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Perioperative Treatment Strategies for Lung Cancer in 2025: A Paradigm Shift

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Perioperative management of resectable non-small cell lung cancer (NSCLC) has evolved significantly with the integration of immune checkpoint inhibitors and targeted therapies. This review synthesizes current evidence from key clinical trials, highlighting the improved survival outcomes achieved with neoadjuvant and perioperative chemoimmunotherapy in oncogene-wildtype NSCLC, as well as adjuvant tyrosine kinase inhibitors (TKIs) in epidermal growth factor receptor (EGFR)- and anaplastic lymphoma kinase (ALK)-altered tumours. While neoadjuvant immunotherapy has demonstrated high pathological response rates and long-term survival benefits, perioperative strategies may offer added value in selected subgroups. The ADAURA and ALINA trials have established adjuvant osimertinib and alectinib as new standards of care in oncogene-driven disease. Unresolved questions remain regarding optimal treatment sequencing, duration, and patient selection. Emerging tools such as circulating tumour DNA and artificial intelligence hold promise for refining risk stratification and guiding individualized treatment approaches.

Introduction

Lung cancer remains a leading cause of cancer-related mortality, with surgery offering curative potential for early-stage resectable non-small cell lung cancer (NSCLC).[1] Approximately 25–30% of patients present with resectable disease, yet up to 55% experience recurrence despite surgery. Historically, adjuvant cisplatin-based chemotherapy provided modest survival benefits, with a 5-year absolute survival benefit of 5.4% for stage II–III disease.[2] Perioperative therapy—encompassing neoadjuvant, adjuvant, or combined approaches—aims to eradicate micrometastases and improve long-term outcomes. The integration of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) into perioperative regimens has redefined standards of care, enabling tailored approaches based on molecular profiling.[3] This review evaluates the latest evidence shaping perioperative strategies for both subgroups.

NSCLC Without Oncogene Addiction

Adjuvant Treatment

Adjuvant immunotherapy has significantly advanced the treatment landscape for resectable NSCLC. Two pivotal studies, the IMpower010 and PEARLS/KEYNOTE-091 trials, have reshaped current clinical practice by demonstrating the efficacy of ICIs following mandatory platinum-doublet chemotherapy. The IMpower010 trial evaluated adjuvant atezolizumab in patients with stage II–IIIA NSCLC following platinum-based chemotherapy, with treatment given for one year. This study revealed substantial benefits in disease-free survival (DFS) and overall survival (OS) among programmed cell death ligand 1 (PD-L1)-positive populations, with a DFS hazard ratio (HR) of 0.70 for patients with PD-L1 expression of ≥1% and an impressive HR of 0.43 for those with PD-L1 expression of ≥50%.[4] Additionally, the OS was significantly improved, with HRs of 0.71 for PD-L1 expression of ≥1% and 0.43 for PD-L1 expression of ≥50%.[5] These

compelling results led to regulatory approvals from the US Food and Drug Administration (FDA) for atezolizumab in patients with PD-L1 expression of ≥1% and from the European Medicines Agency (EMA) for those with PD-L1 expression of ≥50%. In contrast, the PEARLS/KEYNOTE-091 trial assessed pembrolizumab as an adjuvant therapy in stage II-III NSCLC, regardless of PD-L1 expression. Pembrolizumab demonstrated a DFS improvement in the overall population, achieving an HR of 0.76, which resulted in its approval by both the FDA and EMA for stage II-III NSCLC irrespective of PD-L1 status.[6] With discordance to the above studies, the more recent CCTG BR31 trial investigated adjuvant durvalumab in patients with PD-L1 expression of ≥25%; however, it did not show a significant DFS benefit.[7] A potential explanation for this discrepancy lies in the superior performance of the control arm in CCTG BR31, which reported a DFS of 54 months compared to 37 months in the IMpower010 study and 42 months in the PEARLS/KEYNOTE-091 trial, possibly reflecting differences in surgical quality.

Neoadjuvant and Perioperative Treatment

Neoadjuvant and perioperative strategies have significantly advanced the treatment landscape for resectable NSCLC. **Table 1** summarizes the neoadjuvant and perioperative trials with key results.

The CheckMate 816 trial remains the only Phase III trial evaluating an exclusively neoadjuvant approach, combining nivolumab with chemotherapy, which demonstrated a 37% reduction in the risk of disease recurrence or death (HR: 0.63; p=0.0052) and a 24.0% pathologic complete response (pCR) rate versus 2.2% with chemotherapy alone.[8] Four-year follow-up data revealed sustained event-free survival (EFS) benefits, and a recent news release confirmed a statistically significant improvement in OS.[9,10]

Similarly, the CheckMate 77T trial evaluated a perioperative strategy, adding one year of adjuvant nivolumab to neoadjuvant nivolumab-chemotherapy, and achieved a 42% reduction in EFS risk (HR: 0.58; 95% confidence interval [CI]: 0.42–0.81) and a 25.3% pCR rate versus 4.7% with neoadjuvant chemotherapy alone.[11]

In the absence of head-to-head trials comparing neoadjuvant to perioperative nivolumab, a cross-trial analysis suggested EFS improvement of a perioperative over a neoadjuvant-only approach, particularly in patients without pCR and PD-L1 <1% subgroups (HR: 0.38).[12] However, in this study patients were censored from surgery rather than being analyzed using a full intention-to-treat approach. It included only those who received at least one cycle of adjuvant nivolumab, excluding approximately 20% of patients from the CheckMate 77T trial who did not proceed to adjuvant treatment and had a poorer overall prognosis. This selection bias favoured the perioperative strategy by artificially enhancing its outcomes, thereby reducing the reliability of the analysis.

An individual patient data (IPD) meta-analysis of prospective clinical trials evaluating neoadjuvant or perioperative chemoimmunotherapy demonstrated that patients achieving a major pathological response or pCR had significantly improved EFS. However, EFS was similar between patients treated in experimental arms that included adjuvant immunotherapy and those who received neoadjuvant treatment alone.[13]

The KEYNOTE 671 trial, which utilized perioperative pembrolizumab, demonstrated both EFS (HR: 0.59) and OS benefits (HR: 0.63), with 48-month OS rates of 68.0% versus 56.7% compared to placebo.[14]

The AEGEAN trial is a Phase III study investigating perioperative durvalumab with neoadjuvant chemotherapy in resectable stage II-IIIB NSCLC. The combination significantly improved EFS (HR: 0.68) and achieved a higher pCR rate (17.2% vs. 4.3%) compared to chemotherapy alone, with a manageable safety profile.[15]

These studies have had a practice-changing impact on the management of resectable NSCLC. The FDA has approved nivolumab with platinum-doublet chemotherapy as a neoadjuvant option, as well as pembrolizumab and durvalumab for perioperative use. Similarly, Health Canada has approved nivolumab with chemotherapy for neoadjuvant treatment and pembrolizumab in a perioperative regimen. However, the role of neoadjuvant chemoimmunotherapy across different stages of resectable NSCLC remains a topic of debate. While the International Association for the Study of Lung Cancer (IASLC) community reached a consensus on recommending its use for stage IIIA and IIIB resectable lung cancer, regardless

Trial name	Phase	Regimen	Key findings	pCR Rate
CheckMate 816[9]	III	Neoadjuvant nivolumab + chemotherapy	EFS HR: 0.63 (37% risk reduction) OS significant improvement (numbers not yet released)	24% vs. 2.2%
CheckMate 77T[11]	III	Perioperative nivolumab + chemotherapy	EFS HR: 0.58 (42% risk reduction)	25.3% vs. 4.7%
KEYNOTE-671[14]	III	Perioperative pembrolizumab + chemotherapy	EFS HR: 0.58 OS HR: 0.63 (48-month OS: 68% vs. 56.7%)	18.1% vs. 4.0%
AEGEAN[15]	III	Perioperative durvalumab + chemotherapy	EFS HR 0.68; OS trends pending	17.2% vs. 4.3%
IMpower010[5]	III	Adjuvant atezolizumab post-chemo	DFS HR: 0.66 (PD-L1 ≥1%)	N/A
KEYNOTE-091[6]	III	Adjuvant pembrolizumab post-chemotherapy	DFS HR: 0.76 (all comers)	N/A
NADIM II[18]	II	Neoadjuvant nivolumab + chemotherapy → adjuvant nivolumab	3-year OS: 81.9% vs. 55.7%	36.8% vs. 6.9%
Neotorch[19]	III	Perioperative toripalimab + chemotherapy	EFS HR: 0.40	24.8% vs. 1.0%
RATIONALE-315[20]	III	Perioperative tislelizumab + chemotherapy	EFS HR: 0.56	MPR of 56% vs. 15%
SAKK 16/14[21]	II	Neoadjuvant chemotherapy → durvalumab	MPR: 60%	18.2%

Table 1. Key Perioperative Immunotherapy Trials in NSCLC; *courtesy of Ramy Samaha, MD, Jonathan Spicer, MD, and Normand Blais, MD.*

Abbreviations: pCR: pathologic complete response, **EFS:** event-free Survival, **HR:** hazard ratio, **MPR:** major pathologic response, **N/A:** not available, **OS:** overall survival, **DFS:** disease-free survival

of PD-L1 expression, no consensus was achieved for stage II.[16] Support for neoadjuvant chemoimmunotherapy in stage II NSCLC comes from a meta-analysis by Sorin et al., which demonstrated a significant improvement in EFS, with an HR of 0.71 for stage II and 0.54 for stage III. In this analysis, the benefit was observed across all PD-L1 expression groups, with HRs of 0.74 for PD-L1 <1%, 0.56 for PD-L1 1–49%, and 0.40 for PD-L1 >50%.[17]

NSCLC With Oncogene Addiction

Epidermal Growth Factor Receptor (EGFR)-Mutant NSCLC

Before the introduction of targeted therapies for early-stage lung cancer, studies showed no difference in prognosis between patients with an EGFR mutation and those with wild-type EGFR.[22]

The ADAURA trial is a Phase III study that assessed the role of adjuvant osimertinib in EGFR-mutant NSCLC. It included patients with

stage IB (≥3 cm), II, and IIIA disease (7th TNM classification), with 60% receiving adjuvant chemotherapy before randomization to osimertinib or placebo for three years. The trial's primary endpoint, DFS in patients with stage II–III disease, showed that osimertinib significantly reduced recurrence with an HR of 0.23. The benefit extended across all enrolled patients (stage IB–IIIA) with an HR of 0.27. Additionally, OS improved across all stages, both in patients who received adjuvant chemotherapy and those who did not.

One key advantage of adjuvant osimertinib is its ability to lower the incidence of brain metastases, indicating a potential shift in the natural history of the disease. However, discontinuing treatment increases the risk of brain progression, implying that osimertinib may delay rather than eliminate recurrence. Furthermore, at the time of progression, only 43% of patients in the placebo arm received osimertinib, despite it being the standard treatment for metastatic EGFR-mutant NSCLC, reflecting limited crossover in the trial.

In summary, the ADAURA trial established adjuvant osimertinib as an effective strategy for reducing recurrence and improving survival in early-stage EGFR-mutant NSCLC, thus leading to its FDA approval in December 2020 and Health Canada approval in April 2021. However, questions remain regarding the optimal duration of therapy, long-term outcomes, and whether the treatment is truly curative or primarily delays disease progression(23–25).[23-25]

The NeoADAURA trial is an ongoing study evaluating osimertinib alone or in combination with chemotherapy in the neoadjuvant setting.[26]

ALK-Altered NSCLC

The Phase III ALINA trial investigated the use of adjuvant alectinib in patients with ALK-positive NSCLC. The study enrolled individuals with stage IB (≥4 cm), II, and IIIA disease, who were randomized to receive alectinib for two years compared to adjuvant chemotherapy. The primary endpoint, DFS in stage II–III patients, showed statistically significant improvement in the alectinib arm with an HR of 0.24. This benefit extended across all disease stages (IB–IIIA). In this trial, the OS data is not yet mature for analysis. Additionally, 76% of patients in the chemotherapy arm received an ALK-TKI upon progression, which may impact the long-term survival outcomes of this trial.[27]

Therefore, the ALINA trial confirmed the effectiveness of adjuvant alectinib in improving DFS in stage II-III ALK-positive NSCLC, thus leading to its FDA approval on April 18, 2024, and Health Canada approval on June 27, 2024.

The ALNEO trial is a Phase II study investigating the role of alectinib in the perioperative setting, with two neoadjuvant cycles and 24 adjuvant cycles. The primary endpoint is major pathologic response (MPR).[28]

Unmet Needs

The optimal sequencing of systemic therapy in resectable NSCLC remains an open question. Specifically, whether perioperative strategies offer superior outcomes compared to pure neoadjuvant approaches is yet to be determined. The ongoing ETOP 25–23 ADOPT-Lung trial is designed to address this issue by assessing the added value of adjuvant immunotherapy with durvalumab following neoadjuvant chemoimmunotherapy, focusing on its impact on DFS in patients with completely resected stage IIB–IIIB (N2) NSCLC. However, as the trial is still in the recruitment phase, definitive results may emerge at a time when the standard of care has already evolved.[29]

Current treatment decisions are primarily guided by clinical staging, which does not account for the presence of micrometastatic disease—a potential driver of recurrence. This raises the question whether biological markers could enable a more personalized therapeutic approach. Circulating tumour DNA (ctDNA) has emerged as a promising tool for stratifying patients, particularly in identifying those who may be candidates for treatment de-escalation. Nevertheless, the lack of standardized assays and the limited sensitivity—often leading to high false-negative rates—limit its standalone clinical utility. Molecular residual disease (MRD) assessment has shown promise in identifying patients with a high likelihood of cure, especially among those with consistently undetectable ctDNA over time.[30] Yet, as demonstrated in the AEGEAN trial, up to 20% of patients who achieved ctDNA clearance still experienced disease recurrence, underscoring its limitations as a definitive predictor of cure. Importantly, the persistence of detectable ctDNA has been associated with poor outcomes and may help identify patients who could benefit from treatment intensification.[31] Further supporting this approach, a post-hoc analysis of the ADAURA trial

suggested that ctDNA-based MRD monitoring could anticipate disease recurrence, particularly after discontinuation of adjuvant osimertinib. In most cases, MRD detection preceded DFS events, indicating its potential to guide extended adjuvant therapy in selected patients.[32] In summary, while MRD assays offer high specificity, their suboptimal sensitivity limits their current role in guiding treatment de-escalation strategies.

Moreover, artificial intelligence (AI) can play a major role in treatment decisions. Deep learning algorithms have demonstrated high accuracy in predicting post-surgical disease progression, offering potentially valuable insights for clinical decision-making following resection.[33]

Conclusion and Future Directions

The landscape of early-stage non-small cell lung cancer (NSCLC) treatment continues to evolve, presenting several challenges. One key issue is the lack of standardized guidelines and the need for a unified approach to diagnosis and treatment. As diagnostic precision improves, the creation of smaller molecular subgroups complicates clinical trial enrollment and treatment selection. Additionally, overlapping therapeutic strategies may lead to competing options for similar patient populations, raising questions about how best to determine optimal treatment pathways. Additionally, the financial burden associated with longer and more complex treatments should not be overlooked, as it may impact treatment accessibility and patient adherence.

To standardize the management of operable stage II/III NSCLC across Canada, a set of Canadian consensus recommendations has been published to provide evidence-based guidance for clinical practice.[34]

Looking ahead, AI could play a key role in refining treatment selection. Advanced predictive models may help clinicians determine which emerging therapies offer the greatest benefit for individual patients, enabling more precise and effective treatment decisions in an increasingly complex therapeutic landscape.

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