

# Contemporary Strategies: Incorporating Immunotherapy into Stage 3 Non-small Cell Lung Cancer Treatment

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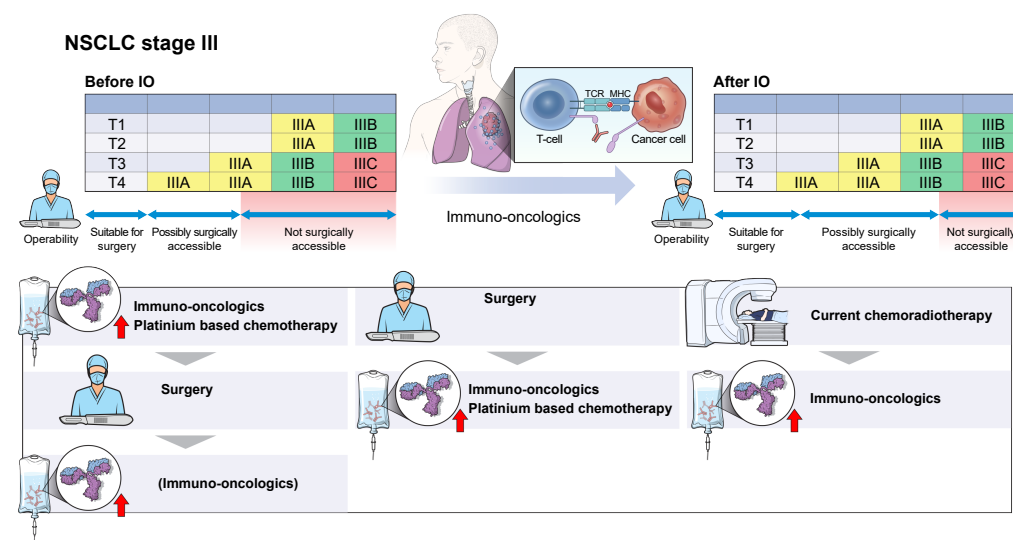
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## Abstract

Stage 3 non-small cell lung cancer (NSCLC) exhibits significant diversity, making it challenging to define an optimal treatment. A collaborative multidisciplinary approach is essential in crafting individualized treatments. Previously, targeted therapies and immunotherapies were commonly used to treat patients with advanced and metastatic lung cancer. Such treatments are now being extended to individuals considered surgery, as well as patients once considered unsuitable for surgery. These changes have increased surgical success and substantially reduced postoperative recurrence. However, the possibility of severe adverse effects from immunotherapy can deter some patients from performing surgery. It is essential to carefully explore the clinical traits and biomarkers of patients who may benefit the most from immunotherapy, and patients for whom immunotherapy should not be prescribed. In summary, it's crucial to effectively integrate the latest immunotherapy in treating stage 3 NSCLC patients, thereby increasing their opportunities for surgical intervention, and ensuring they receive the best possible care.

**Keywords:** Immunotherapy; Non-Small Cell Lung Cancer; Consolidation; Surgery; Adjuvant Treatment; Neoadjuvant Treatment

## Take Home Message

Stage III non-small cell lung cancer (NSCLC) patients exhibit significant heterogeneity, allowing for the application of various treatments in diverse sequences. With recent advancements, it's now possible to integrate immunotherapy or targeted therapy with surgical interventions for stage III NSCLC patients. Consequently, it's crucial to endeavor, through multidisciplinary collaboration, to identify and implement the most tailored treatment strategy for each individual.

## Introduction

During the past decade, there have been substantial advances in lung cancer treatments. Targeted therapies, immunotherapies, stereotactic body irradiation, and refinements in video-assisted thoracic surgery have significantly enhanced the outcomes. Even patients with advanced or metastatic lung cancer often maintain high quality of life and exhibit prolonged survival. However, despite these advancements, many patients still confront challenges such as post-surgery or post-radiation recurrence, resistance to chemotherapy, and brain metastasis. Thus, lung cancer remains the primary cause of cancer-related mortality<sup>1</sup>.

For patients with stage 1 and 2 NSCLC, surgery is performed whenever possible, and adjuvant chemotherapy may be prescribed if needed. For patients with stage 4 NSCLC, the primary approach is anticancer therapy; palliative radiation treatment or salvage surgery may be considered if necessary. However, the factors involved for patients with stage 3 NSCLC are more complex; careful consideration of various treatment options is required<sup>1,2</sup>. Stage 3 has been divided into sub-stages 3A, 3B, and 3C with distinct 5-year survival rates (36%, 26%, and 13%, respectively)<sup>3</sup>. Multidisciplinary care is needed to select the most suitable treatment for each individual. The conventional approach for patients with stage 3 NSCLC considered unsuitable for surgery has been concurrent chemoradiation followed by a waiting period to observe the treatment outcomes. However, considering the recent introduction of adjuvant immunotherapies and targeted therapies after surgery or radiation, lung cancer treatment outcomes have further improved<sup>4</sup>. This improvement has encouraged clinicians to carefully consider the selection of an optimal treatment. Several studies by the multidisciplinary teams of various hospitals have revealed extensive variations in the staging and treatment of patients with stage 3A NSCLC. While some variations may be inevitable when dealing with challenging patients, more

principled treatment is needed<sup>5</sup>.

In this review, we discuss the current treatment guidelines and practices for patients with stage 3 NSCLC, as well as treatment strategies that have recently been actively investigated, with a focus on pre- and post-surgery immunotherapies and the corresponding treatment outcomes<sup>2,3,6-12</sup>.

## Changes in and Implications of TNM Staging

In the American Joint Committee on Cancer 8th edition of lung cancer staging, a greater emphasis is placed on the detailed T stage classification, compared with the previous edition. In the 7th edition, tumors  $\geq 7$  cm were classified as T3; in the 8th edition, they are classified as T4. Similarly, cases exhibiting invasion of the diaphragm were classified as T3 in the 7th edition; in the 8th edition, they are classified as T4<sup>13</sup>. In contrast, cases involving lesions within 2 cm of the main bronchial carina were classified as T3 in the 7th edition; in the 8th edition, that distance has been removed, and all cases involving invasion of the main bronchus are now classified as T2<sup>13,14</sup>. These changes are likely attributable to advances in surgery and radiation treatment. Some cancers previously classified as T2N2M0 or T3N2M0/stage 3A are now classified as T3N2M0 or T4N2M0/stage 3B. Thus, it is essential to review research conducted in the era of the 7th edition to appropriately apply the staging criteria of the 8th edition in clinical practice<sup>5</sup>.

## NSCLC Stage 3: Comprehensive Disease Spectrum and Multifaceted Treatment Modalities

Stage 3 NSCLC presents a wide variety of cases, each with numerous potential treatment strategies. Stage 3 includes cancers ranging from T4N0M0 (with rather large tumors but no lymph node metastases) to T4N3M0 (with large tumors and multilevel lymph node metastases) that render surgical interventions impossible and radiotherapy difficult. NSCLC can be broadly classified as resectable, potentially resectable, or unresectable<sup>1,2,15,16</sup>. In a modified Delphi study involving 30 physicians from diverse specialties who responded to a 76-item questionnaire, a significant majority of participants (up to 93%) reached a consensus on the following treatment approaches<sup>16</sup>. The panel recommended surgery followed by (neo)adjuvant chemotherapy for single-station disease patients<sup>16</sup>. For those with multi-station N2 disease, the panel suggested surgery

with concurrent chemoradiotherapy (CCRT), followed by adjuvant immunotherapy<sup>16</sup>.

One study showed that a tri-modal approach significantly improved survival and the relapse free survival in patients with locally advanced NSCLC, emphasizing the importance of multidisciplinary decision<sup>17</sup>. Perioperative platinum-based chemotherapy increased such survival by 5.4% compared with surgical monotherapy, while the complications of grade 3 or higher developed in >60% of patients. However recent study revealed major pathological responses to neoadjuvant chemotherapy in about 22% of patients with non-squamous NSCLC<sup>16,18,19</sup>.

One study of 8,110 patients treated in 52 South Korean institutions from 2014 to 2016 assessed the treatment preferences and outcomes of patients with stage 3 lung cancer. Patients with stage 3A NSCLC favored surgery (24.4%); the 2-year survival rate was 45.3%, and surgery was especially beneficial for patients with squamous cell carcinoma. Patients with stage 3B and 3C survived better if they underwent CCRT compared with monotherapies; the survival rates were 27.0% and 24.8%, respectively. Overall, CCRT consistently led to better survival in patients with later stages of cancer<sup>20</sup>.

For patients with stage 3 NSCLC who are eligible for surgery, neoadjuvant chemotherapy or chemoradiation is typically advised, particularly when they exhibit N2 involvement or superior sulcus tumors. If pre-surgery chemotherapy is not prescribed, postoperative adjuvant chemotherapy is recommended. For tumors considered unresectable, the suggested treatment is CCRT. If the disease does not progress after CCRT, durvalumab should be considered<sup>21</sup>.

## Evolution of Standard Management and New Concerns about Patients with Stage 3 NSCLC

Recently, targeted therapies such as estimated glomerular filtration rate (EGFR)-tyrosine kinase inhibitors and immunotherapies have led to promising outcomes in metastatic lung cancer, and when prescribed as adjuvants after surgery or CCRT. The ADAURA (ClinicalTrials.gov identifier: NCT02511106) study showed significant improvements in the 5-year survival rates of patients with stage 1B, 2, and 3A who had EGFR exon 19 deletions or L858R mutations and received osimertinib for 3 years after surgery, compared with such patients who received placebo<sup>4</sup>. Similarly, the A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced,

Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC) study revealed substantial improvements in the survival rates of patients with stage 3 NSCLC who had tumor cell programmed death-ligand 1 (PD-L1) expression levels  $\geq 1\%$  and received 1 year of durvalumab consolidation therapy after CCRT, compared with controls<sup>6,22,23</sup>. More recently, immunotherapies used as neoadjuvants, adjuvants, or both, improved the survival of patients with stage 3 lung cancer who had undergone surgical resection. Perioperative immune checkpoint inhibitors (ICIs) rendered patients with potentially resectable tumors eligible for surgery and reduced postoperative recurrence in high-risk cases<sup>7</sup>. However, ICI therapy may trigger hyper-progression or severe adverse events that render some patients ineligible for surgery. Moreover, the radiological distinction between tumor progression and immune system-related responses, such as inflammation and tumor cell death after ICI treatment, can be challenging<sup>24</sup>. Several studies have identified cases in which tumor sizes increased after ICI treatment, but examination of resected tissues revealed a major pathological response (i.e., <10% cancer cells) or complete pathological response (i.e., no cancer cells). Further in-depth research is required<sup>6,9,10,12</sup>. We have organized the treatment guideline for stage 3 NSCLC patients according to the approval and reimbursement status in South Korea as of January 2024 (Figure 1).

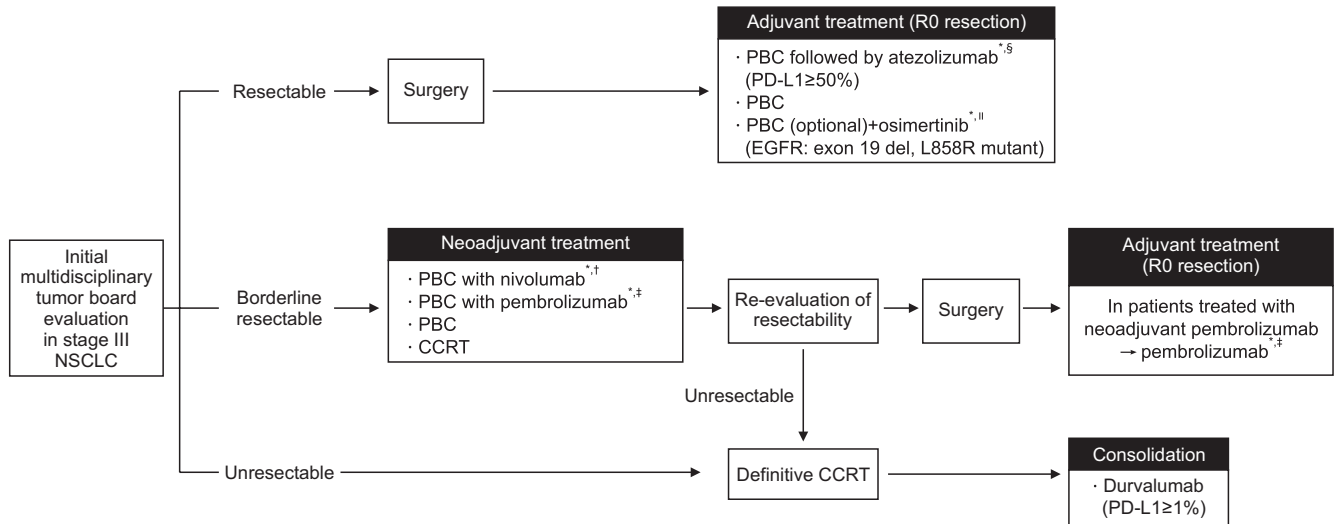
## Criteria for Adjuvant and Neoadjuvant Therapy in Stage 3 NSCLC Treatment

Deciding between adjuvant and neoadjuvant treatment is not a straightforward issue. However, if the tumor size is large or the tumor is adjacent to surrounding blood vessels and bronchi, making it potentially resectable, opting for neoadjuvant treatment might be more beneficial.

### 1. Neoadjuvant treatment

In neoadjuvant treatment for stage 3 NSCLC, targeted treatment is ideal for patients with identifiable genetic mutations in EGFR and anaplastic lymphoma kinase. Immunotherapy offers promising effect to some patients but should be avoided in those with active autoimmune conditions, underlying immunodeficiency, or a history of severe immune-related side effects. Radiation is used to reduce tumor size in locally advanced, potentially resectable tumors. It's contraindicated for patients with significantly impaired lung function, those

**Figure 1.** Recommended guideline in patients with stage 3 non-small cell lung cancer (NSCLC) according to approval and reimbursement in South Korea (as of January 2024). Initial multidisciplinary tumor board evaluation in stage 3 NSCLC is essential for evaluating resectability. Resectable or borderline resectable cases may be considered for adjuvant treatment or neoadjuvant treatment. Unresectable stage 3 patients can be treated with definitive concurrent chemoradiation therapy (CCRT) followed by consolidation with durvalumab. \*Approval but non-reimbursement; <sup>†</sup>Since October, 2022; <sup>‡</sup>Since December, 2023; <sup>§</sup>Since November 2022; <sup>||</sup>Since February 2021. PBC, platinum-based chemotherapy; PD-L1: programmed death-ligand 1; EGFR: estimated glomerular filtration rate.



who have previously received the maximum safe radiation dose.

Finally, CCRT is aimed at shrinking locally advanced tumors in patients with a robust health status. It's not recommended for patients with compromised performance status, significant other illnesses, or markedly impaired lung function. Careful patient evaluation is essential to balance the potential benefits of these treatments against their risks. Indications and contraindications for each treatment are listed in Table 1.

## 2. Adjuvant treatment

In stage 3 NSCLC patients who have achieved an R0 resection post-surgery, considering adjuvant therapy with ICIs like atezolizumab or pembrolizumab is a viable strategy. Additionally, osimertinib treatment can be a suitable option for those with specific mutations such as the EGFR exon 19 deletion or the exon 21 L858R substitution. For patients with R1 surgical margins, initiating sequential or concurrent chemoradiation is recommended. In cases of R2 margins, concurrent chemoradiation becomes imperative. These strategies are crucial for addressing any remaining disease and enhancing overall patient prognosis.

Although there are no absolute contraindications for administering ICIs as adjuvant therapy after surgery in NSCLC patients, certain conditions warrant careful consideration. Patients with pre-existing autoimmune

diseases, underlying interstitial lung diseases such as idiopathic pulmonary fibrosis, or compromised pulmonary function due to conditions like severe chronic obstructive pulmonary disease or combined pulmonary fibrosis and emphysema, should be assessed thoroughly. Furthermore, immunotherapy should be approached with caution in patients with immunosuppression. Each case should be evaluated individually by a multidisciplinary team to weigh the benefits and risks of treatment.

Contraindications for adjuvant radiotherapy or chemoradiotherapy after surgery primarily include poor overall health or a low performance status, severe coexisting conditions such as advanced heart, lung, or kidney diseases, and incomplete recovery or complications related to recent surgery. Particularly, patients with prior radiation to the same area and those with severe pulmonary dysfunction may experience further deterioration with radiotherapy. This is especially critical if a large portion of the lung requires irradiation, as it can exacerbate respiratory insufficiency and compromise overall respiratory function (Table 1).

## Clinical Research Regarding Perioperative ICI Therapies

Recently, perioperative treatments using ICIs have been extensively researched; many positive results have

**Table 1.** Guidelines for neoadjuvant therapy eligibility and exclusions in stage 3 NSCLC treatment

Treatment type	Indications	Contraindications
Targeted treatment	Specific genetic mutations present (EGFR, ALK)	Lack of targetable mutations Previous adverse reactions or resistance to similar therapies
Immunotherapy	1) Nivolumab+Chemotherapy: $\geq 4$ cm or LN metastasis (+) regardless of PD-L1 expression 2) Pembrolizumab+Chemotherapy: resectable stage 2, 3A, 3B followed by pembrolizumab adjuvant treatment	Active autoimmune conditions Immunodeficiency History of severe immune-related side effects
Radiation	Locally advanced, potentially resectable tumors	Markedly impaired lung function Exceeding prior radiation treatment
Concurrent chemoradiotherapy	Locally advanced tumors for downsizing pre-surgery Patients with robust health status	Compromised performance status Significant other illnesses Markedly impaired lung function

NSCLC: non-small cell lung cancer; EGFR: estimated glomerular filtration rate; ALK: anaplastic lymphoma kinase; LN: lymph node; PD-L1: programmed death-ligand 1.

been reported (Table 2). A 2018 *New England Journal of Medicine* paper evaluating neoadjuvant nivolumab treatment was the first such study; 21 patients with stage 1, 2, and 3 cancers, including seven patients with stage 3A cancers (33%), were enrolled<sup>7</sup>. The pathological response was high (42.8%). Notably, although increases in tumor size were evident on computed tomography, some cases revealed no cancer cells on pathological examination; thus, it was difficult to assess the effects of ICI treatment using computed tomography alone<sup>8,12</sup>. In the later Neo-Adjuvant Immunotherapy (NADIMII) study, neoadjuvant nivolumab in combination with cytotoxic chemotherapy led to a significant increase in the proportion of patients undergoing definitive surgery (93%, compared with 69% for patients receiving cytotoxic therapy alone)<sup>24</sup>. In the CheckMate 816 Phase 3 study, patients with stage 1B (tumors  $\geq 4$  cm) to stage 3A NSCLC who received nivolumab plus platinum-doublet chemotherapy exhibited significant improvements in event-free survival, overall survival, and pathological complete response<sup>12</sup>. The Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010) study revealed that atezolizumab prescribed after adjuvant chemotherapy improved disease-free survival among patients with resected stage 2–3A NSCLC, especially among patients with  $\geq 1\%$  PD-L1-positive tumor cells; 11% of patients experienced grade 3 and 4 adverse events related to atezolizumab, and 1% of such patients experienced grade 5 events<sup>10</sup>. The Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-

3475-091/KEYNOTE-091) (PEARLS) study revealed that the median disease-free survival was 53.6 months among patients receiving pembrolizumab, compared with 42.0 months in the placebo group (hazard ratio [HR], 0.76;  $p=0.0014$ ). In the population with a PD-L1 tumor proportion score of 50% or higher, neither the pembrolizumab group nor the placebo group achieved a median disease-free survival. Adverse events of grade 3 or higher were observed in 34% of the pembrolizumab group and 26% of the placebo group<sup>25</sup>. The KEYNOTE-671 study evaluated pembrolizumab as both a neoadjuvant treatment and an adjuvant treatment. At 24 months, the event-free survival rates were 62.4% in the pembrolizumab group and 40.6% in the placebo group (HR, 0.58;  $p<0.001$ ); the overall survival rates were 80.9% and 77.6%, respectively. The pembrolizumab group exhibited considerably more major pathological and complete responses. Grade 3 or higher adverse events were more common in the pembrolizumab group (44.9%) than in the placebo group (37.3%)<sup>26</sup>.

## Ongoing Clinical Research Regarding Perioperative Therapies

There are so many ongoing clinical trials including phase I, II, and III in stage 3 NSCLC patients. We summarized the phase II and III clinical trials that have produced or are expected to produce significant results and will soon be available for clinical application.

### 1. Ongoing clinical trials of perioperative therapies for patients with resectable stage 3 NSCLC

Neoadjuvant and/or adjuvant ICI treatment has im-



**Table 2.** Clinical research results regarding perioperative ICI therapies

Study Year	Phase/Enrollment	Treatment	Effect	Reference
2018 (Consolidation), PACIFIC	Phase 3, PD-L1 (+) III (n=713)	Consolidation post-CCRT; durvalumab bi-weekly for up to 12 months	12-mo PFS: 55.9% vs. 35.3%; 18-mo PFS: 44.2% vs. 27%	<sup>23</sup>
2021 (Adjuvant ICI), IMPOWER 010	Phase 3, IB-III A (n=227)	Adjuvant atezolizumab post-chemotherapy (up to 16 cycles)	DFS among all: HR, 0.79; 95% CI, 0.64–0.96; p=0.020	<sup>10</sup>
2022 (Neoadjuvant ICI), CheckMate 816	Phase 3, IB-III A (n=358)	Nivolumab+platinum- doublet chemo q3w for 3 cycles; 4 adjuvant cycles of chemo/radiation	Median EFS: nivolumab+chemo (31.6 mo; 95% CI, 30.2–NR); chemo alone (20.8 mo; 95% CI, 14.0–26.7); p=0.005	<sup>12</sup>
2022 (Adjuvant), PEARLS/ KEYNOTE-091	Phase 3, IB-III A (n=1,955)	Adjuvant pembrolizumab q3w for up to 18 cycles	Median DFS: pembrolizumab (53.6 mo; 95% CI, 39.2–NR); placebo (42.0 mo; 95% CI, 31.3–NR)	<sup>25</sup>
2023 (Neo+Adjuvant), KEYNOTE-671	Phase 3 II, III A, III B (n=397)	Neoadjuvant pembrolizumab+chemo; adjuvant pembrolizumab vs. neoadjuvant chemo	EFS at 24 mo (pembrolizumab 62.4%, control 40.6%; HR, 0.58); OS at 24 mo (pembrolizumab 80.9%, control 77.6%, p=0.02)	<sup>26</sup>

ICI: immune checkpoint inhibitor; PACIFIC: A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy; PD-L1: programmed death-ligand 1; CCRT: concurrent chemoradiotherapy; PFS: progression-free survival; IMPOWER: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer; DFS: disease-free survival; HR: hazard ratio; CI: confidence interval; q3w: means every 3 weeks; EFS: event-free survival; NR: not reached; PEARLS/KEYNOTE-091: Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer; OS: overall survival.

proved the clinical outcomes of patients with resectable stage 3 NSCLC. Various clinical trials of neoadjuvant or adjuvant ICI treatments before and after surgery are ongoing; several ICIs serve as monotherapies, are combined with chemotherapy, or are added to both other new agents and chemotherapy (Table 3). A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer (AEGEAN) study evaluated the efficacies of neoadjuvant and adjuvant durvalumab (ICI monotherapy). In the IMPOWER 030, CheckMate 77T, and Neoadjuvant and Adjuvant Treatment in Resectable Non-small Cell Lung Cancer (NeoCOAST-2) trials, participants received ICI (atezolizumab or nivolumab) and chemotherapy combinations, or ICIs combined with chemotherapy and other drugs such as tiragolumab (an anti-T-cell immunoglobulin and ITIM domain [TIGIT] monoclonal antibody [mAb]), oleclumab (an anti-CD73 antibody), or monalizumab (an anti-natural killer group 2 member A-blocking [NKG2A] mAb) as neoadjuvant and/or adjuvant treatments. These trials used event-free survival, pathological complete response, major

pathological response, and overall survival as primary or secondary endpoints.

## 2. Ongoing clinical trials of chemoradiation-based therapies for patients with unresectable stage 3 NSCLC

For patients with unresectable stage 3 NSCLC, durvalumab consolidation treatment became the standard of care after the PACIFIC study; several clinical trials exploring consolidation therapy after CCRT are in progress. The efficacies of combinations of programmed cell death protein 1 (PD-1)/PD-L1 inhibitors (atezolizumab, durvalumab, nivolumab, or pembrolizumab) and other drugs (anti-TIGIT mAb, anti-CD73 antibody, anti-NKG2A-blocking mAb, anti-cytotoxic T-lymphocyte associated protein 4 [CTLA4] inhibitor, and/or a selective inhibitor of poly [ADP-ribose] polymerase [PARP]1/2) are being evaluated as consolidation treatments for patients with unresectable stage 3 NSCLC (Table 4).

**Table 3.** Summary of ongoing and recently completed clinical trials of perioperative therapies in patients with resectable stage 3 non-small cell lung cancer

(Setting) Trial title	Drug	Stage	Primary outcome	Trial phase	Trial number
(Neoadjuvant) IMPOWER 030	Atezolizumab	2, 3A, or select 3B (T3N2 only)	EFS	Phase 3	NCT03456063
(Neo+adjuvant) AEGEAN	Durvalumab	Stage 2A to select (i.e., N2) stage 3B	pCR, EFS	Phase 3	NCT03800134
(Neo+adjuvant) CheckMate 77T	Nivolumab	Stage 2A (>4 cm) to 3B (T3N2)	EFS	Phase 3	NCT04025879
(Adjuvant) MERMAID-1	Durvalumab	Stage 2–3	DFS	Phase 3	NCT04385368

IMPOWER: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer; EFS: event-free survival; NCT: national clinical trial; AEGEAN: A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Non-small Cell Lung Cancer; pCR: pathologic complete remission; MERMAID-1: Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II–III Non-small Cell Lung Cancer (NSCLC); DFS: disease-free survival.

**Table 4.** Summary of ongoing and recently completed clinical trials of chemoradiation-based therapies in patients with unresectable stage 3 non-small cell lung cancer

Trial title	Drug	PD-L1	Primary outcome	Trial phase	Trial number
SKYSCRAPER-03	Atezolizumab and tiragolumab	Any PD-L1	PFS	Phase 3	NCT04513925
PACIFIC-8	Durvalumab+domvanalimab	PD-L1 $\geq$ 1%	PFS	Phase 3	NCT05211895
PACIFIC-9	Durvalumab with oleclumab or durvalumab with monalizumab	Any PD-L1	PFS	Phase 3	NCT05221840
CheckMate73L	Nivolumab and ipilimumab	Any PD-L1	PFS	Phase 3	NCT04026412
KEYLYNK-012	Pembrolizumab with or without olaparib	Any PD-L1	PFS, OS	Phase 3	NCT04380636
KEYVIBE-006	Pembrolizumab/vibostolimab	Any PD-L1	PFS, OS	Phase 3	NCT05298423

PD-L1: programmed death-ligand 1; SKYSCRAPER: A Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Participants With Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC); PFS: progression-free survival; NCT: national clinical trial; PACIFIC: A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy; KEYLYNK: Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC); OS: overall survival; KEYVIBE: Study of Pembrolizumab/Vibostolimab (MK-7684A) in Combination With Concurrent Chemoradiotherapy Followed by Pembrolizumab/Vibostolimab Versus Concurrent Chemoradiotherapy Followed by Durvalumab in Participants With Stage III Non-small Cell Lung Cancer.

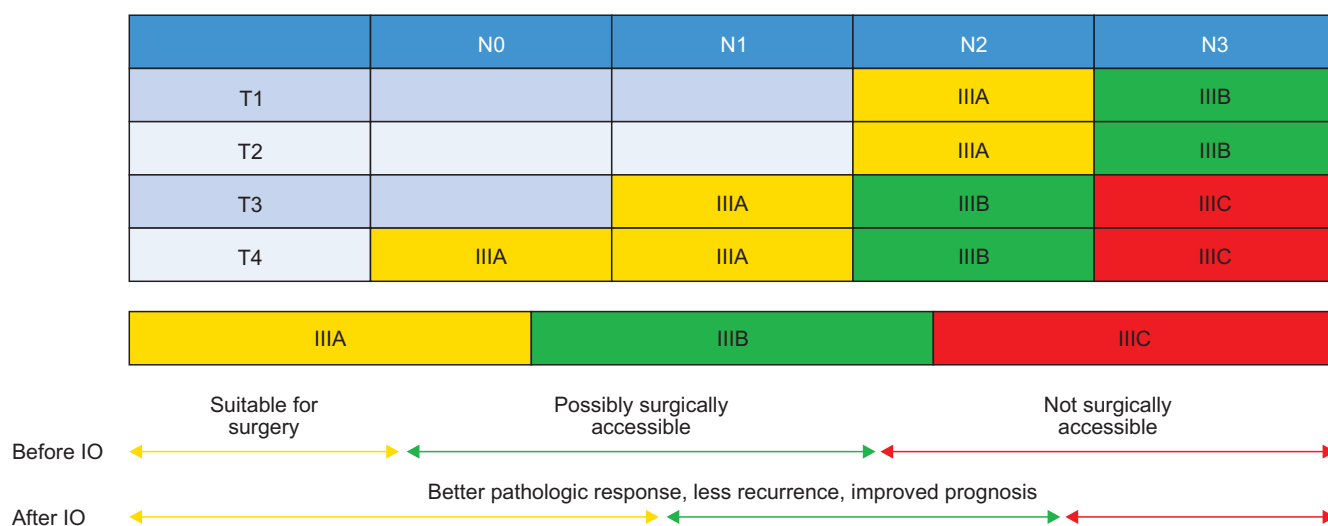
## Discussion

Stage 3 NSCLC is a multifaceted condition; it is difficult to always ensure the best possible outcomes<sup>2-4,9,22,26</sup>. Such patients are subjected to multimodal interventions associated with therapeutic risks and adverse events; it is challenging to enhance long-term survival. For stage 3 NSCLCs that can be surgically excised, no consensus optimal multimodal strategy has emerged; patient preferences, collaborative decision-making, and multidisciplinary team proficiency are key factors

that influence the preferred treatment<sup>2,3,13,17,27</sup>. When stage 3 NSCLC is non-operable, CCRT is the recommended therapy. Durvalumab has become a standard post-treatment for patients with stage 3 non-operable NSCLC and  $\geq$ 1% PD-L1-positive tumor cells who have undergone two rounds of platinum-infused CCRT. This approach may further improve the outcomes of patients with stage 3 NSCLC<sup>23</sup>.

Considering the recent introductions of immunotherapies and targeted therapies in neoadjuvant and adjuvant settings, more patients with NSCLC stage 3 now

**Figure 2.** Innovative breakthroughs with immune checkpoint inhibitor therapy for stage 3 non-small cell lung cancer. Utilizing immunotherapy in both neoadjuvant and adjuvant settings has expanded the pool of patients suitable for surgical treatments. This approach has enhanced the post-surgical pathologic response in stage 3 patients, resulting in decreased relapse rates and an improved overall prognosis. IO: immuno-oncology.



consider surgery, and the postoperative prognosis has improved<sup>1,4,7,10-12,25,28-30</sup>. However, some patients may experience severe ICI-associated adverse events; there is a need to conduct additional research regarding ICI indications and relevant biomarkers.

In the contemporary landscape of advanced systemic therapies, a precise definition of resectable stage 3 NSCLC is urgently required to ensure consistent planning by multidisciplinary teams and to facilitate robust comparisons across trials exploring multimodal treatment strategies for various subsets of patients with stage 3 NSCLC<sup>13,21</sup>. Stage 3 tumors previously considered unresectable may become resectable after appropriate induction therapy. Surgical interventions may enhance survival by facilitating locoregional control. During the navigation of evolving treatment paradigms, tumor-specific attributes become increasingly relevant to personalized treatment decisions for patients with stage 3 NSCLC<sup>1-4,9,22,26</sup>.

## Conclusion

NSCLC stage 3 presents with marked heterogeneity, leading to diverse therapeutic strategies and outcomes in contemporary oncology. Consequently, NSCLC demands an integrated approach involving multiple disciplines for optimal management (Figures 1, 2). Notably, when surgical intervention is achievable, the prognosis for patients tends to be more favorable. Recent advancements include the incorporation of

immunotherapeutic agents into the treatment regimen for stage 3 NSCLC, marking a significant stride in the field. Current research landscapes also feature a myriad of ongoing clinical trials exploring further potential benefits and applications. Nonetheless, ICIs are not devoid of adverse events, and certain patients may remain unsuitable for surgical procedures. Thus, there's an imperative to further delineate the clinical markers and biomarkers that can guide patient selection for ICI therapies.

## Authors' Contributions

Conceptualization: Chung C. Methodology: all authors. Data curation: all authors. Validation: all authors. Writing - original draft preparation: all authors. Writing - review and editing: all authors. Approval of final manuscript: all authors.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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