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RESEARCH ARTICLE

Emerging Evidence from Landmark Clinical Trials on Perioperative Immunotherapy in Resectable Non-Small Cell Lung Cancer

Emily M. Mackay MD, MSc[1] and Anna L. McGuire MD, MSc*[,1,2,3]

1. Division of Thoracic Surgery, Department of Surgery, University of British Columbia, Vancouver, BC, Canada.
2. Division of Thoracic Surgery, Department of Surgery, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada.
3. Vancouver Coastal Health Research Institute, Vancouver General Hospital, Vancouver, BC, Canada.

***Correspondence:** anna.mcguire@vch.ca

ABSTRACT

Non-small cell lung cancer (NSCLC) remains one of the most prevalent cancers worldwide, with high rates of local and distant recurrence limiting survival even after curative-intent surgical resection. Traditional adjuvant chemotherapy benefits only 5% of patients, and as such additional treatment modalities are urgently needed to improve NSCLC patient outcomes. Systemic therapy with PD1 and PDL1 immune check-point inhibitors (ICIs) has emerged as a promising treatment option in many types of solid malignancies, including lung cancer. Encouraging results from immunotherapy trials in metastatic lung cancer populations, and now newer results from ongoing clinical trials in early stage locally advanced lung cancers, suggested an evolving role for perioperative immune checkpoint inhibition in resectable NSCLC. In this review we examine the latest advances in the landscape of clinical trials on immunotherapy in resectable NSCLC. We discuss the key findings and specific clinical challenges related to neoadjuvant administration of these immune therapies in the CheckMate816, Impower030, AEGEAN and KEYNOTE671 phase III clinical trials. The role of adjuvant ICI is also discussed examining the ANVIL, Impower010, and PEARLS trials. By understanding the remaining unanswered questions and clinical dilemmas that exist in this rapidly evolving field for ICIs in early stage NSCLC, clinicians may provide patients options which may markedly improve survival outcomes for this life-threatening disease.

Introduction

Lung cancer remains the second most common cancer worldwide with over 2.2 million newly diagnosed cases reported annually. In addition to the high incidence rates, lung cancer also accounts for the highest proportion of cancer-related deaths globally[1]. NSCLC is the most common histologic type, comprising 80-85% of lung cancer cases, with adenocarcinoma being the most common subtype within this group[2].

Despite advancements in early diagnosis and implementation of lung cancer screening programs, most patients with lung cancer are still diagnosed at an advanced stage with 5-year survival rates reported at only 5% when distant disease is evident at the time of initial presentation[3]. Survival rates and treatment options increase with earlier diagnosis of lung cancer. Traditionally, the primary treatment for stage I-IIIA lung cancer has been surgical resection, followed by adjuvant systemic therapy for resected stage IB-IIIA disease. Systemic therapy, in the form of a cisplatin-based chemotherapy regimen, has been demonstrated to increase 5-year overall survival (OS) by only 5% in patients with completely resected stage II-IIIA lung cancer[4]. Due to the persistently high rates of post-surgical local and distant recurrence, additional therapies in the neoadjuvant and adjuvant settings have been urgently sought to improve patient outcomes.

The programmed cell death 1 (PD-1) pathway, a key component of immunosuppression in the tumour microenvironment, represents the target of cancer immunotherapies for many different tumour types. Blockade of the PD-1 pathway including blockade of its ligands, PD-L1 and PD-L2, has shown significant response rates for numerous advanced malignancies. Currently, the most commonly used monoclonal antibodies for blocking the PD-1 pathway are pembrolizumab, nivolumab, atezolizumab, and durvalumab. These immunotherapies have been used as first-line and subsequent-line treatments for more than 15 types of advanced malignancies, including lung cancer[5].

In lung cancer specifically, immune checkpoint inhibition of the PD-1 pathway was first explored in the setting of advanced NSCLC. Typically, the treatment for patients with metastatic NSCLC at diagnosis was platinum-doublet chemotherapy and/or targeted therapies for those patients with targetable genetic mutations. Over the past decade, numerous randomized controlled trials (RCTs) were conducted investigating the use of immune checkpoint inhibitors in patients with progression of disease on first-line therapy. Given the success in this setting, further trials subsequently investigated their use in first-line settings, either alone or in combination with standard chemotherapy regimens. A meta-analysis of 20 RCTs in the advanced NSCLC population demonstrated significantly prolonged OS and progression free survival (PFS) when immune checkpoint inhibition therapy was combined with chemotherapy[6]. Immunotherapy is now the mainstay of treatment for metastatic NSCLC with current guidelines recommending systemic therapy plus immunotherapy as first-line therapy for patients with advanced disease in tumours with PD-L1 expression >1% that are negative for actionable molecular mutations[7].

With the improvements seen in OS and PFS in patients with advanced lung cancers, the use of immunotherapy agents has been broadened to patients with earlier stage lung cancers. Numerous promising RCTs are currently ongoing exploring the use of immune checkpoint inhibition. In this review, we will summarize the emerging evidence from landmark trials for perioperative immunotherapy in resectable NSCLC, first focusing on trials being conducted in the neoadjuvant setting, followed by a summary of the current adjuvant trials.

Neoadjuvant immunotherapy in resectable NSCLC

The use of neoadjuvant immunotherapy in resectable NSCLC has shown promising results in multiple phase 1 and 2 trials, generating further interest and ongoing investigation with several larger prospective phase 3 trials that are currently underway[10]. These trials involve combinations of therapies including mono-immunotherapy, dual-immunotherapy, and immunotherapy plus traditional chemotherapy. The phase 2 trials conducted thus far have demonstrated major pathologic response (MPR; typically defined as less than 10% viable tumour) and pathologic complete response (pCR; absence of viable tumour) rates that are greater when immunotherapy agents are combined with chemotherapy, mirroring findings from the metastatic lung cancer population[10]. Tumours with mutations in epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) have been excluded from most of these trials given results from prior investigations in the metastatic lung cancer setting where immunotherapy was less effective in patients with these driver mutations[8].

Several proposed advantages exist with delivery of immunotherapy in the induction setting. These include earlier administration of anti-cancer agents targeting the primary tumour along with any

existing micrometastatic disease, activated immune response by intact tumour and lymph nodes potentially providing a longer lasting immune response, and the ability to assess the tumour's pathologic response to that specific immune checkpoint inhibitor in order to guide further post-surgical therapies.

In addition to the benefits of pre-operative administration of immunotherapy, several concerns also exist. Side effects from the treatment may affect timing to operation, possibly leading to disease progression if the delay to surgery is significant. Toxicities associated with treatment may also pre-dispose the patient to more complications in the peri-operative period. From a surgical perspective, concern has been raised regarding the technical challenges that may arise after the administration of neoadjuvant immunotherapy as hilar and mediastinal dissections may become more challenging secondary to inflammatory reactions in these tissues[8]. Early pilot studies, such as the safety and feasibility trial examining neoadjuvant nivolumab in resectable stage I-IIIA NSCLC (NCT02259621), found that administration of this PD-1 inhibitor was associated with few side effects, did not impact timing to surgery, and additionally induced a MPR in a significant proportion of patients[9]. Phase 2 trials such as this one have supported further, larger scale investigations into induction immunotherapy and its safety and efficacy in this patient population.

Assessing response to neoadjuvant immunotherapy

Another area of ongoing investigation in the realm of neoadjuvant immunotherapy in resectable NSCLC is the ability to accurately predict response to treatment. This has implications for tailoring therapy to the patient's and tumour's genetic profile, guiding appropriate post-resection therapy, and for clinical trial design and drug development. The traditional endpoint of OS is a challenging one to use in neoadjuvant trials as results are not obtained for many years following completion of treatment. MPR and pCR are frequently used as surrogate markers for OS in the neoadjuvant setting, as samples from tumour specimens can be pathologically examined before and after induction therapy, providing a more rapid indication of treatment effectiveness. MPR has been shown to correlate with lung cancer mortality, but both MPR and pCR have yet to be validated as surrogate endpoint markers in lung cancer specific outcomes necessitating that clinical trials continue to use OS and PFS as a component of their endpoints[8].

Several phase 2 trials are underway examining pathologic response to neoadjuvant immunotherapy. The NADIM II study (NCT03838159) is a randomized, open-label trial being conducted at multiple sites in Spain. This study is examining pCR in lung and lymph nodes in patients treated with nivolumab plus standard chemotherapy versus chemotherapy alone in stage IIIA and select IIIB (T3N2) NSCLC. Tumours with mutations in *EGFR* or *ALK* are excluded from the study, and estimated study completion is November 2028[10]. Another phase 2 trial in the United States, the LCMC3 study (NCT02927301), is examining MPR after neoadjuvant atezolizumab in patients with resectable stage IB to select IIIB (T3-4N2) NSCLC. Estimated completion time for this study is May 2024[11].

In addition to pathologic response in tumour and lymph node specimens, several prospective, multi-center trials are also ongoing to evaluate biomarker response to neoadjuvant immunotherapy. One such trial is REAL-NADIM (NCT05382052), a nationwide study being conducted in Spain. This observational study is enrolling patients with stage IIIA NSCLC that will receive neoadjuvant treatment prior to surgical resection. Circulating tumour DNA (ctDNA) levels will be measured before neoadjuvant treatment, at the end of the treatment cycle before surgery, immediately after surgery, 6 months after surgery, and at first disease progression. The primary outcome measure is to assess whether there is a significant association between ctDNA clearance after neoadjuvant treatment and progression free survival (PFS)[12]. From trials such as these, we will gain further understanding of accurate measures of response to neoadjuvant immunotherapy and hopefully expedite therapy development for this patient population that urgently needs improvement in outcomes.

Current phase 3 neoadjuvant immunotherapy trials in resectable NSCLC

Due to promising results from multiple phase 2 trials demonstrating benefit from induction immunotherapy, with acceptable safety profiles and minimal impact to operative difficulty, several phase 3 trials have commenced and are currently ongoing (Table 1). Results from these various trials are anticipated over the next several years, with study completion dates ranging from 2024 to 2028.

The CheckMate 816 study (NCT02998528) is a global, randomized, phase 3 trial comparing neoadjuvant nivolumab plus ipilimumab or nivolumab plus platinum-based chemotherapy versus chemotherapy alone in patients with operable stage IB-IIIA NSCLC. No

adjuvant therapy is given in this study protocol. Tumours with *EGFR* or *ALK* mutations are excluded. The primary outcome measures are event-free survival (EFS) and pCR. Estimated study completion date is November 2028[13].

The IMpower030 study (NCT03456063) is a global, randomized, phase 3 trial comparing neoadjuvant atezolizumab versus placebo in combination with standard platinum-based chemotherapy in patients with resectable stage IIA, IIIA, or select IIIB (T3N2) NSCLC. Adjuvant therapy in the form of atezolizumab or best supportive care is allowed. Activating mutations in *EGFR* or *ALK* are excluded from the study population. The primary outcome measure is EFS and estimated study completion is November 2024[14].

The AEGEAN study (NCT03800134) is a global, randomized, phase 3 trial comparing neoadjuvant durvalumab versus placebo in combination with platinum-based chemotherapy in patients with resectable stage IIA to select stage IIIB (N2 disease) NSCLC. Adjuvant therapy in the form of durvalumab or best supportive care is allowed. Of note, tumours with mutations in *EGFR* or *ALK* were not excluded from this study, a unique aspect of this RCT compared to the other neoadjuvant trials currently underway. The primary outcome measures are pCR and EFS. Estimated study completion is April 2024[15].

The KEYNOTE-671 study (NCT03425643) is a global, randomized, phase 3 trial comparing neoadjuvant pembrolizumab versus placebo in combination with platinum-based chemotherapy in patients with resectable stage II to select IIIB (T3-4N2) NSCLC. Adjuvant therapy in the form of pembrolizumab or placebo is given within this study protocol. *EGFR* and *ALK* mutation status was not recorded in the study protocol. Primary outcome measures are EFS and OS and estimated study completion is June 2026[16].

The CA209-77T study (NCT04025879) is a global, randomized, phase 3 trial comparing neoadjuvant nivolumab versus placebo in combination with platinum doublet chemotherapy in patients with resectable stage II to select IIIB (T3N2) NSCLC. Adjuvant therapy in the form of nivolumab or placebo is given within this study protocol. Tumours with *EGFR* and *ALK* activating mutations were excluded. Primary outcome measure is EFS and estimated study completion is September 2024[17].

Lastly, a phase 3, randomized trial being conducted in China (NCT04379635) is comparing neoadjuvant tislelizumab versus placebo in combination with platinum-based chemotherapy in patients with resectable stage II-IIIA NSCLC. Adjuvant therapy in the form of tislelizumab or placebo is given within this study protocol. Tumours with *EGFR* and *ALK* gene mutations were excluded. Primary outcome measures are MPR and EFS. Estimated study completion is November 2025[18].

Table 1. Phase 3 clinical trials currently ongoing on neoadjuvant immunotherapy in resectable NSCLC.

Trial Name/ Study Identifier	Phase	Stage	Standard Therapy	Neoadjuvant Intervention	Primary endpoints
CheckMate 816 (NCT02998528)	3	IB-IIIA	Platinum-based chemotherapy	Nivolumab	EFS pCR
IMpower030 (NCT03456063)	3	IIA- select IIIB (T3N2)	Platinum-based chemotherapy	Atezolizumab	EFS
AEGEAN (NCT03800134)	3	IIA-select IIIB (N2 disease)	Platinum-based chemotherapy	Durvalumab	EFS pCR
KEYNOTE-671 (NCT03425643)	3	IIA-select IIIB (T3-4N2)	Platinum-based chemotherapy	Pembrolizumab	EFS OS
CA209-77T (NCT04025879)	3	II-select IIIB (T3N2)	Platinum-based chemotherapy	Nivolumab	EFS
NCT04379635	3	II-IIIA	Platinum-based chemotherapy	Tislelizumab	MPR EFS

Adjuvant immunotherapy in resectable NSCLC

The role for adjuvant immunotherapy in resected NSCLC is currently unknown and is under investigation with several large RCTs with estimated trial completion dates ranging from 2024 to 2027 (Table 2).

The ANVIL study (NCT02595944) is a phase 3, nationwide, clinical trial currently ongoing in the United States. This trial compares the addition of one year of adjuvant nivolumab, with or without standard adjuvant chemotherapy, in patients with resected stage IB-IIIA NSCLC to observation alone.

Patients in this trial must be wildtype for *EGFR* or *ALK*. The endpoints for this study are OS and disease-free survival (DFS) and estimated study completion date is September 2025[19].

The IMpower010 study (NCT02486718) is a phase 3, global, randomized trial comparing adjuvant atezolizumab to observation alone in patients with stage IB-IIIA resected NSCLC who have also received adjuvant standard chemotherapy. Following completion of adjuvant systemic therapy, patients are randomized 1:1 to receive either atezolizumab or best supportive care. The primary endpoint is this trial is DFS and estimated study completion is December 2027[20].

The PEARLS study (NCT02504372) is a randomized, phase 3 trial comparing adjuvant pembrolizumab to placebo in patients with resected stage IB-IIIA NSCLC with or without standard adjuvant chemotherapy. The primary endpoint is this trial is DFS and estimated study completion is February 2024[21].

Lastly, the National Cancer Institute of Canada study (NCT02273375) is a global, randomized, phase 3 trial comparing adjuvant durvalumab versus placebo in patients with resected stage IB-IIIA NSCLC after adjuvant chemotherapy. The primary endpoint is this trial is DFS and estimated study completion is January 2024[22]. The results from the currently ongoing adjuvant immunotherapy trials are eagerly anticipated and will help guide future treatment of patients with resectable NSCLC.

Table 2. Clinical trials currently ongoing for adjuvant immunotherapy in resectable NSCLC.

Trial Name/ Study Identifier	Phase	Stage	Therapy	Primary endpoints
ANVIL (NCT02595944)	3	IB (4cm) -IIIA	Nivolumab (versus placebo) +/- platinum-based chemotherapy	OS DFS
IMpower010 (NCT02486718)	3	IB (4cm) -IIIA	Atezolizumab (versus observation) + platinum-based chemotherapy	DFS
PEARLS (NCT02504372)	3	IB (4cm) -IIIA	Pembrolizumab (versus placebo) +/- platinum-based chemotherapy	DFS
NCT02273375	3	IB (4cm) -IIIA	Durvalumab (versus placebo) +/- platinum-based chemotherapy	DFS

Determining who will benefit from immunotherapy

It remains to be determined which patients with resectable NSCLC will maximally benefit from immunotherapy agents targeting the PD-1 pathway. Varying levels of efficacy have been seen in this patient population and biomarkers are needed to identify patients that are most likely to respond to these therapies. Heterogeneity within the multiple histologic subtypes of NSCLC as well as within individual tumour microenvironments are likely responsible for the differences in response rates seen from PD-1 pathway inhibition.

Multiple clinical trials have examined expression levels of PD-L1 and response to immune checkpoint inhibition. Higher expression of PD-L1 has been correlated with increased benefit from inhibition of the PD-1 pathway in several trials, but other studies have demonstrated benefit regardless of expression level. Currently, PD-L1 expression is the most widely used biomarker for predicting response to immunotherapy in this population, but many others exist such as tumour mutational burden and tumour-infiltrating lymphocytes that have also been shown to correlate with response to treatment[23]. As our knowledge base increases, an expanding repertoire of biomarkers will likely be available to accurately stratify patients to appropriate immune mediated therapies based on their individual tumour microenvironments.

Conclusions

As evidenced by the review of the current landscape above, immunotherapy is emerging as a promising treatment modality in resectable NSCLC with benefits in both neoadjuvant and adjuvant settings. The results of the ongoing phase 3 clinical trials are eagerly awaited as this will help guide improved treatment in this patient population that currently has relatively poor prognosis despite surgery and adjuvant systemic therapy.

With increased understanding of the tumour microenvironment over the past decade from basic science research, and the clinical insights gained from trial outcomes, more questions continue to arise. The question of which mode of immunotherapy is better from an immunology standpoint – induction therapy versus adjuvant therapy - remains. The ideal window between completion of induction immunotherapy and surgical

intervention is unknown. Assessing response to neoadjuvant immunotherapy radiographically also remains a challenge as inflammation following induction therapy has been described with re-staging imaging appearing to suggest progression of disease when this is not necessarily the case. Finally, the biomarker profile that accurately predicts who will maximally benefit from various adjuvant immunotherapies has yet to be characterized.

Despite these unanswered questions and clinical dilemmas, immune checkpoint inhibition has shown great promise in the field of metastatic, and more recently resectable, NSCLC and provides hope for better outcomes in this patient population.

Conflicts of interest statement

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