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Review

The Role of Smoking History in the Efficacy of Neoadjuvant and Perioperative Therapy for Lung Cancer

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Simple Summary

This narrative review examines the efficacy of various neoadjuvant and perioperative therapies for lung cancer in relation to patient smoking history (current, former, and never-smokers). It also explores the molecular mechanisms that may contribute to treatment response among current, former, and never-smokers. In particular, this review evaluates findings from major clinical trials examining the efficacy of chemotherapy, immunotherapy, chemoimmunotherapy, and targeted therapies. Although smoking history may influence treatment outcomes, current evidence remains limited by the small number of never-smokers included in clinical trials and the lack of direct comparisons by smoking status. This review highlights the importance of considering smoking history alongside molecular and clinical characteristics when developing personalized strategies for the treatment of lung cancer. Furthermore, it identifies gaps in current research and emphasizes the need for future studies to better understand how smoking history may guide treatment selection.

Abstract

Lung cancer is one of the leading causes of cancer-related mortality worldwide, and neoadjuvant therapy has become a cornerstone in the management of resectable non-small-cell lung cancer (NSCLC). Growing evidence suggests that smoking history is an important clinical and biological factor that influences response to neoadjuvant treatment. This review synthesizes epidemiologic, translational, and clinical evidence, including findings from landmark clinical trials. It aims to evaluate the efficacy of neoadjuvant chemotherapy, immunotherapy, targeted therapy, and multimodal treatment strategies according to smoking status. Furthermore, this review examines the molecular and immunologic mechanisms underlying the differential treatment responses observed among current, former, and never-smokers. Ultimately, there is an increasing need to conduct prospective smoking-stratified studies and integrate smoking history into medical practice to develop more personalized neoadjuvant therapies for patients with lung cancer.

Keywords: never-smoker; non-small-cell lung cancer; lung cancer; neoadjuvant therapy; perioperative therapy; United States

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1. Introduction

Lung cancer continues to represent one of the greatest challenges in oncology and remains the leading cause of cancer-related mortality worldwide, despite advances in early detection and treatment strategies [1].

Although smoking is a predominant risk factor for developing lung cancer, approximately 25% of all lung cancers occur in individuals who have never smoked, and lung cancer in never-smokers (LCINS) is recognized as the fifth leading cause of cancer-related mortality globally and the eighth leading cause of cancer-related mortality in the United States (US) [2]. Notably, the incidence of lung cancer has remained stable or increased in many regions of the US, despite declining tobacco use. This emphasizes the importance of addressing LCINS. Growing evidence indicates that tumors arising in never-smokers differ substantially from smoking-associated lung cancers. Compared with tumors from individuals with smoking history, LCINSs are more frequently adenocarcinomas, occur disproportionately in women and individuals of Asian ancestry, and commonly harbor targetable oncogenic driver alterations [2]. LCINS is also characterized by lower tumor mutational burden, lower rates of programmed death-ligand 1 (PD-L1) expression, and fewer tobacco-related mutational signatures. All of these factors may influence responsiveness to systemic therapies, particularly immune checkpoint inhibitors (ICIs) [2]. These biological differences suggest that smoking history reflects more than an epidemiologic risk factor and is an important element in determining the most appropriate therapy for lung cancer patients and predicting therapeutic response.

The management of resectable NSCLC has evolved considerably over the past decade. Although complete surgical resection remains the foundation of curative treatment, recurrence after surgery remains common because occult micrometastatic disease is often present at diagnosis [3]. As a result, perioperative and neoadjuvant systemic therapy has become essential in treating patients with stage II–III lung cancer [4–9]. Studies have established platinum-based neoadjuvant chemotherapy as a strategy capable of improving survival compared with surgery alone. However, the overall benefit has been relatively modest [10].

In the past decade, introducing ICIs into the neoadjuvant setting has transformed the treatment landscape for resectable NSCLC. The phase III CheckMate-816 trial was the first to demonstrate that adding nivolumab to platinum-doublet chemotherapy before surgery significantly improved pathological complete response (pCR), event-free survival (EFS), and long-term overall survival (OS) compared to chemotherapy alone [11]. This established neoadjuvant chemoimmunotherapy as a new standard of care for eligible patients. Subsequent landmark trials have consistently reinforced these findings across different checkpoint inhibitors. The KEYNOTE-671 trial demonstrated significant improvements in EFS and OS with perioperative pembrolizumab plus chemotherapy [5], while CheckMate 77T showed that perioperative nivolumab significantly increased rates of pCR and prolonged EFS [6]. Similarly, the AEGEAN trial demonstrated superior pathological response (PR) and EFS with perioperative durvalumab combined with neoadjuvant chemotherapy compared to chemotherapy alone [7]. Supportive evidence from the phase II NADIM II trial further demonstrated substantial improvements in pCR, PFS, and OS with perioperative nivolumab-based therapy in patients with resectable stage IIIA/IIIB NSCLC [8]. These studies have established perioperative chemoimmunotherapy as the preferred treatment approach for many patients with resectable stage II–IIIB NSCLC. Despite these advances, not all patients derive the same degree of benefit from neoadjuvant immunotherapy-based regimens. One factor that has received increasing attention is smoking history, which is closely linked to the molecular and immunologic characteristics of NSCLC. Smoking is associated with higher tumor mutational burden, increased neoantigen formation, and greater tumor immunogenicity, whereas tumors arising in never-smokers are more frequently driven by oncogenic alterations and generally exhibit a more immunologically "cold" environment [12].

These biological differences raise the possibility that smoking history may influence the effectiveness of neoadjuvant therapy for lung cancer and contribute to the variability

in treatment outcomes observed across clinical trials and within medical practice. Although analyses according to smoking status have been reported in several contemporary neoadjuvant trials, these findings have not been systematically integrated, and the clinical implications remain uncertain. A comprehensive understanding of how smoking history affects PR and survival outcomes in lung cancer patients is therefore needed to better interpret existing evidence and identify patients most likely to benefit from various neoadjuvant treatment strategies.

This review consolidates the current evidence at the molecular and therapeutic levels regarding the role of smoking history—including never, former, and current smoking status—in the efficacy of neoadjuvant therapy for lung cancer. The definitions of never, former, and current smokers are in accordance with the Centers for Disease Control and Prevention [13]. A never-smoker is classified as an adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime. A former smoker is classified as an adult who has smoked at least 100 cigarettes in his or her lifetime but had quit smoking at the time of information collection, and a current smoker is an adult who has smoked 100 cigarettes in his or her lifetime and currently smokes cigarettes.

This review will discuss how smoking influences the tumor microenvironment at the molecular level and how these mechanisms may underlie differential responses to treatment. Lastly, we will explore the implications of smoking history for future biomarker development, clinical trial design, and personalized treatment selection.

2. Background

2.1. Smoking History Defines Distinct Biological Subtypes of Lung Cancer

Although smoking remains the leading cause of lung cancer worldwide, LCINS is increasingly recognized as a biologically distinct subtype of NSCLC with unique clinicopathologic and molecular characteristics. These differences extend beyond the absence of smoking exposure and suggest that smoking-associated and never-smoker-associated NSCLC develop through distinct carcinogenic pathways. The histologic subtype is one of the most evident distinctions between these populations. Adenocarcinoma is the predominant histologic subtype among never-smokers, whereas squamous cell carcinoma (SqCC) and small cell lung cancer (SCLC) occur disproportionately in individuals with a history of tobacco use [14].

Large pooled analyses have demonstrated that cigarette smoking increases the risk of all major histologic subtypes of lung cancer; however, the magnitude of risk varies considerably according to histology [15]. Compared with adenocarcinoma, smoking shows a much steeper dose–response relationship with SqCC and SCLC [15]. In one pooled analysis of more than 13,000 lung cancer cases, it was found that the odds of current male smokers who consume more than 30 cigarettes per day developing SqCC and SCLC were 100 times higher than those of never-smokers [15], whereas the odds were roughly 22 times higher for developing adenocarcinoma [15]. Although lung cancer risk begins to decline soon after smoking cessation, it remains significantly elevated compared to that of never-smokers, even after more than 35 years of abstinence, highlighting the long-lasting carcinogenic effects of tobacco exposure [15].

Evidence also suggests that smoking influences the biological behavior of tumors during the earliest stages of carcinogenesis [16]. In patients with stage I lung adenocarcinoma, lung tumors derived from smokers exhibited significantly higher expression of the proliferation marker Ki-67 and the anti-apoptotic protein survivin than tumors derived from never-smokers, indicating increased cellular proliferation and resistance to apoptosis during early tumor development. Notably, these differences were no longer observed in stage II and III disease, raising the possibility that the influence of smoking on these molecular markers

may vary according to tumor stage [16]. Collectively, these findings indicate that smoking history is associated with distinct clinicopathologic phenotypes rather than solely reflecting different levels of carcinogen exposure, providing a unique foundation for understanding differences in treatment response observed between smokers and never-smokers.

2.2. Oncogenic Drivers Characterize Smokers and Never-Smokers

NSCLC in smokers and never-smokers has shown distinct molecular landscapes and oncogenic driver alterations. Never-smoker-associated tumors are enriched for actionable driver mutations, particularly *EGFR* mutations and *EML4-ALK* rearrangements [17], whereas smoking-associated tumors more commonly harbor *KRAS* and *TP53* mutations [Figure 1]. Notably, activation of either oncogenic pathway arising from an *EGFR* mutation for never-smokers and *KRAS* mutations for smokers appears sufficient to drive malignant transformation without selective pressure for additional driver mutations. Across many studies, *EGFR* and *KRAS* mutations have commonly been identified among never-smokers and smokers, respectively [12]. This provides strong evidence that the tumors of never-smokers and smokers arise through distinct molecular pathways, as activation of either oncogenic pathway appears to be sufficient to drive malignant transformation without selective pressure for additional driver mutations.

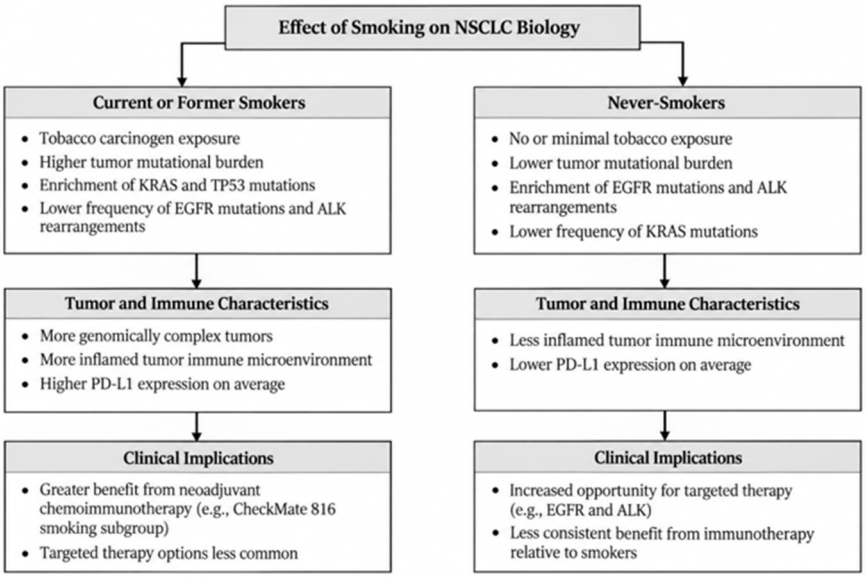


Figure 1. Differences in molecular and immune characteristics between smokers and never-smokers with non-small-cell lung cancer (NSCLC) and their potential influence on response to neoadjuvant therapy.

Furthermore, increasing tobacco exposure is associated with a lower frequency of *EGFR* mutations overall, while common activating mutations, including exon 19 deletions and L858R, occur predominantly in never-smokers [18]. In contrast, uncommon single and complex *EGFR* mutations are more frequently observed in smokers, suggesting that tobacco carcinogens generate a broader and more heterogeneous mutational profile [19]. Consistent with these observations, *EGFR* mutations are more frequently identified in women, older individuals, and never-smokers. Smoking history similarly influences the spectrum of *KRAS* alterations. Mutations in G12C and G12V of the *KRAS* gene are commonly found in smoking individuals, whereas alternative *KRAS* variants are encountered more frequently in never-smokers, indicating different underlying mutagenic processes [20].

In addition, geographic differences further highlight the heterogeneity of never-smoker NSCLC. Among never-smokers with lung adenocarcinoma, *EGFR* and *TP53* mutations are more common in East Asian patients, while *KRAS* mutations are 3.8 times more common

in North American and European patients [21]. These findings suggest that geography can play a role in influencing oncogenic mechanisms behind lung cancer development.

Overall, tumors of never-smokers are typically driven by targetable kinase alterations and smoking-associated tumors characterized by KRAS- and TP53-dominant molecular profiles. These distinct oncogenic driver profiles have important implications when reflecting on therapy, as they influence tumor mutational burden (TMB), immune recognition, and responsiveness to targeted therapies and immune checkpoint blockade, all of which may contribute to differences in outcomes following neoadjuvant treatment.

2.3. Smoking Reshapes the Genomic Landscape of NSCLC

Beyond differences in individual driver mutations, smoking profoundly alters the global genomic architecture of NSCLC (Figure 1). Tobacco carcinogens induce extensive DNA damage, resulting in substantially greater genomic complexity in smoking-associated tumors than in those arising in never-smokers. An important factor contributing to this difference is TMB, which is found to be seven times higher in smokers than in never-smokers—reflecting the accumulation of somatic mutations caused by chronic tobacco exposure [22]. Along with increased mutation burden, there tends to be greater chromosomal instability, including more frequent copy-number alterations and widespread loss of heterozygosity (LOH), particularly involving the human leukocyte antigen (HLA) loci responsible for antigen presentation [23].

In contrast, loss of HLA heterozygosity is uncommon in never-smokers, consistent with their lower mutational burden and reduced generation of tumor-specific neoantigens. This suggests that smoking-associated tumors generate a broader repertoire of neoantigens for immune recognition than tumors of never-smokers.

The genomic consequences of tobacco exposure are also reflected in distinct mutational signatures. Smoking-associated tumors exhibit characteristic *TP53* mutations consisting of G→T (C>A) transversions, a mutational pattern strongly linked to DNA adducts formed by polycyclic aromatic hydrocarbons (PAHs), a component of cigarette smoke [24].

In addition to this pattern, transcriptomic analyses have further identified differential gene expression according to smoking status, including significantly higher expression of AKR1B10 in lung tumors of smokers [25]. AKR1B10, a member of the aldo-keto reductase family involved in the metabolism of reactive aldehydes, promotes cancer cell survival and has been suggested to play a role in initiating lung cancer [26].

Polymorphisms in carcinogen-metabolizing enzymes, including CYP1A1, CYP1B1, and GSTT1, have been associated with altered lung cancer risk, with several variants demonstrating stronger associations in never-smokers than in individuals with a history of tobacco exposure [16]. For example, the CYP1A1 Ile462Val (A2455G) polymorphism has been associated with a significantly increased risk of lung cancer in Caucasian never-smoking individuals, CYP1B1 Leu432Val polymorphism is associated with a modest increase in risk, and the CYP1A1 MspI (T3801C) polymorphism has not been shown to significantly increase lung cancer risk [27].

Similarly, inherited variants in DNA repair genes, such as XRCC1, ERCC1, ERCC2 (XPD), OGG1, and XRCC3, and mismatch repair genes including MLH1 have been linked to impaired DNA repair and an increased susceptibility to lung cancer [28]. For instance, the XRCC1 Arg399Gln polymorphism is associated with an increased risk of lung cancer, particularly in never-smokers. Studies suggest that individuals with reduced DNA repair capacity, as measured by blood tests, have an approximately 1.9-fold increased risk of developing lung cancer despite never smoking. This risk is even higher among those exposed to secondhand smoke or those with a family history of lung cancer [29]. This suggests that inherited defects may compensate for the absence of direct tobacco-induced

mutagenesis. In addition to variations in DNA repair genes, lung cancers derived from smokers and never-smokers differ in the expression of DNA repair proteins, particularly those involved in nucleotide excision repair [22].

Recent genomic profiling studies have further demonstrated that lung cancers arising in smokers and never-smokers can be classified into distinct molecular subtypes based on patterns of somatic copy-number variation. The "piano" subtype, which predominates in never-smokers, is characterized by a low tumor mutational burden, lack of somatic copy-number alterations, long telomeres, frequent *KRAS* mutations, high intratumor heterogeneity, and relatively slow tumor growth [12]. In contrast, the "mezzo-forte" subtype demonstrates chromosome arm-level amplifications, frequent *EGFR* mutations, and HLA loss of heterozygosity, whereas the "forte" subtype exhibits extensive whole-genome doubling and marked chromosomal instability [12]. These molecular subtypes further support the concept that smoking-associated and never-smoker NSCLC types developed through distinct pathways with a combination of genetic, epigenetic and environmental factors contributing to these pathways. Smoking-associated tumors accumulate substantially greater genomic damage and mutational diversity than tumors arising in never-smokers, generating a biologically distinct genomic landscape that is likely to influence tumor immunogenicity and ultimately, responsiveness to neoadjuvant therapy.

2.4. Current Neoadjuvant Treatment Landscape

2.4.1. Evolution from Surgery to Perioperative Systemic Therapy

Complete surgical resection has historically been the cornerstone of curative treatment for patients with resectable NSCLC [30]. However, surgery alone is insufficient for many patients because micrometastases may be frequently present at diagnosis, contributing to recurrence post-operatively despite removal of the tumor [31]. This is seen when examining the decline in survival in patients as lung cancer stage progresses since the metastases can progress at the time of resection. After surgical resection, five-year survival rates decreased from approximately 92% for resected stage IA1 disease to 36% for stage IIIA disease [31].

To improve long-term outcomes, platinum-based adjuvant chemotherapy became the standard postoperative systemic treatment after demonstrating a survival advantage compared with surgery alone [32]. Various randomized control trials, such as the IALT [33], JBR.10 [34], CALGB 9633 [35], and ANITA [36], helped confirm the benefit of adjuvant cisplatin-based chemotherapy. The LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis helped confirm the benefit of platinum-based adjuvant chemotherapy, demonstrating an increase in the 5-year survival rate of 4% five years from the start of treatment with addition of chemotherapy [37].

These modest benefits prompted the development of neoadjuvant chemotherapy, with a meta-analysis conducted in 2014 by the NSCLC Meta-analysis Collaborative Group. The group found that neoadjuvant chemotherapy significantly improves overall survival, delays recurrence to sites other than the lung, and improves recurrence-free survival in resectable NSCLC [36]. However, as further advances progressed, neoadjuvant chemoimmunotherapy emerged with the NADIM phase II trial (perioperative nivolumab and chemotherapy) in 2019 [8] and was subsequently confirmed in the CheckMate 816 phase III trial (neoadjuvant chemoimmunotherapy with nivolumab) [11] in 2022. Neoadjuvant chemoimmunotherapy provides various theoretical and practical advantages over postoperative therapy. Administering systemic therapy before surgery enables earlier treatment of micrometastates, increases the likelihood of tumor downstaging and complete resection, and provides an opportunity to evaluate pathological response directly within the resected tumor.

Furthermore, pathological endpoints such as major pathological response (MPR) and pCR have emerged as valuable surrogate markers for long-term clinical outcomes, facilitating more rapid assessment of treatment efficacy.

2.4.2. Precision Neoadjuvant Therapy: Targeted Therapy and Chemoimmunotherapy

With further recognition of the molecular heterogeneity of NSCLC, there have been further developments toward biomarker-driven strategies. Perioperative management has evolved from having a standardized treatment approach toward implementing individualized strategies guided by patients' tumor biology. Molecular profiling is now routinely performed to identify actionable oncogenic alterations, particularly EGFR-activating mutations, ALK, ROS1, and RET rearrangements, because patients with these driver mutations derive limited benefit from immune checkpoint inhibitors and may instead benefit from targeted therapies.

The field of neoadjuvant targeted therapy for EGFR-mutated resectable NSCLC is emerging, with the recent phase III NeoADAURA trial providing strong evidence of the efficacy of neoadjuvant osimertinib alone or with platinum-based chemotherapy [38]. Moreover, researchers are currently conducting the NAUTIKA1 trial (NCT04302025), a phase II umbrella study evaluating multiple cohorts of biomarker-matched targeted therapies in the neoadjuvant setting for patients with resectable, oncogene-driven NSCLC harboring ALK, ROS1, NTRK, RET, or BRAF alterations [39]. In addition to these advances, there is increasing evidence on the efficacy of combining ICIs with platinum-based chemotherapy. This regimen presents complementary effects, with chemotherapy destructing fast-growing cancer cells while promoting release of their antigens and ICIs blocking proteins that cancer cells use to evade T cells This enhances antitumor immune responses while simultaneously reducing tumor burden before surgery.

2.4.3. The Emergence of Neoadjuvant Chemoimmunotherapy

The introduction of ICIs into the neoadjuvant setting has transformed the management of resectable NSCLC. The landmark phase III CheckMate 816 trial established neoadjuvant nivolumab plus platinum-doublet chemotherapy as a new standard of care after demonstrating significant improvements in pCR, EFS, and ultimately OS compared with chemotherapy alone [11].

These findings were subsequently reinforced by multiple phase II and III trials [Table 1]. NADIM II demonstrated substantially higher rates of pCR with improvements in PFS and OS in patients with stage IIIA/IIIB NSCLC receiving perioperative nivolumab plus chemotherapy [8].

Table 1. Selected ongoing clinical trials investigating biomarker-driven neoadjuvant therapies in resectable non-small-cell lung cancer (NSCLC).

Selected Trials	Molecular Alteration	Treatment Tested	Trial Status
NAUTIKA1 (NCT04302025)	ALK, ROS1, NTRK, RET, BRAF V600E, KRAS G12C	Neoadjuvant biomarker-matched targeted therapy followed by surgery	Recruiting
NeoADAURA (NCT04351555)	EGFR exon 19 deletion or L858R	Neoadjuvant osimertinib ± chemotherapy vs. chemotherapy alone	Active, not recruiting; results reported
ALNEO (NCT05015010)	ALK rearrangement	Neoadjuvant alectinib followed by surgery	Active, not recruiting
NEOpredict-EGFR (NCT06784791)	Activating EGFR mutations	Preoperative amivantamab ± carboplatin/ pemetrexed	Recruiting

Similarly, the phase III KEYNOTE-671 (perioperative pembrolizumab) [5], AEGEAN (perioperative durvalumab) [7], and CheckMate 77T (perioperative nivolumab) [6] trials consistently demonstrated that adding immune checkpoint inhibition to platinum-based chemotherapy significantly improved PR and EFS in patients with resectable stage II–IIIB NSCLC. However, an important distinction is that CheckMate 816 evaluated neoadjuvant chemoimmunotherapy alone, whereas the other trials incorporated immunotherapy in both the neoadjuvant and adjuvant settings. KEYNOTE-671 became the first randomized phase III trial to demonstrate a statistically significant overall survival benefit with perioperative chemoimmunotherapy in the treatment of stage II-IIIB NSLCS, while the final analysis of CheckMate 816 subsequently confirmed a durable overall survival advantage with neoadjuvant nivolumab plus chemotherapy. In CheckMate 816, neoadjuvant nivolumab plus platinum-doublet chemotherapy significantly improved pCR (24% vs. 2%) and EFS (median 31.6 vs. 20.8 months), and OS was significantly longer with a 10 percentage-point absolute difference maintained over 5 years.

These landmark studies consistently demonstrated improvements in pCR, MPR, and EFS across multiple PD-1/PD-L1 inhibitors, establishing perioperative chemoimmunotherapy as the preferred treatment strategy for eligible patients with resectable NSCLC. Along with these advancements, researchers are examining the potential application of molecular profiling, circulating tumor DNA (ctDNA), and surrogate pathological endpoints to develop more personalized neoadjuvant and perioperative therapies.

Despite these advances, not all patients respond equally well to neoadjuvant chemoimmunotherapy. Emerging evidence suggests that clinical and biological characteristics—including PD-L1 expression, oncogenic driver mutations, TMB, and smoking history—may influence response to treatment. Among these factors, smoking history is growing in recognition as an important determinant of response to neoadjuvant therapy, as it closely influences the biology of the tumor and patient's immune system.

3. Methods

A narrative literature review was conducted by searching PubMed, Google Scholar, Embase, and Scopus. The search included studies published between 2000 and the present. Keywords were used in various combinations, including "lung cancer," "neoadjuvant therapy," "smoking," and "never-smoker."

Eligible studies included original research articles, review articles, meta-analyses, retrospective and prospective studies, clinical trials, and epidemiological investigations published in peer-reviewed journals. Non-peer-reviewed publications were excluded. Articles were selected based on their relevance to the themes addressed in this review, including the current neoadjuvant treatment landscape for lung cancer, the efficacy of neoadjuvant therapies (including chemotherapy, immunotherapy, chemoimmunotherapy, targeted therapy, and radiation therapy), and the biological mechanisms underlying treatment response according to smoking history.

The selected literature was narratively synthesized and organized by theme. The review begins with an overview of the epidemiology of lung cancer among current, former, and never-smokers, followed by the evolution of neoadjuvant therapy for lung cancer. It then summarizes landmark clinical trials evaluating the major neoadjuvant treatment modalities and examines treatment outcomes according to smoking status. Subsequently, the review explores the molecular and immunologic mechanisms that may explain the differential responses to neoadjuvant therapies observed among smokers and never-smokers. Finally, it synthesizes the current evidence to identify limitations and knowledge gaps, discuss future directions, and provide recommendations for integrating smoking history into biomarker-informed, personalized neoadjuvant treatment strategies for patients with lung cancer.

4. Results

4.1. Role of Smoking History in the Effectiveness of Neoadjuvant Chemoimmunotherapy

Smoking history has emerged as a potential factor influencing response to neoadjuvant chemoimmunotherapy in resectable NSCLC. In most clinical trials evaluating responses to various chemoimmunotherapy regimens, formal subgroup analyses directly comparing treatment outcomes between smokers and never-smokers were not reported. However, several trials provided separate outcome measures for these patient populations. Accordingly, this review examines the reported outcomes among smokers and never-smokers to provide an exploratory assessment of potential differences in treatment response [Table 2]. Although these findings do not constitute direct statistical comparisons, they may offer preliminary insights into the influence of smoking history on therapeutic efficacy and highlight the need for future studies incorporating formal comparative subgroup analyses.

Across multiple landmark phase III trials, differences in pathological complete response (pCR) and event-free survival (EFS) outcomes have been observed between patients with and without a smoking history following the addition of immune checkpoint inhibitors to platinum-based chemotherapy. Although some studies reported numerically greater improvements among current or former smokers, these subgroup analyses were exploratory and included relatively few never-smokers. Therefore, these findings should be considered hypothesis-generating rather than evidence of a definitive difference in treatment efficacy between smoking groups.

When interpreting the outcomes of the trials conducted to assess the efficacy of various types of neoadjuvant and perioperative therapy for lung cancer, it is important to distinguish between the trials that implemented either a neoadjuvant or perioperative treatment approach. CheckMate 816 evaluated chemoimmunotherapy administered before surgery, whereas KEYNOTE-671, AEGEAN, CheckMate 77T, Neotorch, and NADIM II also included adjuvant immunotherapy. Moreover, some of these trials excluded patients with EGFR mutations or ALK rearrangement from their study. Several factors should be considered when interpreting findings from studies that excluded patients with these molecular alterations.

Because EGFR mutations and ALK rearrangements are more frequently observed in never-smokers, excluding patients with these known alterations may limit how well the enrolled never-smoker population represents the broader population of never-smokers with NSCLC. Furthermore, smoking history is associated with several other clinical and molecular characteristics, including tumor histology, PD-L1 expression, tumor mutational burden, sex, and ancestry, which may also influence treatment outcomes. Moreover, an exclusion criterion of EGFR mutations/ALK rearrangement does not mean that all enrolled patients were confirmed to have EGFR/ALK-wild-type tumors.

The CheckMate 816 trial (NCT02998528), which evaluated the efficacy of neoadjuvant nivolumab with chemotherapy, provides additional insights into how smoking history could influence treatment outcomes [11]. CheckMate 816 enrolled adults with treatment-naïve, resectable stage IB–IIIA NSCLC and good performance status (ECOG 0–1) while excluding those with prior anti-cancer therapy, autoimmune disease, or active, known, or uncontrolled infections such as hepatitis/HIV. Patients with known EGFR mutations or ALK rearrangements were excluded. Both smokers and never-smokers demonstrated numerically higher rates of pCR with chemoimmunotherapy than with chemotherapy alone, although the reported absolute improvements differed between smoking-status subgroups. In smokers, the addition of nivolumab increased the pCR rate from 2.5% to 25.6%, representing an absolute improvement of 23.1 percentage points, whereas the improvement in never-smokers was considerably smaller and associated with wider confidence intervals. However, a limitation is that the sample size was smaller for never smokers [11]. Although these findings suggest potential differences in pathological response based on smoking history, the exploratory

nature of these analyses and the small number of never-smokers limit the ability to draw definitive conclusions about differences in treatment efficacy between the two groups.

Table 2. Selected Trials with Treatment Outcomes of Smokers vs. Never-Smokers.

Selected Trials	Phase	Sample Size	Treatment Tested	Outcomes in Smokers (Current/Former)	Outcomes in Never-Smokers
CheckMate-816 (NCT02998528) [11]	III	358 (179 vs. 179) Current/former smokers: 318 Never smoker: 39	Neoadjuvant nivolumab + platinum-doublet chemotherapy ×3 vs. chemotherapy alone	EFS (HR 0.68; 95% CI 0.48–0.96), pCR (HR: 23.1, 95% CI 15.9–30.5), benefit broadly consistent across subgroups (median EFS 31.6 vs. 22.4; pCR 25.6 vs. 2.5); smokers comprise large majority of sample size	Never-smokers are a small subgroup (pCR 10.5 vs. 0); benefit limited by sample size
KEYNOTE-671 [5] (NCT03425643)	III	797 (397 vs. 400)	Perioperative pembrolizumab (neoadjuvant + adjuvant) + cisplatin-based chemotherapy vs. chemotherapy alone	Statistic not explicitly mentioned. Observed that smokers appeared to derive greater benefit than never-smokers. However, subgroups were small.	Statistic not explicitly mentioned
AEGEAN (NCT03800134) [7]	III	802 randomized Current smoker: 190 Former smoker: 443 Never smoker: 107	Perioperative durvalumab (neoadjuvant + adjuvant) + platinum-based chemotherapy vs. chemotherapy alone	Benefit seen across all smoking subgroups, with the greatest EFS/pCR benefit in current and former smokers (current smokers: 52% reduction in risk of disease progression, recurrence, or death compared to placebo with chemotherapy; former smokers: 21% reduction)	Benefit present but of lesser magnitude (24% reduction); wide CI partially due to small sample size
NADIM II (NCT03838159) [8]	II	86 (57 vs. 29; 2:1) Former smoker: 30 Current smoker: 51 Never smoker: 5	Neoadjuvant nivolumab + carboplatin/paclitaxel ×3 → adjuvant nivolumab vs. chemotherapy alone (stage IIIA–B)	Marked benefit (pCR 37% vs. 7%; 24-mo OS 85% vs. 63%); study sample predominantly smokers	Not reported
CheckMate 77T (NCT04025879) [6]	III	461 (1:1) Current or former smoker: 417 Never smoker: 44	Perioperative nivolumab (neoadjuvant + adjuvant) + platinum-doublet chemotherapy vs. chemotherapy alone	EFS and pCR benefit consistent across reported subgroups (overall EFS HR 0.58, 95% CI 0.42–0.81); pCR 25.3% vs. 4.7%; 18-mo EFS 70.2% vs. 50.0%)	The never-smoker subgroup did not demonstrate a clear benefit in EFS with perioperative nivolumab.
NeoADAURA (NCT04351555) [38]	III	358 (osimertinib + chemo 121; osimertinib alone 117; placebo + chemo 120)	Neoadjuvant osimertinib ± platinum chemotherapy vs. chemotherapy + placebo (EGFR-mutated, stage II–IIIB)	Not reported	Not reported
NAUTIKA1 (NCT04302025) [39]	II		Platform trial of neoadjuvant/ perioperative biomarker-matched therapy	Not reported	Not reported

In addition to the CheckMate 816 trial, the KEYNOTE-671 trial (NCT03425643) examined the role of perioperative pembrolizumab in early-stage non-small-cell lung cancer [5].

KEYNOTE-671 included previously untreated patients with resectable stage II–IIIB NSCLC, ECOG status of 0–1, and adequate organ function, and excluded specific tumor types such as superior sulcus tumors, solid organ transplant recipients, prior immunotherapy, and clinically significant autoimmune or interstitial lung disease. EGFR- and ALK-positive patients were not formally excluded, and a small number were enrolled (roughly 3.5% with EGFR and 3% with ALK alterations in the treatment arm). Participants with a current smoking status had a statistically significant improvement in median EFS with pembrolizumab plus chemotherapy compared to with chemotherapy alone, with the median EFS not yet reached during the study period in the pembrolizumab arm [5]. However, never-smokers did not demonstrate a significant improvement in EFS with pembrolizumab plus chemotherapy. This may be due to the small sample size of 44 never-smokers in the study, making formal conclusions difficult. Although the number of never-smokers enrolled was relatively small, these findings raise the possibility of differences in the survival benefit of perioperative pembrolizumab according to smoking history, warranting further investigation in larger studies [5].

The AEGEAN trial (NCT03800134) demonstrated a comparable trend among patients with resectable NSCLC [7]. AEGEAN required patients to be ≥18 years old with previously untreated, resectable stage IIA–select IIIB (N2) NSCLC and to have at least one lesion not previously irradiated at baseline, no prior exposure to immune-mediated therapy, and adequate tissue for molecular testing while excluding those with stage IIIB-N3/IIIC/IV disease, history of allogeneic organ transplantation, another primary malignancy, prior immunotherapy, and autoimmune or inflammatory disorders. Patients with EGFR mutations or ALK rearrangements were excluded. Among current smokers, perioperative durvalumab plus chemotherapy was associated with a 52% reduction in the risk of disease progression, recurrence, or death compared with placebo plus chemotherapy. This finding may suggest a potential benefit of this treatment regimen among current smokers.

Similarly, former smokers also demonstrated a favorable numerical 21% reduction in risk compared to placebo, although statistical significance was not reached. Never-smokers similarly showed a numerical benefit of reduction of 24%; however, the confidence interval was wide and crossed unity, likely reflecting the relatively small number of never-smokers included in the study similarly to the KEYNOTE-671 trial. Overall, AEGEAN provides preliminary evidence that smoking-associated tumors, particularly among current smokers, may exhibit a more favorable response to perioperative immune checkpoint inhibition. However, these findings remain exploratory and require further investigation to determine whether the observed differences reflect a true variation in treatment efficacy as per smoking history.

The CheckMate 77T trial (NCT04025879) is another major trial examining the efficacy of perioperative nivolumab in resectable lung cancer [6]. CheckMate 77T enrolled treatment-naïve patients with resectable stage IIA (>4 cm) to IIIB (T3N2) NSCLC, good performance status, and no brain metastases while excluding those with prior anticancer or checkpoint therapy, autoimmune disease or interstitial lung disease, and active HBV/HCV/HIV. Patients with EGFR or ALK mutations were excluded. Among current or former smokers, perioperative nivolumab reduced the risk of disease progression or death by 46%, with median event-free survival not yet reached in the nivolumab arm. In contrast, never-smokers did not demonstrate a significant EFS benefit (HR 1.32; 95% CI, 0.54–3.20). Importantly, only 44 never-smokers were included in this subgroup analysis, limiting statistical power and preventing definitive conclusions regarding the efficacy of treatment in this population.

Along with the CheckMate 77T trial, the Neotorch trial (NCT04158440) examined the efficacy of perioperative toripalimab plus chemotherapy for patients with resectable NSCLC [40]. Neotorch enrolled patients aged 18–70 with histologically confirmed,

resectable stage II, IIIA, or IIIB (N2) NSCLC, an ECOG score of 0–1, and good organ function while excluding those with advanced or metastatic disease, tumors involving the superior sulcus or large cell neuroendocrine carcinoma, and autoimmune disease or active infections. Patients with EGFR mutations or ALK alterations (in non-squamous histology) were excluded from participation. Participants receiving toripalimab plus chemotherapy exhibited higher major PRR (48.5% vs. 8.4%) and pCR compared to the placebo group (24.8% vs. 1.0%), which received placebo plus chemotherapy. However, the study findings were not stratified by smoking history. Similarly, the NADIM II trial (II (NCT03838159), which demonstrated a markedly higher pCR with nivolumab plus chemotherapy compared to chemotherapy alone in stage IIIA/B disease, did not have clear comparisons between smokers and never-smokers. NADIM included treatment-naïve patients with resectable stage IIIA/IIIB NSCLC, ECOG 0–1, and adequate organ function while excluding those with prior immunotherapy, significant autoimmune or infectious disease (including HBV/HCV/HIV), or grade 3–4 interstitial lung disease. Patients with EGFR mutations or ALK translocations were excluded. These landmark trials suggest that patients with a current or former smoking history may experience greater pathological and survival benefits from neoadjuvant or perioperative chemoimmunotherapy than never-smokers. However, these observations remain preliminary and hypothesis-generating. The findings should be interpreted cautiously because smoking-status subgroup analyses were exploratory, and never-smokers represented a small proportion of enrolled patients. Furthermore, the survival benefits observed in perioperative trials cannot be attributed solely to neoadjuvant therapy, as these regimens also included adjuvant immunotherapy. Further prospective studies are needed to determine how smoking history may influence treatment efficacy. Such studies may provide stronger evidence to support the incorporation of smoking history into the selection of neoadjuvant and perioperative treatment strategies.

4.2. Biological Mechanisms Underlying the Differential Efficacy of Neoadjuvant Therapeutic Strategies in Relation to Smoking History

4.2.1. Neoadjuvant Chemoimmunotherapy

Exploratory subgroup analyses suggest that smoking history may be associated with differences in response to neoadjuvant chemoimmunotherapy. These potential differences may be multifactorial and reflect distinct tumor biological characteristics between smoking-associated and never-smoker NSCLC. However, the limited representation of never-smokers in clinical trials warrants cautious interpretation of these findings.

Tobacco-Induced Mutagenesis and Increased Tumor Immunogenicity

The increased mutational burden associated with chronic tobacco exposure may contribute to differences in ICI responsiveness between smokers and never-smokers. Various genetic mutations have been identified across different smoking statuses: never-smokers exhibit a higher prevalence of *EGFR* mutations, while former smokers and current smokers demonstrate a higher incidence of *TP53* mutations [41].

Tobacco carcinogens, particularly polycyclic aromatic hydrocarbons, generate characteristic DNA damage that produces the tobacco-associated mutational signature SBS4, leading to the accumulation of numerous somatic mutations throughout the tumor genome [42]. Some of these mutations may generate neoantigens that can be recognized by the adaptive immune system, potentially contributing to increased tumor immunogenicity.

TMB has emerged as a potential biomarker of response to immune checkpoint blockade, although its predictive utility varies across clinical settings. In lung adenocarcinoma, cumulative pack-years have been associated with increased TMB, while higher TMB has been associated with increased pathological complete response (pCR) rates following neoadjuvant therapy.

Furthermore, various clinical studies have shown that patients with a higher TMB exhibit longer survival and response rates with ICI treatment. Notably, a TMB value ≥10 mutations/Mb has been associated with longer PFS in certain NSCLC cohorts, although the predictive significance of this threshold may vary across treatment settings. Never-smoker NSCLC exhibits a fundamentally different genomic profile. Compared with smoking-associated tumors, never-smoker tumors harbor substantially fewer somatic mutations, possess lower neoantigen loads, and frequently contain actionable oncogenic driver alterations such as EGFR mutations or ALK rearrangements rather than smoking-associated KRAS and TP53 mutations [41]. These molecular differences may contribute to variations in tumor immunogenicity between smoking-associated and never-smoker NSCLC.

Smoking Remodels the Tumor Immune Microenvironment

Beyond its association with increased TMB, smoking may also influence the composition of the tumor immune microenvironment. Analyses integrating clinical cohorts with CyTOF and transcriptomic data demonstrate that tumors from smokers contain higher densities of activated immune cells, such as activated $CD8^+$ cytotoxic T cells, follicular helper $CD4^+$ T cells, γδ T cells, activated dendritic cells, and increased expression of immune-activating chemokines [43]. These features may reflect a more immune-inflamed or "hot" tumor microenvironment, which has been associated with increased responsiveness to immune checkpoint inhibition in certain clinical settings.

In contrast, some studies have reported enrichment of immunosuppressive cell populations, particularly regulatory T cells (Tregs) and M2 macrophages, together with reduced immune activation in tumors arising in never-smokers. Consistent with this observation, $CD45RA^{high}$ $CD4^+$ T cells and $CD45RA^{high}$ $CD8^+$ T cells are enriched in never-smokers [43]. CD45RA is a marker expressed on naïve T cells (cells that have not yet encountered an antigen) and a subset of terminally differentiated effector memory cells [44]. These differences in the tumor immune microenvironment may contribute to variations in sensitivity to PD-1/PD-L1 blockade between smokers and never-smokers. However, the extent to which these immunological characteristics influence responses to neoadjuvant chemoimmunotherapy remains further explored.

Smoking-Associated PD-L1 Expression and Its Potential Influence on Checkpoint Blockade

Smoking also influences expression of PD-L1, one of the principal therapeutic targets of modern immune checkpoint inhibitors. Several clinical studies have reported higher PD-L1 expression in current smokers compared with former smokers or never-smokers, with some studies identifying associations between PD-L1 expression and cumulative smoking exposure [45]. Higher PD-L1 expression likely contributes to the greater efficacy of PD-1/PD-L1 blockade, in combination with chemotherapy, observed in smokers across multiple clinical trials [46,47]. For instance, when examining the effect of PD-1/PD-L1 blockade alone, the phase III KEYNOTE-042 study demonstrated that after 5 years of follow-up, pembrolizumab used as first-line monotherapy continued to provide long-lasting clinical benefits compared with standard chemotherapy in patients with PD-L1-positive, locally advanced or metastatic NSCLC without EGFR or ALK alterations [48]. Moreover, the risk of disease recurrence was highest in patients with PD-L1-negative tumors, while patients with low or high PD-L1 expression experienced progressively lower risks of relapse [49]. These findings demonstrate how PD-L1 expression can also influence the risk of relapse, along with response to therapy.

Mechanistically, examining this effect at the molecular level, cigarette smoke carcinogens, such as benzo(a)pyrene, activate the aryl hydrocarbon receptor (AhR), which directly induces PD-L1 transcription in lung epithelial cells. Experimental models have

demonstrated that inhibition of AhR suppresses smoking-induced PD-L1 expression and enhances antitumor immunity, suggesting that tobacco exposure paradoxically promotes the formation of tumors that become increasingly dependent on the PD-1/PD-L1 immune checkpoint pathway [50].

While it is shown that smoking-associated tumors classically present with higher PD-1 expression than never-smoker-associated tumors, it is important to recognize that some never-smokers may present with a smoking-associated tumor. Among patients with PD-L1 expression ≥50%, never-smokers experienced substantially greater benefit from first-line chemoimmunotherapy than immunotherapy alone, with higher objective response rates (70% vs. 24%) and longer PFS [51]. In contrast, smokers achieved similar outcomes regardless of treatment approach. These findings raise the possibility that adding chemotherapy may provide additional clinical benefit in certain never-smoker populations.

Smoking-associated PD-L1 expression may represent one component of a broader immunogenic phenotype characterized by elevated TMB, increased neoantigen presentation, and enhanced immune cell infiltration, which may contribute to differences in therapeutic responsiveness across smoking statuses. Recent studies also suggest that smoking alters the gut microbiome. Compared with never-smokers, smokers have been reported to exhibit reduced abundance of *Bifidobacterium longum* and enrichment of Gram-negative bacterial taxa associated with increased lipopolysaccharide biosynthesis. These microbial changes have been associated with improved responses to immune checkpoint inhibitors, although their precise mechanistic role remains under investigation [52].

Additional evidence suggests that individuals with heterozygous HLA alleles may be able to present a broader variety of neoantigens generated by smoking-induced somatic mutations, allowing the immune system to recognize and target tumor cells more effectively. Overall, TMB, immune microenvironment, neoantigen load, tobacco smoking-related mutational signatures, AhR-mediated PD-L1 upregulation, and the gut microbiome contribute greatly to improved responsiveness to chemoimmunotherapy in smokers vs. never-smokers with NSCLC.

4.2.2. Neoadjuvant Chemotherapy

Unlike immunotherapy, conventional chemotherapy appears to be more effective in lung cancer patients who are never-smokers than in those with a history of smoking. This difference is likely driven by the cumulative biological effects of chronic tobacco exposure, which promotes several complementary mechanisms of chemoresistance. Cigarette smoke induces the expression of the ATP-binding cassette transporter ABCG2 by activating the PI3K/Akt signaling pathway, increasing the efflux of cytotoxic agents such as doxorubicin and mitoxantrone from tumor cells through the transporter, and reducing accumulation of drugs in the cell [53]. In addition to lowering chemotherapy concentrations within cancer cells, upregulating ABCG2 also expands a cancer stem cell-like population, which has been associated with enhanced resistance to treatment and tumor persistence [54].

In addition to upregulating transporter expression, smoking also impairs one of chemotherapy's principal mechanisms of action—induction of apoptosis. Prolonged exposure to cigarette smoke downregulates the expression of Smad3 through the TGF-β pathway, which subsequently upregulates the anti-apoptotic protein Bcl-2. This shift toward cell survival reduces the ability of carboplatin to induce apoptosis in tumor cells and allows them to withstand platinum-based chemotherapy [55].

Nicotine further reinforces this resistant phenotype by upregulating the MAPK and PI3K/Akt signaling pathways and the X-linked inhibitor of apoptosis protein (XIAP) [56]. Through these pathways, nicotine preserves mitochondrial membrane potential, inhibits caspase-9 activation, and prevents the pro-apoptotic protein Bax from translocating to the

mitochondria [56]. Together, these alterations limit mitochondrial-mediated cell death, allowing malignant cells to survive despite chemotherapy exposure.

In addition to promoting intrinsic cellular resistance, cigarette smoke alters the pharmacokinetics of several anticancer agents. PAHs contained in tobacco smoke induce hepatic drug-metabolizing enzymes, particularly CYP1A1, CYP1A2, and several UDP-glucuronosyltransferases, accelerating the metabolism and clearance of multiple systemic therapies [57]. As a result, smokers may achieve lower circulating drug concentrations and reduced therapeutic exposure despite receiving the same chemotherapy dose as never-smokers. These pharmacokinetic changes further diminish the efficacy of treatment and may contribute to the inferior clinical outcomes consistently observed in smokers receiving chemotherapy.

These biological mechanisms contribute to clinical observations demonstrating a clear dose–response relationship between smoking exposure and chemotherapy resistance. Increased cumulative tobacco exposure is associated with progressively poorer responses to platinum-based chemotherapy, with patients who have smoked 40 or more pack-years exhibiting markedly lower response to treatment than lighter smokers [58].

These findings indicate that chronic tobacco exposure promotes a phenotype in tumors classified by an impaired ability to retain chemotherapy drugs in tumor cells, enhanced survival, resistance to apoptosis, and altered drug metabolism—thereby reducing the effectiveness of neoadjuvant chemotherapy alone.

4.2.3. Neoadjuvant EGFR-Targeted Therapy

The relationship between smoking history and the efficacy of neoadjuvant EGFR-targeted therapy is complex, reflecting differences in tumor molecular characteristics and the potential effects of tobacco exposure on EGFR signaling. EGFR mutations are more common among never-smokers, while smoking-associated lung cancers more frequently harbor TP53 mutations and other tobacco-related genomic alterations [41]. However, EGFR mutations can also occur in smokers, and not all never-smokers have EGFR-mutated tumors. Therefore, the higher proportion of never-smokers enrolled in neoadjuvant EGFR-TKI clinical trials may be explained by the greater prevalence of EGFR mutations in this population, rather than a greater response to treatment based on smoking history alone [39,59].

Beyond differences in mutation prevalence, cigarette smoke promotes resistance to EGFR-targeted therapy through multiple complementary mechanisms. One important pathway involves suppression of the LKB1–AMPK signaling axis. Cigarette smoke has been shown to epigenetically downregulate the expression of LKB1 by methylating the CpG islands of the gene, reducing the activation of AMPK. As AMPK inhibits mTOR, decreased AMPK function can relieve its inhibitory effects on mTOR signaling [59]. These alterations may enhance glycolysis and promote tumor growth despite EGFR inhibition, potentially contributing to reduced sensitivity to EGFR-TKIs in experimental models. Experimental studies have further demonstrated that restoring the activity of AMPK activity can partially overcome this resistance, suggesting that impairing the LKB1/AMPK pathway promotes smoking-associated TKI resistance.

Furthermore, experimental studies suggest that chronic nicotine exposure may reduce the ability of EGFR-TKIs to suppress EGFR phosphorylation, potentially requiring higher drug concentrations to achieve comparable receptor inhibition in lung cancer patients with a smoking history [60]. As a result, despite therapy, the pathways downstream of EGFR, such as the RAS/RAF/MEK, PI3K/AKT, and JAK/STAT pathways, continue to signal [61]. These mechanisms may contribute to differences in EGFR-TKI sensitivity associated with tobacco exposure, although their clinical relevance in the neoadjuvant setting remains to be established.

In addition, cigarette smoke activates several signaling pathways that reduce dependence on canonical EGFR signaling. Reactive oxygen species generated by tobacco smoke stimulate the autocrine release of EGFR ligands, including HB-EGF (HBEGF), amphiregulin, and transforming growth factor-α, while simultaneously promoting the autophosphorylation of EGFR through an Src-dependent non-canonical pathway [60]. These events activate the Ras/Raf/MEK/ERK and PI3K/Akt pathways, allowing tumor cells to proliferate and survive even when EGFR kinase activity is pharmacologically inhibited. Experimental evidence also suggests that cigarette smoke may help cancer cells evade various cell death pathways by disrupting SMAD3-SMAD4 signaling, increasing the expression of the anti-apoptotic protein Bcl-2, and reducing TGF-β-mediated apoptosis. These mechanisms may influence the antitumor effects of EGFR-targeted therapy.

Overall, differences in the prevalence of sensitizing EGFR mutations may affect the proportion of smokers and never-smokers eligible for neoadjuvant EGFR-targeted therapy. Smoking-related changes in EGFR signaling, downstream pathways, and metabolic regulation may also influence sensitivity to EGFR-TKIs. However, further clinical studies are needed to determine whether smoking history affects treatment outcomes among patients with EGFR-mutated tumors receiving neoadjuvant EGFR-targeted therapy.

4.3. Treatment Selection Considerations

With recent advances in neoadjuvant therapy for lung cancer and growing evidence on the differences in response to therapy in association with smoking history, it is important to consider the role of smoking history in treatment selection for patients with resectable NSCLC. Smoking history may provide valuable insight into the underlying molecular and immunological characteristics of a patient's tumor. However, this factor should not be used in isolation to determine treatment. As discussed, exploratory analyses suggest that smoking history may be associated with differences in response to neoadjuvant chemoimmunotherapy, although these findings remain inconclusive. Furthermore, never-smokers are more likely to harbor actionable oncogenic driver alterations, such as EGFR mutations, which may influence eligibility for targeted therapeutic approaches.

The observed differences in treatment efficacy likely reflect the underlying biology of smoking-associated and never-smoker NSCLC rather than smoking itself. These biological differences, including variations in tumor mutational burden, PD-L1 expression, and the prevalence of actionable oncogenic driver alterations, may contribute to differences in treatment response across smoking statuses.

Despite these emerging observations, smoking history should currently be viewed as one component of a broader clinical assessment rather than as a stand-alone predictive biomarker. Treatment selection should continue to rely primarily on established factors, including disease stage, resectability, histologic subtype, molecular profiling, PD-L1 expression, comorbidities, and the patient's suitability for immunotherapy. Within this framework, smoking history may provide additional insight into the expected magnitude of benefit from specific neoadjuvant approaches and may contribute to developing more personalized treatments for patients as further research is conducted.

4.4. Biomarker-Driven Strategies for Never-Smokers

The distinct molecular characteristics of never-smoker NSCLC highlight the need for treatment strategies that extend beyond the standard neoadjuvant chemoimmunotherapy. As explained earlier, compared with smokers, never-smokers are more likely to develop tumors driven by actionable oncogenic alterations, particularly EGFR mutations, while simultaneously exhibiting lower tumor mutational burden, fewer neoantigens, and a less immunogenic tumor microenvironment. As these tumors are substantially more likely

to harbor actionable genomic alterations, testing for molecular markers and driver mutations should be considered an essential step in designing a treatment plan for patients. Understanding these molecular mechanisms could help researchers and clinicians develop treatments that directly target the pathways responsible for tumor growth.

The development of EGFR tyrosine kinase inhibitors (TKIs) has fundamentally changed the management of EGFR-mutated NSCLC. Successive generations of these agents have progressively improved clinical outcomes, culminating in the development of osimertinib (a third-generation irreversible EGFR TKI). The phase III NeoADAURA trial represents a major step toward developing personalized neoadjuvant therapy for never-smokers with EGFR-mutated NSCLC. Patients treated with neoadjuvant osimertinib, either alone or combined with platinum-based chemotherapy, achieved substantially higher MPR (25% with osimertinib monotherapy and 26% for osimertinib plus chemotherapy) than those receiving placebo plus chemotherapy alone (2%) [38].

Considering therapeutic resistance for patient subgroups such as never-smokers, researchers and clinicians are working on developing therapies that remodel the tumor immune microenvironment. These strategies include combining ICIs with oncolytic viruses, adoptive cellular therapies such as tumor-infiltrating lymphocytes, therapeutic cancer vaccines, cytokine-based therapies, or other multimodal immunotherapeutic approaches designed to recruit immune cells into otherwise poorly immune-inflamed tumors [62]. As an alternative to intensifying checkpoint inhibition with immunotherapy and enhancing cell death with chemotherapy, these approaches seek to make immunologically "cold" tumors into tumors more receptive to an antitumor immune response [62].

The management of never-smokers is likely to become increasingly individualized as molecular diagnostics continue to evolve. Integrating smoking history with genomic alterations, PD-L1 expression, TMB, and emerging biomarkers may provide a more comprehensive framework for selecting an appropriate neoadjuvant therapy while minimizing therapeutic toxicity for never-smoking patients.

5. Limitations and Knowledge Gaps

Although accumulating evidence suggests that smoking history influences the efficacy of neoadjuvant therapy in NSCLC, the current literature remains insufficient to establish smoking status as a clinically actionable biomarker. Most of the available evidence originates from post-analyses of randomized clinical trials that were designed to evaluate treatment efficacy rather than differences according to smoking history. Consequently, these analyses were not adequately powered to detect treatment interactions between smokers and never-smokers, particularly because never-smokers represented only a small proportion of participants in most landmark neoadjuvant studies. The resulting wide confidence intervals and limited statistical power among never-smoking participants make it difficult to determine whether the smaller effects of treatment observed among them reflect a true effect of therapy. Future prospective trials should incorporate smoking status in design and a statistical methodology to accurately evaluate treatment across smoking subgroups.

An additional limitation is the lack of uniformity in how smoking exposure is defined across clinical studies. Trials have variably categorized patients as current, former, or never-smokers, while others have incorporated different pack-year thresholds or have not reported cumulative tobacco exposure in detail. These inconsistencies make it more challenging to analyze comparisons across studies and limit the ability to evaluate potential dose–response relationships between smoking intensity and efficacy of treatment.

Current biomarker strategies also remain inadequate for accurately predicting treatment response according to smoking history. Although PD-L1 expression and TMB are routinely used to guide immunotherapy decisions, both biomarkers have important

limitations [63]. Only a subset of patients (46%) with PD-L1 expression levels of ≥50% experience continued benefits from immunotherapy, suggesting that the other 54% of patients with high PD-L1 expression fail to achieve durable responses. However, others with low PD-L1 expression still benefit from chemoimmunotherapy. For instance, for individuals with PD-L1 expression <1%, immunotherapy combined with chemotherapy increased response rates from 14.3% to 32% [64].

TMB alone does not fully capture the complex interactions between smoking exposure, the tumor microenvironment, and host immunity. Emerging biomarkers, including DNA methylation signatures, represent a promising avenue for improving risk stratification [64]. Smoking induces characteristic epigenetic alterations that influence gene expression, immune regulation, and tumor progression, and several methylation markers such as methylation of Synuclein Alpha (SNCA) and Zinc Finger Protein 549 (ZNF549) have demonstrated potential in distinguishing lung cancer from cancer-free smokers using minimally invasive specimens such as sputum [65].

Integrating epigenetic biomarkers with molecular profiling and smoking history may provide a more comprehensive framework for predicting therapeutic response and selecting optimal strategies for neoadjuvant treatment.

Finally, substantial knowledge gaps remain regarding the optimal management of never-smoker NSCLC. Although EGFR-targeted therapy has demonstrated potential in early neoadjuvant trials, long-term survival data remain limited. Ongoing studies, such as NAUTIKA1 [39] and NeoADAURA [38], will help us gain a deeper understanding of the efficacy of inhibiting EGFR as a neoadjuvant therapy for never-smoker NSCLC.

Beyond targeted therapy, novel strategies designed to overcome the relatively immune-cold phenotype of never-smoker tumors, such as combinations of immunotherapy with stereotactic body radiotherapy [66] and epigenetic therapies [67], are currently under exploration. These studies will help shift the treatment landscape from extrapolating therapeutic approaches from predominantly smoking-associated NSCLC to developing personalized evidence-based therapies for never-smoker-associated NSCLC.

6. Future Directions

Despite real progress in neoadjuvant treatment for resectable NSCLC, smoking history and its role in guiding therapy is still uncertain. Much of what we know comes from retrospective or subgroup analyses—studies that were not built to test smoking status as a predictive biomarker in the first place. Prospective trials are needed to determine whether smoking history predicts how a tumor responds to treatment, or whether it is simply a surrogate for underlying molecular and immune features of the cancer. Reporting also needs to be more precise: pack-years, duration of smoking, and time since cessation would tell us far more than the simplicity of current/former/never categories most studies still use. That degree of specificity could clarify how tobacco exposure shapes treatment response and make cross-study comparisons more meaningful [68].

Smoking history alone would not get us there, though. It is one useful data point among several, and pairing it with PD-L1 expression, tumor mutational burden, genomic profiling, and ctDNA is likely to sharpen our ability to match patients to the right approach. As precision oncology matures, a multi-biomarker model will almost certainly outperform any single clinical characteristic on its own [68,69].

Never-smokers present a distinct challenge. Their tumors are more likely to carry actionable driver mutations but tend to have lower mutational burden and a colder immune microenvironment. This helps explain why checkpoint inhibitors work inconsistently in this group. Targeted therapies, antibody–drug conjugates, bispecific antibodies, cancer vaccines,

and adoptive cell therapy all warrant continued study here, and perioperative trials testing these approaches will matter for moving beyond standard chemoimmunotherapy [68,70].

One area is still surprisingly underexplored: what quitting smoking does to treatment outcomes. Cessation is recommended across the board for lung cancer patients, but we do not yet have solid prospective data on whether quitting before or during neoadjuvant therapy changes pathological response, recurrence risk, ctDNA clearance, or survival. Untangling how cessation affects both tumor biology and drug efficacy could open another mechanism for individualizing care [45].

Furthermore, artificial intelligence (AI) has emerged as a promising tool that can be used to integrate clinical, radiological, and molecular data to aid in all stages of cancer care from assessing risk factors for cancer development to prevention, diagnosis, treatment, monitoring of patients. Importantly, AI has shown potential in predicting patients' smoking status as well as their response to neoadjuvant NSCLC therapy. For instance, machine learning models have demonstrated the ability to identify smoking status using clinical and biological characteristics, with various AI-based models having classification accuracies of smoking status ranging from 77% to 85% [71]. These models can be helpful to more clearly understand a patient's exposure to first-hand or second-hand smoking and therefore better evaluate response to neoadjuvant therapy.

Additionally, AI-based radiomics models have shown potential in noninvasively predicting biomarkers associated with immunotherapy response, such as programmed death-ligand 1 (PD-L1) expression, with several CT-based models achieving areas under the receiver operating characteristic curve (AUCs) exceeding 0.75 [72]. This value indicates that these models can moderately well discriminate tumors with low vs. high PD-L1 expression.

Interestingly, AI has demonstrated promising performance in predicting pathological response following neoadjuvant immunochemotherapy in NSCLC. A systematic review and meta-analysis encompassing 23 studies and 2004 patients in validation cohorts reported pooled AUCs of 0.85 and 0.88 for predicting pathological complete response (pCR) and major pathological response (MPR), respectively, outperforming conventional radiological assessment methods [73].

Given the associations between smoking history, tumor mutational burden, oncogenic driver alterations, and the tumor immune microenvironment, incorporating smoking status alongside radiomic, genomic, and clinical features into AI-based predictive models may further improve the identification of patients most likely to benefit from neoadjuvant immunotherapy. However, whether smoking history provides independent predictive value within these models remains insufficiently established. Future prospective studies should investigate the integration of smoking status into AI models to improve treatment selection and more accurately predict NSCLC patients' response to neoadjuvant therapy.

Overall, future management of resectable NSCLC will likely rely on combining clinical characteristics with molecular and immune biomarkers to guide treatment decisions. Rather than serving as a stand-alone predictive biomarker, smoking history should be considered one component of a broader biologic profile that may help optimize patient selection for neoadjuvant therapy.

7. Conclusions

Smoking history plays an integral role in deepening our understanding of lung cancer patients' response to neoadjuvant therapy and in ultimately formulating a neoadjuvant therapy that is believed to most benefit each patient. Smoking history provides insight into the molecular, genomic, and immunologic characteristics that shape therapeutic response. As our understanding of these differences continues to evolve, treatment decisions are likely

to shift away from uniform treatment approaches toward strategies that better account for the biological diversity of lung cancer.

Integrating clinical presentation with molecular and immune profiling will be essential in formulating neoadjuvant treatment approaches. Incorporating genomic alterations, tumor mutational burden, PD-L1 expression, ctDNA, epigenetic signatures, and smoking-associated mutational patterns into composite biomarker panels may improve patient selection and enable more precise use of neoadjuvant therapies.

Continued innovation is particularly needed for never-smoker NSCLC, where conventional immunotherapy-based approaches have demonstrated more variable efficacy. Developing more targeted therapies and further examining antibody–drug conjugates, bispecific antibodies, and other next-generation immunotherapeutic strategies can help address the unique tumor biology of never-smokers.

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Abbreviations

The following abbreviations are used in this manuscript:

ADC	Antibody–Drug Conjugate
CI	Confidence Interval
ctDNA	Circulating Tumor DNA
DNAm	DNA Methylation
EFS	Event-Free Survival
EGFR	Epidermal Growth Factor Receptor
HLA	Human Leukocyte Antigen
MPR	Major Pathological Response
NCCN	National Comprehensive Cancer Network
NSCLC	Non-Small-Cell Lung Cancer
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
pCR	Pathological Complete Response
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
RET	Rearranged During Transfection
ROS1	ROS Proto-Oncogene 1
SBRT	Stereotactic Body Radiotherapy
TKI	Tyrosine Kinase Inhibitor
TMB	Tumor Mutational Burden
AUC	Area Under the Curve

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