Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2025.0589

REVIEW

Opportunities and challenges of immunotherapy for patients with resectable and potentially resectable stage III non-small cell lung cancer

Yuzhen Cui[1,2], Jingdong Xu[1,2], Junxu Wen[3], Jianfeng Peng[3], Jiangao Ren[1,2], Ailing Liu[3], Xiangjiao Meng[3], Zhaoqin Huang[4], Anwen Liu[5]

[1]Nanchang University Queen Mary School, Nanchang 330031, China; [2]Queen Mary University of London, London E1 4NS, UK; [3]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China; [4]Department of Radiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, China; [5]Department of Oncology, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, China

ABSTRACT The integration of immune checkpoint inhibitors has transformed the therapeutic landscape for patients with resectable and potentially resectable stage III non-small cell lung cancer, providing unprecedented opportunities for curative treatment. Several trials have investigated immune checkpoint inhibitors, either alone or in combination with chemotherapy or radiotherapy, as neoadjuvant and/or adjuvant approaches for resectable and potentially resectable stage III non-small cell lung cancer. This comprehensive review elaborates and deeply analyzes the evolving evidence from landmark clinical trials and emerging treatment strategies. Despite these promising outcomes, significant challenges remain, including optimal treatment modality selection, controversy about adjuvant immunotherapy for patients who have already achieved a pathologic complete response, appropriate endpoint evaluation, and biomarker identification. This review also discusses future directions for optimizing immunotherapy integration in patients with resectable stage III non-small cell lung cancer, emphasizing the need for personalized treatment approaches to maximize patient benefit while addressing unanswered clinical questions.

KEYWORDS Non-small cell lung cancer; immunotherapy; chemotherapy; radiotherapy; resectable; potentially resectable; biomarkers

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide[1] with stage III non-small cell lung cancer (NSCLC), representing a locally advanced form of the disease, accounting for 20%–25% of all NSCLC cases[2]. The distinction between resectable and unresectable disease in patients with stage III NSCLC is not always clear. Accordingly, some patients fall into an intermediate category of potentially resectable cases. The treatment landscape for resectable stage III NSCLC has evolved rapidly with recent advances in tumor immunology leading to the identification of new therapeutic agents and modalities, including immune checkpoint inhibitors (ICIs)[3,4].

Numerous phase III clinical trials have been conducted[5-7], yet a systematic synthesis and analysis of the available evidence is lacking[8,9]. This review provides a comprehensive overview of treatment modalities for resectable stage III NSCLC, including consideration of the biological principles underlying immunotherapy implementation[10,11]. In addition, we discuss specific challenges in this field and future strategies for optimizing treatment outcomes in patients with resectable stage III disease through novel therapeutic modalities and approaches.

Correspondence to: Xiangjiao Meng, Zhaoqin Huang and Anwen Liu
E-mail: mengxiangjiao@sina.com, devin813@163.com, and awliu666@163.com
ORCID ID: https://orcid.org/0000-0001-7380-5510, https://orcid.org/0000-0002-2069-3401, https://orcid.org/0009-0004-9534-2317
Received September 26, 2025; accepted March 10, 2026;
published online April 21, 2026.
Available at www.cancerbiomed.org
©2026 The Authors. Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Classification of stage III NSCLC

Stage III NSCLC

Stage III NSCLC can be classified into three distinct categories based on the feasibility of surgical resection: resectable;

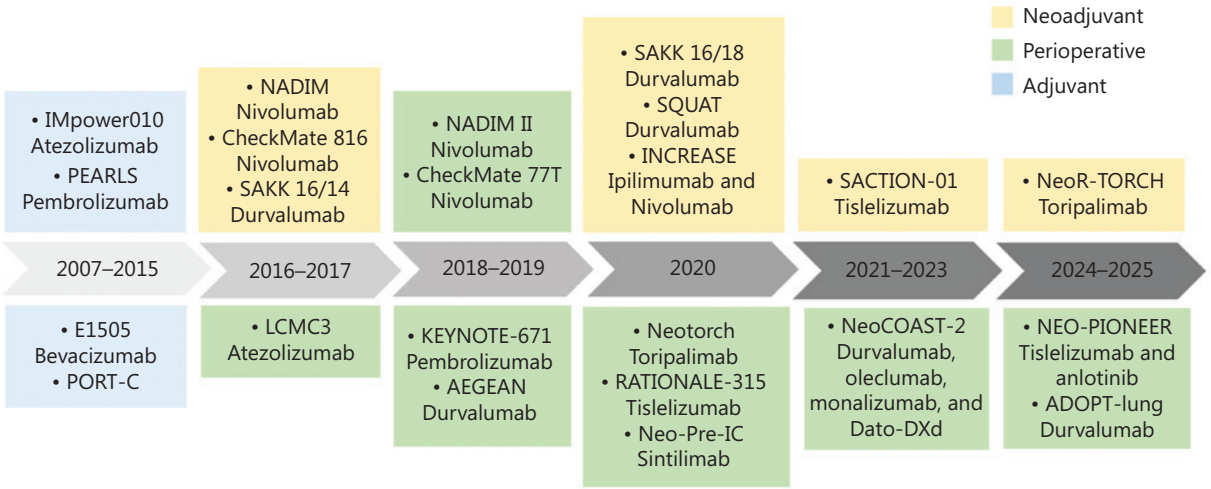


Figure 1 History and representative trials in the development of ICIs in resectable and potentially resectable stage III NSCLC. This timeline illustrates the evolution of ICI trials from 2007 to 2025, categorized by treatment strategy: neoadjuvant (yellow); perioperative (green); and adjuvant (blue). The specific ICI agent(s) used in each trial are indicated. Dato-DXd, datopotamab deruxtecan-dlnk; ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer (figure created using Microsoft PowerPoint).

potentially resectable; and unresectable. This review encompasses discussions of recent therapeutic advances related to resectable and potentially resectable stage III NSCLC (**Figure 1**).

Resectable

Stage III lung cancer is highly heterogeneous. Accordingly, the diagnosis and treatment of NSCLC require precise assessment, decision-making, and implementation. This complex process often necessitates multidisciplinary collaboration and integration. Multidisciplinary team (MDT) management involves a comprehensive evaluation based on the individual circumstances of each patient to formulate the optimal personalized treatment strategy (**Figure 2**). For example, patients eligible for surgery may undergo surgical treatment following neoadjuvant therapy.

Resectable stage III NSCLC primarily encompasses stage IIIA N0–1 and select N2 disease with single-station mediastinal lymph node metastasis where the short-axis diameter of the lymph nodes is < 2 cm, as well as some cases of T4N1 disease (isolated tumor nodules within different ipsilateral lobes). In accordance with the 8th edition of the International Association for the Study of Lung Cancer (IASLC) lung cancer TNM staging recommendations[12-14], resectable stage III NSCLC includes stage IIIA T3N1, T4N0–1, and select T1–2N2 and stage IIIB (T3–4N2) cases. This category also encompasses resectable superior sulcus tumors (T3N1). The use of immunotherapy with surgical treatment strategies for stage III NSCLC can be classified into three categories: neoadjuvant; adjuvant; and perioperative management. Neoadjuvant immunotherapy relies on preoperative antigens, an intact lymphatic system, and patient characteristics, such as PD-L1 expression levels,[15] to enhance the activation of the anti-tumor immune response[11], expand the tumor-specific T-cell population[10,16], and reduce the risk of disease recurrence. Adjuvant therapy, administered after surgery, is usually initiated 3–4 weeks postoperatively. The primary objective of adjuvant therapy is to eliminate any remaining micro-metastatic foci, reducing the likelihood of tumor recurrence and metastasis, and ultimately improving curative outcomes[17].

Potentially resectable NSCLC

The Asian Thoracic Oncology Research Group defines potentially resectable stage III NSCLC as follows: i) tumors have extensively invaded vital structures, rendering the tumor surgically unresectable or compromising essential physiologic functions; and ii) patients who are unlikely to benefit from surgery alone with definitive chemoradiation as the standard therapeutic regimen[18]. Current treatment regimens for these patients may include neoadjuvant induction therapy to achieve tumor downstaging[19]. Following MDT assessment, select stage III patients who achieve adequate tumor downstaging may be considered for surgical resection. In the process of converting potentially resectable patients to radical resection with curative potential, the optimization of therapeutic strategies to ensure improved safety and tolerability is an area requiring further exploration and investigation.

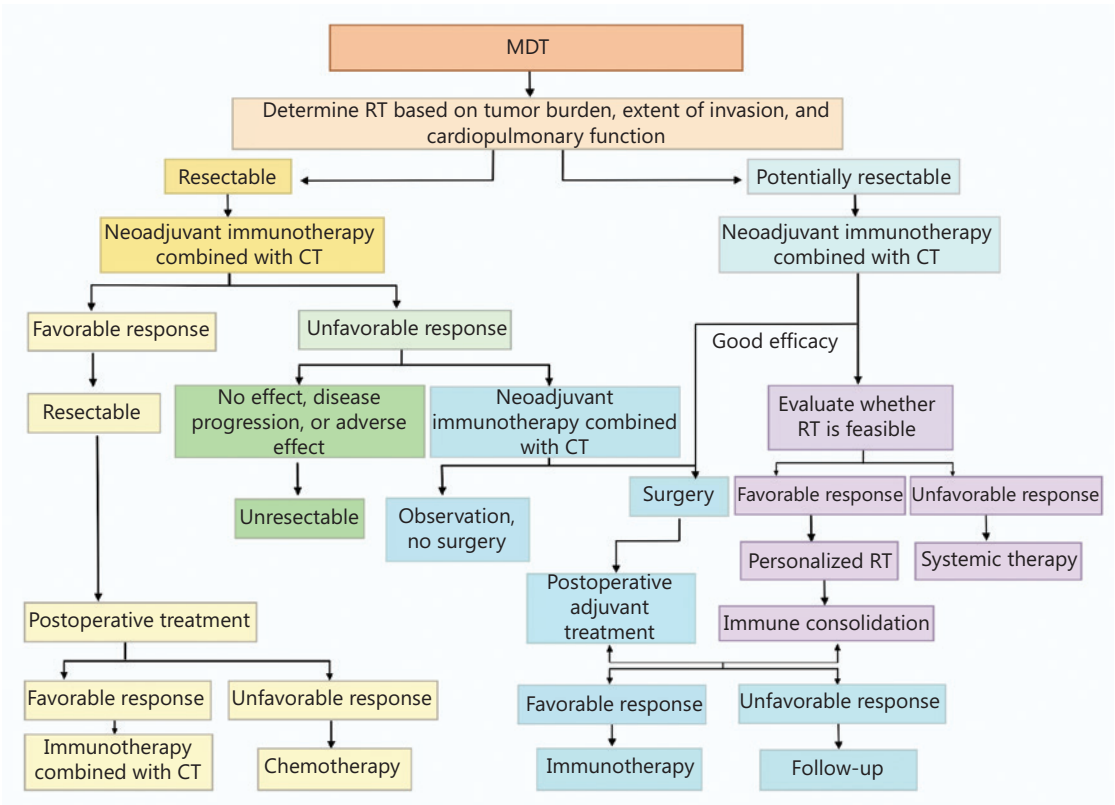


Figure 2 Diagnostic and treatment procedures for patients with resectable and potentially resectable stage III NSCLC. This flowchart outlines the clinical decision-making pathway following multidisciplinary team review. **For resectable disease**, neoadjuvant immunotherapy is administered first. Patients demonstrating a favorable response undergo surgery followed by postoperative treatment. Responders continue immunotherapy combined with CT, while non-responders switch to chemotherapy. Patients with an unfavorable response to initial neoadjuvant therapy are reassessed and may be reclassified as unresectable or receive intensified neoadjuvant immunotherapy combined with CT. Subsequent responders proceed to surgery and postoperative adjuvant treatment with immunotherapy or follow-up based on treatment response. **For potentially resectable disease**, patients achieving a favorable response to neoadjuvant immunotherapy proceed to surgery. Otherwise, the feasibility of RT is evaluated. Responders to RT receive personalized radiotherapy and immune consolidation therapy, while non-responders receive systemic therapy. Treatment is continuously adjusted based on therapeutic efficacy and tolerability. CT, chemotherapy; CRT, chemoradiotherapy; MDT, multidisciplinary team; NSCLC, non-small cell lung cancer; RT, radiotherapy (figure created using MedPeer).

Promising results in resectable stage III NSCLC

Immunotherapy demonstrates promising therapeutic potential in resectable stage III NSCLC. Several novel treatment modalities aimed at further improving the survival outcomes of stage III patients have been developed (**Figure 3**). Numerous large-scale trials have been conducted evaluating these treatment modalities to identify the optimal treatment approaches (**Table 1**).

Neoadjuvant immunotherapy combined with chemotherapy

Several studies have focused on neoadjuvant immunotherapy in the clinical setting of stage III NSCLC. Early studies have reported promising outcomes of neoadjuvant immunotherapy for resectable NSCLC[20], in which the combination of neoadjuvant immunotherapy and chemotherapy has attracted widespread attention because of significant efficacy[15]. Several critical clinical trials have confirmed the feasibility of this therapeutic approach[21-24].

The NADIM trial was a landmark study evaluating the feasibility of this therapeutic modality. Forty-six patients with stage IIIA NSCLC were enrolled; patients harboring EGFR/ALK mutations were excluded. Patients received three cycles of neoadjuvant nivolumab (PD-1 antibody) combined with chemotherapy, followed by resection. Notably, 63% of patients achieved a pathologic complete response (pCR)[21]. The intention-to-treat (ITT) population (46 patients) had a 5-year progression-free survival (PFS) rate of 65.0% [95% confidence interval (CI) = 49.4–76.9] and a 5-year overall survival (OS) rate of 69.3% (95% CI = 53.7–80.6), indicating long-term benefits[25].

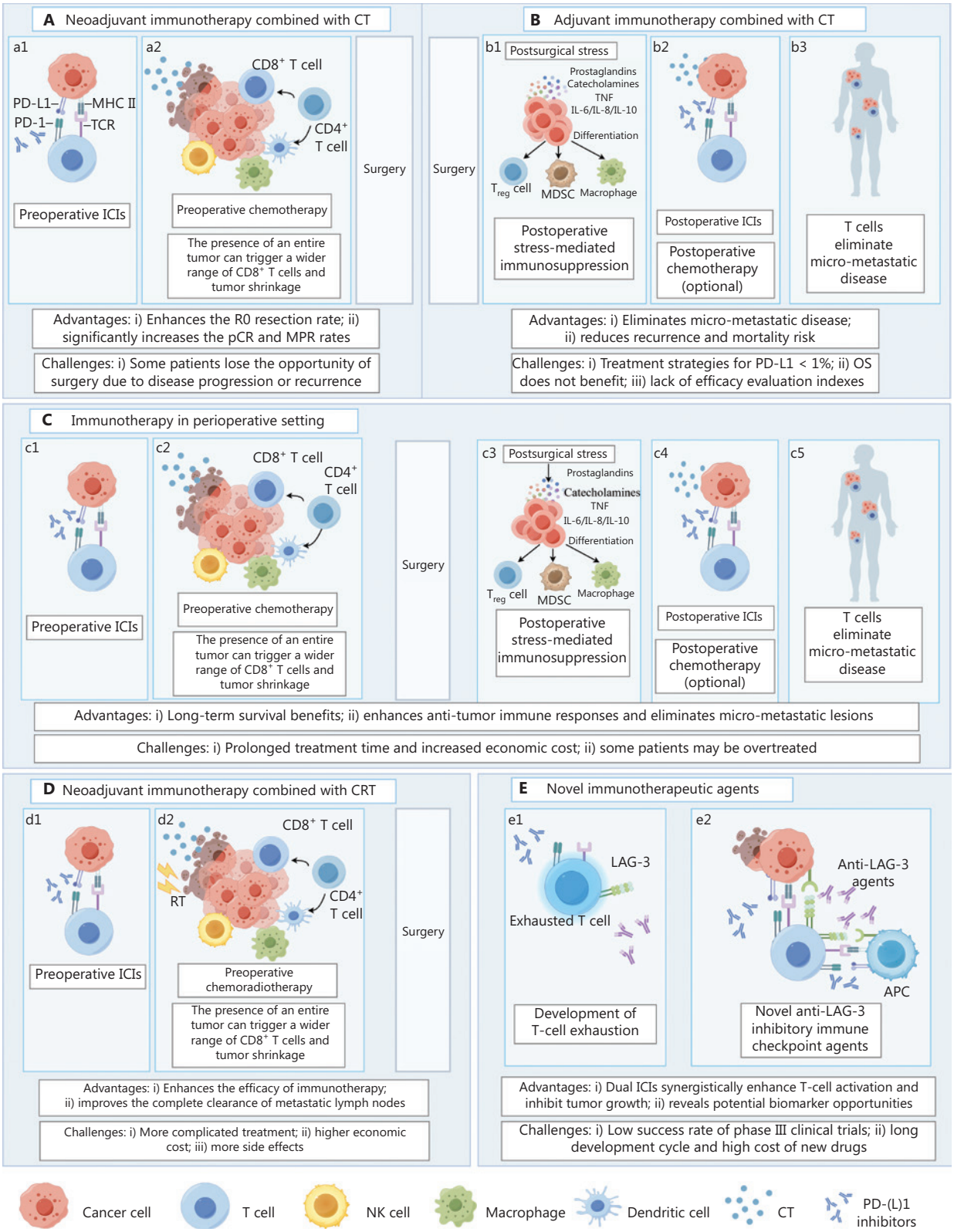


Figure 3 Therapeutic strategies and biological principles of ICI therapy in resectable stage III NSCLC. This schematic illustrates the treatment workflow, underlying biological mechanisms and respective advantages and challenges of different strategies for implementing ICI

therapy in resectable stage III NSCLC (A–E). A. **Neoadjuvant immunotherapy combined with CT:** (a1) PD-1 expressed on T cells engages PD-L1 on tumor cells and antigen-presenting cells, suppressing MHC-II-restricted antigen recognition and TCR-mediated cytotoxicity, thereby inhibiting T-cell proliferation and establishing an immunosuppressive tumor microenvironment. Preoperative ICIs targeting the PD-1/PD-L1 axis restore T-cell signaling and anti-tumor effector function. (a2) Preoperative chemotherapy induces immunogenic cell death, releasing tumor-associated antigens that activate $CD4^+$ T cells to promote dendritic cell maturation while stimulating $CD8^+$ T-cell proliferation and differentiation. Concurrently, chemotherapy enhances NK cell and macrophage infiltration into the tumor. The resulting robust immune response promotes tumor regression and facilitates surgical resection. B. **Adjuvant immunotherapy combined with chemotherapy:** (b1) Surgical trauma triggers the release of prostaglandins, catecholamines, TNF, and IL-6/IL-8/IL-10, which promote differentiation toward Tregs, MDSCs, and immunosuppressive macrophages, establishing a postoperative stress-mediated immunosuppressive microenvironment. (b2) Residual cancer cells may reactivate PD-1/PD-L1-mediated immune suppression. Postoperative ICIs restore T-cell-mediated anti-tumor immunity, and optional adjuvant chemotherapy further enhances T-cell activation through immunogenic cell death. (b3) Activated T cells eliminate systemic micro-metastatic foci and reduce recurrence risk. C. **Perioperative immunotherapy:** (c1) As described in panel A, T-cell function is suppressed through tumor PD-L1/PD-1 signaling; preoperative ICIs block this inhibitory axis. (c2) As described in panel A, preoperative chemotherapy combined with ICIs generates broad, multicellular anti-tumor immune responses that promote tumor regression, followed by surgical resection. (c3) As depicted in panel B, surgical trauma establishes an immunosuppressive microenvironment. (c4) Perioperative immunotherapy continues ICI administration immediately postoperatively, thereby continuously blocking the PD-1/PD-L1 axis. Sustained postoperative ICIs with optional adjuvant chemotherapy maintain T-cell anti-tumor activity. (c5) Activated T cells eliminate systemic micro-metastatic disease. D. **Neoadjuvant immunotherapy combined with CRT:** (d1) As described in panel A, T-cell function is suppressed by PD-L1/PD-1 signaling; preoperative ICIs block this inhibitory axis. (d2) Radiotherapy combined with chemotherapy and ICIs may enhance the activation of $CD8^+$ T cells, $CD4^+$ T cells, NK cells, and macrophages, promoting tumor regression and creating favorable conditions for surgical resection. E. **Novel immunotherapeutic agents:** (e1) Under chronic antigen stimulation within the tumor microenvironment, T cells progressively undergo exhaustion, upregulating multiple co-inhibitory receptors, including PD-1 and *LAG-3*. (e2) Tumor cells engage PD-1 and *LAG-3* on exhausted T cells, establishing multiple co-inhibitory signaling pathways that limit the efficacy of PD-1 blockade alone. Combined inhibition of *LAG-3* and PD-1 achieves synergistic reversal of T-cell exhaustion. APC, antigen presenting cell; CT, chemotherapy; CRT, chemoradiotherapy; ICI, immune-checkpoint inhibitor; IL, interleukin; *LAG*, lymphocyte activation gene; MDSC, myeloid-derived suppressor cell; MHC II, major histocompatibility complex class II; MPR, major pathologic response; NK cell, natural killer cell; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathologic complete response; TCR, T-cell receptor; TNF, tumor necrosis factor (figure created using FigDraw).

The results of the subsequent large-scale randomized controlled CheckMate 816 trial further confirmed the objective efficacy of nivolumab. The CheckMate 816 trial was the first phase III study involving neoadjuvant chemoimmunotherapy. The FDA approved the combination therapy in March 2022 based on the positive results in this trial. The results of this study revealed a significantly increased pCR rate of 24% compared to 2.2% for chemotherapy ($P < 0.001$) and major pathologic response [MPR] (36.9% *vs.* 8.9%)[22]. Notably, marked improvement was observed in patients with stage III NSCLC, in whom the pCR reached 23.0% (*vs.* 0.9%). The 4-year event-free survival (EFS) rates were 49% and 38%, respectively, while the 5-year OS rates were 65.4% and 55%, respectively[7,26]. Although the incidence of grade 3 and 4 treatment-related adverse events (TRAEs) in the chemoimmunotherapy group was as high as 33.5%, the surgical resection rates were comparable between groups (83% *vs.* 75%), indicating acceptable perioperative safety. Furthermore, a meta-analysis revealed that neoadjuvant chemoimmunotherapy did not significantly increase the rate of serious adverse events compared to chemotherapy alone (18.0% *vs.* 12.3%; $P = 0.32$), suggesting manageable toxicity profiles[27]. These results indicated that neoadjuvant nivolumab combined with chemotherapy may significantly improve pathologic and survival outcomes with manageable toxicity.

A phase II SAKK 16/14 study evaluated the addition of durvalumab (PD-L1 antibody) to neoadjuvant chemotherapy. Fifty-five patients underwent surgical resection; 34 (62%) achieved an MPR, while 10 (18%) achieved a pCR[23]. The median EFS was 4.0 years, while the median OS was not reached.

The optimal number of cycles for neoadjuvant immunochemotherapy has emerged as an important issue based on the favorable outcomes of this treatment modality, which was addressed in a retrospective study involving 115 patients[28]. The MPR rates were 44.8%, 61.4%, 66.7%, and 40.0% for patients who received 2, 3, 4, and ≥ 5 neoadjuvant immunochemotherapy cycles, respectively ($P = 0.189$). This study demonstrated that an extended neoadjuvant immunochemotherapy regimen of 3–4 cycles was associated with higher MPR rates compared to 2 cycles. Notably, even in patients who achieved a complete or partial response (CR or PR) on imaging, extending treatment to 3–4 cycles remained

Table 1 Clinical trials of ICIs in resectable stage III non-small-cell lung cancer

Trial	Treatment	Phase	Patients	*n*	mEFS (months)	pCR (%)	MPR (%)	mDFS (months)	OS
Neoadjuvant									
NEOSTAR (NCT03158129)	Arm I: NIVO (3 mg/kg) + Ipilimumab (1 mg/kg) + CT → Surgery Arm II: NIVO (3 mg/kg) + CT → Surgery	2	I-IIIA	44	NR	29.0 *vs*. 9.0	38.0 *vs*. 22.0	NA	mOS NR
NeoTAP01 (NCT04304248)	CT + Toripalimab (240 mg q3w × 3 cycles) → Surgery	2	IIIA-IIIB	33	NR (2-year EFS 67.9%)	50.0	66.7	NR	NR
TD-FOREKNOW (NCT04338620)	Arm I: CT + Camrelizumab (200 mg × 3 cycles) → Surgery Arm II: CT + Placebo (3 cycles) → Surgery	2	IIIA-IIIB	94	NR (2-year EFS 76.9% *vs* 67.6%)	32.6 *vs*. 8.9	65.1 *vs*. 15.6	NR (2-year DFS 78.4% *vs*. 71.7%)	NA
CheckMate 816 (NCT02998528)	Arm I: CT + NIVO (360 mg q3w × 3 cycles) → Surgery Arm II: CT + Placebo (q3w × 3 cycles) → Surgery	3	IB-IIIA	358	54.8 *vs*. 20.9	24.0 *vs*. 2.2	36.9 *vs*. 8.9	NA	5-year OS 65.4% *vs*. 55.0%
NADIM (NCT03081689)	CT + NIVO (360 mg q3w × 3 cycles) → Surgery	2	IIIA	46	77.1	63.0	83.0	NA	5-year OS 69.3%
SAKK 16/14 (NCT02572843)	CT → Durvalumab (750 mg q2w × 2 cycles) → Surgery → Durvalumab (750 mg q2w up to 1 year)	2	IIIA (N2)	67	48.0	18.2	61.8	NA	NA
SACTION-01 (NCT05319574)	SBRT + Tislelizumab (200 mg q3w × 2 cycles) + CT → Surgery	2	II-IIIB	46	NR	52.2	76.1	NA	18-month OS 92.9%
SQUAT (WJOG12119L)	CT + Durvalumab (1500 mg q4w × 2 cycles) + RT → Surgery → Durvalumab	2	IIIA–IIIB (N2)	61	NA	23.0	63.0	NA	2-year OS 76.0%
Adjuvant									
IMpower010 (NCT02486718)	Arm I: Surgery → CT → Atezolizumab (1200 mg q3w × 16 cycles) Arm II: Surgery → CT → Placebo (q3w × 16 cycles)	3	IB (≥ 4 cm)-IIIA	1,280	NA	NA	NA	68.5 *vs*. 37.3	5-year OS 76.8% *vs*. 67.5%
KEYNOTE-091/PEARLS (NCT02504372)	Arm I: Surgery → CT → Pembrolizumab (200 mg q3w up to 1 year) Arm II: Surgery → CT → Placebo (q3w up to 1 year)	3	IB-IIIA	1,177	NA	NA	NA	53.8 *vs*. 43.0	3-year OS 82.0% *vs*. 80.0%
E1505 (NCT00324805)	Arm I: Surgery → CT → Bevacizumab (15 mg/kg q3w up to 1 year) Arm II: Surgery → CT → Placebo (q3w up to 1 year)	3	IB (≥ 4 cm)-IIIA	1,501	NA	NA	NA	40.6 *vs*. 42.9	mOS 85.8m *vs*. NR

Table 1 Continued

Trial	Treatment	Phase	Patients	*n*	mEFS (months)	pCR (%)	MPR (%)	mDFS (months)	OS
LUNG ART (NCT00410683)	Arm I: Surgery → PORT (54 Gy in 27 or 30 daily fractions) Arm II: Surgery → Followed periodically (for up to 10 years)	3	IIIA-N2	501	NA	NA	NA	30.5 *vs*. 22.8	3-year OS 66.5% *vs*. 68.5%
PORT-C (NCT00880971)	Arm I: Surgery → CT (4 cycles) → PORT (50 Gy) Arm II: Surgery → CT (4 cycles)	3	IIIA-N2	364	NA	NA	NA	22.1 *vs*. 18.6	3-year OS 78.3% *vs*. 82.8%
Perioperative									
TOP 1501 (NCT02818920)	Pembrolizumab (200 mg IV × 2 cycles) → Surgery → Pembrolizumab (4 cycles)	2	IB-IIIA	35	88% achieved R0 resection	12.0	28.0	NA	NA
LCMC3 (NCT02927301)	Atezolizumab (1200 mg q3w × 2 cycles) → Surgery → optional Atezolizumab (1200 mg q3w up to 1 year)	2	IB-IIIB	181	NA	7.0	20.0	NA (3-year DFS 64.0% *vs*. 83.0%)	3-year OS 89.0% *vs*. 77.0%
NADIM II (NCT03838159)	Arm I: CT + NIVO (360 mg q3w × 3 cycles) → Surgery → NIVO (480 mg q4w up to 6 mo.) Arm II: CT → Surgery	2	IIIA-IIIB	90	NA	37.0 *vs*. 7.0	53.0 *vs*. 14.0	NA	2-year OS 85.0% *vs*. 63.6%
AEGEAN (NCT03800134)	Arm I: CT + Durvalumab (1500 mg q3w × 4 cycles) → Surgery → Durvalumab (1500 mg q4w × 12 cycles) Arm II: CT + Placebo→ Surgery →Placebo	3	IIA-IIIB	825	NR *vs*. 30.0	17.2 *vs*. 4.3	33.3 *vs*. 12.3	NA	mOS NR *vs*. 53.2 m
KEYNOTE-671 (NCT03425643)	Arm I: CT + Pembrolizumab (200 mg IV q3w × 4 cycles) → Surgery → Pembrolizumab (200 mg IV q3w × 13 cycles) Arm II: CT + Placebo → Surgery → Placebo	3	IIA–IIIB (N2)	786	47.2 *vs*. 18.3	18.1 *vs*. 4.0	30.2 *vs*. 11.0	NA	4-year OS 67.1% *vs*. 51.5%
Neotorch (NCT04158440)	Arm I: CT + Toripalimab → Surgery → CT + Toripalimab (240 mg) → Toripalimab (240 mg q3w × 13 cycles) Arm II: CT + Placebo → Surgery → CT + Placebo	3	IIIA/B/C (70% stage III patients)	404	NR *vs*. 15.1 (Stage III)	24.8 *vs*. 1.0 (Stage III)	48.5 *vs*. 8.4 (Stage III)	NA	2-year OS 81.2% *vs*. 74.3%
CheckMate 77T (NCT04025879)	Arm I: CT + NIVO → Surgery → NIVO Arm II: CT + Placebo → Surgery → Placebo	3	IIA–IIIB (N2)	461	NR *vs*. 18.4	25.3 *vs*. 4.7	35.4 *vs*. 12.1	NA	NA

Table 1 Continued

Trial	Treatment	Phase	Patients	*n*	mEFS (months)	pCR (%)	MPR (%)	mDFS (months)	OS
RATIONALE-315 (NCT04379635)	Arm I: CT + Tislelizumab (200 mg q3w) → Surgery → Tislelizumab (400 mg q6w) Arm II: CT + Placebo → Surgery → Placebo	3	II-IIIA	453	NR *vs.* NR	40.7 *vs.* 5.7	56.2 *vs.* 15.0	NA	2-year OS 88.6% *vs.* 79.4%
NeoCOAST-2 (NCT05061550)	Arm I: CT + Oleclumab + Durvalumab → Surgery → Oleclumab + Durvalumab Arm II: CT + Monalizumab + Durvalumab → Surgery → Monalizumab + Durvalumab Arm III: CT + Volrustomig → Surgery → Volrustomig Arm IV: CT + Dato-DXd + Durvalumab → Surgery → Durvalumab	2	IIA–IIIB	272	NA	Arm I: 20.0 Arm II: 26.7 Arm IV: 34.1	Arm I: 45.0 Arm II: 53.3 Arm IV: 65.9	NA	NA

CT, chemotherapy; mo, months; Dato-DXd, datopotamab deruxtecan-dlnk; ICIs, ICI, immune-checkpoint inhibitors; mEFS, median event-free survival; mOS, median overall survival; mDFS, median disease-free survival; MPR, major pathologic response; *n*, number; NR, not reached; NA, not available; NIVO, nivolumab; ORR, overall response rate; pCR, pathologic complete response; Q3W, every 3 weeks.

beneficial. Furthermore, the results suggested that extending treatment beyond 4 cycles was not associated with further improvement in MPR rates.

Neoadjuvant immunochemotherapy demonstrated superior efficacy in terms of increasing the EFS, OS, MPR, and pCR rates compared to neoadjuvant chemotherapy alone and was associated with higher surgical and R0 resection rates without increasing the incidence of serious adverse events (SAEs) or TRAEs (**Table 2**). Future investigations should continue evaluating the benefits of neoadjuvant immunochemotherapy across different subgroups, particularly as OS data mature, and explore whether specific chemotherapy regimens or immunotherapies are correlated with treatment outcomes in patients receiving neoadjuvant immunochemotherapy.

Neoadjuvant immunotherapy combined with chemoradiotherapy

Given the substantial benefits demonstrated by neoadjuvant chemoimmunotherapy, further optimization is needed to increase the short-term efficacy of combined surgical treatment in patients with locally advanced NSCLC, thereby prolonging patient survival; this goal is a current research focus. Investigators have integrated immunotherapy with chemoradiotherapy to increase survival benefits, minimize treatment-related toxicity, and increase local control rates. Notable trials investigating this approach include the INCREASE trial and the SAKK 16/18 trial[29,30].

The SAKK 16/18 study explored the efficacy and safety of durvalumab in combination with chemotherapy and 3 different dose fractionation radiotherapy schemes (2 Gy/20, 5 Gy/5, and 8 Gy/3 fractions)[30]. Eighty-one percent of the patients underwent surgical resection with R0 resection achieved in 96% of the patients. The pCR rate among evaluated patients was 28%, while the MPR rate for the enrolled patients was 76%. Notably, the moderate fractionation regimen (5 Gy/5 fractions) demonstrated superior efficacy, achieving MPR and pCR rates of 89% and 44%, respectively. There were no significant differences in safety outcomes among the three groups. Further studies are needed to increase the study size and explore the differences.

Durvalumab was administered as the immunotherapeutic agent in the SQUAT (WJOG 12119L) study[31]. Of the 13 enrolled patients, 11 completed neoadjuvant therapy and successfully underwent surgical resection. The primary endpoints revealed an MPR rate of 63% and a pCR rate of 23%. This treatment regimen resulted in a higher MPR rate than reported in other recently published studies involving neoadjuvant chemotherapy combined with immunotherapy. These findings suggested that concurrent chemoradiotherapy combined with single-agent immunotherapy may have strong tumor control potential and result in favorable outcomes. However, the 2-year PFS and OS rates (43% and 76%, respectively)[32]

Table 2 Safety profile of immunotherapy trials in resectable stage III NSCLC

Trial	Treatment	TRAEs (%)	≥ Grade 3 TRAEs (%)	≥ Grade 3 AEs (%)	≥ Grade 3 irAEs (%)
Neoadjuvant					
CheckMate 816	Arm I: CT + NIVO → Surgery Arm II: CT + Placebo → Surgery	82.4 *vs*. 88.6	33.5 *vs*. 36.9	40.9 *vs*. 43.8	1.7 *vs*. 0.0
NADIM	CT + NIVO → Surgery	93.0	30.0	NA	NA
SQUAT	CT + Durvalumab + RT→ Surgery → Durvalumab	100.0	48.0	48.0	≥ Grade 5: 1 patient
Adjuvant					
IMpower010	Arm I: Surgery → CT → Atezolizumab Arm II: Surgery → CT→ Placebo	67.9 *vs*. NA	10.7 *vs*. NA	22.0 *vs*. 11.5	8.0 *vs*. 1.0
KEYNOTE-091	Arm I: Surgery → CT → Pembrolizumab Arm II: Surgery → CT → Placebo	75.0 *vs*. 52.0	15.0 *vs*. 4.0	34.0 *vs*. 26.0	8.0 *vs*. 2.0
Perioperative					
AEGEAN	Arm I: CT + Durvalumab → Surgery → Durvalumab Arm II: CT + Placebo → Surgery → Placebo	86.8 *vs*. 80.7	32.4 *vs*. 32.9	43.6 *vs*. 43.2	4.2 *vs*. 2.5
KEYNOTE-671	Arm I: CT + Pembrolizumab → Surgery → Pembrolizumab Arm II: CT + Placebo → Surgery → Placebo	95.0 *vs*. 94.0	41.0 *vs*. 37.0	26.0 *vs*. 21.0	7.0 *vs*. 2.0
CheckMate 77T	Arm I: CT + NIVO → Surgery → NIVO Arm II: CT + Placebo → Surgery → Placebo	89.0 *vs*. 87.0	32.5 *vs*. 25.2	47.4 *vs*. 43.0	5.7 *vs*. 1.3
Neotorch	Arm I: CT + Toripalimab → Surgery → CT + Toripalimab Arm II: CT + Placebo → Surgery → CT + Placebo	99.5 *vs*. 98.5	63.4 *vs*. 54.0	NA	11.9 *vs*. 3.0
RATIONALE-315	Arm I: CT + Tislelizumab → Surgery → Tislelizumab Arm II: CT + Placebo → Surgery → Placebo	99.1 *vs*. 99.6	73.0 *vs*. 67.3	70.0 *vs*. 67.0	9.3 *vs*. 3.1

AEs, adverse events; CT, chemotherapy; irAEs, immune-related adverse events; NA, not available; NIVO, nivolumab; NSCLC, non-small cell lung cancer; TRAEs, treatment-related adverse events.

indicated that the observed local response advantage has not yet been translated into significant improvements in PFS or OS, and further follow-up and investigation are needed for validation.

The INCREASE trial used a dual chemoradiotherapy-immunotherapy (CRT-IO) regimen [chemotherapy plus simultaneous radiotherapy (50 Gy/25 fractions)] interspersed with ipilimumab and nivolumab[29]. The results indicated a pCR rate of 63%, which was more than twice the rates reported in traditional CRT induction trials[33,34] and recent immunochemotherapy trials[35]. The safety profile was favorable[36]. This regimen exhibited good efficacy but a radiation dose of 50–60 Gy may significantly impact surgical procedures.

Moreover, the SACTION-01 study used a combination regimen with low-dose radiotherapy. Forty-six patients underwent SBRT (8 Gy/3 fractions) in combination with tislelizumab (PD-1 antibody) and chemotherapy[37]. Of the 46 patients, 44 ultimately underwent surgical treatment. The MPR rate was 76.1% with an EFS rate of 90% and an OS rate of 95% at 1 year. The safety profile was also favorable. Only 26.1% of patients experienced ≥ grade 3 TRAEs.

Toripalimab (PD-1 antibody) was used in the NeoRTORCH study (NCT06437977) and the CRT-IO regimen (24 Gy/3 fractions) was compared to the immunotherapy plus chemotherapy regimen. The results of this controlled trial may provide valuable evidence to inform the selection of neoadjuvant chemoradiotherapy versus chemotherapy regimens in future clinical practice.

Despite existing challenges in combining ICI treatment with radiotherapy, the current high pCR/MPR rates and manageable side effects validate the feasibility of this approach. CRT-IO trials, such as INCREASE (pCR 63%) and SAKK 16/18 (pCR 44%), have demonstrated numerically higher response rates compared to CheckMate 816 (pCR 24%), suggesting that radiotherapy may enhance the pathologic response, although these findings require confirmation in large-scale trials given the limited sample sizes. Neoadjuvant therapy aims to reduce tumor burden and improve surgical resection rates and

delay recurrence and extend the disease-free survival (DFS). Furthermore, as illustrated by the SQUAT study, higher pathologic response rates may not translate into survival benefits, highlighting the need for randomized controlled trials with mature survival data to establish the definitive role of radiotherapy in neoadjuvant immunotherapy.

Immunotherapy as an adjuvant setting in resectable stage III NSCLC

Adjuvant cytotoxic chemotherapy has traditionally been the recommended treatment for resected locally advanced NSCLC and high-risk patients. A meta-analysis revealed a 5.8% increase in the DFS rate and a 5.4% increase in the OS rate over a 5-year period with adjuvant chemotherapy[38]. Several large phase III clinical trials, including IMpower010 and KEYNOTE-091[39,40], as well as other trials (**Table 1**), have explored the use of adjuvant ICI therapy.

The IMpower010 trial included 1280 patients who underwent surgical resection and chemotherapy. The participants were randomly assigned to receive or not receive atezolizumab (PD-L1 antibody)[39]. In the population with a PD-L1 ≥ 1%, the 5-year DFS rate was 53.2% in the immunotherapy group compared to 42.7% in the chemotherapy alone group. This trend continued to translate to a favorable OS outcome. This benefit was more pronounced in the PD-L1 tumor cell (TC) ≥ 50% subgroup [hazard ratio (HR) = 0.42] with a 5-year OS rate of 84.8%. No unexpected safety signals were observed[41]. Therefore, the European Medicines Agency (EMA) supports the use of atezolizumab solely for patients with stage II–IIIA NSCLC in whom PD-L1 expression is ≥ 50%, while the Food and Drug Administration (FDA) approves atezolizumab for patients with a PD-L1 ≥ 1% following surgical resection and platinum-based chemotherapy.

Pembrolizumab has recently been approved as adjuvant monotherapy following tumor resection and platinum-based chemotherapy based on positive results from a phase III clinical trial. The KEYNOTE-091 (PEARLS) trial confirmed this finding[40]. Importantly, patients were enrolled regardless of PD-L1 expression status in this study, creating a more heterogeneous population for biomarker analysis. Adjuvant pembrolizumab was associated with an improved DFS compared to placebo (median DFS of 53.6 *vs*. 42.0 months; HR = 0.76, 95% CI = 0.63–0.91; $P = 0.0014$). However, despite the significant benefit in the overall population, the difference in DFS among patients with a PD-L1 ≥ 50% was not statistically significant. The DFS HRs for the PD-L1 < 1%, 1%–49%, and ≥ 50% subgroups were 0.78 (95% CI = 0.58–1.03), 0.67 (95% CI = 0.48–0.92), and 0.82 (95% CI = 0.63–1.05), respectively[42].

The IMpower010 and KEYNOTE-091 trials stratified patients based on PD-L1 TC expression. The improvement in DFS following immunotherapy was associated with higher PD-L1 expression according to the IMpower010 subgroup analysis with patients in whom PD-L1 expression was ≥ 50% experiencing a more pronounced benefit (HR = 0.43, 95% CI = 0.27–0.68)[41]. However, this pattern was not noted in the KEYNOTE-091 trial[42] (**Figure 4**). These divergent findings suggested that in the clinical setting of adjuvant immunotherapy for NSCLC, higher PD-L1 expression does not necessarily correlate with greater efficacy of adjuvant immunotherapy.

These findings may be attributable to the substantial heterogeneity within KEYNOTE-091. First, the study enrolled patients with stage IB–IIIA disease regardless of PD-L1 status and this broad eligibility criterion may have introduced baseline imbalances. Second, the trial design lacked adequate standardization. Specifically, approximately 14% of the patients did not receive adjuvant chemotherapy[40] and surgical techniques varied across centers with respect to the extent of lymph node dissection and resection margin quality. These factors likely increased the within-subgroup variance and diminished the statistical power. In contrast, heterogeneity was reduced in IMpower010 through mandatory chemotherapy, stage II–IIIA restriction, and stringent R0 verification[39]. In addition, the distinct tumor microenvironment in early-stage lung cancer following surgical resection warrants consideration. Adjuvant immunotherapy targets minimal residual disease after R0 resection when the tumor burden is relatively low and the biological characteristics may differ from the primary tumor. PD-L1 testing limitations should also be considered. The two studies used different assay platforms (SP263 *vs*. 22C3), potentially identifying biologically distinct populations at the same threshold[43]. Moreover, tumor specimens for testing are derived from surgical resection and may not adequately represent tumor heterogeneity. When coupled with the spatiotemporal heterogeneity of PD-L1 expression, the predictive value in minimal residual disease remains debatable. Statistically, the PD-L1 ≥ 50% subgroup in KEYNOTE-091 enrolled only 333 patients, which may have been underpowered to detect moderate associations with potential unidentified confounding factors influencing the interpretation of results. Given the divergent predictive role of PD-L1 between these two phase III clinical trials, the results do not support extrapolation to guide the application of other ICIs and emphasize the urgent need for more precise biomarkers and individualized therapeutic approaches to avoid overtreatment.

Immunotherapy in a perioperative setting in resectable stage III NSCLC

Perioperative treatment comprises neoadjuvant immunotherapy prior to surgery, followed by adjuvant therapy to enhance treatment efficacy. This integrated approach combines ICI treatment with chemotherapy to achieve optimal tumor reduction and systemic disease management before

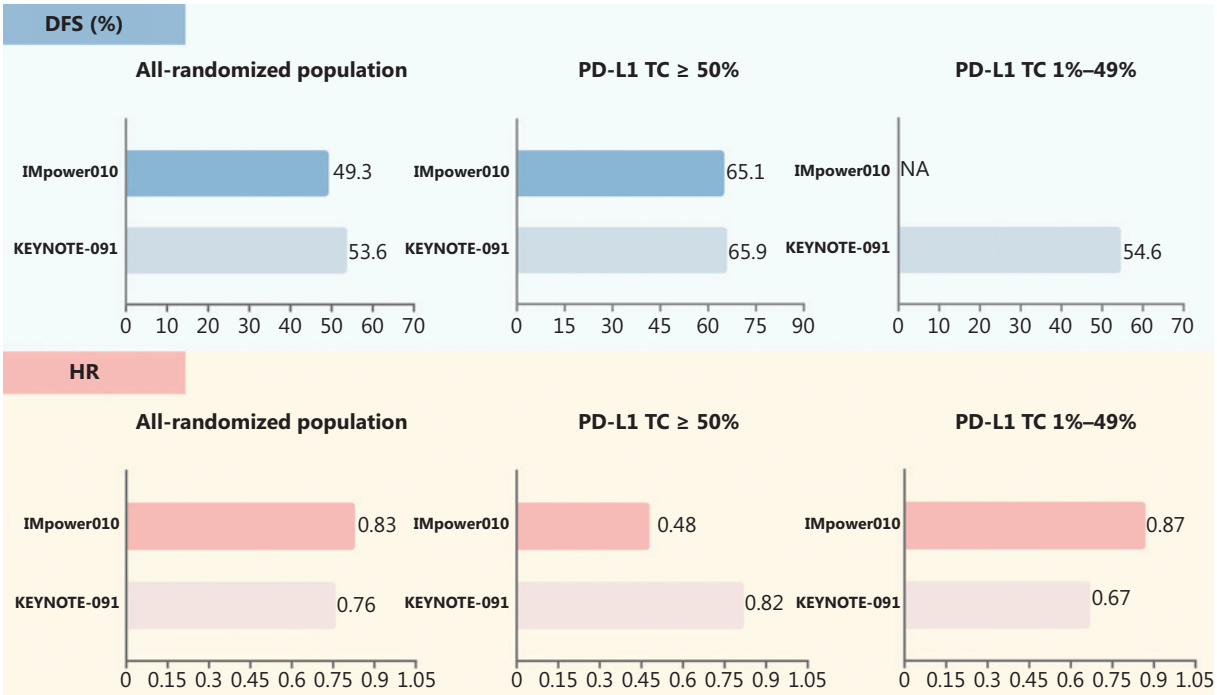


Figure 4 Summary of the main outcomes of clinical trials evaluating adjuvant therapy strategies in resectable stage III NSCLC. The figure compares DFS outcomes and HR between IMpower010 (atezolizumab) and KEYNOTE-091 (pembrolizumab) trials across three subgroups. **In the DFS rate figure**, KEYNOTE-091 showed comparable or superior results to IMpower010 in the all-randomized population, while IMpower010 demonstrated higher efficacy in the PD-L1 TC ≥ 50% subgroup, although the KEYNOTE-091 DFS rates remained consistent across subgroups. **In the HR value figure**, both trials demonstrated clinical benefit (HR < 1.0), particularly in the IMpower010 PD-L1 TC ≥ 50% subgroup. These data underscore the importance of PD-L1 expression in predicting adjuvant immunotherapy efficacy. DFS, disease-free survival; HR, hazard ratio (figure created using BioRender.com).

surgery. By maintaining therapeutic efficacy postoperatively, this strategy has the potential to eradicate residual micro-metastatic disease not eliminated by preoperative neoadjuvant treatment.

A key question is whether perioperative combination treatment yields improved pathologic responses and how this affects surgical outcomes. The NADIM II study, a follow-up to the NADIM trial, further demonstrated the objective efficacy of nivolumab in patients with resectable stage III NSCLC. This randomized phase II trial enrolled 86 patients with stage IIIA–B disease and extended the NADIM regimen by incorporating 6 months of adjuvant nivolumab following neoadjuvant chemoimmunotherapy and surgery[21,44]. The surgical rate in the combination therapy group was 93.0% compared to 69.0% in the chemotherapy group. This trial demonstrated that neoadjuvant immunotherapy significantly prolonged PFS (2-year PFS, 67.2% *vs.* 40.9%, HR = 0.47) and OS (2-year OS, 85.0% *vs.* 63.6%, HR = 0.43), which were assessed as non-α-controlled secondary endpoints[45].

The feasibility of perioperative ICI treatment has been supported by the following five additional recent randomized phase III clinical trials: KEYNOTE-671; AEGEAN; Neotorch; RATIONALE-315, and CheckMate 77T (**Figure 5**). Durvalumab was administered as perioperative treatment in the AEGEAN study[46]. The pCR rates were 17.2% and 4.3% in the durvalumab and placebo groups, respectively (95% CI = 8.7%–17.6%; $P = 0.000036$)[47]. The corresponding median EFS times were not reached (NR) and 30.0 months (HR = 0.69). The median DFS was not reached in either group (HR = 0.66) with the durvalumab group demonstrating DFS outcomes significantly superior to the placebo group. Although the OS data are not available yet, a trend toward an OS benefit favoring the durvalumab group was detected[48].

The KEYNOTE-671 trial used pembrolizumab and is currently the only phase III perioperative clinical trial designating both OS and EFS as co-primary endpoints[49]. In contrast, the AEGEAN, Neotorch, and RATIONALE-315 studies[46,50,51] focused primarily on pCR, MPR, and EFS as endpoints without incorporating OS. The pembrolizumab group had a significantly longer median EFS compared to the placebo group (47.2 *vs.* 18.3 months) with a significantly improved 3-year OS rate of 71.3% (*vs.* 64%; HR = 0.72)[6]. The FDA subsequently approved pembrolizumab for the indication of neoadjuvant/

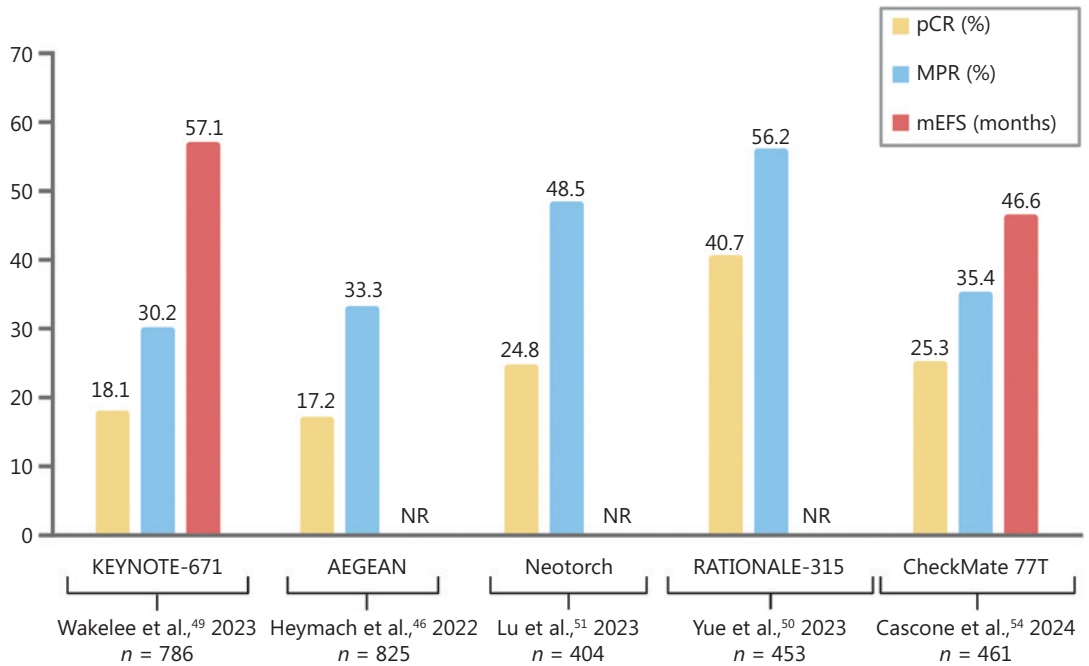


Figure 5 Summary of perioperative ICI clinical trial outcomes in resectable stage III NSCLC. The figure summarizes key efficacy outcomes from five major perioperative immunotherapy trials. These data highlight consistent benefits of perioperative immunochemotherapy across different ICI agents with pathologic response rates correlating with improved survival outcomes. ICI, immune-checkpoint inhibitor; MPR, major pathologic response; mEFS, median event-free survival; NR, not reached; NSCLC, non-small cell lung cancer; pCR, pathologic complete response (figure created using BioRender.com).

adjuvant immunotherapy in patients with resectable stage II–IIIB NSCLC[52].

The success of multiple large-scale trials has prompted a critical discourse regarding the optimal neoadjuvant duration of therapy (3 or 4 cycles). Notably, comparable pCR rates were noted between the 4-cycle CheckMate 77T regimen (25.3%) and the 3-cycle CheckMate 816 regimen (24.0%). A strong correlation between pCR and EFS was demonstrated in both trials[53,54]. These findings suggested that three cycles may be sufficient in most cases with the decision regarding an additional fourth cycle warranting individualization based on clinical considerations.

Another critical question is whether the significant pathologic responses achieved through perioperative treatment can translate into improved long-term prognostic outcomes. Given the heterogeneity in study designs and chemotherapeutic regimens, cross-study comparisons should be interpreted with caution. The CheckMate 816 trial reported a hazard ratio of 0.68 for disease progression, recurrence, and death, whereas the HR reported in the KEYNOTE-091 trial was 0.76. These findings suggested that neoadjuvant ICI therapy has a pivotal role in treatment outcomes. The next research priority involves determining whether perioperative approaches confer additional benefits beyond the benefits achieved by either neoadjuvant or adjuvant monotherapy alone.

Potentially resectable stage III NSCLC

The incorporation of immunotherapy into neoadjuvant treatment has allowed a significant proportion of patients with stage III NSCLC, who were previously at the borderline of resectability, to achieve tumor downstaging[55]. This approach has ultimately provided such patients with the opportunity for curative surgical resection.

The Neo-Pre-IC study included 30 patients with potentially resectable disease who received perioperative sintilimab plus chemotherapy. Notably, the downstaging rate was as high as 80% (95% CI = 65.7%–94.3%), indicating that the combination method can effectively convert potentially resectable NSCLC into resectable NSCLC. The 2-year OS rate was 83.3% and the 2-year DFS rate was 75% (95% CI = 56%–94%)[56]. Furthermore, the neoadjuvant treatment demonstrated an acceptable safety profile with favorable tolerability.

One study evaluated the efficacy of neoadjuvant PD-1/PD-L1 inhibitors combined with chemotherapy in patients with borderline resectable or unresectable stage III NSCLC. A total of 112 patients with T4 and/or N2–N3 disease were included in this study. Of the 112 patients, 75% successfully underwent surgical resection, 29% achieved a pCR, and 42.2% achieved an MPR with a median EFS of 52.6 months. Patients

with high PD-L1 expression and a high tumor mutational burden achieved the most favorable pathologic response rates[57]. This study broadens the population of patients who may benefit from neoadjuvant therapy and underscores the importance of evaluation within an MDT setting.

The INCREASE trial included patients with potentially resectable T3–4N0–1 NSCLC treated with the CRT-IO regimen. Among patients in whom the MDT assessment deemed the tumor only marginally resectable, the radiation dose was increased to a maximum of 60 Gy[29]. A total of 83% of patients underwent surgery and subsequent pathologic assessment. The MPR and pCR rates significantly increased to 79% and 63%, respectively, with manageable safety profiles[36]. Extended follow-up is needed to further evaluate long-term toxicity.

Low-dose radiotherapy (LDRT), which has been shown to exert specific immunomodulatory effects with relatively low toxicity in prior studies, may balance treatment efficacy and toxicity. The NCT05157542 trial evaluated the tolerability threshold of neoadjuvant chemotherapy combined with LDRT and reported that the optimal radiotherapy dose among the different cohorts was 30 Gy/15 fractions. All patients achieved tumor downstaging following completion of the planned neoadjuvant therapy. The MPR and pCR rates were both 33.3% in cohort 1 (10 Gy/5 fractions), 66.7% and 0.0% in cohort 2 (20 Gy/10 fractions), respectively, and 100.0% and 66.7% in cohort 3, respectively (30 Gy/15 fractions). No additional safety concerns were reported[58]. Larger scale studies are warranted to further validate the safety and efficacy of this combination regimen.

Optimal neoadjuvant treatment approaches remain under investigation for potentially resectable patients. Whether concurrent chemoradiotherapy followed by durvalumab or neoadjuvant/perioperative chemotherapy combined with immune checkpoint inhibitors followed by surgery represents the superior approach for patients with bulky or multi-station N2 disease remains a matter of debate. This uncertainty underscores the importance of individualized MDT discussions and the need for further research to refine risk stratification.

Challenges and controversies

Selection of the optimal treatment modality for resectable stage III NSCLC

Currently, three immunotherapy approaches have demonstrated significant benefits for patients with resectable stage III NSCLC. Selecting a treatment strategy that maximizes the therapeutic advantages and long-term survival outcomes of immunotherapy is therefore of critical importance. Neoadjuvant immunotherapy can improve the R0 resection rate and achieving pCR after neoadjuvant therapy can provide substantial survival benefits to patients. Our single-arm meta-analysis comparing different neoadjuvant regimens revealed that ICI combined with chemotherapy achieved promising pathologic response rates (MPR, 44.5%; pCR, 26.5%; **Figure 6**)[22,45,49-51,54,59,60]. However, this approach may lead to disease progression or significant adverse effects, potentially resulting in patients losing the opportunity for surgery. Surgery was cancelled for 15.6% of patients in the combination group of the CheckMate 816 study, mainly because of disease progression[22]. Therefore, for patients with a PD-L1 ≥ 1%, neoadjuvant immunotherapy should be prioritized for continuous monitoring of disease progression. Notably, in our single-arm meta-analysis, emerging neoadjuvant strategies demonstrated even higher efficacy. ICI combined with radiotherapy achieved remarkable pathologic response rates (MPR, 73.8%; pCR, 45.5%)[31,37,61], likely attributable to enhanced local tumor control and potentially reduced systemic toxicity by radiotherapy. Similarly, ICI combined with anti-VEGF agents and chemotherapy showed considerable efficacy (MPR, 64.5%; pCR, 39.2%; **Figure 6**)[62-66], representing a promising future direction, although phase III randomized controlled trials are required to validate these findings.

Adjuvant therapy may not compromise the effectiveness of surgery and it has the potential to eliminate micro-metastatic disease not eradicated by preoperative (chemo-)immunotherapy[17]. However, the IMpower010 study indicated that adjuvant therapy is significantly beneficial only for patients with PD-L1 levels ≥ 1%[41]. In contrast to adjuvant therapy, neoadjuvant immunotherapy combined with chemotherapy has demonstrated benefit, even in patients with PD-L1 expression < 1%, whereas adjuvant therapy has not yielded a significant OS benefit and lacks assessment metrics, such as the objective response rate (ORR). Current research suggests that adjuvant therapy may not be the optimal choice for patients with stage III NSCLC. For patients who can tolerate systemic therapy or have PD-L1 expression < 1%, perioperative treatment should be strongly considered.

The 'sandwich' approach has shown long-term benefits as a perioperative treatment approach, demonstrating significant improvements in pCR/MPR and EFS in patients with both squamous and non-squamous NSCLC. While this approach may currently be the optimal choice for patients with stage III NSCLC, the high cost, economic burden, and reimbursement challenges may limit widespread clinical application. Omitting adjuvant therapy in some patients could prevent overtreatment and unnecessary economic burden. Currently, the need for postoperative adjuvant treatment in patients who achieve a pCR with neoadjuvant immunotherapy combined with chemotherapy is still under debate. Analyses from the CheckMate 77T and CheckMate 816 trials indicate that patients with a PD-L1 < 1% and pCR negativity show additional EFS benefits from perioperative nivolumab treatment and it is recommended that these patients receive postoperative adjuvant therapy[53]. Through propensity score weighting analysis, key baseline characteristics between the CheckMate 816 and CheckMate 77T studies were adjusted to achieve

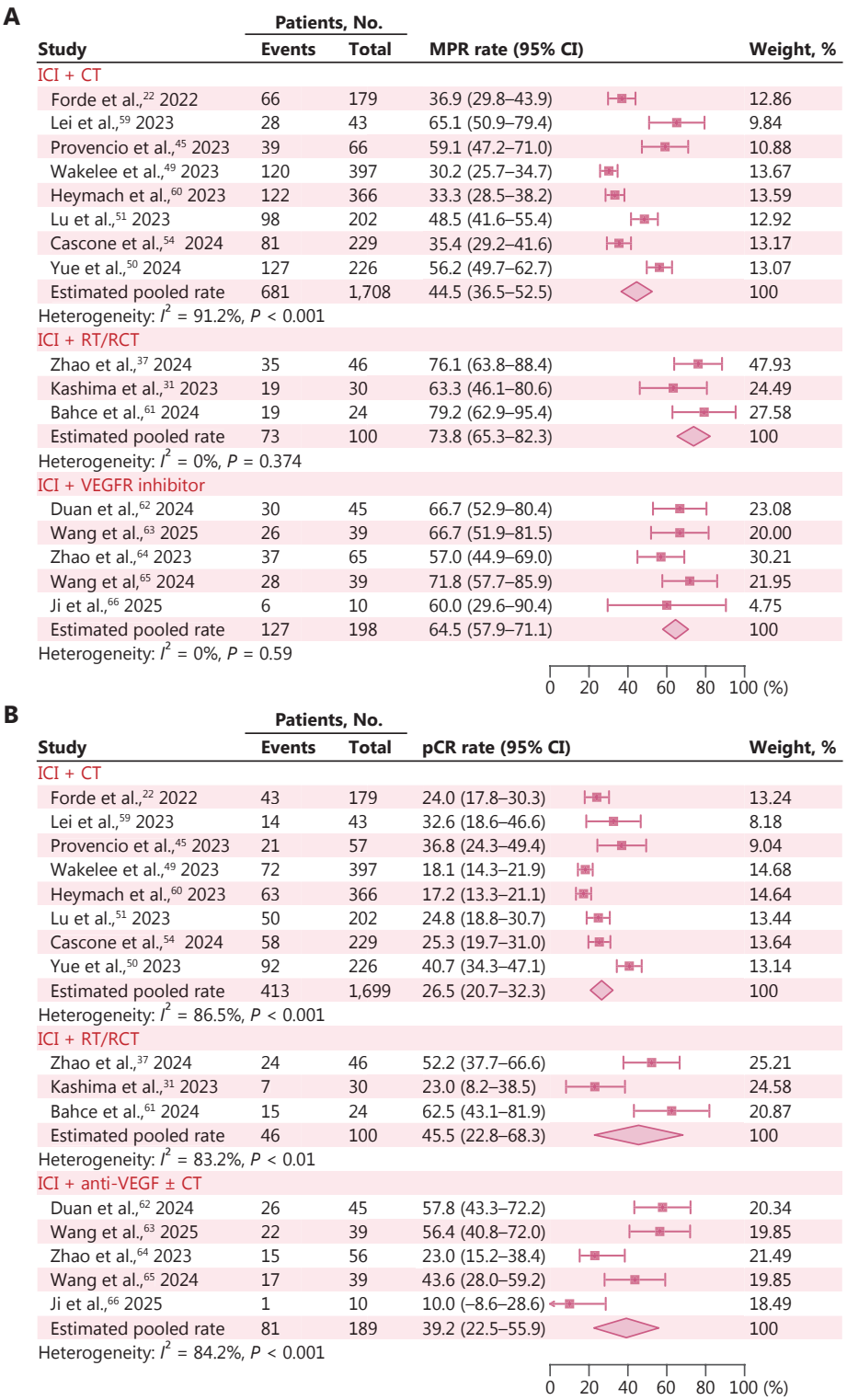


Figure 6 Single-arm meta-analysis of pCR and MPR rates with neoadjuvant immunotherapy-based combinations in resectable NSCLC. This meta-analysis summarizes and compares the efficacy of three neoadjuvant treatment strategies: immunotherapy combined with chemotherapy, immunotherapy combined with radiotherapy, and immunotherapy combined with VEGFR inhibitors. (A) Forest plot of MPR rates stratified by treatment strategy ICI + CT, ICI + RT/RCT, and ICI + anti-VEGF ± CT. (B) Forest plot of pCR rates stratified by treatment strategy ICI + CT, ICI

+ RT/RCT, and ICI + anti-VEGF ± CT inhibitor. CT, chemotherapy; ICI, immune checkpoint inhibitor; MPR, major pathologic response; NSCLC, non-small cell lung cancer; pCR, pathologic complete response; RT, radiotherapy; RCT, chemoradiotherapy; VEGF, vascular endothelial growth factor (figure created using the R Project and Adobe Illustrator).

balance, revealing that perioperative treatment reduced disease recurrence/death risk by 39% compared to neoadjuvant treatment alone. The LCMC3 study results revealed that patients who received postoperative adjuvant immunotherapy had significantly improved DFS compared to patients who did not receive adjuvant treatment with OS also showing improvement[67]. Therefore, continuation of adjuvant treatment after neoadjuvant immunotherapy confers survival benefits whether a pCR is or is not achieved. The continuation of adjuvant immunotherapy is recommended for patients receiving preoperative neoadjuvant immunotherapy when feasible based on several phase III perioperative immunotherapy trials. Moreover, individualized discussion of optimal treatment selection for patients within the MDT is encouraged with participation in clinical trials addressing treatment de-escalation and intensification opportunities.

Appropriate primary endpoint selection

Improvement in survival is the most crucial consideration in the evaluation framework of a therapeutic regimen. OS is regarded as the gold standard for evaluating treatment efficacy but large sample sizes and longer follow-up periods are usually needed. As a result, the evaluation of perioperative immunotherapy in patients with NSCLC requires timely and robust surrogate clinical endpoints.

The MPR and pCR are commonly used primary endpoints in trials evaluating neoadjuvant ICIs[68]. Meta-analyses have demonstrated that the pCR is an effective predictor of OS outcomes in the context of neoadjuvant chemotherapy and MPR is also associated with OS[69]. Although the MPR and pCR can assess local tumor regression following treatment, the MPR and pCR cannot be used to evaluate the eradication of distant occult disease. Even patients assessed as having achieved pCR or MPR may still experience distant disease recurrence. Indeed, the risk of distant metastasis might even exceed the risk of local recurrence (48.1% *vs*. 23.9%, respectively, in patients with stage III NSCLC)[70]. Although there is a clear correlation between pCR and OS, confirming the value of pCR as a prognostic indicator and validity as a surrogate for OS after neoadjuvant therapy is controversial. pCR appears to represent a reasonable surrogate endpoint that is strongly correlated with OS based on existing evidence.

DFS/EFS, defined as the interval from randomization to disease recurrence, distant metastasis, or death, is a critical endpoint for evaluating the efficacy of adjuvant therapy. However, the interpretation of DFS remains ambiguous. Does DFS indicate control of residual disease leading to delayed recurrence or does DFS imply a complete disease eradication? This distinction has not been definitively resolved. The ADAURA study[71] revealed a significant improvement in DFS with adjuvant osimertinib compared to placebo ($P < 0.001$) with a substantial reduction in the risk of recurrence or death (73% reduction, HR = 0.27). In addition, a significant increase in the 5-year OS benefit was noted (88% *vs*. 78%), providing strong evidence that DFS benefits from adjuvant treatment can translate into OS improvements. While surrogate clinical endpoints, including MPR, pCR, and DFS, have achieved acceptance in clinical research involving stage III NSCLC perioperative treatment, debate persists whether short-term survival benefits translate to improved OS. Further long-term data are needed to clarify the precise correlations between these measures and OS.

Strategies for the precise evaluation of treatment efficacy

The most widely used imaging modality in the context of neoadjuvant immunotherapy is PET/CT. During the neoadjuvant immunotherapy phase, PET/CT findings are evaluated using the iPERCIST criteria, which assess metabolic changes in tumors based on PET/CT scan findings[72].

The advantages of PET/CT include the systemic and non-invasive methodology, molecular-level precision, and targeted approach. PET/CT is expected to become an important adjunctive tool for the non-invasive evaluation of PD-L1 expression. Immuno-PET/CT has undergone rapid advances and deferoxamine-mediated chelation of anti-PD-L1 antibodies with ^{89}Zr has been successfully applied in tumor-bearing mouse models to visualize changes in PD-L1 expression before and after chemotherapy[73]. In addition, PET/CT-derived metabolic parameters provide insight for predicting dynamic changes in PD-L1 status. ^{18}F-FDG PET/CT is used to assess metabolic parameters in humans and studies have demonstrated relationships between these parameters and PD-L1 expression[74].

There can be discrepancies between imaging and pathologic findings in clinical practice. Evaluations based on the RECIST criteria may not always correspond with pathologic assessments. This discrepancy is manifested primarily in cases in which RECIST indicates progression or stability, while pathologic evaluation reveals partial or even complete response[75]. Some patients may initially be staged as having stage II NSCLC

owing to the absence of radiologically detectable lymph node involvement. However, lymph nodes may be discovered during surgery, leading to postoperative reclassification as stage III NSCLC[76]. Adjuvant therapy is preferred to address residual lymph node disease and micro-metastatic foci for upstaged patients who have already undergone surgery.

Molecular residual disease (MRD) detection serves as a crucial tool for assessing minimal residual disease after treatment. Circulating tumor DNA (ctDNA)-based MRD detection has emerged as a pivotal tool for treatment response evaluation, recurrence monitoring, and prognostic assessment in patients with early-stage NSCLC[77] but considerable technical limitations remain. The low mutant allele frequency in ctDNA necessitates ultrahigh-sensitivity detection approaches. In addition, MRD detection in solid tumors is limited by tumor heterogeneity, complicating the design of detection panels. Given the limitations of imaging and MRD detection in precise efficacy assessment, multimodal evaluation systems are a novel research direction. In a multicenter retrospective study utilizing CT imaging combined with deep learning, an imaging biomarker model (LUNAI-fCT) was developed for predicting pCR following neoadjuvant immunochemotherapy in patients with NSCLC[78]. Multimodal fusion models have demonstrated superior accuracy in pCR prediction compared to unimodal approaches.

With the development of artificial intelligence (AI), more precise capabilities and applications are gradually being identified. Radiologists and histopathologists have successfully used machine learning (ML) and deep learning (DL) approaches to maximize sensitivity, specificity, and accuracy, especially in the evaluation of lung cancer[79-81]. Large NSCLC datasets of whole slide images and genomic profiles can be used to train robust AI algorithms, improving the efficiency, accuracy, and consistency of histopathologic assessment. Increasingly sophisticated AI prediction models, such as lung cancer risk and prognostic prediction models[82,83], are continually being developed. Related studies have shown that combined models integrating clinical features with AI-based DL scores effectively predict MPR in patients with NSCLC following neoadjuvant chemoimmunotherapy [internal validation: area under the receiver operating characteristic curve (AUC) = 0.77, 95% CI = 0.64–0.89; and external validation: AUC = 0.75, 95% = CI 0.62–0.87]. AI prediction models may significantly support future evaluation of treatment efficacy.

Future integration of multimodal models incorporating clinical, pathologic, radiologic, and molecular biomarkers with ML algorithms and the exploration of novel biomarkers is expected to improve therapeutic efficacy assessment and prediction accuracy, enabling precision individualized treatment for patients with stage III NSCLC. Dynamic monitoring approaches, including continuous MRD surveillance and temporal radiomic analysis, are anticipated to provide novel perspectives for efficacy evaluation. These integrated technologies will enable clinicians to precisely monitor disease progression and develop targeted individualized treatment strategies, ultimately improving therapeutic outcomes and patient prognosis.

Potential of chemotherapy-free treatment strategies

Recent studies have demonstrated the considerable effectiveness of combining immunotherapy with chemotherapy. However, the addition of immunotherapy, particularly when paired with anti-angiogenic agents, can increase toxicity compared to standard chemotherapy[84]. The impact of surgery on pulmonary function and the increased toxicity from chemotherapy have resulted in adverse reactions in many patients, potentially leading to missed opportunities for further treatment. Greater than 40% of patients with NSCLC are elderly patients with poor performance status and/or multiple co-morbidities with poor treatment tolerance[85]. Many of these patients are considered unsuitable for first-line platinum-based treatment regimens and are often excluded from first-line clinical trials[86]. This group represents an important yet insufficiently studied population of patients with NSCLC and significant unmet medical needs. Therefore, actively exploring a chemotherapy-free approach for neoadjuvant therapy may lead to new solutions.

The LCMC3 study evaluated the efficacy and safety of atezolizumab without chemotherapy[67]. Neoadjuvant atezolizumab treatment resulted in an MPR rate of 20% for stage IB–III NSCLC and with at least 3 years of follow-up, the 3-year OS rate was 80%. Anti-angiogenic agents combined with PD-1 inhibitors may offer a strategy to maintain the pathologic response while minimizing toxicity for chemotherapy-intolerant patients. Exploring this approach, the phase II AK112-205 trial evaluated ivonescimab (AK112), a PD-1/VEGF bispecific antibody, as neoadjuvant monotherapy or combined with chemotherapy in resectable NSCLC. Monotherapy achieved MPR and pCR rates of 60% and 30%[65], respectively, which were notably higher than the 20% MPR reported in the LCMC3 study but lower than the combination group (MPR, 71.8%; pCR, 43.6%). A phase II study evaluated camrelizumab plus apatinib (a VEGFR-2 inhibitor) as neoadjuvant therapy for resectable stage IIA–IIIB NSCLC, yielding an MPR rate of 57% and a pCR rate of 23%[64]. The NCT04379739 study further validated this approach by comparing camrelizumab plus chemotherapy versus camrelizumab plus apatinib in PD-L1-positive patients. The apatinib combination resulted in a significantly higher MPR rate than chemotherapy (60% *vs.* 25%) with fewer grade ≥ 3 adverse events (10% *vs.* 25%)[66]. These findings suggested that chemotherapy-free regimens combining ICIs with anti-angiogenic agents may achieve superior efficacy with reduced toxicity in PD-L1-positive patients, potentially providing a promising treatment option for this subgroup.

Although phase III trials, such as KEYNOTE-024[87] and HARMONi-2[88], have suggested that the chemotherapy-free approach may be feasible for select patients with advanced unresectable NSCLC, the prevailing evidence for resectable patients still favors neoadjuvant immunotherapy combined with chemotherapy. At present, a chemotherapy-free strategy has not been established as a standard approach for this patient subset.

Subsequent treatment after effective induction therapy for patients with potentially resectable NSCLC: surgical resection or radiotherapy?

Neoadjuvant immunochemotherapy has emerged as the recommended treatment approach for patients with potentially resectable NSCLC. In the INCREASE trial, 92.3% of patients underwent surgical resection with pCR and MPR rates of 63% and 79%, respectively, among patients who underwent surgical resection[36]. Similarly, the Neo-Pre-IC study demonstrated a downstaging rate of 80% in patients with potentially resectable stage IIIA/IIIB NSCLC treated with sintilimab in combination with chemotherapy. Among patients who underwent surgery, 65% and 40% achieved MPR and pCR, respectively[89]. Several experimental findings suggested that when neoadjuvant treatment is efficacious in potentially resectable disease, the long-term benefits of surgical resection may outweigh the less invasive nature of radiation therapy.

Novel immunotherapeutic agents

Lymphocyte-activation gene 3 (*LAG-3*) is recognized as a crucial immune checkpoint with PD-1/PD-L1 and CTLA-4[90]. Relatlimab, an anti-*LAG-3* antibody, has demonstrated clinical efficacy in some patients with advanced NSCLC[91]. The NEOpredict-Lung study demonstrated that the combination of relatlimab and nivolumab can elicit profound, rapid, and durable pathologic responses in patients with resectable stage III NSCLC[92]. In this trial, the response rates were comparable between the two treatment groups. The 2-year OS and DFS rates for the monotherapy group were 92.3% and 75.3%, respectively, whereas the OS and DFS rates were 88.6% and 69.1%, respectively, for the combination therapy group. All patients successfully underwent surgery with a significantly higher lymph node downstaging rate in the combination therapy group (66.7% *vs.* 28.6%). The safety profile was acceptable[93]. A phase II umbrella trial evaluated neoadjuvant chemotherapy plus tislelizumab (TIS), TIS combined with ociperlimab [anti-T cell immunoreceptor with Ig and ITIM domains (TIGIT)], or TIS combined with LBL-007 (anti-*LAG-3*) in patients with resectable NSCLC. In patients with a PD-L1 TC ≥ 50%, TIS monotherapy and TIS-based combinations yielded favorable MPR and pCR rates. In contrast, the addition of supplementary immunotherapy to TIS plus chemotherapy conferred no additional benefit for patients with a PD-L1 TC < 50%[94]. Stratified treatment strategies based on histology and PD-L1 expression should be explored in future studies to optimize therapy for low-expression populations and identify optimal combination regimens.

The NeoCOAST-2 study evaluated the efficacy and safety of durvalumab combined with various novel agents and chemotherapy in the perioperative setting[95]. The pCR rates were 20.0%, 26.7%, and 34.1% in Arm 1 (combined with oleclumab), Arm 2 (combined with monalizumab), and Arm 4 (combined with Dato-DXd), respectively, while the MPR rates were 45.0%, 53.3%, and 65.9%, respectively. The safety profiles were manageable across all treatment groups.

A wide range of therapeutic agents targeting multiple pathways are available for the treatment of NSCLC. As more novel drugs and combination regimens are developed, further clinical data are eagerly anticipated.

Selection and application of biomarker prediction

Establishing a hierarchy of biomarker priority is essential in the clinical management of resectable stage III NSCLC. In current practice, first-line testing of oncogenic driver mutations is required to guide targeted therapy, followed by PD-L1 assessment (≥ 50% threshold) to determine immunotherapy eligibility, and increasingly, ctDNA-based MRD for postoperative risk stratification. A PD-L1 status ≥ 50% currently has the highest clinical priority for the selection of patients for adjuvant atezolizumab[39]. Given the rapidly changing NSCLC treatment environment, new biomarkers that offer dynamic insights beyond tissue-based assessment are urgently needed.

MRD is a crucial biomarker for predicting postoperative recurrence in patients with NSCLC and is detected primarily through ctDNA or circulating tumor cells. The CheckMate 816 trial revealed that among 89 patients who received nivolumab plus chemotherapy, ctDNA clearance was associated with higher pCR rates (46% *vs.* 0%) and a longer EFS (median NR *vs.* 18.9 months)[22]. Similarly, patients with undetectable ctDNA levels in the NADIM study had significantly improved PFS and OS outcomes[44]. These results suggested that ctDNA testing following neoadjuvant chemoimmunotherapy may have important prognostic value and could provide a basis for further individualized treatment. The IMpower010 study demonstrated that patients with ctDNA-negative status had better DFS outcomes after surgery than ctDNA-positive patients in the setting of adjuvant therapy[96]. However, patients with stage II–IIIA disease, regardless of ctDNA clearance status, benefited from adjuvant ICI treatment. Only patients with persistent ctDNA positivity and a PD-L1 < 1% exhibited no significant improvement in DFS (HR = 0.88, 95% CI = 0.40–1.91)[97]. The LUNGCA-1 trial revealed that postoperative ctDNA-based MRD was significantly associated with disease recurrence

(HR = 11.1)[98]. Among MRD-positive patients, those who received adjuvant therapy had better recurrence-free survival (RFS) than patients who did not receive treatment (HR = 0.30; $P = 0.008$). Adjuvant therapy did not prolong the RFS in MRD-negative patients.

Landmarking analysis refers to the selection of a specific postoperative time point as a critical observation point for evaluating MRD status. The timing of postoperative landmark detection is crucial because surgery and adjuvant therapy affect ctDNA levels. Studies have shown that ctDNA positivity at postoperative day 3 was significantly associated with reduced RFS (HR = 5.31)[99]. Another study revealed that ctDNA levels measured 1 month postoperatively showed a significantly stronger correlation with DFS than ctDNA levels measured at days 3–7, although this difference was observed primarily among MRD-positive groups ($P = 0.018$) rather than MRD-negative groups[100]. Plasma samples should ideally be collected 3–7 days postoperatively for initial patient assessment based on these findings. Only when MRD status is positive at days 3–7 should additional samples be collected at 1 month for further evaluation with the 1-month result serving as the definitive MRD status.

Therefore, perioperative MRD monitoring has the potential to predict recurrence risk and inform adjuvant treatment decisions. However, the widespread clinical adoption of these biomarkers is currently hindered by substantial standardization challenges. Key technical limitations include inter-assay variability among anti-PD-L1 antibodies and the requirement for ultrahigh-sensitivity platforms to accurately detect low-abundance ctDNA in early-stage disease. Furthermore, tumor heterogeneity remains a barrier to consistent detection panel design across different clinical settings. Under these prevailing constraints, in the setting of adjuvant immunotherapy, MRD serves primarily as a prognostic indicator rather than a predictive biomarker of immunotherapeutic efficacy[97] but further validation is needed. Future studies should prioritize the standardization of precise dynamic evaluation methodologies and the establishment of clinical-grade validation frameworks to facilitate the development of truly individualized treatment strategies.

Conclusions

Recent data, regulatory approvals, and ongoing trials are transforming the standard of care. Improving the curative potential for patients with stage III NSCLC should be a key goal in managing this frequently fatal disease. Indeed, this goal appears more achievable with the introduction of ICIs.

Landmark studies, such as the CheckMate 816 trial, demonstrated significant benefits of neoadjuvant immunochemotherapy over chemotherapy alone in resectable stage III NSCLC, marking the beginning of a new era in neoadjuvant immunotherapy for NSCLC. Our single-arm meta-analysis further supported the favorable efficacy of neoadjuvant immunochemotherapy. The combination of ICI with radiotherapy demonstrated numerically higher pathologic response rates, while ICI combined with antiangiogenic agents also showed promising therapeutic potential. The IMpower010 trial demonstrated improved DFS in association with adjuvant immunotherapy. These trials have prompted debate regarding which treatment strategy is optimal for specific patient populations. We propose the following clinical practice recommendations for resectable stage III NSCLC based on existing evidence. Neoadjuvant immunochemotherapy (3–4 cycles) followed by surgery should be prioritized for patients in whom the PD-L1 TC is ≥ 1% with continuous monitoring for disease progression. Perioperative treatment is recommended for patients tolerating systemic therapy or with a PD-L1 < 1%. Continuing adjuvant therapy after neoadjuvant immunotherapy appears to confer survival benefits independent of achieving a pCR, particularly for patients with a PD-L1 < 1% who do not achieve a pCR. Individualized discussion of optimal treatment selection within the MDT is encouraged for all patients.

While the outlook for the use of ICIs in the treatment of stage III NSCLC is promising, challenges remain in the judicious application of ICIs. High-priority areas include establishing appropriate endpoints for stage III NSCLC. The limitations of current alternative endpoints in assessing distant occult metastasis and addressing ambiguous deficiencies are also underscored. Given the unique clinical needs and vulnerability of patients intolerant of chemotherapy, developing chemotherapy-free regimens is crucial. Optimizing perioperative treatment strategies is also important because the optimal number of cycles for neoadjuvant immunotherapy plus chemotherapy is unclear and requires individualized adjustment. Whether all patients require such intensive treatment regimens is uncertain, highlighting the need for precise stratification criteria and treatment escalation or de-escalation strategies. Moreover, for potentially resectable patients, international consensus on resectability criteria integrating anatomic, functional, and molecular features is urgently needed. Despite the preliminary efficacy of immunotherapy in this population, prospective randomized, controlled trials (RCTs) are required to clarify the comparative efficacy of immunotherapy versus definitive concurrent chemoradiotherapy across different subgroups and to establish evidence-based selection criteria. The discordance between radiologic findings and pathologic outcomes with the uncertainty regarding the need for adjuvant therapy in patients who achieve apCR highlights the importance of routine ctDNA-based MRD detection to guide adaptive treatment strategies. These adaptive strategies include treatment escalation for MRD-positive patients to eradicate micro-metastatic disease and potential de-escalation for patients with a pCR and MRD negativity to minimize toxicity. The development of AI-based multimodal predictive models that integrate radiomics, digital

pathology, and ctDNA analysis approaches to predict pathologic response and immunotherapy efficacy is another key area for exploration.

Overall, identifying strategies that meaningfully improve survival outcomes in patients with resectable stage III NSCLC remains a long-term challenge. Nevertheless, conventional therapies are continuously being refined through ongoing research. In biomarker-selected populations, next-generation immunotherapies, such as *LAG-3* inhibitors, TIGIT inhibitors, and antibody-drug conjugates (ADCs), have shown promise in specific subgroups, particularly patients with a PD-L1 TC ≥ 50% who may demonstrate the most favorable responses. In addition, LDRT combined with immunotherapy has demonstrated notable synergistic anti-tumor effects with manageable toxicity. Prospective trials (e.g., NCT05157542 and SACTION-01) are exploring the perioperative application. These novel agents and strategies are expected to continue improving outcomes for patients with resectable stage III NSCLC.

Grant support

This work was supported by a grant from the Natural Science Foundation of Shandong Province (Grant No. ZR2023LZL001).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yuzhen Cui, Xiangjiao Meng, Zhaoqin Huang, Anwen Liu.
Collected the data: Ailing Liu.
Contributed data or analysis tools: Junxu Wen.
Performed the analysis: Jianfeng Peng, Jiangao Ren.
Wrote the paper: Yuzhen Cui, Jingdong Xu.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019; 144: 1941-53.
2. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010; 28: 2181-90.
3. Jain P, Jain C, Velcheti V. Role of immune-checkpoint inhibitors in lung cancer. Ther Adv Respir Dis. 2018; 12: 1753465817750075.
4. Pistamaltzian NF, Georgoulias V, Kotsakis A. The role of immune checkpoint inhibitors in advanced non-small cell lung cancer. Expert Rev Respir Med. 2019; 13: 435-47.
5. Felip E, Altorki N, Vallieres E, Vynnychenko IO, Akopov A, Martinez-Marti A, et al. IMpower010: Overall Survival Interim Analysis of a Phase III Study of Atezolizumab vs Best Supportive Care in Resected NSCLC. World Conference on Lung Cancer; 2022.
6. Spicer J, Gao S, Liberman M, Kato T, Tsuboi M, Lee S, et al. LBA56 overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage non-small-cell lung cancer (NSCLC). Ann Oncol. 2023; 34: S1297-8.
7. Spicer J, Girard N, Provencio M, Wang C, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816. J Clin Oncol. 2024; 42: LBA8010.
8. Marinelli D, Nuccio A, Di Federico A, Ambrosi F, Bertoglio P, Faccioli E, et al. Improved event-free survival after complete or major pathologic response in patients with resectable NSCLC treated with neoadjuvant chemoimmunotherapy regardless of adjuvant treatment: a systematic review and individual patient data meta-analysis. J Thorac Oncol. 2025; 20: 285-95.
9. Banna GL, Hassan MA, Signori A, Giunta EF, Maniam A, Anpalakhan S, et al. Neoadjuvant chemo-immunotherapy for early-stage non-small cell lung cancer: a systematic review and meta-analysis. JAMA Netw Open. 2024; 7: e246837.
10. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science. 2016; 351: 1463-9.
11. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science. 2020; 367: eaax0182.
12. Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, et al. The IASLC lung cancer staging project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol. 2015; 10: 990-1003.
13. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, et al. The international association for the study of lung cancer lung cancer staging project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. J Thorac Oncol. 2015; 10: 1675-84.
14. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016; 11: 39-51.
15. Sorin M, Prosty C, Ghaleb L, Nie K, Katergi K, Shahzad MH, et al. Neoadjuvant chemoimmunotherapy for NSCLC: a systematic review and meta-analysis. JAMA Oncol. 2024; 10: 621-33.
16. Liu J, Blake SJ, Yong MC, Harjunpää H, Ngiow SF, Takeda K, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. Cancer Discov. 2016; 6: 1382-99.

17. Bakos O, Lawson C, Rouleau S, Tai LH. Combining surgery and immunotherapy: turning an immunosuppressive effect into a therapeutic opportunity. J Immunother Cancer. 2018; 6: 86.
18. Tan WL, Chua KLM, Lin CC, Lee VHF, Tho LM, Chan AW, et al. Asian thoracic oncology research group expert consensus statement on optimal management of stage III NSCLC. J Thorac Oncol. 2020; 15: 324-43.
19. Wong LY, Liou DZ, Roy M, Elliott IA, Backhus LM, Lui NS, et al. The impact of immunotherapy use in stage IIIA (T1-2N2) NSCLC: a nationwide analysis. JTO Clin Res Rep. 2024; 5: 100654.
20. Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med. 2018; 378: 1976-86.
21. Provencio M, Nadal E, Insa A, García-Campelo MR, Casal-Rubio J, Dómine M, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020; 21: 1413-22.
22. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med. 2022; 386: 1973-85.
23. Rothschild SI, Zippelius A, Eboulet EI, Savic Prince S, Betticher D, Bettini A, et al. SAKK 16/14: durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small-cell lung cancer—a multicenter single-arm phase II trial. J Clin Oncol. 2021; 39: 2872-80.
24. Shao M, Yao J, Wang Y, Zhao L, Li B, Li L, et al. Two vs three cycles of neoadjuvant sintilimab plus chemotherapy for resectable non-small-cell lung cancer: neoSCORE trial. Signal Transduct Target Ther. 2023; 8: 146.
25. Provencio M, Nadal E, Insa A, García Campelo R, Casal J, Dómine M, et al. Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2024; 25: 1453-64.
26. Forde PM, Spicer JD, Provencio M, Mitsudomi T, Awad MM, Wang C, et al. Overall survival with neoadjuvant nivolumab plus chemotherapy in lung cancer. N Engl J Med. 2025; 393: 741-52.
27. Jiang J, Wang Y, Gao Y, Sugimura H, Minervini F, Uchino J, et al. Neoadjuvant immunotherapy or chemoimmunotherapy in non-small cell lung cancer: a systematic review and meta-analysis. Transl Lung Cancer Res. 2022; 11: 277-94.
28. Deng H, Liang H, Chen J, Wang W, Li J, Xiong S, et al. Preoperative immunochemotherapy for locally advanced non-small cell lung cancer: an analysis of the clinical outcomes, optimal number of cycles, and peripheral immune markers. Transl Lung Cancer Res. 2022; 11: 2364-81.
29. Dickhoff C, Senan S, Schneiders FL, Veltman J, Hashemi S, Daniels JM, et al. Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable T3-4N0-1 non-small cell lung cancer: the INCREASE trial. BMC cancer. 2020; 20: 764.
30. Mauti LA, Finazzi T, Holer L, Bettini A, König D, Früh M, et al. SAKK 16/18: Immune-modulatory radiotherapy to enhance the effects of neoadjuvant PD-L1 blockade after neoadjuvant chemotherapy in patients with resectable stage III (N2) non-small cell lung cancer (NSCLC)—a multicenter phase II trial. J Clin Oncol. 2023; 41: 8547-7.
31. Hamada A, Soh J, Hata A, Nakamatsu K, Shimokawa M, Yatabe Y, et al. Phase II study of neoadjuvant concurrent chemo-immuno-radiation therapy followed by surgery and adjuvant immunotherapy for resectable stage IIIA-B (discrete N2) non-small-cell lung cancer: SQUAT trial (WJOG 12119L). Clin Lung Cancer. 2021; 22: 596-600.
32. Toyooka S, Hamada A, Soh J, Hata A, Nakamatsu K, Shimokawa M, et al. OA12.04 neoadjuvant concurrent chemo-immuno-radiation therapy followed by surgery for stage III-N2 NSCLC: SQUAT trial (WJOG 12119L). J Thorac Oncol. 2024; 19: S36-S37.
33. Eberhardt WEE, De Ruysscher D, Weder W, Le Péchoux C, De Leyn P, Hoffmann H, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol. 2015; 26: 1573-88.
34. Daly ME, Singh N, Ismaila N, Antonoff MB, Arenberg DA, Bradley J, et al. Management of stage III non-small-cell lung cancer: ASCO guideline. J Clin Oncol. 2022; 40: 1356-84.
35. Kernstine KH, Moon J, Kraut MJ, Pisters KM, Sonett JR, Rusch VW, et al. Trimodality therapy for superior sulcus non-small cell lung cancer: Southwest Oncology Group-Intergroup Trial S0220. Ann Thorac Surg. 2014; 98: 402-10.
36. Dickhoff C, Heineman D, Schneiders F, Houda I, Veltman J, Hashemi S, et al. OA06.04 surgery after neoadjuvant immuno-chemoradiotherapy in (borderline) resectable NSCLC: results from the INCREASE trial. J Thorac Oncol. 2023; 18: S56-7.
37. Zhao Z-R, Liu S-L, Zhou T, Li Z-C, Wu J-D, Xi M, et al. Stereotactic body radiation therapy with sequential immunochemotherapy as neoadjuvant therapy in resectable non-small cell lung cancer (SACTION-01 study). J Clin Oncol. 2023; 41: 8540-0.
38. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE collaborative group. J Clin Oncol. 2008; 26: 3552-9.
39. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet. 2021; 398: 1344-57.
40. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol. 2022; 23: 1274-86.
41. Felip E, Altorki N, Zhou C, Vallières E, Martínez-Martí A, Rittmeyer A, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. Ann Oncol. 2023; 34: 907-19.
42. Paz-Ares L, O'Brien MER, Mauer M, Dafni U, Oselin K, Havel L, et al. VP3-2022: Pembrolizumab (pembro) versus placebo

for early-stage non-small cell lung cancer (NSCLC) following complete resection and adjuvant chemotherapy (chemo) when indicated: randomized, triple-blind, phase III EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study. Ann Oncol. 2022; 33: 451-3.

43. Hirsch FR, McElhinny A, Stanforth D, Ranger-Moore J, Jansson M, Kulangara K, et al. PD-L1 immunohistochemistry assays for lung cancer: results from phase 1 of the blueprint PD-L1 IHC assay comparison project. J Thorac Oncol. 2017; 12: 208-22.
44. Provencio M, Serna-Blasco R, Nadal E, Insa A, García-Campelo MR, Casal Rubio J, et al. Overall survival and biomarker analysis of neoadjuvant nivolumab plus chemotherapy in operable stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). J Clin Oncol. 2022; 40: 2924-33.
45. Provencio M, Nadal E, González-Larriba JL, Martínez-Martí A, Bernabé R, Bosch-Barrera J, et al. Perioperative nivolumab and chemotherapy in stage III Non-Small-Cell lung cancer. N Engl J Med. 2023; 389: 504-13.
46. Heymach JV, Mitsudomi T, Harpole D, Aperghis M, Jones S, Mann H, et al. Design and rationale for a phase III, double-blind, placebo-controlled study of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab for the treatment of patients with resectable stages II and III non-small-cell lung cancer: the AEGEAN trial. Clin Lung Cancer. 2022; 23: e247-e51.
47. Mitsudomi T, Heymach JV, Reck M, Taube JM, Gao S, Horio Y, et al. OA12.05 surgical outcomes with neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in resectable NSCLC (AEGEAN). J Thorac Oncol. 2023; 18: S71-S2.
48. Reck M, Gale D, Zhu Z, Harpole D, Taube J, Mitsudomi T, et al. LBA49 associations of ctDNA clearance (CL) during neoadjuvant Tx with pathological response and event-free survival (EFS) in pts with resectable NSCLC (R-NSCLC): expanded analyses from AEGEAN. Ann Oncol. 2024; 35: S1239.
49. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. N Engl J Med. 2023; 389: 491-503.
50. Yue D, Wang W, Liu H, Chen Q, Chen C, Zhang J, et al. LBA58 Pathological response to neoadjuvant tislelizumab (TIS) plus platinum-doublet (PtDb) chemotherapy (CT) in resectable stage II-IIIA NSCLC patients (pts) in the phase III (Ph3) RATIONALE-315 trial. Ann Oncol. 2023; 34: S1299.
51. Lu S, Wu L, Zhang W, Zhang P, Wang W, Fang W, et al. Perioperative toripalimab + platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): interim event-free survival (EFS) analysis of the phase III NEOTORCH study. J Clin Oncol. 2023; 41: 425126-6.
52. Food and Drug Administration. FDA Approves Neoadjuvant/adjuvant Pembrolizumab for Resectable Non-small Cell Lung Cancer. FDA; 2023.
53. Forde PM, Peters S, Donington J, Meadows-Shropshire S, Tran P, Lucherini S, et al. PL02.08 Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816. J Thorac Oncol. 2024; 19: S2.
54. Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, et al. Perioperative nivolumab in resectable lung cancer. N Engl J Med. 2024; 390: 1756-69.
55. Hu H, Zou S, Xu R, Ichiki Y, De Ruysscher D, Yu F, et al. Conversion therapy from N3 unresectable lung adenocarcinoma to radical surgery: a case report. Ann Transl Med. 2019; 7: 590.
56. Sun C, Wang X, Xu Y, Shao G, Chen X, Liu Y, et al. Efficiency and safety of neoadjuvant PD-1 inhibitor (sintilimab) combined with chemotherapy in potentially resectable stage IIIA/IIIB non-small cell lung cancer: Neo-Pre-IC, a single-arm phase 2 trial. EClinicalMedicine. 2024; 68: 102422.
57. Ricciuti B, Fusco F, Cooper A, Garbo E, Pecci F, Aldea M, et al. Neoadjuvant PD-1 and PD-L1 blockade with chemotherapy for borderline resectable and unresectable stage III non-small cell lung cancer. JAMA Oncol. 2025; 11: 735-41.
58. Li J, Lu S, Tian Y, Jiang L, Li L, Xie SH, et al. Neoadjuvant low-dose radiotherapy plus durvalumab and chemotherapy for potentially resectable stage III NSCLC: a phase IB dose-escalation study. Radiother Oncol. 2024; 196: 110316.
59. Lei J, Zhao J, Gong L, Ni Y, Zhou Y, Tian F, et al. Neoadjuvant Camrelizumab plus platinum-based chemotherapy vs chemotherapy alone for Chinese patients with resectable stage IIIA or IIIB (T3N2) non-small cell lung cancer: the TD-FOREKNOW randomized clinical trial. JAMA Oncol. 2023; 9: 1348-55.
60. Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, et al. Perioperative durvalumab for resectable non-small-cell lung cancer. N Engl J Med. 2023; 389: 1672-84.
61. Bahce I, Dickhoff C, Schneiders FL, Veltman J, Heineman DJ, Hashemi SMS, et al. Single-arm trial of neoadjuvant ipilimumab plus nivolumab with chemoradiotherapy in patients with resectable and borderline resectable lung cancer: the INCREASE study. J Immunother Cancer. 2024; 12: e009799.
62. Duan H, Shao C, Luo Z, Wang T, Tong L, Liu H, et al. Perioperative sintilimab and neoadjuvant anlotinib plus chemotherapy for resectable non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 2 trial (TD-NeoFOUR trial). Sig Transduct Target Ther. 2024; 9: 296.
63. Wang M, Liu W, Guo H, Long H, Yu B, Zhao G, et al. Perioperative penpulimab-based combination therapy in patients with resectable non-small cell lung cancer (ALTER-L043): an open-label, multicenter, randomized, phase II trial. Sig Transduct Target Ther. 2026; 11: 21.
64. Zhao J, Zhao L, Guo W, Wang S, Tao X, Li L, et al. Efficacy, safety, and biomarker analysis of neoadjuvant camrelizumab and apatinib in patients with resectable NSCLC: a phase 2 clinical trial. J Thorac Oncol. 2023; 18: 780-91.
65. Wang C, Zhao X, Zhang L, Yue D, Zhang Z, Wang M, et al. OA01.06 A phase II study of perioperative ivonescimab alone or combined with chemotherapy in resectable non-small cell lung cancer. J Thorac Oncol. 2024; 19: S10.
66. Ji S, Sheng Z, Bian D, Bao M, Jin K, Zhang W, et al. Neoadjuvant camrelizumab plus chemotherapy or apatinib for resectable stage IIA-IIIA NSCLC: a multicenter, two-arm, phase II exploratory trial. BMC Med. 2025; 23: 429.

67. Chaft JE, Oezkan F, Kris MG, Bunn PA, Wistuba II, Kwiatkowski DJ, et al. Neoadjuvant atezolizumab for resectable non-small cell lung cancer: an open-label, single-arm phase II trial. Nat Med. 2022; 28: 2155-61.
68. Mountzios G, Remon J, Hendriks LEL, García-Campelo R, Rolfo C, Van Schil P, et al. Immune-checkpoint inhibition for resectable non-small-cell lung cancer – opportunities and challenges. Nat Rev Clin Oncol. 2023; 20: 664-77.
69. Nie R, Chen F, Provencio M, Wang Y, van den Ende T, van Laarhoven HWM, et al. Predictive value of radiological response, pathological response and relapse-free survival for overall survival in neoadjuvant immunotherapy trials: pooled analysis of 29 clinical trials. Eur J Cancer. 2023; 186: 211-21.
70. Hui Z, Men Y, Hu C, Kang J, Sun X, Bi N, et al. Effect of postoperative radiotherapy for patients with PIIIA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy: the phase 3 PORT-C randomized clinical trial. JAMA Oncol. 2021; 7: 1178-85.
71. Herbst RS, Wu YL, John T, Grohe C, Majem M, Wang J, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. J Clin Oncol. 2023; 41: 1830-40.
72. Tazdait M, Mezquita L, Lahmar J, Ferrara R, Bidault F, Ammari S, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: comparison of RECIST 1.1, iRRECIST and iRECIST criteria. Eur J Cancer. 2018; 88: 38-47.
73. Truillet C, Oh HLJ, Yeo SP, Lee CY, Huynh LT, Wei J, et al. Imaging PD-L1 expression with immunoPET. Bioconjug Chem. 2018; 29: 96-103.
74. Hughes DJ, Josephides E, O'Shea R, Manickavasagar T, Horst C, Hunter S, et al. 1283P predicting PD-L1 expression using [18F] FDG PET/CT in early stage non-small cell lung cancer (NSCLC). Ann Oncol. 2023; 34: S741.
75. Liang W, Cai K, Chen C, Chen H, Chen Q, Fu J, et al. Expert consensus on neoadjuvant immunotherapy for non-small cell lung cancer. Transl Lung Cancer Res. 2020; 9: 2696-715.
76. Rusch VW, Hawes D, Decker PA, Martin SE, Abati A, Landreneau RJ, et al. Occult metastases in lymph nodes predict survival in resectable non-small-cell lung cancer: report of the ACOSOG Z0040 trial. J Clin Oncol. 2011; 29: 4313-9.
77. Chaudhuri AA, Chabon JJ, Lovejoy AF, Newman AM, Stehr H, Azad TD, et al. Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. Cancer Discov. 2017; 7: 1394-403.
78. Ye G, Wu G, Qi Y, Li K, Wang M, Zhang C, et al. Non-invasive multimodal CT deep learning biomarker to predict pathological complete response of non-small cell lung cancer following neoadjuvant immunochemotherapy: a multicenter study. J Immunother Cancer. 2024; 12: e009348.
79. Wu Z, Wang L, Li C, Cai Y, Liang Y, Mo X, et al. DeepLRHE: a deep convolutional neural network framework to evaluate the risk of lung cancer recurrence and metastasis from histopathology images. Front Genet. 2020; 11: 768.
80. Gillies RJ, Schabath MB. Radiomics improves cancer screening and early detection. Cancer Epidemiol Biomarkers Prev. 2020; 29: 2556-67.
81. El Ayachy R, Giraud N, Giraud P, Durdux C, Giraud P, Burgun A, et al. The role of radiomics in lung cancer: from screening to treatment and follow-up. Front Oncol. 2021; 11: 603595.
82. Siah KW, Khozin S, Wong CH, Lo AW. Machine-learning and stochastic tumor growth models for predicting outcomes in patients with advanced non-small-cell lung cancer. JCO Clin Cancer Inform. 2019; 3: 1-11.
83. Lynch CM, Abdollahi B, Fuqua JD, de Carlo AR, Bartholomai JA, Balgemann RN, et al. Prediction of lung cancer patient survival via supervised machine learning classification techniques. Int J Med Inform. 2017; 108: 1-8.
84. Liu L, Bai H, Wang C, Seery S, Wang Z, Duan J, et al. Efficacy and safety of first-line immunotherapy combinations for advanced NSCLC: a systematic review and network meta-analysis. J Thorac Oncol. 2021; 16: 1099-117.
85. Lilenbaum RC, Cashy J, Hensing TA, Young S, Cella D. Prevalence of poor performance status in lung cancer patients: implications for research. J Thorac Oncol. 2008; 3: 125-9.
86. De Marinis F, Bria E, Baas P, Tiseo M, Camerini A, Favaretto AG, et al. Treatment of unfit patients with advanced non-small-cell lung cancer: definition criteria according an expert panel. Clin Lung Cancer. 2015; 16: 399-405.
87. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 2019; 37: 537-46.
88. Zhou C, Chen J, Wu L, Wang L, Liu B, Yao J, et al. PL02.04 phase 3 study of ivonescimab (AK112) vs. pembrolizumab as first-line treatment for PD-L1-positive advanced NSCLC: primary analysis of harmoni-2. J Thorac Oncol. 2024; 19: S1.
89. Sun C, Liu Y, Zhang P, Wang X, Xu Y, Lin X, et al. Interim analysis of the efficiency and safety of neoadjuvant PD-1 inhibitor (sintilimab) combined with chemotherapy (nab-paclitaxel and carboplatin) in potentially resectable stage IIIA/IIIB non-small cell lung cancer: a single-arm, phase 2 trial. J Cancer Res Clin Oncol. 2023; 149: 819-31.
90. Aggarwal V, Workman CJ, Vignali DAA. LAG-3 as the third checkpoint inhibitor. Nat Immunol. 2023; 24: 1415-22.
91. Girard N, Burotto M, Paz-Ares LG, Reck M, Schenker M, Lingua A, et al. LBA53 nivolumab (NIVO) plus relatlimab with platinum-doublet chemotherapy (PDCT) vs NIVO + PDCT as first-line (1L) treatment (tx) for stage IV or recurrent NSCLC: results from the randomized phase II RELATIVITY-104 study. Ann Oncol. 2024; 35: S1243-4.
92. Schuler M, Cuppens K, Plönes T, Wiesweg M, Du Pont B, Hegedus B, et al. Neoadjuvant nivolumab with or without relatlimab in resectable non-small-cell lung cancer: a randomized phase 2 trial. Nat Med. 2024; 30: 1602-11.

93. Cuppens K, Baas P, Wiesweg M, Du Pont B, Ploenes T, Theegarten D, et al. OA01.05 neoadjuvant nivolumab with or without relatlimab in resectable NSCLC: additional analysis and extended follow-up. J Thorac Oncol. 2024; 19: S9.
94. Zhang Y, Chen H. MA04.01 no versus systematic mediastinal LN dissection for GGO-dominant lung adenocarcinoma: a multicenter, phase III, non-inferiority RCT. J Thorac Oncol. 2025; 20: S65-6.
95. Cascone T, Florian G, Bonanno L, Lieberman M, Bylicki O, Insa A, et al. PL02.07 neocoast-2: efficacy and safety of neoadjuvant durvalumab (D) + novel anticancer agents + CT and adjuvant D ± novel agents in resectable NSCLC. J Thorac Oncol. 2024; 19: S1-S2.
96. Felip E, Srivastava M, Reck M, Wakelee H, Altorki NK, Vallieres E, et al. 1O IMpower010: ctDNA status in patients (pts) with resected NSCLC who received adjuvant chemotherapy (chemo) followed by atezolizumab (atezo) or best supportive care (BSC). Immuno Oncol Technol. 2022; 16: 100106.
97. Zhou C, Das Thakur M, Srivastava MK, Zou W, Xu H, Ballinger M, et al. 2O IMpower010: Biomarkers of disease-free survival (DFS) in a phase III study of atezolizumab (atezo) vs best supportive care (BSC) after adjuvant chemotherapy in stage IB-IIIA NSCLC. Ann Oncol. 2021; 32: S1374.
98. Xia L, Mei J, Kang R, Deng S, Chen Y, Yang Y, et al. Perioperative ctDNA-based molecular residual disease detection for non-small cell lung cancer: a prospective multicenter cohort study (LUNGCA-1). Clin Cancer Res. 2022; 28: 3308-17.
99. Chen K, Zhao H, Shi Y, Yang F, Wang LT, Kang G, et al. Perioperative dynamic changes in circulating tumor DNA in patients with lung cancer (DYNAMIC). Clin Cancer Res. 2019; 25: 7058-67.
100. Chen K, Yang F, Shen H, Wang C, Li X, Chervova O, et al. Individualized tumor-informed circulating tumor DNA analysis for postoperative monitoring of non-small cell lung cancer. Cancer Cell. 2023; 41: 1749-62.e6.

Cite this article as: Cui Y, Xu J, Wen J, Peng J, Ren J, Liu A, et al. Opportunities and challenges of immunotherapy for patients with resectable and potentially resectable stage III non-small cell lung cancer. Cancer Biol Med. 2026; 23: 865-887. doi: 10.20892/j.issn.2095-3941.2025.0589