www.ajcr.us /ISSN:2156-6976/ajcr0161261

Original Article

Risk factors for immunoresistance in advanced non-small cell lung cancer and the advantages of targeted therapy in improving prognosis

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Received October 17, 2024; Accepted January 17, 2025; Epub February 15, 2025; Published February 28, 2025

Abstract: Objectives: The advent of immunotherapy has transformed the therapeutic landscape for advanced non-small cell lung cancer (NSCLC); nonetheless, the emergence of resistance to immunotherapy poses a considerable obstacle. Our research sought to identify factors contributing to immunotherapy resistance and to assess the effectiveness of subsequent treatments in patients with advanced NSCLC who have been exposed to immune checkpoint inhibitors (ICIs). Methods: This retrospective study analyzed data from 232 individuals with advanced NSCLC who were treated with ICIs during January 2020 to December 2023. Based on their response to ICIs, these patients were classified into two groups: immunoresistance group (IM group) and non-immunoresistance group (NIM group). Data collected included demographics, clinical parameters, cytokine profiles, tumor mutational burden (TMB), PD-L1 expression, overall survival (OS), progression-free survival (PFS), and adverse events. The association between risk factors and immunoresistance were assessed, and second-line treatment outcomes were evaluated. Results: Key risk factors for immunoresistance included lower TMB, higher levels of interleukin-10 (IL-10), and PD-L1 expression ≥ 50%. TMB was inversely correlated with immunoresistance (rho = -0.838, $P < 0.001$). In multivariate analysis, IL-10 remained a significant risk factor (OR = 33.654, $P = 0.021$), whereas TMB was protective (OR = 0.786, $P < 0.001$). Second-line targeted therapy significantly improved OS (8.72 ± 2.02 months) and PFS (5.37 ± 2.15 months) compared to chemotherapy (OS: 7.93 ± 2.13 months; PFS: 4.86 ± 1.68 months) ($P < 0.05$). The targeted therapy group experienced distinct side effects, notably increased hypertension and hand-foot syndrome, while chemotherapy group had higher rates of fatigue ($P < 0.05$). Conclusion: Immunoresistance in advanced NSCLC is influenced by IL-10, TMB, and PD-L1 expression. Targeted therapies offer superior outcomes than chemotherapy, though side effect management remains crucial.

Keywords: Non-small cell lung cancer, immunoresistance, immune checkpoint inhibitors, tumor mutational burden, biomarkers, second-line treatment

Introduction

Lung cancer remains the leading cause of cancer-related deaths globally, with non-small cell lung cancer (NSCLC) comprising roughly 85% of all diagnosed cases [1]. Despite significant advancements in treatment modalities over the past few decades, the prognosis for patients with advanced NSCLC remains challenging, largely due to the development of resistance to conventional therapies, including immune checkpoint inhibitors (ICIs). The introduction of ICIs, especially those that target the programmed cell death protein 1 (PD-1) and its ligand (PD-L1), has markedly altered the therapeutic approach for NSCLC. By leveraging the patient's immune system to better fight the cancer, these treatments block the signaling pathways that cancer cells employ to evade immune detection, thus amplifying the body's innate immune response against the tumor [2].

However, the clinical utility of ICIs was frequently compromised by the emergence of immunoresistance, significantly diminishing the potential survival benefits in a diverse range of pa-

tient subgroups. One of the major challenges in the field is the development of immunoresistance, which can occur through various mechanisms, including genetic alterations, immune microenvironment changes, and metabolic adaptations [3]. Understanding the complex mechanisms underlying this resistance is critical for optimizing therapeutic regimens and improving patient outcomes. Immunoresistance in NSCLC emerges through a multifaceted interplay of tumor-intrinsic factors, such as genetic and epigenetic alterations, and tumor-extrinsic factors, including alterations in the tumor microenvironment and systemic immune responses. Tumor mutational burden (TMB) has recently garnered attention as a promising biomarker for predicting response to ICIs. A high TMB is thought to be associated with increased neoantigen production, which enhances tumor immunogenicity and sensitivity to checkpoint blockade therapies. Nonetheless, debates linger over its predictive accuracy, especially in the context of NSCLC, necessitating further elucidation of its role in immunoresistance pathways [4].

In addition to TMB, cytokines within the tumor microenvironment are increasingly recognized for their contribution to immune evasion and resistance dynamics. Cytokines such as interleukin-10 (IL-10) and interferon-gamma (IFN-γ) have been implicated in modulating immune responses in a manner that can both suppress and sustain tumor-promoting mechanisms. IL-10, often associated with an immunosuppressive milieu, may mitigate the efficacy of immunotherapies by fostering regulatory T cell activity and hindering the function of cytotoxic T lymphocytes [5]. Conversely, while IFN-γ is commonly linked to potent antitumor responses, its chronic presence may inadvertently enhance immunoresistance by upregulating checkpoint molecules like PD-L1 on tumor cells, thereby facilitating immune escape [6]. These intricate pathways underscore the need for a comprehensive approach in identifying and validating reliable prognostic markers of immunotherapy resistance.

Alongside refining our understanding of immunoresistance, another critical challenge in evaluating second-line treatments for NSCLC patients who exhibit disease progression following ICI therapy. Traditional chemotherapy and targeted therapies remain the mainstay of second-line treatment strategies. However, their relative efficacy varies significantly, influenced by multiple factors including the distinct molecular and pathophysiological profiles of each cancer. Notwithstanding their efficacy, these treatments are accompanied by diverse adverse-effect profiles that necessitate careful management to optimize patient well-being and clinical outcomes [7]. Consequently, investigating the efficacy and tolerability of second-line treatments through evidence-based research is essential for informing clinical decision-making.

This study aims to comprehensively analyze the risk factors associated with immunoresistance in advanced NSCLC, while systematically comparing the clinical efficacy of various second-line therapeutic regimens. This research introduces several innovative aspects: 1) Integrated biomarker analysis, including TMB, IL-10, and PD-L1, for a deeper understanding of immunoresistance. 2) Multivariate analysis to identify independent risk factors. 3) Demonstration of the superiority of targeted therapy over chemotherapy in overall survival (OS) and progression-free survival (PFS), with distinct side-effect profiles.

Methods

Patient selection

Ethics statement: Approval for this study was obtained from the Institutional Review Board and Ethics Committee of the People's Hospital Affiliated with Fujian University of Traditional Chinese Medicine. Given the retrospective nature of the study, the requirement for informed consent was waived. This decision was based on the use of only de-identified patient data, which ensures that there is no potential for harm to participants and does not impact their medical care.

Study design: This retrospective analysis included 232 patients diagnosed with advanced NSCLC who received ICI therapy at the People's Hospital Affiliated with Fujian University of Traditional Chinese Medicine from January 2020 to December 2023. The dataset compiled for this study included demographic details, routine blood test results, plasma inflammatory cytokine levels, tumor characteristics and microenvironment, OS, PFS, and adverse events. All information was obtained retrospectively from the institution's medical record system.

Inclusion and exclusion criteria: Inclusion criteria: 1) a diagnosis of advanced NSCLC in accordance with the NCCN Clinical Practice Guidelines in Oncology [8]; 2) aged 18 years or older; 3) presence of at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) [9]; 4) receipt of at least one cycle of ICI therapy; and 5) subsequent enrollment in second-line treatment following ICI therapy.

Exclusion criteria: 1) prior receipt of other forms of immunotherapy; 2) second-line treatment not consisting of chemotherapy or targeted therapy; 3) presence of autoimmune or infectious diseases; 4) concurrent malignancies that could potentially influence treatment outcomes; 5) brain metastasis or spinal cord compression; and 6) incomplete medical records.

Data extraction

Grouping criteria: In compliance with the protocols established by the Society for Immunotherapy of Cancer [10], patients were classified as having developed resistance if their tumors did not decrease in size but instead increased, or if new lesions appeared after a specified course of treatment. This resistance was further categorized into primary resistance, secondary resistance, and progression following the discontinuation of treatment for any reason. Primary resistance was characterized by disease progression after receiving ICI treatment for at least six weeks (two cycles) but no more than six months. Conversely, secondary resistance refers to disease progression after an initial clinical benefit, which includes either an objective response or stable disease (SD) persisting for six months or longer.

Patients were classified into different groups based on the development of immune resistance. The immune resistance group (IM group) consisted of 105 patients who exhibited resistance, while the non-immune resistance group (NIM group) included 127 patients who did not develop resistance. Additionally, the entire cohort was further divided based on their second-line treatment regimens. Patients who received chemotherapy as their second-line treatment were placed in the chemotherapy group, and those who received targeted therapy were categorized into the targeted therapy group (**Figure 1**).

Assessment of patient's disease condition: The Eastern Cooperative Oncology Group (ECOG) performance status was utilized to assess patients' overall health and treatment tolerance based on their physical activity levels. This scoring system was divided into six categories (0-5). 0: Fully active individuals with no restrictions on daily activities; 1: Individuals who can walk and perform light activities, such as housework or office tasks, but cannot engage in strenuous labor; 2: Individuals capable of self-care and ambulation, who were unable to work but can remain active for over half of their waking hours; 3: Individuals limited to minimal self-care and confined to a bed or chair for more than half the day; 4: Completely incapacitated individuals who were bedridden or chair-bound and unable to care for themselves; and 5: Deceased individuals. The inter-rater reliability for this assessment was measured as Cohen's $\kappa = 0.486$ [11].

The TNM staging system [12] was used to assess the extent of tumor progression. As an internationally recognized classification method, it categorizes tumor advancement, with higher stages indicating more advanced disease. The T (Tumor) category assesses the size and local extent of the primary tumor, divided into four levels: T1, T2, T3, and T4, with higher numbers signifying larger tumors and greater local invasion. The N (Node) category details regional lymph node involvement, classified into N0, N1, N2, and N3, where higher numbers denote more extensive lymph node involvement. The M (Metastasis) category signifies whether there is a presence or absence of distant metastasis, with M0 denoting no metastasis and M1 indicating the presence of metastasis.

TMB was evaluated using high-throughput sequencing technology, specifically with the NextSeq sequencer (Illumina, Inc., USA). Data processing was conducted utilizing the Burrows-Wheeler Aligner (BWA) and the Genome Analysis Toolkit (GATK).

Blood routine test: Venous blood samples (8 ml) were obtained from patients in the morning following an overnight fast after the administration of ICI treatment. The samples were centrifuged at 3000 r/min for 10 minutes using a low-temperature high-speed centrifuge (TLD

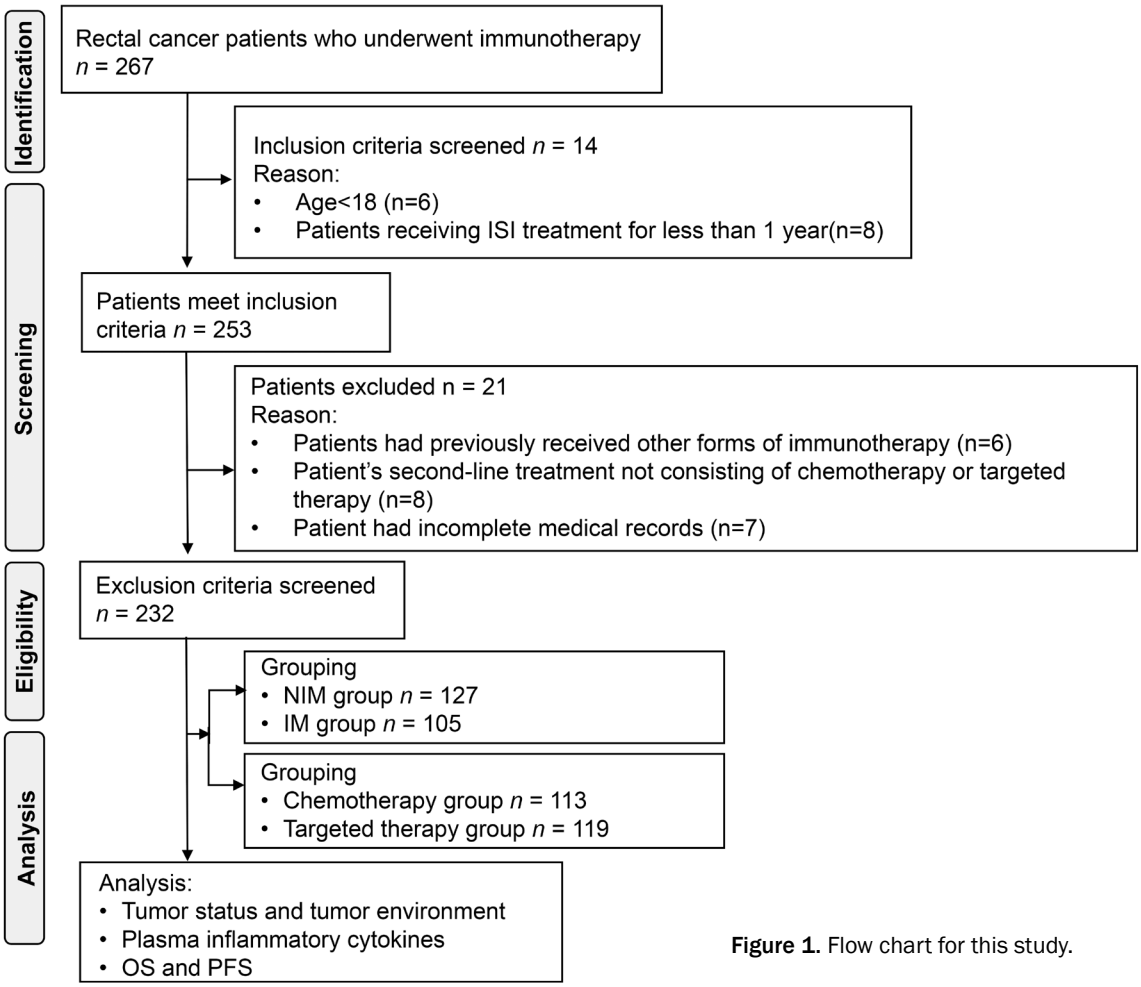

Figure 1. Flow chart for this study.

12A, Xiangxi Scientific Instrument Factory, Hunan, China). The separated plasma was then stored at -80°C. Red blood cell (RBC) and white blood cell counts, along with hemoglobin (HB) levels, were measured using a blood cell analyzer (SYSMEX SE-9000, Sysmex Corporation, Japan). Albumin levels were determined using an automated biochemical analyzer (Seamaty SD1, Chengdu Smart Technology Co., Ltd., China).

Detection of inflammatory cytokines and programmed cell death ligand 1 (PD-L1): The plasma concentrations of PD-L1 and inflammatory cytokines, such as interferon-γ (IFN-γ), IL-6, IL-8, and IL-10, were quantified using ELISA kits (JK-E3181; JK-E2757; JK-E2762; JK-E2737; JK-E2765; Shanghai Jingkang Biotechnology Co., Ltd., China). The optical density (OD) values were measured at 450 nm with a microplate reader (Molecular Devices, CA, USA) to determine the expression levels of these cytokines.

Outcome measures

Primary outcome measures: OS (Overall Survival): Defined as the duration from the initiation of first-line immunotherapy to the date of death due to any cause. Patients who remained alive at the last follow-up were censored on that date.

PFS (Progression-Free Survival): Defined as the interval from the start of first-line immunotherapy to the earliest recorded instance of disease progression or death, whichever comes first. Patients without evidence of progression or death were censored at the time of their last follow-up.

Secondary outcome measures: TMB, IL-10, PD-L1 (post-first-line immunotherapy testing).

Statistical analysis

Data cleaning and management: Prior to statistical analyses, a systematic data cleansing pro-

cess was undertaken to ensure the integrity of dataset. This procedure invloved identifying and resolving issues such as inconsistencies, inaccuracies, or missing information within the data collection. The cleaning process included eliminating duplicate records, rectifying input mistakes, and addressing gaps in the data. For handling missing data, we utilized Python 3.6.0 along with specialized libraries including pandas, numpy, seaborn, random, and missingno. We initially applied mean imputation, followed by stochastic regression imputation. For this, a KDTree was constructed from the complete dataset to identify nearest neighbors and calculate weighted averages of missing values.

To mitigate any selection bias that might arise from missing data, we kept its proportion under 5% and performed sensitivity analyses to evaluate the impact of different assumptions about missing data on the outcomes. Specifically, for cases lost to follow-up, we calculated outcomes under both best-case and worst-case scenarios. If these extreme scenarios did not significantly affect the study conclusions, it indicated that the missing data had little influence on the reliability of the findings. All subsequent analyses were based on the dataset after imputing missing values.

Statistical analysis: The calculation of the minimum sample size was conducted using G* Power 3.1.9.7, opting for the "Difference between two independent means (two groups)" scenario suitable for t-tests. With a significance level (α) at 0.05 and a desired power (1 - β) of 0.95, it was determined that at least 88 patients were required for the study. The formula used for this calculation is:

$$n = [(Z1-\alpha/2 + Z1-\beta)/d]^2 \times [p1 (1-p1) + p2 (1-p2)]$$

Data analysis was performed using SPSS 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were reported as [n (%)]. The chi-square test was applied when the sample size ≥ 40 and theoretical frequency (T) ≥ 5. For instances where the theoretical frequency was between 1 and 5, adjustments to the chi-square test were made. Fisher's exact test was employed for smaller samples or when T < 1.

Continuous variables were first tested for normal distribution using the Shapiro-Wilk test. Normally distributed continuous variables were described as (X ± s), whereas non-normally distributed data were analyzed using the Wilcoxon rank-sum test and reported as [median (25th quartile, 75th quartile)]. A *P*-value below 0.05 indicated statistical significance. Correlation between continuous variables was assessed using Pearson correlation, and for categorical variables, Spearman correlation was used. Univariate and multivariate analyses were also carried out to identify risk factors associated with immune resistance in advanced NSCLC patients.

Results

Comparison of baseline data between the IM and NIM groups

The demographic characteristics of NIM and IM groups were compared (**Table 1**). The mean age of participants in the NIM and IM groups was 63.63 ± 8.38 years and 65.19 ± 7.77 years, respectively (*P* = 0.146). Gender distribution was similar in both groups, with 44.09% females and 55.91% males in the NIM group, compared to 44.76% females and 55.24% males in the IM group (*P* = 0.919). Ethnically, the majority were Han, with 81.1% in the NIM group and 79.05% in the IM group (*P* = 0.696). BMI was comparable between groups, with means of 24.64 ± 2.83 kg/m^2 for the NIM and 24.24 ± 2.25 kg/m^2 for the IM group (*P* = 0.232). The ECOG performance status was 0 in 65.35% of the NIM group and 62.86% in the IM group (*P* = 0.693). Regarding lifestyle factors, a history of smoking was reported by 65.35% of the NIM group and 68.57% of the IM group (*P* = 0.604), while alcohol consumption history was observed in 33.86% and 37.14% of individuals in each group, respectively (*P* = 0.602). The prevalence of comorbidities, including hypertension (43.31% vs. 45.71%) and diabetes (14.96% vs. 12.38%), was similar between the two groups. Educational attainment and marital status did not differ significantly, as 77.17% of the NIM group and 75.24% of the IM group had at least a college education, and 55.91% of the NIM group versus 53.33% of the IM group were married (*P* > 0.05). Analysis of the ratio of family income to poverty, TNM stage, pathological type, and lymphatic metastasis showed no significant differences (*P* > 0.05) between the two groups. These findings indicate that demographic and clinical characteristics were evenly distributed between the two groups.

Table 1. Comparison of demographic characteristics between two groups

	NIM group (n = 127)	IM group (n = 105)	t/χ^2	P
Age (years)	63.63 ± 8.38	65.19 ± 7.77	1.459	0.146
Female/Male	56 (44.09%)/71 (55.91%)	47 (44.76%)/58 (55.24%)	0.010	0.919
Ethnicity (Han/Other)	103 (81.1%)/24 (18.9%)	83 (79.05%)/22 (20.95%)	0.153	0.696
BMI (kg/m^2)	24.64 ± 2.83	24.24 ± 2.25	1.198	0.232
ECOG performance status (0/≥ 1)	83 (65.35%)/44 (34.65%)	66 (62.86%)/39 (37.14%)	0.156	0.693
Smoking history (Yes/No)	83 (65.35%)	72 (68.57%)	0.268	0.604
Drinking history (Yes/No)	43 (33.86%)	39 (37.14%)	0.271	0.602
Hypertension (Yes/No)	55 (43.31%)	48 (45.71%)	0.135	0.713
Diabetes (Yes/No)	19 (14.96%)	13 (12.38%)	0.322	0.571
Educational level (High school or below/College or above)	29 (22.83%)/98 (77.17%)	26 (24.76%)/79 (75.24%)	0.118	0.731
Marital Status (Married/Unmarried)	71 (55.91%)/56 (44.09%)	56 (53.33%)/49 (46.67%)	0.153	0.695
RIP (< 1/1-3/3)	31 (24.41%)/52 (40.94%)/44 (34.65%)	28 (26.67%)/50 (47.62%)/27 (25.71%)	2.196	0.334
TNM stage (≤ II/> II)	46 (36.22%)/81 (63.78%)	34 (32.38%)/71 (67.62%)	0.375	0.540
Pathological Type (Squamous/Adenocarcinoma/Large Cell Lung cancer)	53 (41.73%)/30 (23.62%)/44 (34.65%)	42 (40%)/28 (26.67%)/35 (33.33%)	0.284	0.867
Lymphatic Metastasis (Yes/No)	54 (42.52%)	49 (46.67%)	0.400	0.527

NIM: Non-immunoresistance; IM: Immunoresistance; BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group performance status; RIP: the ratio of family income to poverty; TNM: tumor node metastasis classification.

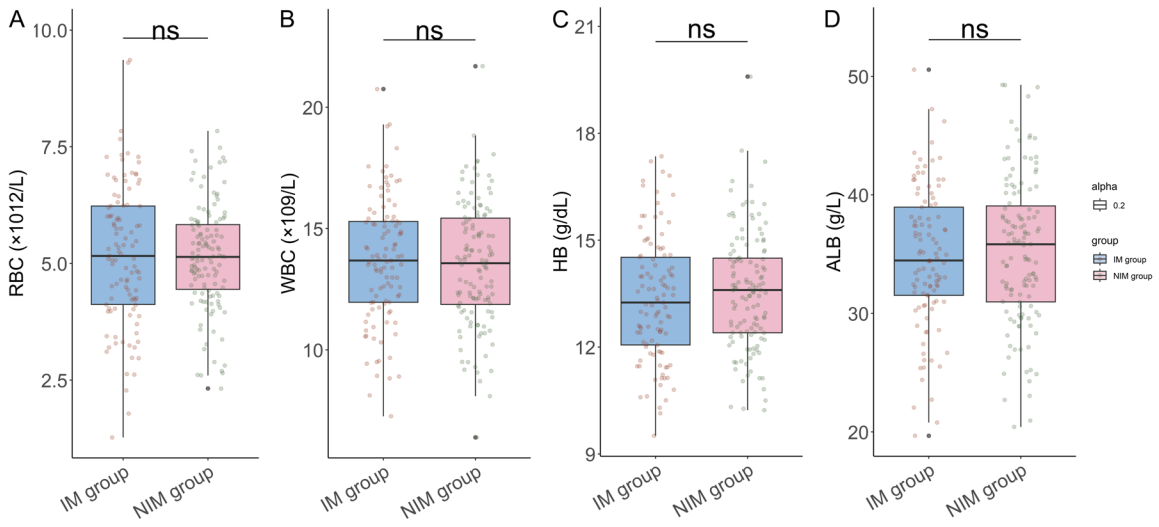

Figure 2. Comparison of routine blood test between two groups. A. Level of RBC; B. Level of WBC; C. Level of HB; D. Level of ALB. RBC: red blood cell; WBC: white blood cell; HB: hemoglobin; ALB: albumin. ns: no statistically significant difference. *: P < 0.05; **: P < 0.01; ns: not significant.

Comparison of blood routine results between the two groups

As displayed in **Figure 2**, the mean RBC count was 5.13 ± 1.12 × 10^{12}/L in the NIM group and 5.18 ± 1.51 × 10^{12}/L in the IM group (P = 0.770). Similarly, the white blood cell (WBC) counts were comparable, with means of 13.52 ± 2.54 × 10^{9}/L for the NIM group and 13.68 ± 2.58 × 10^{9}/L for the IM group (P = 0.627). HB levels were 13.56 ± 1.63 g/dL in the NIM group compared to 13.33 ± 1.74 g/dL in the IM group (P = 0.314). Finally, albumin (ALB) levels showed means of 35.26 ± 6.18 g/L and 34.72 ± 5.87 g/L in the NIM and IM groups, respectively (P = 0.495). These results indicate that the routine blood test parameters were comparable between the two groups, suggesting no baseline hematological differences associated with immune resistance status.

IFN-γ levels were notably higher in the IM group (5.42 ± 0.21 pg/mL) compared to the NIM group (5.33 ± 0.25 pg/mL) (P = 0.003), suggesting a possible association with immune resistance (**Figure 3**). Additionally, IL-10 levels were elevated in the IM group (1.03 ± 0.21 pg/mL) versus the NIM group (0.97 ± 0.21 pg/mL) (P = 0.033), indicating its potential role in resistance mechanisms. Conversely, no significant differences were observed in IL-4 (0.93 ± 0.27 pg/mL vs. 0.95 ± 0.21 pg/mL; P = 0.568) and IL-6 (1.81 ± 0.19 pg/mL vs. 1.84 ± 0.12 pg/mL; P = 0.232) levels between the groups. These results suggest that certain cytokines, notably IFN-γ and IL-10, might be implicated in immune resistance in this patient population.

Comparison of tumor status and tumor environment between the two groups

The Tumor Mutational Burden (TMB) was markedly elevated in the NIM group, averaging 101 ± 15, compared to the IM group which had a mean of 56 ± 14 (**Table 2**). Additionally, the analysis revealed a notably higher incidence of high PD-L1 expression (≥ 50%) among patients in the IM group compared to the NIM group (20% vs. 7.09%; P = 0.004), suggesting a potential association between elevated PD-L1 expression and immunoresistance. However, the threshold for PD-L1 expression was lowered to ≥ 5%, no significant discrepancy was observed between the groups, with 25.2% of patients in the NIM group and 28.57% in the IM group had PD-L1 expression at this level (P = 0.563). This finding indicates that while high PD-L1 expression and lower TMB appear to be linked with immune resistance, less pronounced PD-L1 expression does not effectively distinguish between the groups.

Correlation analysis of risk factors for the development of immune resistance in advanced NSCLC

Correlation analysis revealed several significant relationships between immune resistance

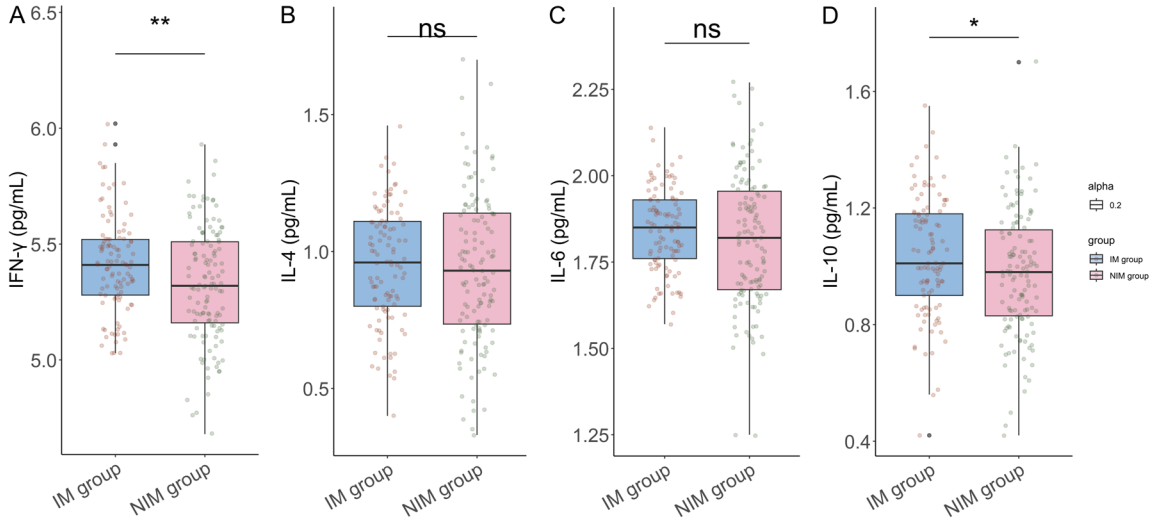

Figure 3. Comparison of plasma inflammatory cytokines between two groups. A. Level of IFN-γ; B. Level of IL-6; C. Level of IL-8; D. Level of IL-10. IFN-γ: interferon-γ; IL-6: interleukin-6; IL-8: interleukin-8; IL-10: interleukin-10. ns: no statistically significant difference; ns: not significant.

Table 2. Comparison of tumor status and tumor environment between two groups

	NIM group (n = 127)	IM group (n = 105)	t/χ^2	P
TMB	101 ± 15	56 ± 14	23.434	< 0.001
PD-L1+ (≥ 5%)	32 (25.2%)	30 (28.57%)	0.334	0.563
PD-L1+ (≥ 50%)	9 (7.09%)	21 (20%)	8.513	0.004

NIM: Non-immunoresistance; IM: Immunoresistance; TMB: Tumor mutational burden; PD-L1: Programmed death-ligand 1.

Table 3. Correlation analysis of risk factors with immune resistance in advanced NSCLC

	rho	P
IFN-γ (pg/mL)	0.166	0.011
IL-10 (pg/mL)	0.145	0.027
TMB	-0.838	*P* < 0.001
PD-L1+ (≥ 50%)	0.192	0.003

IFN-γ: Interferon-γ; IL-10: Interleukin-10; TMB: Tumor mutational burden; PD-L1: Programmed death-ligand 1; NSCLC: Non-small cell lung cancer.

and various biomarkers and clinical parameters (**Table 3**). Among these, TMB was found to have a robust negative correlation with immune resistance, as indicated by a Spearman's rho value of -0.838 (*P* < 0.001). This finding suggests that patients with lower TMB are more likely to develop resistance to immunotherapy.

Furthermore, high PD-L1 expression (≥ 50%) was moderately positively correlated with immune resistance, with a rho value of 0.192 (*P* = 0.003), suggesting an increased likelihood of immune resistance in patients with elevated PD-L1 expression levels. Additionally, weak but statistically significant positive correlations were found between immune resistance and both IFN-γ levels (rho = 0.166, *P* = 0.011) and IL-10 levels (rho = 0.145, *P* = 0.027).

Univariate analysis of risk factors for the development of immune resistance in advanced NSCLC

The univariate analysis identified several significant predictors of immune resistance in advanced NSCLC (**Table 4**). IFN-γ was associated with an increased likelihood of immune resistance, with a coefficient of 1.676 (*P* = 0.005) and an odds ratio (OR) of 5.346 (95% CI, 1.701-17.755), indicating a more than fivefold risk increase. Similarly, IL-10 demonstrated a significant impact (coefficient = 1.358, *P* = 0.035), with an OR of 3.889 (95% CI, 1.122-14.095), suggesting IL-10 was a substantial risk factor. TMB was inversely associated with immune resistance (coefficient = -0.218, P < 0.001), showing a protective role with an OR of 0.804 (95% CI, 0.742-0.853), signifying that higher TMB was linked to lower resistance risk. High PD-L1 expression (≥ 50%) was also a significant predictor (coefficient = 1.187, *P* =

Table 4. Univariate analysis of risk factors for the development of immune resistance in advanced NSCLC patients

	Coefficient	Std. Error	Wald	*P* Value	OR	95% CI
IFN-γ (pg/mL)	1.676	0.596	2.812	0.005	5.346	1.701-17.755
IL-10 (pg/mL)	1.358	0.643	2.112	0.035	3.889	1.122-14.095
TMB	-0.218	0.035	6.215	< 0.001	0.804	0.742-0.853
PD-L1+ (≥ 50%)	1.187	0.423	2.805	0.005	3.278	1.470-7.868

IFN-γ: Interferon-γ; IL-10: Interleukin-10; TMB: Tumor mutational burden; PD-L1: Programmed death-ligand 1; NSCLC: Non-small cell lung cancer.

Table 5. Multivariate analysis of various factors

	Coefficient	Std. Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
IFN-γ (pg/mL)	1.181	1.685	0.701	0.483	3.258	0.120	88.520
IL-10 (pg/mL)	3.516	1.523	2.308	0.021	33.654	1.700	666.198
TMB	-0.240	0.043	-5.636	< 0.001	0.786	0.723	0.855
PD-L1+ (≥ 50%)	0.256	0.835	0.306	0.759	1.291	0.252	6.631

IFN-γ: Interferon-γ; IL-10: Interleukin-10; TMB: Tumor mutational burden; PD-L1: Programmed death-ligand 1.

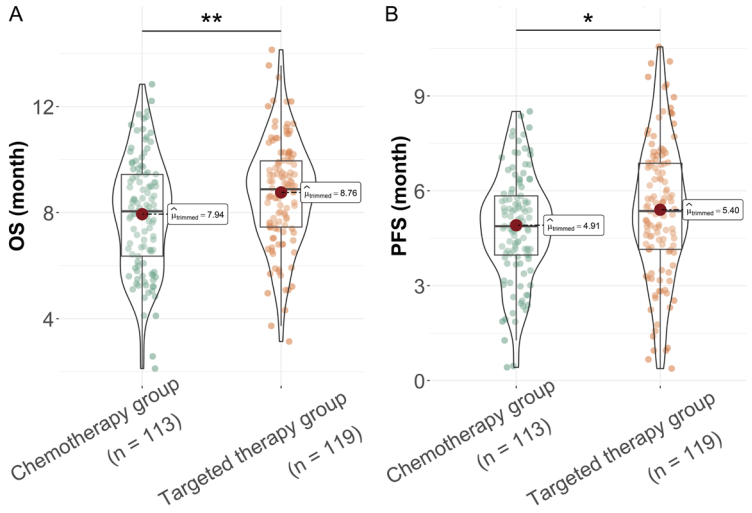

Figure 4. Comparison of OS and PFS between two groups. A. OS; B. PFS. OS: overall survival; PFS: progression-free survival. *: $P < 0.05$; **: $P < 0.01$.

0.005) with an OR of 3.278 (95% CI, 1.470-7.868), further indicating its role in immune resistance. These results underscore the critical influence of IFN-γ, IL-10, TMB, and PD-L1 in shaping immune resistance in advanced NSCLC.

Multivariate analysis of risk factors for the development of immune resistance in advanced NSCLC

In the multivariate analysis (**Table 5**), IL-10 emerged as a significant risk factor for immune resistance, showing a coefficient of 3.516 (P = 0.021) and an odds ratio (OR) of 33.654 (95% CI, 1.700-666.198), indicating a substantial increase in immune resistance risk. TMB maintained its inverse association with immune resistance (coefficient = -0.240, $P < 0.001$), with an OR of 0.786 (95% CI, 0.723-0.855), underscoring its protective role. Conversely, IFN-γ and high PD-L1 expression (≥ 50%) showed no significant impact in the multivariate model. Specifically, IFN-γ had a coefficient of 1.181 (P = 0.483) with an OR of 3.258 (95% CI, 0.120-88.520), and PD-L1 had a coefficient of 0.256 (P = 0.759) with an OR of 1.291 (95% CI, 0.252-6.631). These results highlight IL-10 and TMB as pivotal factors in the development of immune resistance, while IFN-γ and PD-L1 did not have significant contributions in the multivariate context.

Evaluation of different second-line treatment methods for advanced NSCLC

In assessing second-line treatments for advanced NSCLC, patients on targeted therapy showed significantly better outcomes compared to those on chemotherapy (**Figure 4**). The average OS was notably longer in the targeted

Table 6. Comparison of adverse events between chemotherapy group and targeted therapy group

	Chemotherapy group (n = 113)	Targeted therapy group (n = 119)	χ^2	P
Fatigue	55 (48.67%)	34 (28.57%)	9.904	0.002
Hypertension	6 (5.31%)	19 (15.97%)	6.846	0.009
Hypercholesterolemia	8 (7.08%)	18 (15.13%)	3.771	0.052
Hand-foot syndrome	1 (0.88%)	10 (8.4%)	7.254	0.007
Anorexia	42 (37.17%)	54 (45.38%)	1.611	0.204
Weight loss	12 (10.62%)	27 (22.69%)	6.038	0.014
Mucositis oral	39 (34.51%)	27 (22.69%)	3.981	0.046
Others	58 (51.33%)	46 (38.66%)	3.763	0.052

therapy group at 8.72 ± 2.02 months versus 7.93 ± 2.13 months in the chemotherapy group (P = 0.004), indicating improved survival. Similarly, PFS was enhanced in the targeted therapy group, with 5.37 ± 2.15 months compared to 4.86 ± 1.68 months in the chemotherapy group (P = 0.044). These results highlight that targeted therapy provides superior benefit in both survival measures.

Concerning side effects, fatigue was more common in the chemotherapy group, affecting 48.67% of patients, compared to 28.57% in the targeted therapy group (P = 0.002), suggesting a reduction in this adverse effect with targeted therapies (**Table 6**). However, hypertension occurred more frequently in the targeted therapy group at 15.97%, compared to 5.31% in the chemotherapy group (P = 0.009). Additionally, hand-foot syndrome incidence was higher in the targeted therapy group (8.4%) than in the chemotherapy group (0.88%) (P = 0.007). Weight loss also appeared more often in the targeted therapy group, reported in 22.69% of patients compared to 10.62% in the chemotherapy group (P = 0.014). Oral mucositis was more prevalent in the chemotherapy group (34.51%) than in the targeted therapy group (22.69%) (P = 0.046). Other adverse events like hypercholesterolemia and anorexia did not show significant differences between groups, with P values of 0.052 and 0.204, respectively. These findings suggest that while targeted therapies offer an improved survival benefit compared to chemotherapy, they are associated with a distinct side effect profile, including a higher incidence of hypertension, hand-foot syndrome, and weight loss. Conversely, chemotherapy was linked to a higher frequency of fatigue and oral mucositis.

Discussion

This study provides valuable insights into the risk factors for immunoresistance in advanced NSCLC patients. Immunoresistance remains a significant challenge in NSCLC therapy, particularly for patients undergoing immune checkpoint inhibitor (ICI) treatment. By exploring the components contributing to this resistance, our findings contribute to a deeper understanding of the mechanisms involved, which can inform more effective, tailored treatment strategies.

A key finding from our study is the association between a lower TMB and increased immunoresistance. TMB has emerged as a critical biomarker in predicting response to immunotherapy, as high TMB generally correlates with a higher neoantigen load, making tumors more recognizable to the immune system, thus enhancing the efficacy of ICIs [13]. Our findings support this understanding, illustrating a strong inverse correlation between TMB and immunoresistance, signifying that tumors with lower mutational burden may evade immune detection more effectively, leading to resistance.

Conversely, elevated levels of certain inflammatory cytokines, such as IL-10, were implicated in promoting an immunosuppressive tumor microenvironment. IL-10 is known for its role in modulating the immune response, often dampening the activity of effector T cells while promoting regulatory T cell activity, which serves to inhibit anti-tumor immune responses [14]. In our analysis, high levels of IL-10 were linked with increased risk for immunoresistance. Previous studies have also discussed the relationship between IL-10 and immune resistance, suggesting that tumors often exploit immunosuppressive cytokines to evade immune surveillance [15]. Targeting these cytokines may

hold therapeutic potential in restoring immune responses to tumors and overcoming resistance.

The association between elevated IFN-γ levels and immunoresistance reveals intricate feedback mechanisms at play. IFN-γ is generally known to promote antitumor immunity [16]; however, its presence at high levels could indicate compensatory mechanisms by the tumor to counteract an oncogenic immune response [17]. Persistent exposure to IFN-γ can induce upregulation of immune checkpoints like PD-L1 on tumor cells, rendering them less susceptible to cytotoxic T cell activity over time [18]. This might elucidate why we observed no significant impact of high PD-L1 expression in the multivariate context, suggesting that PD-L1 expression alone, without accounting for cytokine milieu, does not fully capture the complexity of immune evasion in NSCLC.

The role of PD-L1 as a predictive marker for immunotherapy response has been extensively debated. Our study supports its relevance, with greater PD-L1 expression correlating with immunoresistance; however, it also highlights limitations of relying solely on PD-L1 as an indicator. Tumor response to ICIs was likely shaped by a combination of PD-L1 expression, TMB, and cytokine environment, suggesting a more integrative approach in biomarker assessment may yield better predictions of therapeutic outcomes in NSCLC [19].

In evaluating the efficacy of second-line treatments, our findings align with the growing body of evidence that targeted therapies can surpass traditional chemotherapy in prolonging OS and PFS in advanced NSCLC patients who show resistance to first-line treatments [20]. The differential side-effect profiles observed between the two treatment groups are noteworthy. The lower incidence of fatigue in the targeted therapy group was consistent with chemotherapy's known systemic effects, which often lead to greater overall toxicity and patient discomfort. On the other hand, the higher prevalence of hypertension and hand-foot syndrome associated with targeted therapy highlights the need for vigilance and monitoring specific to these side effects.

The translational implications of these findings suggest an opportunity for using combination therapies concurrently targeting multiple resistance pathways [21, 22]. For instance, integrating agents that diminish the immunosuppressive milieu - such as IL-10 inhibitors - with current checkpoint inhibitors could potentiate antitumor responses and delay the onset of resistance [23, 24]. Additionally, therapeutic strategies aiming to modify TMB, either through genetic or pharmacological approaches, might optimize long-term outcomes by tipping the balance back towards immune recognition and attack [25, 26].

Furthermore, these insights also raise the possibility of personalized treatment protocols, where specific biomarker profiles dictate the choice and sequence of therapy [27, 28]. Patients with high IL-10 or PD-L1 levels, paired with low TMB, could be flagged for early intervention with tailored combination therapies, leveraging both direct antitumor effects and modulation of the tumor microenvironment [29, 30].

Beyond the molecular and therapeutic implications, this study underscores the importance of comprehensive clinical assessments prior to selecting second-line treatments for NSCLC patients [31, 32]. The decision-making process should incorporate a robust evaluation of the patient's overall health status, potential adverse effects, and quality-of-life considerations, striving to optimize therapeutic efficacy while minimizing the impact on patient well-being [33, 34].

As we deliberate on these findings, it's crucial to acknowledge the study's limitations, including its retrospective design and potential selection biases. Future investigations should employ prospective methodologies and seek to validate these associations within larger, more diverse cohorts. Additionally, exploring the genetic and epigenetic landscape alongside immune profiling might provide deeper insights into how tumors adapt and resist immune-based therapies. While this study offers valuable insights into the risk factors and treatment efficacy related to immunoresistance in advanced NSCLC, several limitations should be acknowledged [35, 36]. Primarily, the retrospective design introduces selection bias, as the data were collected from existing medical records, which might not capture all relevant clinical nuances. The sample size, though adequate for

preliminary findings, limits the generalizability of the results across broader and more diverse populations. Moreover, the study's reliance on specific biomarkers, such as TMB and cytokine levels, without incorporating a comprehensive genetic or epigenetic analysis, might overlook other pivotal factors influencing immunoresistance, such as the lymphocyte-to-monocyte ratio (LMR) and the neutrophil-to-lymphocyte ratio (NLR). This may restrict the comprehensiveness of our analysis. Additionally, while our findings provide correlations, they do not establish causation, underscoring the need for further mechanistic studies to validate and expand upon these observations [37]. Future research should aim for prospective designs, larger cohorts, and incorporate a more integrated biomarker assessment to surmount these limitations and substantiate our conclusions.

Conclusion

In conclusion, this study reinforces the multifaceted nature of immunoresistance in advanced NSCLC and highlights the importance of an integrated biomarker-driven approach to predict and overcome resistance pathways. The exploration of cytokine modulation, alongside traditional markers of mutational burden and expression, presents a promising frontier in tailoring cancer immunotherapy, with the goal of not just prolonging survival, but achieving sustainable, long-term remissions in NSCLC patients. This nuanced understanding of tumor biology must guide both current clinical practices and future research endeavors in our pursuit of more efficacious oncology treatment paradigms.

Acknowledgements

This study was supported by the Zhejiang Province Science and Technology Project of Medicine and Health (2021KY085).

Disclosure of conflict of interest

None.

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References

[1] Miller M and Hanna N. Advances in systemic therapy for non-small cell lung cancer. BMJ 2021; 375: n2363.

[2] Tang S, Qin C, Hu H, Liu T, He Y, Guo H, Yan H, Zhang J, Tang S and Zhou H. Immune checkpoint inhibitors in non-small cell lung cancer: progress, challenges, and prospects. Cells 2022; 11: 320.

[3] Naimi A, Mohammed RN, Raji A, Chupradit S, Yumashev AV, Suksatan W, Shalaby MN, Thangavelu L, Kamrava S, Shomali N, Sohrabi AD, Adili A, Noroozi-Aghideh A and Razeghian E. Tumor immunotherapies by immune checkpoint inhibitors (ICIs); the pros and cons. Cell Commun Signal 2022; 20: 44.

[4] Otano I, Ucero AC, Zugazagoitia J and Paz-Ares L. At the crossroads of immunotherapy for oncogene-addicted subsets of NSCLC. Nat Rev Clin Oncol 2023; 20: 143-159.

[5] Mountzios G, Remon J, Hendriks LEL, García-Campelo R, Rolfo C, Van Schil P, Forde PM, Besse B, Subbiah V, Reck M, Soria JC and Peters S. Immune-checkpoint inhibition for resectable non-small-cell lung cancer - opportunities and challenges. Nat Rev Clin Oncol 2023; 20: 664-677.

[6] Lazzari C, Spagnolo CC, Ciappina G, Di Pietro M, Squeri A, Passalacqua MI, Marchesi S, Gregorc V and Santarpia M. Immunotherapy in early-stage non-small cell lung cancer (NSCLC): current evidence and perspectives. Curr Oncol 2023; 30: 3684-3696.

[7] Salem ME, Bodor JN, Puccini A, Xiu J, Goldberg RM, Grothey A, Korn WM, Shields AF, Worrilow WM, Kim ES, Lenz HJ, Marshall JL and Hall MJ. Relationship between MLH1, PMS2, MSH2 and MSH6 gene-specific alterations and tumor mutational burden in 1057 microsatellite instability-high solid tumors. Int J Cancer 2020; 147: 2948-2956.

[8] Mino-Kenudson M, Schalper K, Cooper W, Dacic S, Hirsch FR, Jain D, Lopez-Rios F, Tsao MS, Yatabe Y, Beasley MB, Yu H, Sholl LM, Brambilla E, Chou TY, Connolly C, Wistuba I, Kerr KM and Lantuejoul S; IASLC Pathology Committee. Predictive biomarkers for immunotherapy in lung cancer: perspective from the International Association for the Study of Lung Cancer Pathology Committee. J Thorac Oncol 2022; 17: 1335-1354.

[9] Hou W, Yi C and Zhu H. Predictive biomarkers of colon cancer immunotherapy: present and future. Front Immunol 2022; 13: 1032314.

[10] Shiri AM, Zhang T, Bedke T, Zazara DE, Zhao L, Lücke J, Sabihi M, Fazio A, Zhang S, Tauriello DVF, Batlle E, Steglich B, Kempski J, Agalioti T, Nawrocki M, Xu Y, Riecken K, Liebold I, Brock-

mann L, Konczalla L, Bosurgi L, Mercanoglu B, Seeger P, Küsters N, Lykoudis PM, Heumann A, Arck PC, Fehse B, Busch P, Grotelüschen R, Mann O, Izbicki JR, Hackert T, Flavell RA, Gagliani N, Giannou AD and Huber S. IL-10 dampens antitumor immunity and promotes liver metastasis via PD-L1 induction. J Hepatol 2024; 80: 634-644.

[11] Liang X, Gao H, Xiao J, Han S, He J, Yuan R, Yang S and Yao C. Abrine, an IDO1 inhibitor, suppresses the immune escape and enhances the immunotherapy of anti-PD-1 antibody in hepatocellular carcinoma. Front Immunol 2023; 14: 1185985.

[12] Knopf P, Stowbur D, Hoffmann SHL, Hermann N, Maurer A, Bucher V, Poxleitner M, Tako B, Sonanini D, Krishnamachary B, Sinharay S, Fehrenbacher B, Gonzalez-Menendez I, Reckmann F, Bomze D, Flatz L, Kramer D, Schaller M, Forchhammer S, Bhujwalla ZM, Quintanilla-Martinez L, Schulze-Osthoff K, Pagel MD, Fransen MF, Röcken M, Martins AF, Pichler BJ, Ghoreschi K and Kneilling M. Acidosis-mediated increase in IFN-γ-induced PD-L1 expression on cancer cells as an immune escape mechanism in solid tumors. Mol Cancer 2023; 22: 207.

[13] Wang L, Luo Y, Ren S, Zhang Z, Xiong A, Su C, Zhou J, Yu X, Hu Y, Zhang X, Dong X, Meng S, Wu F, Hou X, Dai Y, Song W, Li B, Wang ZM, Xia Y and Zhou C. A phase 1b study of ivonescimab, a programmed cell death protein-1 and vascular endothelial growth factor bispecific antibody, as first- or second-line therapy for advanced or metastatic immunotherapy-naive NSCLC. J Thorac Oncol 2024; 19: 465-475.

[14] Moliner L, Spurgeon L and Califano R. Controversies in NSCLC: which second-line strategy after chemo-immunotherapy? ESMO Open 2023; 8: 100879.

[15] Jiang T, Wang P, Zhang J, Zhao Y, Zhou J, Fan Y, Shu Y, Liu X, Zhang H, He J, Gao G, Mu X, Bao Z, Xu Y, Guo R, Wang H, Deng L, Ma N, Zhang Y, Feng H, Yao S, Wu J, Chen L, Zhou C and Ren S. Toripalimab plus chemotherapy as second-line treatment in previously EGFR-TKI treated patients with EGFR-mutant-advanced NSCLC: a multicenter phase-II trial. Signal Transduct Target Ther 2021; 6: 355.

[16] Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, D'Amico TA, DeCamp M, Dilling TJ, Dowell J, Gettinger S, Grotz TE, Gubens MA, Hegde A, Lackner RP, Lanuti M, Lin J, Loo BW, Lovly CM, Maldonado F, Massarelli E, Morgensztern D, Ng T, Otterson GA, Pacheco JM, Patel SP, Riely GJ, Riess J, Schild SE, Shapiro TA, Singh AP, Stevenson J, Tam A, Tanvetyanon T, Yanagawa J, Yang SC, Yau E, Gregory K and Hughes M. Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2022; 20: 497-530.

[17] Armato SG 3rd and Nowak AK. Revised modified response evaluation criteria in solid tumors for assessment of response in malignant pleural mesothelioma (Version 1.1). J Thorac Oncol 2018; 13: 1012-1021.

[18] Kluger HM, Tawbi HA, Ascierto ML, Bowden M, Callahan MK, Cha E, Chen HX, Drake CG, Feltquate DM, Ferris RL, Gulley JL, Gupta S, Humphrey RW, LaVallee TM, Le DT, Hubbard-Lucey VM, Papadimitrakopoulou VA, Postow MA, Rubin EH, Sharon E, Taube JM, Topalian SL, Zappasodi R, Sznol M and Sullivan RJ. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce. J Immunother Cancer 2020; 8: e000398.

[19] Neeman E, Gresham G, Ovasapians N, Hendifar A, Tuli R, Figlin R and Shinde A. Comparing physician and nurse eastern cooperative oncology group performance status (ECOG-PS) ratings as predictors of clinical outcomes in patients with cancer. Oncologist 2019; 24: e1460-e1466.

[20] Lambregts DMJ, Bogveradze N, Blomqvist LK, Fokas E, Garcia-Aguilar J, Glimelius B, Gollub MJ, Konishi T, Marijnen CAM, Nagtegaal ID, Nilsson PJ, Perez RO, Snaebjornsson P, Taylor SA, Tolan DJM, Valentini V, West NP, Wolthuis A, Lahaye MJ, Maas M, Beets GL and Beets-Tan RGH. Current controversies in TNM for the radiological staging of rectal cancer and how to deal with them: results of a global online survey and multidisciplinary expert consensus. Eur Radiol 2022; 32: 4991-5003.

[21] Picard E, Verschoor CP, Ma GW and Pawelec G. Relationships between immune landscapes, genetic subtypes and responses to immunotherapy in colorectal cancer. Front Immunol 2020; 11: 369.

[22] Newell F, Pires da Silva I, Johansson PA, Menzies AM, Wilmott JS, Addala V, Carlino MS, Rizos H, Nones K, Edwards JJ, Lakis V, Kazakoff SH, Mukhopadhyay P, Ferguson PM, Leonard C, Koufariotis LT, Wood S, Blank CU, Thompson JF, Spillane AJ, Saw RPM, Shannon KF, Pearson JV, Mann GJ, Hayward NK, Scolyer RA, Waddell N and Long GV. Multiomic profiling of checkpoint inhibitor-treated melanoma: identifying predictors of response and resistance, and markers of biological discordance. Cancer Cell 2022; 40: 88-102, e107.

[23] McGrail DJ, Pilié PG, Rashid NU, Voorwerk L, Slagter M, Kok M, Jonasch E, Khasraw M, Heimberger AB, Lim B, Ueno NT, Litton JK, Ferrarotto R, Chang JT, Moulder SL and Lin SY.

High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types. Ann Oncol 2021; 32: 661-672.
[24] Song W, Wang Y, Li G, Xue S, Zhang G, Dang Y and Wang H. Modulating the gut microbiota is involved in the effect of low-molecular-weight Glycyrrhiza polysaccharide on immune function. Gut Microbes 2023; 15: 2276814.
[25] Huynh T, Reed C, Blackwell Z, Phelps P, Herrera LCP, Almodovar J, Zaharoff DA and Wolchok J. Local IL-10 delivery modulates the immune response and enhances repair of volumetric muscle loss muscle injury. Sci Rep 2023; 13: 1983.
[26] Golebski K, Layhadi JA, Sahiner U, Steveling-Klein EH, Lenormand MM, Li RCY, Bal SM, Heesters BA, Vilà-Nadal G, Hunewald O, Montamat G, He FQ, Ollert M, Fedina O, Lao-Araya M, Vijverberg SJH, Maitland-van der Zee AH, van Drunen CM, Fokkens WJ, Durham SR, Spits H and Shamji MH. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response. Immunity 2021; 54: 291-307, e297.
[27] Yaguchi T, Goto Y, Kido K, Mochimaru H, Sakurai T, Tsukamoto N, Kudo-Saito C, Fujita T, Sumimoto H and Kawakami Y. Immune suppression and resistance mediated by constitutive activation of Wnt/β-catenin signaling in human melanoma cells. J Immunol 2012; 189: 2110-2117.
[28] He XY, Liu BY, Xu C, Zhuo RX and Cheng SX. A multi-functional macrophage and tumor targeting gene delivery system for the regulation of macrophage polarity and reversal of cancer immunoresistance. Nanoscale 2018; 10: 15578-15587.
[29] Wu L, Hong X, Yang C, Yang Y, Li W, Lu L, Cai M, Cao D, Zhuang G and Deng L. Noncanonical MAVS signaling restrains dendritic cell-driven antitumor immunity by inhibiting IL-12. Sci Immunol 2023; 8: eadf4919.
[30] Ren J, Li N, Pei S, Lian Y, Li L, Peng Y, Liu Q, Guo J, Wang X, Han Y, Zhang G, Wang H, Li Y, Jiang J, Li Q, Tan M, Peng J, Hu G, Xiao Y, Li X, Lin M and Qin J. Histone methyltransferase WHSC1 loss dampens MHC-I antigen presentation pathway to impair IFN-γ-stimulated antitumor immunity. J Clin Invest 2022; 132: e153167.
[31] Jorgovanovic D, Song M, Wang L and Zhang Y. Roles of IFN-γ in tumor progression and regression: a review. Biomark Res 2020; 8: 49.
[32] Shang M, Yang H, Yang R, Chen T, Fu Y, Li Y, Fang X, Zhang K, Zhang J, Li H, Cao X, Gu J, Xiao J, Zhang Q, Liu X, Yu Q and Wang T. The folate cycle enzyme MTHFD2 induces cancer immune evasion through PD-L1 up-regulation. Nat Commun 2021; 12: 1940.
[33] Herzfeldt AK, Gamez MP, Martin E, Boryn LM, Baskaran P, Huber HJ, Schuler M, Park JE and Swee LK. Complementary CRISPR screen highlights the contrasting role of membrane-bound and soluble ICAM-1 in regulating antigen-specific tumor cell killing by cytotoxic T cells. Elife 2023; 12: e84314.
[34] Le Saux O, Ardin M, Berthet J, Barrin S, Bourhis M, Cinier J, Lounici Y, Treilleux I, Just PA, Bataillon G, Savoye AM, Mouret-Reynier MA, Coquan E, Derbel O, Jeay L, Bouizaguen S, Labidi-Galy I, Tabone-Eglinger S, Ferrari A, Thomas E, Ménétrier-Caux C, Tartour E, Galy-Fauroux I, Stern MH, Terme M, Caux C, Dubois B and Ray-Coquard I. Immunomic longitudinal profiling of the NeoPembrOv trial identifies drivers of immunoresistance in high-grade ovarian carcinoma. Nat Commun 2024; 15: 5932.
[35] Hermanowicz J, Sieklucka B, Nosek K and Pawlak D. Intracellular mechanisms of tumor cells' immunoresistance. Acta Biochim Pol 2020; 67: 143-148.
[36] Montaño-Samaniego M, Bravo-Estupiñan DM, Méndez-Guerrero O, Alarcón-Hernández E and Ibáñez-Hernández M. Strategies for targeting gene therapy in cancer cells with tumor-specific promoters. Front Oncol 2020; 10: 605380.
[37] Huang X, Li XY, Shan WL, Chen Y, Zhu Q and Xia BR. Targeted therapy and immunotherapy: diamonds in the rough in the treatment of epithelial ovarian cancer. Front Pharmacol 2023; 14: 1131342.