Progress in perioperative immunotherapy for lung cancer and analysis of therapy (Review)

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Abstract. Surgical treatment has long been the preferred approach for lung cancer. In recent years, postoperative adjuvant immunotherapy following surgical treatment has demonstrated good efficacy. Building on this foundation, the introduction of neoadjuvant immunotherapy prior to surgery has also reported promising results in a number of clinical trials. The aim of the present review was to summarize recent research findings associated with perioperative immunotherapy for lung cancer, including key outcomes from both neoadjuvant and adjuvant therapies. The discussion of the results of the present review primarily addressed efficacy, safety, survival data and programmed death-ligand 1 subgroup analyses. Furthermore, the advantages and limitations of different treatment modalities, including monotherapies and combination therapies, were discussed. Furthermore, the present review incorporated discussions on the applicability of biomarkers in perioperative immunotherapy, the role of immunotherapy combined with other treatments during the perioperative period, mechanisms of resistance and potential solutions to these challenges. In conclusion, the present review offers a systematic examination of the theoretical foundations of perioperative immunotherapy for lung cancer, simultaneously presenting key clinical evidence (including neoadjuvant therapy, adjuvant therapy and 'sandwich' combination regimens), diverse combination strategies (chemotherapy and radiotherapy), the current status of biomarker applications and challenges in underlying drug resistance mechanisms for perioperative immunotherapy. It proposes a dynamic monitoring model and clinical decision pathway for omission of adjuvant immunotherapy in non-small cell lung cancer. Lastly, based upon the latest evidence-based medical research, the present review aims to provide clinicians and researchers with comprehensive decision-making references and scientific guidance.

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1. Introduction

Lung cancer remains the leading cause of cancer-associated mortalities globally, with 2.48 million novel cases and 1.81 million mortalities, recorded in 2022. A model projection released by the International Agency for Research on Cancer under the World Health Organization indicates that new cases of lung cancer will increase by 41% by the year 2050, primarily driven by population aging in China and India. Notably, the nationwide low-dose computed tomography (CT) screening initiative in China has increased the number of cases of early-stage diagnosis by ~12% since 2023 (1-3).

Epidemiological data from 19 countries has revealed that non-small cell lung cancer (NSCLC) accounts for 90.3% of all cases of lung cancer (4). Although surgical resection remains the main curative approach for early-stage and resectable locally advanced NSCLC, postoperative 5-year survival rates remain suboptimal: These have been reported to be 68% for stage IB and 36% for stage IIIA disease, respectively (5). Although traditional adjuvant chemotherapy has been reported to modestly reduce the risk of recurrence, its clinical benefits appear to have reached a plateau, since only a 5% improvement

in 5-year survival rates has been recorded (6), with additional limitations including chemotherapy-associated toxicity and the absence of validated predictive biomarkers. Notably, 30-55% of patients experience locoregional recurrence or distant metastasis postoperatively (7), underscoring the key need for effective eradication of minimal residual disease (MRD) and the activation of systemic immune surveillance to improve outcomes.

The advent of immune checkpoint inhibitors (ICIs) targeting programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) has revolutionized treatment paradigms for advanced NSCLC (8). Key phase III trials, including KEYNOTE-024 and CheckMate 227 (9,10), have demonstrated notable overall survival (OS) benefits with ICI monotherapy or combination regimens in metastatic settings. These breakthroughs have prompted an investigation of immunotherapy in different perioperative settings, aiming to remodel the tumor immune microenvironment through neoadjuvant or adjuvant approaches to achieve synergistic locoregional-systemic control.

Early exploratory studies, such as the LCMC3 and CheckMate 159 studies (11,12), were able to establish the feasibility of neoadjuvant immunotherapy. The landmark CheckMate 816 trial first demonstrated in a phase III setting that the use of the checkpoint inhibitor nivolumab plus chemotherapy led to a marked improvement in both the pathological complete response (pCR) rates and event-free survival (EFS) rates compared with chemotherapy alone in resectable NSCLC, marking the transition of perioperative immunotherapy from the conceptual stage to clinical practice (13).

Subsequent trials, including the KEYNOTE-671 (14) and AEGEAN (15) trials, further advanced combination strategies, achieving pCR rates >30% and demonstrating durable survival benefits with postoperative adjuvant immunotherapy. Similar progress in adjuvant immunotherapy has emerged from the IMpower010 trial, where treatment with atezolizumab led to an improved 3-year disease-free survival (DFS) rate (increased to 60%) compared with chemotherapy in PD-L1^{+} (≥1%) patients with stage II-IIIA cancer (16), whereas the KEYNOTE-091 trial established a DFS benefit for pembrolizumab in PD-L1-unselected cases. These findings have been incorporated into major guidelines, including those of the National Comprehensive Cancer Network (NCCN) and the International Association for the Study of Lung Cancer (IASLC) (17-19).

Nevertheless, several challenges persist in this rapidly evolving field. First, the selection of biomarkers remains contentious: The CheckMate 816 trial revealed marked pCR rate disparities comparing between the PD-L1 ≥1% and PD-L1 <1% subgroups (13), whereas the KEYNOTE-091 trial revealed PD-L1-independent DFS benefits. Secondly, safety optimization of combination strategies warrants urgent attention, as exemplified by the 32% grade 3-4 adverse event (AE) rate with dual immunotherapy that was observed in the CheckMate 77T trial (20). Furthermore, the limited efficacy of ICIs noted in epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase (ALK)-altered NSCLC needs to be followed up with mechanistic studies (21). Lastly, long-term follow-up data are required to fully characterize the impact of immune-associated AEs (irAEs) on perioperative outcomes (22).

Currently, the paradigm of perioperative management is expanding toward integrated systemic approaches that target not only tumor cells, but also the microenvironment of the host. Increasing evidence has highlighted the pivotal role of systemic inflammation and metabolic dysregulation in modulating treatment efficacy; for example, an elevated neutrophil-to-eosinophil ratio was reported to be associated with impaired OS [hazard ratio (HR)=1.74] and progression-free survival (PFS; HR=1.53) rates across malignancies, reflecting pro-tumorigenic inflammation that may undermine immunotherapeutic responses (23). In addition, metabolic syndrome, which is characterized by chronic inflammation and insulin resistance, has been reported to increase cancer risk via adipokine dysregulation and oxidative stress, thereby suggesting that metabolic interventions may potentially act synergistically with ICIs (24).

Concurrently, novel biomarkers are refining patient stratification. The cachexia index, which integrates skeletal muscle mass, albumin and neutrophil-associated lymphocytes, predicts survival rates (OS, HR=2.03) independently of tumor stage, thereby offering a multidimensional assessment of the nutritional-inflammation status (25). Despite these emerging tools; however, PD-L1, as a biomarker, retains its clinical relevance in cases of advanced NSCLC: A high expression (≥50%) of PD-L1 remains predictive of notably increased ICI responsiveness, warranting a further exploration of its dynamic changes in perioperative settings (26). These insights align with other therapeutic advances that have recently been made; for example, meta-analyses have confirmed that adjuvant PD-1/PD-L1 inhibitors reduce the recurrence-free survival (RFS) risk across solid tumors (HR=0.72), thereby supporting their broader application beyond PD-L1 selection (27).

Future research efforts should prioritize precision medicine through the application of multi-omics approaches [for example, single-cell sequencing and spatial transcriptomics (28)] to decipher dynamic tumor-immune microenvironment interactions, to develop circulating tumor DNA (ctDNA)-based MRD monitoring systems and to explore novel therapeutic combinations [for example, immunotherapy with targeted agents (29) or epigenetic modulators (30)] to overcome drug resistance. Real-world evidence will be key to the validation of treatment paradigms in special populations. Subsequently, the present review will systematically examine recent advances that have been made in perioperative immunotherapy through four dimensions, namely clinical applications, combination strategies, biomarker development and future challenges, with the aim of providing information for evidence-based clinical decision-making in the future.

2. Literature identification strategy

The present narrative review has compiled evidence from pivotal clinical trials published between January 1, 2007 and August 31, 2025, using the search terms 'perioperative immunotherapy', 'neoadjuvant/adjuvant', 'lung cancer' and 'clinical trial'. Key sources included the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com) databases, proceedings from major oncology conferences (for example, those organized by American Society of Clinical Oncology (ASCO) (31-33) and European Society

for Medical Oncology (ESMO) (34) and IASLC (35,36) and American Association of Cancer Research (AACR) (37) and the Clinical Trials website (clinicaltrials.gov) (for ongoing trials). Phase III randomized controlled trials (for example, CheckMate816 and KEYNOTE-671) were prioritized, along with practice-changing phase II studies that have informed recent guideline updates (for example, the updates made to version 7.2025; NCCN (18) and Neoadjuvant and Adjuvant Treatments for Early-Stage Resectable NSCLC Consensus Recommendations From IASLC (19). In addition, emphasis was placed on perioperative outcomes (regarding parameters such as the pCR and the EFS/OS rate), biomarker correlates (PD-L1 and ctDNA) and the safety profiles of immunotherapy combinations.

3. Theoretical basis and mechanism of perioperative immunotherapy

The cancer-immunity cycle, a fundamental biological process governing immune-mediated tumor recognition and eradication, comprises seven sequential steps, namely tumor antigen release, antigen presentation, T-cell activation, T-cell trafficking to tumor sites, tumor-infiltrating T-cell recognition of cancer antigens, tumor cell killing and the establishment of immunological memory. ICIs primarily function by counteracting immunosuppressive signals within the tumor microenvironment (TME), thereby reactivating antitumor immune responses (Fig. 1) (38-44). However, the seven steps in the cancer-immunity cycle of lung cancer tumors are notably specific and different perioperative immunotherapy approaches work through a range of different mechanisms (Table I) (45-50).

4. Clinical practice and evidence of perioperative immunotherapy

Exploration of neoadjuvant monotherapy immunotherapy. The exploration of ICIs in neoadjuvant therapy began with early single-agent clinical studies, aimed at evaluating their potential to induce pathological remission and assessing their safety. Although neoadjuvant immunotherapy combined with chemotherapy has become the predominant strategy, research on neoadjuvant monotherapy immunotherapy continues to provide key insights into the biological effects of immunotherapy and patient selection.

In the CheckMate 159 trial (12), the major pathological response (MPR) rate of nivolumab monotherapy was reported to reach 45% and patients with a high tumor mutational burden (TMB) exhibited notable pathological remission. Furthermore, the 5-year RFS risk for PD-L1$^+$ patients was reduced by 64% (HR=0.36), whereas the MPR rate for PD-L1$^-$ patients was 30%, demonstrating that PD-L1$^-$ patients could also derive certain benefit from the therapy. Furthermore, the LCMC3 study (11) further validated the feasibility of neoadjuvant immunotherapy monotherapy. The MPR rate of atezolizumab monotherapy was reported to be 20%, although this increased significantly to 33% in the PD-L1 ≥50% subgroup compared with only 11% in the tumor proportion score (TPS) <1% group (P=0.01). The MPR rate in the TMB ≥16 mutant/Mb subgroup was also 33%, whereas it was only 13% in the low TMB group (P=0.12), highlighting the synergistic screening potential of dual markers. Furthermore, compared with traditional neoadjuvant chemotherapy studies that had an MPR rate of 19% and a treatment-related AE (TRAE) rate of 57%, (51), the MPR rate of neoadjuvant monotherapy immunotherapy increased to 20-45%, with markedly reduced toxicity. The incidence of grade 3 TRAEs was 11-23%, which was notably lower than the 60% incidence of TRAEs observed in neoadjuvant chemotherapy. Notably, the surgical delay rate in the LCMC3 study was extremely low. Similarly, in the NEOSTAR monotherapy group (52), the MPR rate was 22%, while the pCR rate was 9%, both markedly higher compared with those of patients receiving traditional chemotherapy. However, there remained a gap in the efficacy of monotherapy compared with the dual immunotherapy combination: For example, the MPR rate of the nivolumab plus ipilimumab combination increased to 38%, whereas that of the monotherapy group was only 22% and the dual immunotherapy combination also led to the induction of higher levels of effector T cell infiltration, with a 50% increase in CD8$^+$ T cells compared with neoadjuvant immunotherapy monotherapy (P=0.033) (34,52-54).

In general, the pCR of the neoadjuvant monotherapy immunotherapy was reported to be low (generally of the order of <10-15%). Furthermore, the pCR was notably lower compared with that of immunotherapy combined with chemotherapy; for example, the MPR in the CheckMate 816 trial was reported to be 24%. It should be noted that the majority of the single-agent studies had small sample sizes and limited representativeness (Table II).

Advances in neoadjuvant immunotherapy combined with chemotherapy. At present, a combination of ICIs and chemotherapy has become the standard regimen for the neoadjuvant treatment of resectable NSCLC (55). This strategy works by enhancing tumor antigen release via chemotherapeutic-induced immunogenic cell death (ICD) and synergistically activating systemic antitumor immune responses with ICIs, thereby causing marked improvements in pathological remission rates and long-term survival.

CheckMate 816 trial. Global studies have demonstrated that the pCR rate of nivolumab in combined chemotherapy was 24%, markedly higher compared with the 2.2% reported for the chemotherapy control group and the MPR rate was 34%, also much higher compared with the MPR rate of 12% recorded for the chemotherapy control group. Of note, the pCR rate of Chinese patients was as high as 25% (13,56). Furthermore, in the LungMate 002 study (50), the pCR rate for the neoadjuvant toripalimab plus chemotherapy subgroup was reported to be as high as 27.8% and the MPR rate was as high as 55.6%. Patients with high baseline expression of chitinase 3-like protein 1 (CHI3L1) [according to the immunohistochemical (IHC) score] exhibited significantly improved pCR and survival outcomes (for OS, HR=0.17 and P=0.017), demonstrating that CHI3L1 can serve as an independent predictive marker. By contrast, the pCR rate for neoadjuvant immunotherapy alone was only 10-15%, whereas the pCR improvement following neoadjuvant immunotherapy combined with chemotherapy was notable (the combination therapy group achieved 27.8% pCR in LungMate 002, while the pCR rate in the combination

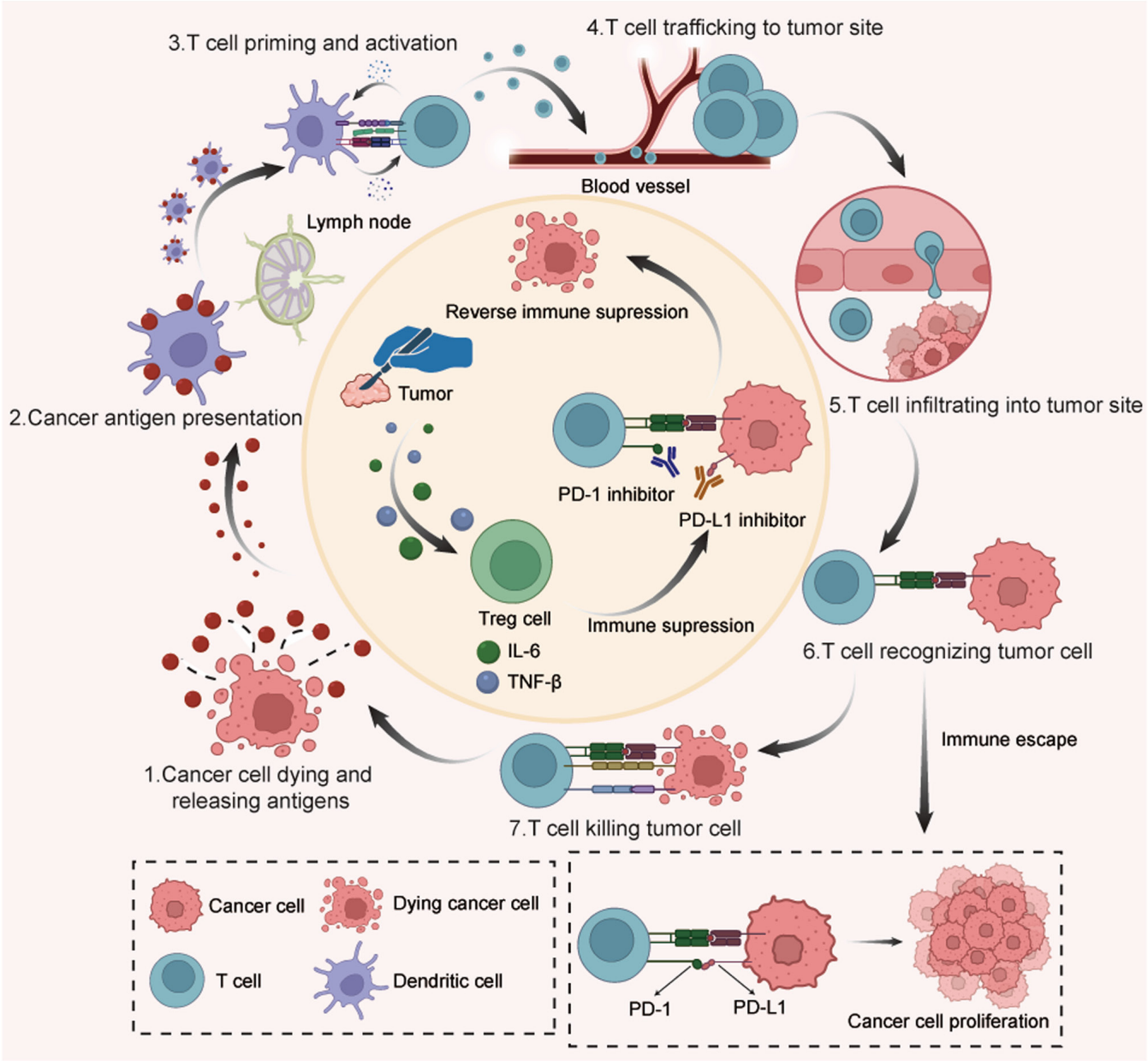

Figure 1. Mechanism of tumor immune cycle. 1) When tumor cells die, they release tumor antigens, which are then captured by DCs in the lymph nodes. 2) Antigen presentation, where dendritic cells process and present tumor antigens to naïve T cells. 3) Priming and activation of naïve T cells: The naïve T cells receive an antigenic signal (from dendritic cells) and a co-stimulatory signal (e.g., CD28/B7), subsequently differentiating into effector T cells. 4) After CD40L on the T-cell surface binds to CD40 on the DC surface, this 'reverse signaling' potently acts back upon the DC. This further upregulates the expression of co-stimulatory molecules such as B7 on the dendritic cell, thereby establishing a positive feedback loop for T cell activation. 5) Migration of activated T cells: Effector T cells exit the lymph node, enter the bloodstream and traffic towards the tumor site guided by chemokine signals. 6) Under the influence of chemokines, T cells first undergo firm adhesion to the vascular endothelium. They then deform and transmigrate through the junctions between endothelial cells to enter the tumor immune microenvironment. 7) Process of T-cell recognition of tumor cells, wherein effector T cells identify tumor-specific antigens presented on the major histocompatibility complex molecules of the tumor cells through their T cell receptors. 8) Cytotoxic killing of tumor cells by T cells. Effector T cells induce cancer cell apoptosis either by secreting cytotoxic mediators like perforin and granzymes, or by activating the death receptor pathway such as Fas/FasL. 9) Lysis of tumor cells that underwent apoptosis and the subsequent release of new tumor antigens, indicating the initiation of a renewed antitumor immunity cycle. 10) Surgery can lead to the formation of an immunosuppressive microenvironment. The physical tissue damage from surgical incision causes the release of Damage-Associated Molecular Patterns (DAMPs); these signals recruit Tregs to the surgical site and, in some cases, drive the conversion of naïve CD4+ T cells into newly induced Tregs. This process establishes a state of local immunosuppression that impedes the antitumor immunity cycle. 11) Mechanism by which immunotherapy reverses immune suppression. The co-inhibitory signaling pathway formed by PD-1 and its primary ligand PD-L1 (B7-H1) impairs the proliferation and cytokine production of effector T cells. PD-1 inhibitors (anti-PD-1 antibodies) bind with high affinity to the PD-1 receptor on T cells, whereas PD-L1 inhibitors (anti-PD-L1 antibodies) bind to the PD-L1 ligand on tumor cells. This intervention physically blocks the PD-1/PD-L1 interaction and subsequent downstream signaling activation. Consequently, the co-stimulatory signals received by T cells are fully transmitted and TCR signal transduction is restored to normal. 12) Immunotherapy, primarily utilizing PD-1/PD-L1 inhibitors, reverses the localized immunosuppression previously caused by surgery. This enables T cells to resume their cytotoxic function against tumor cells via the cancer-immunity cycle, underscoring the critical importance of perioperative immunotherapy in lung cancer. 13) Immune evasion by tumor cells, whereby they avoid immune attack through various immunosuppressive mechanisms (such as PD-L1 overexpression and infiltration of regulatory T cells) or via antigen loss. 14) Proliferative phase following tumor immune escape. Specifically, PD-L1 on tumor cells binds to PD-1 on T cells, delivering an inhibitory signal. This fosters an immunosuppressive micro-environment that microenvironment that allows tumor cells to evade T cell-mediated killing, leading to their uncontrolled expansion uncontrolled expansion. PD-1, programmed cell death protein-1; PD-L1, programmed death ligand 1; DC, dendritic cell; Treg, regulatory T cell.

Table I. Lung cancer-specific mechanism in the cancer-immunity cycle and perioperative immunotherapy measure.

Method	Lung cancer-specific mechanism	Perioperative immunotherapy measure	(Refs.)
Antigen release	In >30% of lung adenocarcinomas, NSCLC-derived TGF-β/IL-10 suppresses antigen release, restricting neoantigen availability	Neoadjuvant immunotherapy combined with chemotherapy forced the release of HMGB1/ ATP by chemically destroying the structure of tumor cells and inhibited the mitochondrial dysfunction caused by TGF-β signaling and compensatory STK11 mutation, thus breaking through the release barrier of lung cancer-specific antigens	(45,46)
Antigen presentation	Dendritic cell priming efficiency is reduced in >40% of NSCLC cases due to impaired antigen presentation caused by HLA class I downregulation	Neoadjuvant immunotherapy triggers immuno therapy triggers IFN-γ release from activated $CD8^+$ T cells. This cytokine then upregulates HLA-I expression on lung cancer cells via the JAK-STAT pathway, thereby reversing the antigen presentation defect	(45,47)
T-cell activation	Antitumor immunity is often compromised by elevated Tregs and MDSCs in the lung tumor microenvironment, particularly in EGFR-mutant lung cancer	During the perioperative period, the combination of PD-1 and CTLA-4 inhibitors promotes T-cell activation via two parallel actions: Blocking the CTLA-4/CD80 axis to reduce Treg-mediated suppression and reversing the impairment of dendritic cell cross-presentation commonly associated with EGFR mutations	(48,49)
T-cell transport	T-cell transport into lung tumors is hindered by VEGF-mediated dysfunctional vasculature and dysregulation of the CXCL12/CXCR4 axis in lung cancer	To restore efficient T-cell transport to tumors, perioperative immunotherapy combined with anti-VEGF therapy normalizes the aberrant lung cancer vasculature by inhibiting VEGF signaling and concurrently counteracts the dysregulated CXCL12/CXCR4 chemotaxis axis	(46,47)
T-cell infiltration	Lung cancer-associated fibroblasts synthesize and secrete large amounts of type III collagen, which encircles tumor cell clusters to form a dense, enveloping structure that acts as a physical barrier, thereby preventing $CD8^+$ T-cell infiltration	Perioperative immunotherapy or operative immunotherapy combined with a TGF-β inhibitor blocked the TGF-β/SMAD pathway, suppressing collagen synthesis and cross-linking in cancer-associated fibroblasts, weakening the physical barrier of the tumor and ultimately restoring $CD8^+$ T- cell infiltration	(48,49)
Tumor identification	Lung cancer cells activate the Wnt/β-catenin signaling pathway, whose activation inhibits the transcription factor NLRC5 (key for MHC-I), leading to the downregulation of specific antigen presentation on the cell surface	Perioperative immunotherapy or operative immunotherapy combined with a CTLA-4 inhibitor blocks the CTLA-4/B7 signaling pathway in lymph nodes. This action liberates naïve T cells from Treg-mediated suppression, enabling their activation and clonal expansion against diverse tumor antigens. Consequently, this broadens the TCR repertoire and enhances the immune system's capacity to recognize a broader spectrum of tumor antigens.	(45,49)

Table I. Continued.

Method	Lung cancer-specific mechanism	Perioperative immunotherapy measure	(Refs.)
Killing of lung cancer cells	The cytotoxic function of T cells against lung cancer is suppressed through Fas-L-mediated induction of T cell exhaustion and concomitant inhibition of granzyme B.	Perioperative immunotherapy combined with an IL-15 agonist enhances the tumor-killing efficacy of CD8+ T cells against lung cancer by activating the JAK3/STAT5 pathway. This activation rescues Fas-L-mediated T cell depletion and augments granzyme B expression.	(46,48,50)

NSCLC, non-small cell lung cancer; TGF-β, transforming growth factor-β; IL-10, interleukin-10; HMGB1, high-mobility group box 1; ATP, adenosine triphosphate; STK11, serine/threonine kinase 11; HLA-I, human leukocyte antigen class I; IFN-γ, interferon-γ; JAK-STAT, Janus kinase-signal transducer and activator of transcription; Tregs, Regulatory T cells; MDSCs, myeloid-derived suppressor cells; EGFR, epidermal growth factor receptor; PD-1, programmed cell death protein-1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cells; VEGF, vascular endothelial growth factor; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; PD-L1, programmed death-ligand 1; SMAD, SMAD family proteins; TCR, T cell receptor; Fas-L, Fas ligand; IL-15, interleukin-15; MHC-I, major histocompatibility complex-I.

therapy group was 24% in CheckMate 816), highlighting the enhanced efficacy of the combined regimen.

Regarding surgical feasibility, in the CheckMate 816 study, the surgery rate for the immunotherapy combined with chemotherapy group was reported to be 83.2% (compared with 75.4% for the chemotherapy alone group) and more minimally invasive surgeries were performed. Furthermore, in the LungMate 002 study, 65.8% of the 76% of the patients who were potentially resectable in the neoadjuvant immunotherapy combined with chemotherapy group were converted into operable patients, achieving a total R0 resection rate of 100% (where 'R0 resection' refers to a surgical outcome where all the cancerous tissue is removed). Additionally, the administration of neoadjuvant immunotherapy combined with chemotherapy achieved a lymph node downstaging rate of 63.9%, suggesting that this regimen led to a marked improvement in surgical feasibility via the reduction of tumor size and downstaging.

In terms of safety, the incidence of grade 3-4 TRAEs in the neoadjuvant immunotherapy combined with chemotherapy group in the CheckMate 816 study was reported to be 33.5%, a percentage that was similar to the reported percentage of 36.9% in the chemotherapy alone group, and neoadjuvant immunotherapy combined with chemotherapy did not lead to increases in the rates of surgical complications or delays. In the LungMate 002 study, the incidence of grade 3-4 TRAEs in neoadjuvant immunotherapy combined with chemotherapy was reported to be 34%. Overall, compared with monotherapy immunotherapy, the chemotoxicity of combined chemotherapy was reported to be slightly higher, although its safety may have been well controlled through standardized management and this toxicity did not markedly affect surgical safety. By contrast, monotherapy immunotherapy may lead to a higher risk of tumor progression due to insufficient efficacy. Subgroup analysis revealed that the pCR rate (partial response to curative therapy) for patients with PD-L1 levels ≥1% in the CheckMate 816 trial was 32.6%, markedly higher compared with the pCR rate of 16.7% observed in the subgroup with PD-L1 levels <1%. In summary, the administration of immunotherapy combined with chemotherapy causes the release of tumor antigens, thereby enhancing immune responses and compensating for the insufficient immune response rate in neoadjuvant monotherapy, which provides a focus in the field of neoadjuvant immunotherapy with more potential benefits than drawbacks (Table II) (11-13,34,57-63).

Synergistic effect of immunotherapy combined with radiotherapy (RT). The combined use of RT and ICIs is based on the principle that RT induces ICD in tumor cells, leading to the release of damage-associated molecular patterns, which, in turn, enhance the antigen-presenting ability of dendritic cells (DCs). ICIs subsequently further alleviate systemic immunosuppression, creating an '*in situ* vaccine' effect (64).

Key studies have validated the clinical potential of this strategy. In the SQUAT trial (65), the MPR rate of the neoadjuvant durvalumab combined with concurrent chemoradiotherapy (50 Gy) was reported to be 63%, which was notably higher compared with the MPR rate of 36.8% reported in the CheckMate 816 trial for neoadjuvant immunotherapy plus chemotherapy. Furthermore, the pCR rate in the SQUAT trial was 23%, similar to the 24% pCR rate noted in the CheckMate 816 trial, indicating that neoadjuvant immunotherapy combined with chemotherapy led to a notable enhancement in the extent of pathological remission (65). In terms of long-term survival, compared with traditional RT, the objective response rate (ORR) for the KEYNOTE-799 regimen with concurrent chemoradiation therapy (cCRT) plus pembrolizumab was 70.5-70.6%, whereas the ORR for the NICOLAS regimen with cCRT plus nivolumab was 73.4%. Both regimens were noted to have higher ORRs compared with the 35-55% range observed in traditional chemoradiotherapy (66,67).

In terms of safety, the SQUAT trial reported a 48% rate of grade 3-4 AEs (including only 1 case of fatality that was associated with the treatment), which was higher compared with that of chemotherapy alone or monotherapy immunotherapy. However, the toxicity profile was reported to be similar to that of historical Neoadjuvant Chemoradiotherapy data (68).

Table II. Clinical trials of neoadjuvant ICIs for lung cancer.

First author, year	Trial (NCT Identifier)	Phase	Stage	No. of patients	ICI	Primary endpoint	pCR rate, %	MPR rate, %	Survival outcomes	(Refs.)
Chaft *et al*, 2022	LCMC3 (NCT02927301)	II	IB-IIIB	181	Atezolizumab	MPR	6.80	20.40	DFS rate, 72%; OS rate, 82%	(11)
Forde *et al*, 2021	CheckMate 159 (NCT02259621)	II	I-IIIA	21	Nivolumab	Safety	10.00	45.00	RFS rate, 60%; OS rate, 80%	(12)
Forde *et al*, 2022	CheckMate-816 (NCT02998528)	III	IB-IIIA	358	Nivolumab	EFS, pCR	24.0 vs. 2.20	36.9 vs. 8.90	EFS rate, 57 vs. 43%; OS rate, 78 vs. 64%; mOS, NR vs.73.7month	(13)
Besse *et al*, 2020	PRINCEPS (NCT02994576)	II	IA-IIIA	30	Atezolizumab	The rate of patients without major toxicities or morbidities	0	14.00	NA	(34)
Zhu *et al*, 2022	LungMate 002 (unregistered)	II	II-III	50	Toripalimab	MPR	27.80	55.60	NA	(57)
Wislez *et al*, 2022	IONFSCO (NCT03030131)	II	IB-IIIA	46	Durvalumab	The complete surgical resection rate	7.00	19.00	DFS rate, 78.3%; OS rate, 89.1%	(58)
Lei *et al*, 2023	TD-FOREKNOW (NCT04338620)	II	IIIA or IIIB	88	Camrelizumab	pCR	32.60 vs. 8.90	65.10 vs. 15.60	EFS rate, 76.9 vs. 67.6%; DFS rate, 78.4 vs.71.7 %	(59)
Liu *et al*, 2023	CTONG 1804 (NCT04015778)	II	IIA or IIIB	48	Nivolumab	MPR	25	50	NA	(60)
Shao *et al*, 2023	neoSCORE (NCT04459611)	II	IB-IIIA	60	Sintilimab	MPR	19.2 vs. 24.1	26.90 vs. 41.40	NR	(61)
Zhang *et al*, 2024	neoSCORE II (NCT05429463)	III	IIA-IIIB	250	Sintilimab	MPR	Ongoing	Ongoing	Ongoing	(62)
NA	LungMate-009 (NCT04728724)	II	III	100	Sintilimab	MPR	Ongoing	Ongoing	Ongoing	(63)

NCT, National Clinical Trial; ICI, immune checkpoint inhibitor; MPR, major pathological response; pCR, pathological complete response; DFS, disease-free survival; mDFS, median disease-free survival; EFS, event-free survival; RFS, recurrence-free survival; OS, overall survival; mOS, median overall survival; NA, not available; NR, not reached.

Furthermore, the most notable AE arising from neoadjuvant immunotherapy combined with RT was shown to be radiation pneumonitis. The incidence of grade 3 or higher pneumonia in the KEYNOTE-799 and NICOLAS combination regimens was 6.9% and up to 10%, respectively. By contrast, the incidence of grade 3 or higher radiation pneumonitis in traditional chemoradiotherapy is typically reported to be between 7 and 20% (69). This suggests that the addition of RT did not exceed the safety threshold. In terms of surgical feasibility, all patients in the SQUAT trial completed their surgeries on schedule, with no reports of surgery delays due to RT.

Regarding the expression of PD-L1, in the KEYNOTE-799 study, the ORR for patients with PD-L1 TPS <1% in cohorts A and B was reported to be 66.7 and 71.4%, respectively, whereas for those patients with PD-L1 ≥1% in cohorts A and B, the ORR was 75.8 and 72.5%, respectively. This demonstrates that there is minimal difference in efficacy among patients with different expression levels of PD-L1. Although the SQUAT trial did not subdivide the PD-L1 groups, the overall MPR rate was still as high as 63%, indicating its broad-spectrum efficacy. However, although the SQUAT trial demonstrated a high MPR rate of 63% for neoadjuvant chemoradiotherapy combined with immunotherapy, the 2-year PFS rate was only 43% and no notable improvements were observed in terms of patient survival. This may suggest that, although RT enhances local immune activation, it may not effectively eliminate MRD. Additionally, the SQUAT trial did not report distant recurrence rates, suggesting that RT might either induce T-cell exhaustion or upregulate PD-L1, thereby weakening the systemic effects of durvalumab and potentially affecting the long-term prognosis of patients.

Postoperative adjuvant immunotherapy. The results from IMpower010 (16), a randomized, multicenter, open-label phase 3 trial, demonstrated that postoperative adjuvant chemotherapy followed by sequential atezolizumab treatment led to a notable reduction in the recurrence risk in the PD-L1 ≥50% subgroup (DFS, HR=0.48; OS, HR=0.47). Compared with the Best Supportive Care (BSC) group, which was reported to have a 5-year DFS rate of only 67.5%, the 5-year DFS rate for the adjuvant atezolizumab treatment group increased to 84.8% and distant metastasis was well controlled. The distant metastasis recurrence rate in the adjuvant atezolizumab treatment group was reported to be 6.8% compared with 12.5% in the BSC group, with particularly good control exerted over brain metastasis recurrence. Furthermore, in another study, KEYNOTE-091 (17), treatment postoperatively with the adjuvant pembrolizumab demonstrated DFS benefits in the overall population (HR=0.76), although this did not reach significance in the PD-L1 ≥50% subgroup (HR=0.82).

In terms of safety, the incidence of grade 3-4 irAEs in the IMpower010 study was only 11%, compared with an incidence of 25% for cisplatin-associated grade 3-4 nausea/vomiting when traditional adjuvant therapy was administered. This suggests that adjuvant immunotherapy is both safer and more tolerable compared with traditional adjuvant chemotherapy. In the KEYNOTE-091 trial, although the incidence of grade 3-4 irAEs was higher (at 34%) among patients receiving postoperative adjuvant immunotherapy, only 4 cases were reported to be associated with myocarditis or pneumonia. This indicated that fatal irAEs are rare and that the majority of irAEs are manageable, rendering them easier to manage compared with the long-term toxicities associated with chemotherapy, such as kidney damage (70) and hearing loss (71). Notably, in both the IMpower010 and the KEYNOTE-091 trials, administering sequential immunotherapy following chemotherapy did not lead to any notable increase in cumulative toxicity, supporting the synergistic model of chemotherapy clearing the immunosuppressive microenvironment combined with immunomodulation (16,17). In addition to the aforementioned postoperative adjuvant immunotherapy, clinical trials of postoperative adjuvant immunotherapy in combination with other regimens, such as INTerpath-002 and SKYSCRAPER-15, have gradually revealed their application prospects (Table III) (16,17,31,32,35-37,72-75).

Adjuvant immunotherapy during the perioperative period. The 'sandwich model' of perioperative immunotherapy for lung cancer comprises a comprehensive strategy that includes preoperative neoadjuvant immunotherapy combined with chemotherapy, surgical resection and postoperative adjuvant immunotherapy to consolidate treatment. This approach aims to activate the immune system preoperatively to shrink tumors and to reduce the stage of cancer, to achieve radical resection during surgery and to continuously eliminate MRD postoperatively.

In the NEOTORCH trial (a randomized, double-blind, placebo-controlled phase 3 trial), the triple therapy group achieved a pCR rate of 24.8%, whereas in the RATIONALE-315 trial (another randomized, double-blind, placebo-controlled phase 3 trial), this rate increased to 56% (76,77). By contrast, in the LCMC3 study, the pCR rate for patients receiving only immunotherapy as neoadjuvant treatment was only 6% (11), and in the CheckMate 816 trial (13), the pCR rate for patients receiving combined immunotherapy and chemotherapy as neoadjuvant treatment was only 24%. Furthermore, in the KEYNOTE-671 study (14), the MPR rate for patients treated with the triple therapy model reached 63.8%, in the RATIONALE-315 trial it was 56% and in the NEOTORCH trial it was 48.5%; by contrast, in the CheckMate 816 study, the MPR rate for patients receiving combined immunotherapy and chemotherapy as neoadjuvant treatment was only 24%, and in the NEOSTAR study, the MPR rate for the single-agent neoadjuvant immunotherapy group was only 22%. This clearly demonstrates that, in terms of pathological remission, the triple therapy model is markedly more effective compared with monotherapy neoadjuvant treatment (13,52,76,77).

Additionally, from the perspective of surgical feasibility, the surgical resection rate for patients treated with the triple therapy model in the KEYNOTE-671 trial was as high as 93%; in the CheckMate 77T study, it was 89%; in the RATIONALE-315 study, it was 91%; whereas in the CheckMate 816 trial, the surgical resection rate for patients receiving combined immunotherapy and chemotherapy as neoadjuvant treatment was only 83.2%. According to the subgroup analysis of CheckMate 816 trial, similarly to the results in the single neoadjuvant setting, the sandwich model also demonstrated a more notable benefit for patients with PD-L1 levels of ≥1%. The EFS HRs were determined to be 0.52 and 0.58 in the CheckMate 77T and KEYNOTE-671 trials, respectively. However, in the subgroup with PD-L1 levels <1%, the HRs increased to 0.73 and 0.65,

Table III. Clinical trials of adjuvant ICIs for lung cancer.

First author, year	Trial (NCT identifier)	Phase	Stage	No. of patients	ICI	Primary endpoint	Survival outcomes	(Refs.)
Felip *et al*, 2021	IMpower010 (NCT02486718)	III	IB-IIIA	1,005	Atezolizumab	DFS	Stage II-IIIA (PD-L1 ≥1%) mDFS, NE vs. 35.3 months; Stage II-IIIA (all) mDFS, 42.3 vs. 35.3 months; Stage IB-IIIA (all) mDFS, NE vs. 37.2 months	(16)
O'Brien *et al*, 2022	KEYNOTE-091 (NCT02504372)	III	IB-IIIA	1,177	Pembrolizumab	DFS	Stage IB-IIIA (PD-L1 ≥50%) mDFS, 67.0 vs. 47.6 months; Stage IB-IIIA (all) mDFS, 53.8 vs. 43.0 months	(17)
Spicer *et al*, 2024	INTerpath-002 (NCT06077760)	III	II, IIIA and IIIB	868	V940 + pembrolizumab	DFS	Ongoing	(72)
Garon *et al*, 2024	CANOPY-A (NCT03447769)	III	II-IIIB	1,382	Canakinumab	DFS	mDFS, 35.0 vs. 29.7months	(73)
Goss *et al*, 2024	ADJUVANT BR.31 (NCT02273375)	III	IB-IIIA	1,415	Durvalumab	DFS	NA	(37)
Zhu *et al*, 2023	DUBHE-L-304 (NCT05487391)	III	II-IIIB	632	QL1706	DFS	Ongoing	(31)
Chaft *et al*, 2017	ANVIL (NCT02595944)	III	IBf-IIIA	903	Nivolumab	DFS and OS	Ongoing	(74)
Calvo *et al*, 2021	NADIM-ADJUVANT (NCT04564157)	III	IB-IIIA	210	Nivolumab	DFS	Ongoing	(32)
NA	SKYSCRAPER-15 (NCT06267001)	III	IIB-IIIB	1,150	Tiragolumab + Atezolizumab	DFS	Ongoing	(75)
Peters *et al*, 2021	MERMAID-1 (NCT04385368)	III	II-III	89	Durvalumab	DFS	Ongoing	(35)
Spigel *et al*, 2021	MERMAID-2 (NCT04642469)	III	II-III	30	Durvalumab	DFS	Ongoing	(36)

NCT, National Clinical Trial; ICI, immune checkpoint inhibitor; MPR, major pathological response; pCR, pathological complete response; DFS, disease-free survival; mDFS, median disease-free survival; EFS, event-free survival; PD-L1, programmed death-ligand 1; NA, not available; NE, not evaluated.

suggesting limited benefits for patients with PD-L1 levels <1%. Nevertheless, the RATIONALE-315 study demonstrated that patients with PD-L1 levels <1% still obtained certain benefit (EFS, HR=0.57). This benefit was primarily due to the unique mechanism of action of tislelizumab, whereby antibody-dependent cell-mediated phagocytosis is reduced, thereby overcoming the limitations of low PD-L1 expression and providing treatment opportunities for these patients.

Notably, tislelizumab has been underutilized in perioperative immunotherapy studies for lung cancer, with potential for enhanced research on this ICI in later stages. Furthermore, compared with the IMpower010 study, in which a simple adjuvant therapy was administered, the survival benefits of the sandwich model were more pronounced. In the NEOTORCH study, the EFS HR for patients treated with the sandwich model was 0.40; in the KEYNOTE-671 study, it was 0.59; and in the RATIONALE-315 study, it was 0.56. By contrast, in studies of adjuvant immunotherapy alone, the DFS HR for all patients receiving postoperative adjuvant immunotherapy in the IMpower010 study was 0.79 and in the KEYNOTE-091 study, the overall DFS HR was 0.76. Although the primary endpoints of the sandwich model study and the adjuvant postoperative

treatment study differed, the EFS parameter includes a broader range of events, such as local recurrence, distant metastasis, second primary cancer and treatment-associated mortality, rendering it more stringent compared with DFS, which only includes recurrence/mortality. However, the sandwich model was still reported to have an improved HR, demonstrating its ability to comprehensively control tumor progression.

It should be noted that, although the sandwich model exhibited a notably increased efficacy compared with simple adjuvant and neoadjuvant immunotherapy, it may face greater challenges in terms of safety management. In the tislelizumab group of the RATIONALE-315 trial, the incidence of irAEs was reported to be 40%, a percentage that was markedly higher than the incidence rate of 18% for irAEs in the chemotherapy group. Furthermore, the incidence of grade 3 or higher neutropenia in the tislelizumab group was as high as 61% and these patients required close monitoring and management. Additionally, administering long-term adjuvant immunotherapy may increase the burden on patients. For example, in the NEOTORCH study, the sandwich model treatment regimen included treatment with 13 cycles of toripalimab. By contrast, the treatment may be prematurely discontinued for certain patients due to toxicity. For example, in the CheckMate 77T study, 35% of the patients did not complete the course of postoperative adjuvant therapy due to intolerance to treatment-associated toxicity (14,20,76,77).

In conclusion, perioperative immunotherapy, which involves tumor shrinkage prior to surgery and continuous immunosuppression following surgery, markedly outperforms preoperative or postoperative adjuvant therapy in terms of pathological remission and survival benefits. It is suitable for most high-risk patients who are able to tolerate toxicity, particularly in the cases of borderline resectable patients, to improve surgical outcomes. For patients with PD-L1 levels ≥1%, it is recommended to prioritize dual immunotherapy or combination chemotherapy. These two treatment regimens were reported to achieve marked pathological remission in the NEOSTAR and RATIONALE-315 studies. Even for the PD-L1$^-$ patients, the sandwich model maintained its superiority compared with postoperative adjuvant therapy; for example, in the CheckMate 77T trial, the EFS HR for patients in the PD-L1 <1 group was only 0.65 (Table IV) (12,15,20,33,76-83).

As discussed previously, employing the sandwich therapy regimen leads to a notable improvement in pathological response rates and survival outcomes, although it also presents greater safety challenges compared with administering monotherapy with neoadjuvant immunotherapy. First, the sandwich therapy regimen is associated with markedly higher rates of TRAEs, particularly irAEs, compared with monotherapy. Furthermore, its extended treatment duration markedly increases the risks of cumulative toxicity, leading to its discontinuation during the adjuvant immunotherapy phase, thereby imposing heavier financial burdens on patients. The current consensus recommends neoadjuvant immunotherapy combined with chemotherapy for all patients with operable stage II-III lung cancer. However, whether postoperative immunotherapy should be upgraded to sandwich therapy remains a subject of ongoing debate (19,55,84). Therefore, the findings of recent studies on perioperative immunotherapy for lung cancer have led to the development of the clinical decision pathway for omission of adjuvant immunotherapy in NSCLC (Fig. 2). The core criteria for pathogenesis-guided adjuvant immunotherapy are pCR with postoperative sustained ctDNA negativity or switching to targeted therapy in driver gene-cases. High-risk patients (namely, those with stage III lung cancer, non-pCR patients and those with high expression of PD-L1) should still complete standardized 1-year adjuvant therapy; however, it must be emphasized that, even in terms of the pCR, patients with squamous cell carcinoma still face a 5-year recurrence risk >30%. Therefore, maintaining full adjuvant therapy is recommended. The current strategy faces challenges due to limitations in pCR assessment (at present, ~8% of micro-metastases are missed) and variations in ctDNA detection sensitivity (currently, the false negative rate is in the range 5-10%). Thus, decision-making regarding exemption requires multidisciplinary team consultation (84-88).

5. Biomarkers

Biological markers perform a key role in perioperative immunotherapy, which is aimed at identifying potential beneficiaries, optimizing treatment decisions and predicting the risk of drug resistance. Currently, the most extensively studied markers are PD-L1 expression, TMB and dynamic monitoring of ctDNAs. However, their clinical application faces numerous challenges. Emerging biomarkers, such as Gene Expression Omnibus (GEO) profiles and tumor-infiltrating lymphocytes (TILs), are beginning to gain prominence.

Traditional biomarkers. In perioperative immunotherapy for lung cancer, PD-L1, ctDNAs and TMB each have unique value as biomarkers, although each of them has its limitations. PD-L1 expression is the most widely used biomarker. The CheckMate 816 study demonstrated that patients with PD-L1 levels of ≥1% had a pCR rate of 32.6%. The KEYNOTE-671 study further confirmed that patients with high PD-L1 expression (TPS ≥50%) received more notable survival benefits. Specifically, in patients treated with the sandwich model, those with low PD-L1 expression (TPS <50%) had an EFS HR of 0.61, whereas those with high PD-L1 expression had an EFS HR of only 0.41 (13,14). However, in the NEOTORCH study, no clear association was identified between EFS benefit and PD-L1 expression. Although the EFS HR values for the subgroup with PD-L1 levels ≥50% and the sandwich model treatment subgroup with a PD-L1 level <50% were 0.31 and 0.35 respectively, neither of these subgroups reached the level of statistical significance, suggesting that PD-L1 expression levels may not serve as an independent predictor of efficacy (77). Furthermore, the spatiotemporal heterogeneity of PD-L1 limits its predictive power, with temporal heterogeneity indicating that PD-L1 expression may vary dynamically with treatment. For example, preoperative neoadjuvant therapy may alter the TME, leading to changes such as TILs and the release of inflammatory factors. This can result in the measured postoperative PD-L1 expression levels in specimens being inconsistent with the baseline levels of patients, thereby reducing the predictive value of PD-L1. The spatial heterogeneity is evident in notable differences in PD-L1 expression being reported among different regions within the same tumor or between the primary lesion and metastatic sites. Therefore,

Table IV. Clinical trials of 'sandwich' combination regimens for lung cancer.

First author, year	Trial (NCT identifier)	Phase	Stage	No. of patients	ICI	Primary endpoint	pCR rate, %		MPR rate, %		Survival outcomes	(Refs.)
							EG	CG	EG	CG		
Spicer *et al*, 2024	KEYNOTE-671 (NCT03425643)	III	II-IIIB	797	Pembrolizumab	EFS, OS	18.1	4.0	30.2	11.0	mEFS, 47.2 vs. 18.3 months; OS rate, 71.3 vs. 64.0%	(14)
Sorscher *et al*, 2024	CheckMate-77 T (NCT04025879)	III	IIA-IIIB	461	Nivolumab	EFS	25.3	4.7	35.4	12.1	mEFS, NR vs. 18.4 months	(20)
Yue *et al*, 2025	RATIONALE-315 (NCT04379635)	III	II-IIIA	453	Tislelizumab	MPR, EFS	40.7	5.7	56.2	15.0	mEFS, NE vs. NE	(76)
Lu *et al*, 2024	Neotorch (NCT04158440)	III	II-III	501	Toripalimab	MPR, EFS	24.8	1.0	48.5	8.4	mEFS, NE vs. 15.1 months; OS rate, 81.2 vs. 74.3%	(77)
Provencio *et al*, 2022	NADIM (NCT03081689)	II	IIIA	46	Nivolumab	PFS	63.0	-	83.0	-	PFS rate, 77.1 %; OS rate, 81.9 %	(78)
Provencio *et al*, 2023	NADIMII (NCT03838159)	II	IIIA-IIIB	86	Nivolumab	pCR	36.8	6.9	52.6	13.8	PFS rate, 67.2 vs. 40.9%; OS rate, 85.0 vs. 63.6%	(79)
Heymach *et al*, 2023	AEGEAN (NCT03800134)	III	IIA-IIIB	802	Durvalumab	pCR, EFS	17.2	4.3	33.3	12.3	mEFS, NR vs. 25.9 months	(15)
Yue *et al*, 2025	RATIONALE-315 (NCT04379635)	III	II-IIIA	453	Tislelizumab	MPR, EFS	40.7	5.7	56.2	15.0	mEFS, NE vs. NE	(76)
NA	ORIENT-99 (NCT05116462)	III	IIB-IIIB	800	Sindilizumab	pCR, EFS	Ongoing		Ongoing		Ongoing	(80)
NA	KN035-CN-017 (NCT06123754)	III	IIIA-IIIB (N2)	390	Envafolimab	MPR, EFS	Ongoing		Ongoing		Ongoing	(81)
Romero Román *et al*, 2021	IMpower-030 (NCT03456063)	III	II-IIIB	451	Atezolizumab	EFS	Ongoing		Ongoing		Ongoing	(82)
Cascone *et al*, 2022	NeoCOAST-2 (NCT05061550)	II	II-IIIB	490	Arm 1, oleclumab + Durvalumab; Arm 2, monalizumab + durvalumab; Arm 3,	pCR, AEs, SAEs	Ongoing		Ongoing		Ongoing	(33)

Table IV. Continued.

First author, year	Trial (NCT identifier)	Phase	Stage	No. of patients	ICI	Primary endpoint	pCR rate, %		MPR rate, %		Survival outcomes	(Refs.)
							EG	CG	EG	CG		
					Volrustomig; Arm 4, Dato-DXd + durvalumab; Arm 5, AZD0171 + durvalumab							
Yan *et al*, 2023	SHR-1316-111-303 (NCT04316364)	III	II-IIIB	537	SHR-1316	MPR, EFS	Ongoing		Ongoing		Ongoing	(83)

NCT, National Clinical Trial; ICI, immune checkpoint inhibitor; MPR, major pathological response; pCR, pathological complete response; DFS, disease-free survival; EFS, event-free survival; PFS, progression-free survival; RFS, recurrence-free survival; OS, overall survival; NA, not available; NR, not reached; EG, experiment group; CG, control group; SAEs, serious adverse events; AEs, adverse events.

biopsy specimens may only reflect local expression status, rather than the overall tumor characteristics (89).

As biomarkers, ctDNAs have performed particularly well with respect to MRD monitoring. The CheckMate 816 subgroup analysis revealed that patients who tested positive for ctDNA post-surgery had an EFS event rate of 72.1% within 12 months, compared with an EFS event rate of only 14.3% for those who tested negative. Furthermore, the exploratory analysis of the KEYNOTE-671 study indicated a positive association between ctDNA clearance and the pCR rate following neoadjuvant immunotherapy. In the ctDNA clearance group where ctDNA was undetectable post-treatment, the pCR rate reached 46.8%, whereas in the non-clearance group, where ctDNA remained detectable post-treatment, the pCR rate was reported to be only 7.7% (11,12). Therefore, the 'TNMB staging' model, combining ctDNA and TNM staging, was proposed in the MEDAL study, in which the results reported that the model was capable of improving the accuracy of recurrence prediction by 28% (90).

TMB is a surrogate indicator of tumor neoantigen load. The CheckMate 227 study demonstrated that, among patients with high TMB (≥10 mut/Mb), those treated with nivolumab plus ipilimumab achieved a median PFS of 7.2 months, whereas it was only 5.5 months in those with low TMB (<10 mut/Mb; HR=0.58). This finding suggests that TMB may serve as a potential predictor of short-term efficacy for immune-combination therapy (10). However, several perioperative studies lack a standardized TMB testing standard (10,11). Whole exome sequencing, which covers ~30,000 genes, does provide a high-precision assessment of TMB, although it is costly and complex, making it difficult to implement the method widely. By contrast, TMB may be inferred from lower-cost targeted panel sequencing, which covers limited genomic regions (typically 1-2 Mb), using the application of fitting algorithms. However, different panel designs can lead to biased results; for example, panels with smaller coverage areas may underestimate TMB values. Furthermore, the TMB thresholds have been reported to vary across different detection platforms; for example, the FoundationOne®CDx platform (Foundation Medicine) detects tissue TMB (tTMB) with a preset threshold of 10, 13 or 16 mut/Mb for tTMB, whereas a preset threshold of 20 mut/Mb is used for blood TMB (bTMB). Although all methods are able to distinguish between high and low TMB levels, inconsistent thresholds have been reported to result in varying clinical benefits. Currently, whole-exome sequencing (WES) and large-panel sequencing are the most commonly used methods for measuring TMB. However, a bridging study involving patients with NSCLC found that 199 missense mutations detected by WES corresponded to a TMB of 10 mut/Mb measured using the FoundationOne CDx (F1 CDx) panel. Although the overall consistency between the two methods reached 84, ~16% of patients may still be misclassified as having low or high TMB due to platform differences. Furthermore, in Cohort C of the BFAST trial, atezolizumab was compared with chemotherapy as first-line therapy for patients with unresectable, advanced-stage NSCLC characterized NSCLC characterized by a bTMB cutoff of ≥10 mut/Mb. Interestingly, in an exploratory analysis where bTMB was evaluated using the F1L CDx assay with an equivalent cutoff of bTMB ≥13.60 mut/Mb, atezolizumab significantly improved

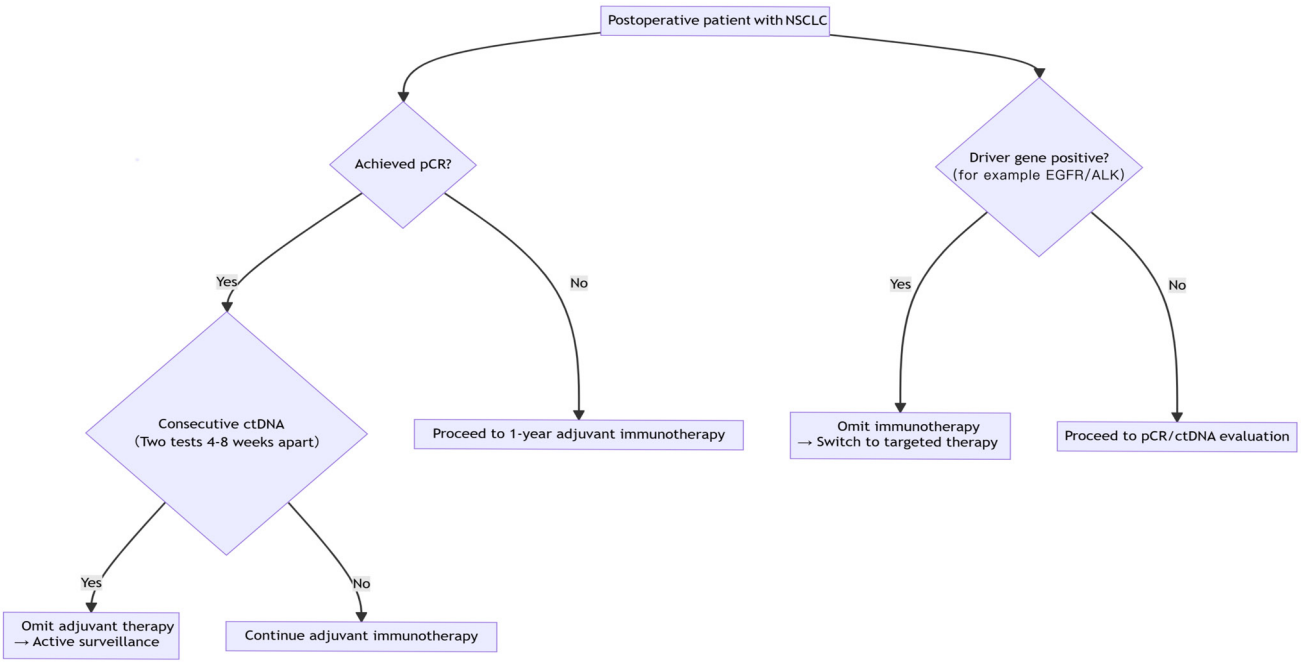

Figure 2. Clinical decision pathway for omission of adjuvant immunotherapy in NSCLC. NSCLC, non-small cell lung cancer; pCR, Pathological complete response; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

PFS compared with chemotherapy. These examples indicate that even within the same population, differences in threshold settings across platforms may result in some patients being unable to be accurately matched with the most suitable treatment regimen (91,92).

Other emerging markers. Gene expression profiling (GEP) analysis comprises an exploration of immune-associated gene expression patterns in the TME using high-throughput sequencing technology, including the analysis of biological markers such as the interferon-γ (IFN-γ) signaling pathway, T cell activation-associated genes [including CD8A and granzyme B (GZMB)] and immunosuppressive molecules [such as TGF-β and indoleamine 2,3-dioxygenase 1 (IDO1)] (93). In the LungMate 002 study, a receiver operating characteristic curve was constructed by comparing the IHC scores of baseline CHI3L1 with the post-treatment pathological remission status. The area under the curve was calculated to be 0.732, indicating that the IHC score of CHI3L1 in baseline tumor samples can predict the treatment response. Patients with high CHI3L1 expression were reported to have an OS HR of 0.17 and a PFS HR of 0.29, suggesting that patients with high CHI3L1 expression had improved survival outcomes. Even in patients with PD-L1^{-} expression, those with high CHI3L1 expression still derived a notable benefit from perioperative immunotherapy, suggesting that CHI3L1 was able to effectively address the prediction 'blind spot' of PD-L1. This is partly because CHI3L1 may influence matrix remodeling by regulating immune-suppressive cells in the TME, thereby enhancing the synergistic effect of chemotherapy combined with immunotherapy.

Furthermore, PD-L1 only reflects the expression of immune checkpoints on the surface of tumor cells and does not fully capture the overall immune activity in the TME. Additionally, in the LungMate 002 study, a high expression of human leukocyte antigen (HLA)-DR was observed in the response group. HLA-DR, a class II major histocompatibility complex (MHC) class II cell surface receptor, performs a key role in antigen presentation and in the activation of CD4^{+} T cells. In this study, a regimen of toripalimab combined with chemotherapy caused the release of tumor antigens by administering chemotherapy, which, when combined with PD-1 inhibitors to block immune checkpoints, led to a synergistic enhancement of HLA-DR-mediated antigen presentation, forming an immune positive feedback loop. Furthermore, it was reported that CHI3L1 is positively associated with HLA-DR expression, suggesting that CHI3L1 may indirectly promote HLA-DR-mediated antigen presentation by regulating tumor matrix remodeling (57). In addition, in the NEOSTAR dual immunotherapy group, a notable increase in GZMB upregulation was observed. This upregulation of GZMB was reported to be associated with the expansion of effector memory T cells (TEM) and tissue-resident memory T cells (TRM) within tumors, suggesting that the upregulation of GZMB may enhance T-cell function. Furthermore, patients with high GZMB expression had a median viable tumor percentage of only ~9% compared with the percentage of 50% observed in the single-agent immunotherapy group. This suggested that GZMB-mediated T-cell toxicity is a key driver of pathological remission. Additionally, in the dual immunotherapy group, the mRNA levels of C-X-C motif chemokine ligand (CXCL) 9 and CXCL10 were markedly elevated. In this study, IHC analysis was also performed, which confirmed that the protein expression levels of CXCL9 and CXCL10 in the tumor tissues were higher compared with those of the dual immunotherapy group, particularly in patients with pathological remission. This may have been due to ipilimumab blocking the inhibitory signals of regulatory T cells (Tregs), thereby enhancing the antigen-presenting capability of the DCs and promoting the secretion of CXCL9/10 (67).

TILs are lymphocytes that migrate from the blood into tumor tissues, where they serve as a key component of the TME. These cells have a dual regulatory role in immune response through their recognition of tumor antigens, which is key to the development, progression and treatment of tumors. TILs primarily include $CD8^+$ T cells, $CD4^+$ T cells, Tregs and natural killer (NK) cells. In the CheckMate 159 study, it was observed that, following immunotherapy, the number of neoantigen-specific T cells in both tumor tissues and peripheral blood were markedly increased. These increases were particularly pronounced in patients who had achieved pCR, suggesting that neoantigen-specific T cells may directly contribute to tumor clearance. Additionally, in the NEOSTAR study, the combined immunotherapy group exhibited a marked increase in the density of $CD8^+$ T cells infiltrating the tumor compared with the monotherapy immunotherapy group. The proportions of TRM and TEM were also increased, whereas the levels of Tregs and myeloid-derived suppressor cells (MDSCs), which are immunosuppressive cells, were decreased. Furthermore, in the LCMC3 study, it was reported that the density of Tregs and MDSCs in the TME was negatively associated with the pathological response; specifically, the enrichment of MDSCs was reported to be notably associated with a low MPR rate for atezolizumab. In addition, it was reported that immunoglobulin-like transcript 2 T cells were also negatively associated with the MPR. The LCMC3 study also demonstrated that the proportions of NK group 2 member D and non-T/NK cells, including γδ T cells or congenital lymphocytes, in baseline peripheral blood were positively associated with the MPR (11,12) (Table V) (32,36,75,79).

In addition to the aforementioned GEP analyses and TILs, the NEOSTAR study also demonstrated that the abundance of *Ruminococcus* and *Akkermansia* in the gut microbiota is notably associated with the MPR of dual immunotherapy. This finding suggests that specific bacterial populations may enhance antitumor effects by modulating systemic immune responses (45), indicating that these specific bacterial populations may have notable potential as biomarkers for perioperative immunotherapy.

Application model of biomarkers in perioperative immunotherapy for lung cancer. Current evidence suggests that integrated biomarker models are able to enhance prediction accuracy (94). Therefore, our research group developed a dynamic monitoring model for perioperative immunotherapy in lung cancer that works through integrating mainstream non-treatment biomarkers.

Neoadjuvant. First, ctDNA clearance rates were assessed in patients with advanced unresectable lung cancer after one cycle of neoadjuvant immunotherapy. Those achieving clearance continued with the original treatment regimen, whereas those without clearance either received an additional cycle of neoadjuvant immunotherapy or switched to immunotherapy combined with chemotherapy (95).

Surgery. During the 4 weeks preceding surgery, changes in the density of the TILs were continuously monitored. Patients with increases in the number of $CD8^+$ TILs of ≥30% were scheduled for surgery as planned, whereas those with less marked increases received either adjuvant RT or targeted therapy. Due to the spatial heterogeneity in tumor biomarker expression (Table VI), intraoperative multi-region sampling (core tumor area and peripheral zone) combined with frozen-section pathology and IHC analysis was performed to stratify patients for risk assessment and guide adjuvant therapy decisions. High-risk patients (who were core MRD^+ with peripheral zone immunosuppression) were recommended adjuvant immunotherapy combined with chemotherapy to enhance the clearance of residual lesions in the core area. By contrast, low-risk patients (who were core MRD^- with peripheral zone immune activation) were advised to receive adjuvant immunotherapy alone in order to reduce chemotherapy toxicity (96).

Adjuvant. Thoracic drainage fluid ctDNA testing was performed within 24 h postoperatively. If patients were reported to be positive (tumor fraction ≥0.01%), early adjuvant therapy was initiated within 72 h. Additionally, TME spatial mapping was used to evaluate postoperative margins. If the number of $CD8^+$ TILs were <100 cells/high-power field at the invasive margins, high-risk areas were marked to guide postoperative RT target design. At 4 weeks post-surgery, plasma ctDNA levels could be used to assess the MRD status. If two consecutive tests exhibit negative results, the adjuvant immunotherapy cycle may be shortened from the standard 16 cycles to 8 cycles. Lastly, patients should undergo regular soluble PD-L1 (sPD-L1) level testing every 3 months. If the sPD-L1 level should increase by 2 times or more compared with baseline values, the adjuvant therapy should be switched to a combination of immunotherapy and anti-angiogenesis treatment [since the increase in the sPD-L1 level is notably associated with increased levels of VEGF in the TME (97)].

6. Progress in immunotherapy combined with other treatments

The combined strategy of perioperative immunotherapy should balance efficacy and safety, particularly considering the impact of treatment on surgical feasibility, postoperative recovery and long-term survival. The following section combines the latest clinical studies to explore the potential and challenges of different combined modes in perioperative therapy. Immunotherapy with dual checkpoint inhibitors, via simultaneously blocking multiple immune suppression pathways, including the PD-1/PD-L1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) pathways, enhances the antitumor immune response, thereby helping to overcome drug resistance to a certain extent. This strategy has been validated in each of the Checkmate 227, Checkmate 568 and Checkmate 817 trials for its efficacy and safety in advanced NSCLC (10,98-100) and its application in perioperative care is currently being actively explored.

In the NEOpredict-Lung study (101), patients who received nivolumab plus relatlimab as neoadjuvant therapy had an MPR rate of 30% and a pCR rate of 17%. Patients in the PD-L1 ≥50% subgroup demonstrated both a further pathological remission and a lower proportion of residual tumor cells. By contrast, in the CheckMate 816 study, the MPR rate for patients receiving neoadjuvant nivolumab plus chemotherapy was only 35.4% and the pCR rate was 25.3% (13), demonstrating that the dual immunotherapy regimen was able to achieve similar pathological remission levels without chemotherapy. In the EAST ENERGY trial (89), the dual immunotherapy regimen

Table V. Predictive and prognostic biomarkers in perioperative immunotherapy for NSCLC.

Biomarker	Detection method positive criteria	pCR/MPR prediction	Survival association	Clinical utility	Limitations	(Refs.)
Inflammatory gene signature	RNA-seq	pCR AUC=0.72	OS HR=0.39	1. It fills the prediction gap for patients with PD-L1 TPS <1% 2. Patients with low expression of the inflammatory gene signature. Response may require combination immunomodulators to enhance the inflammatory	1. It requires bioinformatics analysis and is difficult for clinical laboratories to carry out 2. There are no large trials to confirm the clinical value of inflammatory gene signatures	(32)
ctDNA clearance	Tumor-informed ctDNA clearance rate NGS ≥90%	pCR PPV= 92%	OS HR=0.33	1. It is emerging MRD monitoring standards 2. It is an early predictor of the efficacy of perioperative immunotherapy 2. High detection costs 3. Patients with undetected ctDNA may require enhanced adjuvant therapy	1. Preoperative/postoperative paired testing is required to increase the burden on patients	(36,75)
TILs density ($CD8^+$)	Multiplex IHC TILs ≥50 per HPF	MPR OR=4.2	EFS HR=0.44	1. Patients with high TILs density had an improved response to immunotherapy among different pathologists 2. Patients with low TILs density may require combination of Immunotherapy and chemotherapy	1. There are differences in the evaluation of TILs density 2. Need for multiple biopsies, low patient acceptance	(36,75)
HLA genotype	NGS (HLA-I/II type)-	HLA-A*02:0; pCR OR=3.1	HLA-I heterozygosity missing DFS HR=0.51	1. It can be used as a personalized prediction for Asian patients 2. It differences may be the reason for different immune responses in different patients	1. Predictive value is ethnically different 2. HLA typing requires special laboratory resources	(36)
TMB	WES/NGS TMB ≥10 mut/Mb	pCR AUC=0.59	Limited data	1. It fills the prediction gap for patients with PD-L1 TPS <1% 2. Patients with high TMB may benefit from combination of immunotherapy and chemotherapy 3. Weak predictive power	1. High detection costs 2. Different platforms have different testing standards	(36)

Table V. Continued.

Biomarker	Detection method positive criteria	pCR/MPR prediction	Survival association	Clinical utility	Limitations	(Refs.)
PD-L1 TPS	IHC PD-L1 TPS≥1%	pCR OR=2.1 (95% CI, 1.6-2.8)	DFS HR=0.62	1. It is NCCN level 1 evidence 2. It can guide the choice of immunotherapy monotherapy or immunotherapy combined with chemotherapy	1. Time heterogeneity 2. Spatial heterogeneity	(36,79)

PD-L1, programmed death-ligand 1; TPS, tumor proportion score; IHC, immunohistochemistry; pCR, pathological complete response; CI, confidence interval; OR, odds ratio; DFS, disease-free survival; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; TMB, tumor mutational burden; WES, whole exome sequencing; NGS, next-generation sequencing; AUC, area under the curve; ctDNA, circulating tumor DNA; PPV, positive predictive value; OS, overall survival; MRD, minimal residual disease; HLA, human leukocyte antigen; TILs, tumor-infiltrating lymphocytes; HPF, high-power field; MPR, major pathological response; RNA-seq, RNA sequencing.

demonstrated even more notable advantages, with an MPR rate of 50% and a pCR rate of 25% for patients receiving neoadjuvant pembrolizumab plus ramucirumab. Additionally, the dual immunotherapy regimen also demonstrated promising results in terms of surgical feasibility. In the NEOpredict-Lung study, patients who received nivolumab plus relatlimab as neoadjuvant therapy achieved a 100% surgical completion rate and a 95% R0 resection rate, with no delays due to treatment toxicity. By contrast, in the CheckMate 77T study, the surgical completion rate for patients receiving neoadjuvant nivolumab combined with chemotherapy was only 77.7% and certain patients required adjustments to their surgical plans due to bone marrow suppression.

Regarding the safety of the dual immunotherapy regimen, in the NEOpredict-Lung trial, patients receiving nivolumab plus relatlimab neoadjuvant therapy were reported to have only a 13% incidence of TRAEs of grade 3 or higher and experienced no chemotherapy-associated toxicities (such as neutropenia). Additionally, irAEs were mainly associated with thyroid dysfunction, with a 40% incidence rate in the dual immunotherapy group and rare serious events, such as pneumonia, which occurred in <2% of cases. By contrast, in the CheckMate 77T study, the incidence of TRAEs of grade 3 or higher was as high as 32.5%, accompanied by notable chemotherapy-associated toxicities, including a 10.1% incidence of neutropenia. Although the dual immunotherapy regimen was associated with higher levels of pathological remission in the PD-L1 level ≥50% group, it still provided notable benefits to patients with PD-L1 levels <1%; for example, in the NEOpredict-Lung study, the MPR rate for patients with PD-L1 levels <1% was 16.7%. Overall, the dual immunotherapy regimen avoids the risks of bone marrow suppression and gastrointestinal toxicity associated with chemotherapy, reduces the risk of postoperative infections and delayed recovery and is particularly suitable for elderly or poorly tolerated patients.

Furthermore, the EAST ENERGY study demonstrated that blocking ramucirumab with VEGFR-2 antagonists led to a reshaping of the TME, an enhancement of $CD8^+$ T-cell infiltration and a prolongation of the duration of the immune response. However, the double immunization regimen still needs to be investigated in phase III trials for the purpose of directly comparing the double immunization regimen with the combination of chemotherapy and immunotherapy to further clarify its advantages (10,102).

At present, although no separate studies have been published on perioperative immunotherapy combined with targeted therapy for lung cancer, a potential synergistic antitumor mechanism exists between immunotherapy and targeted therapy. The MARIPOSA-2 study (103) evaluated the efficacy of the EGFR-mesenchymal/epithelial transition factor (MET) bispecific antibody amivantamab in combination with chemotherapy and lazertinib in patients with advanced EGFR-mutated NSCLC. The results demonstrated that the median PFS in the combined treatment group reached 8.3 months, the median intracranial PFS was 12.8 months and the ORR was 63%. This data demonstrates that amivantamab combined with targeted therapy and chemotherapy has notable efficacy in treating advanced EGFR-mutated NSCLC, suggesting the translational potential of immunotherapy combined with targeted

Table VI. Microenvironmental, biomarker and clinical differences in tumor core zone and tumor edge zone.

Region	TME characteristics	Differences in biomarkers	Clinical implications
Tumor core zone	Tumors are characterized by high cellular density, sparse vasculature and limited oxygen supply	High PD-L1 expression is predominantly found on tumor cells, concurrent with a low density of $CD8^+$ TILs in the TME	Immune inhibitory microenvironment has poor response to immunotherapy
Tumor edge zone	Tumors are characterized by low cellular density, a well-vascularized network and ample oxygen supply.	High PD-L1 expression is predominantly found on immune cells, concurrent with a high density of $CD8^+$ TILs in the TME	Immune activation microenvironment has a good response to immunotherapy

PD-L1, programmed death-ligand 1; TIL, tumor-infiltrating lymphocytes; TME, tumor immune microenvironment.

therapy in perioperative lung cancer treatment. In particular, the enhanced intracranial activity of lazertinib may prevent occult brain metastasis progression during surgery; in addition, lazertinib inhibits the EGFR signaling pathway, thereby reducing the levels of immune-suppressive cytokines such as IL-6 and VEGF, which has the effects of improving the TME and enhancing the synergistic effect with immunotherapy. Furthermore, the CheckMate 370 (104) and TATTON (105) studies also explored the potential of immunotherapy in combination with targeted therapy in advanced NSCLC and the results obtained from these studies also have the potential to be applied to perioperative immunotherapy in lung cancer in the future.

Furthermore, novel immunomodulators target non-PD-1/PD-L1 immune checkpoints to modulate key signaling pathways in the TME, thereby offering a novel direction for perioperative immunotherapy. The NeoTRACK study (106) explored the use of atezolizumab in combination with the novel T cell immunoreceptor with Ig and ITIM domains (TIGIT) inhibitor, tiragolimab, during perioperative care. Tiragolimab is a novel monoclonal antibody that targets the TIGIT receptor, which functions as an inhibitory immune checkpoint receptor primarily expressed on the surface of activated T and NK cells. By binding to the ligand CD155, which is highly expressed on the surface of tumor and antigen-presenting cells, TIGIT transmits inhibitory signals, leading to T-cell exhaustion and NK cell dysfunction. However, a synergistic inhibitory effect also exists between TIGIT and the PD-1/PD-L1 pathway. Blocking TIGIT helps relieve the dual inhibition of T cells and NK cells, thereby enhancing the antitumor immune response. In models of PD-1/PD-L1 inhibitor resistance, TIGIT inhibition has been reported to restore the function of exhausted T cells, thereby overcoming immune escape. This research is currently ongoing (106) and may potentially lead to applications in perioperative immunotherapy for lung cancer in the future.

7. Resistance

Although perioperative immunotherapy for lung cancer has been reported to be effective and safe in the aforementioned clinical trials, long-term resistance to immunotherapy remains a notable concern, particularly for patients requiring postoperative adjuvant immunotherapy. Generally, the mechanisms of immunotherapy resistance can be categorized into primary and secondary modes of resistance. The core of primary drug resistance lies in the 'cold' nature of the TME, characterized by insufficient immune cell infiltration. This is primarily due to disordered tumor vascular structures and defects in the secretion of chemokines such as CXCL9/10, which prevent $CD8^+$ T cells from effectively infiltrating the tumor. Additionally, mutations or epigenetic silencing in genes associated with antigen presentation, such as β-2 microglobulin and transporter associated with antigen processing 1/2, result in the absence of MHC class I molecule expression, thereby creating a 'blind spot' for immune recognition and leading to an immunosuppressive state against the tumor cells. Furthermore, this immunosuppressive state is exacerbated by the infiltration of immune-suppressing cells, such as Tregs and MDSCs. These cells create an inhibitory TME by secreting cytokines such as IL-10 and TGF-β and they continue to support tumor cell survival through abnormal activation of the Wnt/β-catenin or PI3K/AKT signaling pathways (107-109). If the tumor evades the initial immune attack, secondary drug resistance will gradually develop. Initially, drug-resistant subclones of the tumor achieve immune escape through mutations in driver genes, such as the EGFR T790M mutation and MET amplification or through epigenetic remodeling that leads to the loss of neoantigens due to DNA hypermethylation. Furthermore, tumor cells enhance glycolysis via the Warburg effect, leading to lactic acid accumulation in the TME, which directly inhibits T-cell function. Additionally, abnormal tryptophan metabolism mediated by IDO1 depletes key amino acids in the local TME, which further disrupts the antitumor immune response. Epigenetic regulation either alters the accessibility of immune-associated genes through chromatin modifications that are mediated via histone deacetylases or dynamically regulates the expression of immune checkpoints such as PD-L1 through non-coding RNA networks, including circular RNA/N6-methyladenosine modifications, thereby forming a multi-dimensional drug resistance barrier. These mechanisms are interlinked, ultimately leading to a decline in the clinical response to immunotherapy (Fig. 3) (110-112).

Offering neoadjuvant dual immunotherapy for lung cancer may be a viable approach to overcome drug resistance in the future. The NEOSTAR study demonstrated that, in patients

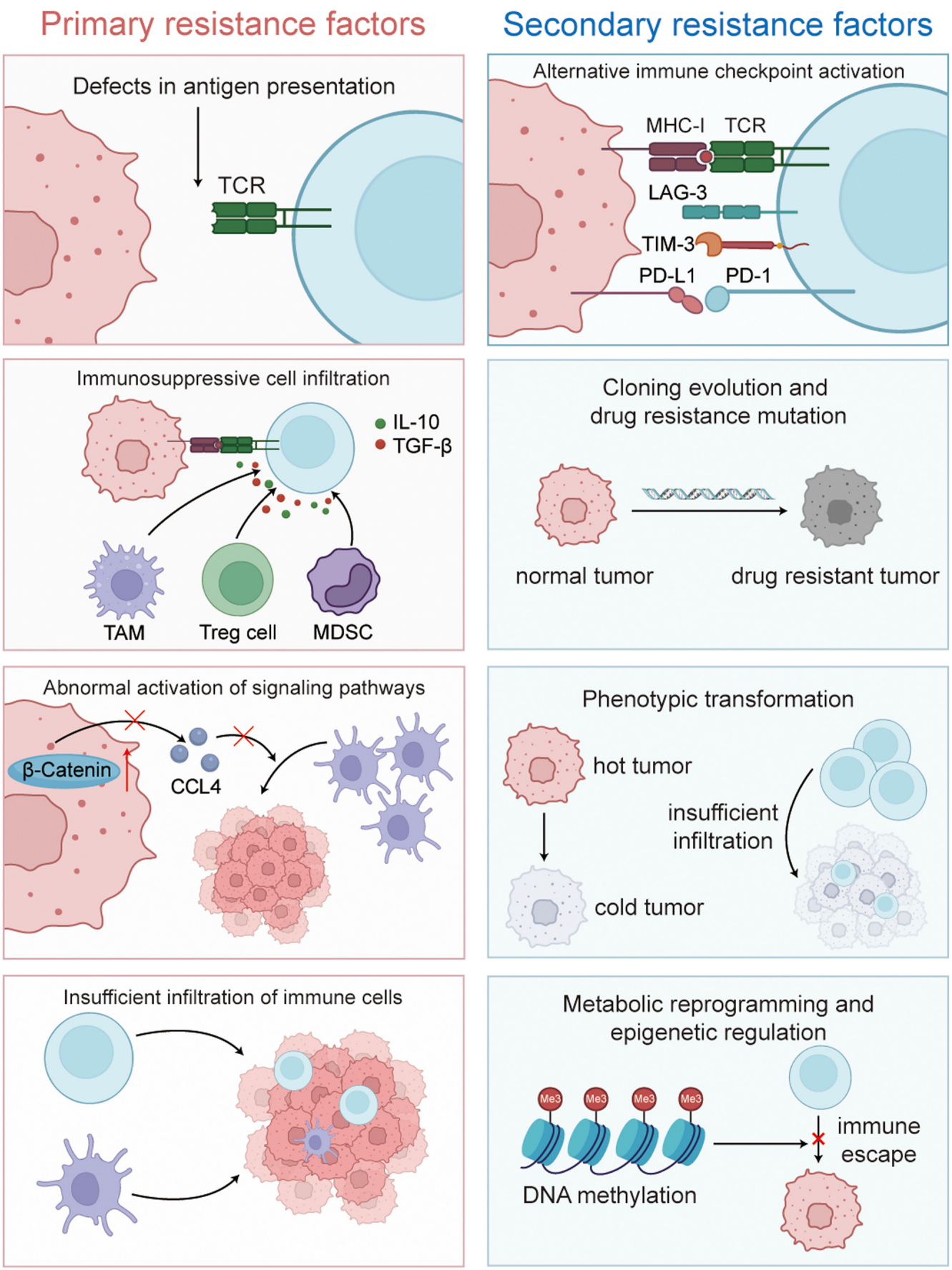

Figure 3. Mechanism of tumor immune resistance. TCR, T cell receptor; TAM, tumor-associated macrophages; Treg, regulatory T cells; MDSC, myeloid-derived suppressor cells; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein-1; LAG-3, lymphocyte-activation gene 3; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; MHC-I, major histocompatibility complex class I; IL-10, interleukin-10; TGF-β, transforming growth factor-β; CCL4, C-C motif chemokine ligand 4.

treated with neoadjuvant nivolumab plus ipilimumab, tumor tissue samples that were analyzed using multi-color immunofluorescence technology exhibited a marked reduction in Treg cell infiltration. By contrast, the density of Tregs in the neoadjuvant nivolumab monotherapy group did not markedly change either prior to or after treatment. These findings suggest that this neoadjuvant dual immunotherapy approach effectively leads to an improvement in the immune rejection state, possibly due to the high expression of CTLA-4 on the surface of Treg cells. A combination of ipilimumab and other CTLA-4 inhibitors may effectively deplete Treg cells, thereby improving drug resistance (113). Furthermore, since the C-C motif chemokine ligand 2-CC chemokine receptor 2 (CCL2-CCR2) signaling axis is key to the functional specialization of MDSCs, clinical studies have reported that CCR2 antagonists are able to reduce infiltration of the MDSCs (114-116). At present, the LCMC3 study is being followed up with novel research aimed at validating the use of CCR2 antagonists in combination with PD-1 inhibitors for the perioperative treatment of lung cancer (114). Additionally, lymphocyte activation gene 3 (LAG-3), which is highly expressed in exhausted T cells, binds to the T cell receptor-CD3 complex, leading to an inhibition of T-cell activation by disrupting the interaction between co-receptors and the Src kinase family member Lck, thereby negatively regulating immune function. Clinical trials have demonstrated that a combination of the LAG-3 inhibitor relatlimab and the checkpoint inhibitor nivolumab is able to reverse T-cell exhaustion (117-119). The team responsible for the NEOSTAR study aims to further explore such combination therapies to improve drug resistance (120).

8. Conclusions and perspectives

In conclusion, perioperative immunotherapy has fundamentally reshaped the therapeutic paradigm for resectable NSCLC. The present systematic analysis has revealed that multimodal strategies, particularly the 'sandwich approach' (namely, neoadjuvant chemoimmunotherapy to surgery to adjuvant immunotherapy), demonstrate notably increased pathological response parameters (pCR, 24.8-56 vs. ≤24% in the neoadjuvant-only patient cohort) and survival benefits (EFS HR, 0.40-0.59 vs. 0.76-0.79 in the adjuvant-only group). Notably, the present review has established two key advancements: i) By integrating the current traditional biomarkers and emerging biomarkers, a dynamic monitoring model has been proposed to overcome the spatial and temporal heterogeneity of PD-L1 and a biomarker-guided perioperative immunotherapy regimen was also implemented to achieve truly personalized treatment for patients; and ii) a clinical decision pathway for the omission of adjuvant immunotherapy in NSCLC: The sandwich protocol increases irAEs (≥3 irAEs: chemotherapy group, 40 vs. 18%) and we propose a decision process to determine whether adjuvant immunotherapy should be exempted following neoadjuvant immunotherapy combined with chemotherapy.

Three main topics are involved here; first, concerning biomarker optimization, PD-L1 thresholds remain contentious (for example, the NEOTORCH trial demonstrated no EFS association with PD-L1), whereas TMB standardization is impeded by platform variability (for example, by comparing the FoundationOne®CDx tTMB with bTMB thresholds). Second, as far as oncogenic driver limitations are concerned, ICIs exhibit minimal efficacy in EGFR/ALK-altered NSCLC, thereby necessitating the development of novel combination therapies. Third, regarding long-term irAE impacts, immune-associated sequelae (for example, radiation pneumonitis in 10% of the patients in the NICOLAS trial) require extended follow-up to define surgical/quality-of-life trade-offs.

Four key areas require further exploration in terms of the goal of working toward precision perioperative therapy. The first future direction for research is dynamic biomarker integration, whereby multi-omics models (spatial transcriptomics plus ctDNA) will be developed to track real-time immune remodeling. The second area is novel combination strategies; for example, studying target immunosuppressive niches with TGF-β/IDO1 inhibitors and strengthening antigen presentation via the use of HLA-DR agonists (as validated in the LungMate 002 trial responders). Thirdly, future studies should investigate personalized toxicity mitigation, as in the case of target GEO signatures (for example, IFN-γ pathway genes) to predict irAE susceptibility. Lastly, real-world validation studies are necessary in order to establish registries for special populations (for example, elderly/oligometastatic populations) and to refine clinical guidelines (such as the NCCN/ESMO guidelines).

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Authors' contributions

GL, XM and HL conceived the present review. XM reviewed the literature and drafted the manuscript. HL provided financial support. XM, LL, HZ and ZL reviewed the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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