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PD-1 Blockade in Early-Stage Lung Cancer

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Abstract

Early-stage non–small cell lung cancer is a potentially curable disease, but with relapse rates exceeding 50% with standard treatments, this is a patient population in critical need of therapy innovation. Immunotherapy with immune checkpoint blockade has revolutionized the treatment strategy for advanced lung cancer. However, the role of this therapy in earlier-stage disease is largely unknown. The study of immunotherapy in earlier-stage disease has many advantages, including assessment of pathologic response and incorporation of translational scientific analyses to evaluate antitumor immune responses. Multiple clinical trials are currently under way, with promising early results.

INTRODUCTION

Lung cancer is responsible for the greatest number of deaths across all cancer subtypes. Non–small cell lung cancer (NSCLC) accounts for ~84% of lung cancer diagnoses, and at diagnosis ~57% have metastasized, ~22% have spread to regional lymph nodes, and ~16% are localized (1). Despite ostensibly curative surgery for localized or locoregional disease, the five-year survival rate for this population is roughly 56%, and 30–60% of NSCLC patients undergoing surgery develop metastatic disease (1, 2). This highlights a critical need for innovative therapeutics in this patient population.

Over the past decade, the advent of checkpoint inhibition immunotherapy has revolutionized the treatment paradigm of many advanced malignancies, chief among them melanoma, lung, genitourinary, and head and neck. While there are many novel agents in development, the main checkpoint inhibitors in clinical practice include antibodies modulating cytotoxic T lymphocyte–associated protein 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1). CTLA-4 is a glycoprotein expressed on the surface of T cells that inhibits T cell activation by binding the B7-1 and B7-2 costimulatory molecules expressed by antigen-presenting cells, leaving them unavailable to costimulate T cell activation through binding to CD28 on T cells (3). PD-L1, expressed on the tumor surface, binds the PD-1 receptor on T cells and in so doing downregulates the T cell immune response (4). CTLA-4 and PD-(L)1 antibodies act centrally and in the periphery, respectively, to stimulate immune activation.

ANTI-PD-(L)1 CHECKPOINT BLOCKADE IN METASTATIC NON–SMALL CELL LUNG CANCER

Anti-PD-(L)1 antibody immunotherapy has become a mainstay in the treatment of metastatic NSCLC. Historically, survival for patients with metastatic NSCLC has been poor, ranging from a median of 8 to 12 months with conventional cytotoxic chemotherapy (5, 6).

Beginning in 2015, data from the CHECKMATE, KEYNOTE, and POPLAR/OAK randomized phase III clinical trials successively resulted in approval of nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), and atezolizumab (anti-PD-L1), respectively, as single agents for treatment of patients who experience tumor progression on or after prior chemotherapy for metastatic NSCLC (7–11).

Subsequent studies have demonstrated marked improvements in survival with upfront use of these agents alone and in combination with chemotherapy. PD-L1 protein expression on the surface of tumor cells is predictive of benefit from anti-PD-(L)1 therapy in metastatic NSCLC (12). Approximately 70% of newly diagnosed patients with metastatic NSCLC have tumors with ≥1% PD-L1 expression on the surface of cells, while 30% have tumors with ≥50% PD-L1 expression (13). The KEYNOTE-024 trial demonstrated that in treatment-naïve NSCLC patients with PD-L1 expression >50% who were treated with pembrolizumab, survival was more than doubled (30 months versus 14.2 months, $p = 0.002$) compared with the previous standard-of-care chemotherapy, while toxicity was lessened, resulting in the US Food and Drug Administration (FDA)'s approval for pembrolizumab in this patient population (14, 15). More recently, results of the phase II KEYNOTE-021G trial led to preliminary approval of pembrolizumab in combination with carboplatin/pemetrexed as first-line therapy in nonsquamous NSCLC patients (16). This was validated by the phase III trial KEYNOTE-189, which demonstrated an approximate doubling in survival for patients who received upfront pembrolizumab with chemotherapy over chemotherapy alone (17). Similarly, increased efficacy has been reported with other combinations of chemotherapy with anti-PD-(L)1 therapy for both squamous and nonsquamous metastatic

NSCLC (18, 19). Studies also suggest efficacy of first-line combination immunotherapy with nivolumab and the anti-CTLA-4 antibody ipilimumab in patients with a high tumor mutation burden (20). However, how these combinations will be incorporated into the treatment paradigm of metastatic NSCLC remains to be seen owing to the relative complexity and cost of tumor mutation burden testing. Not only has checkpoint immunotherapy resulted in improved response rates and overall survival, but the sustained duration of response appears to approach cure in some patients, suggesting that ongoing antitumor immune surveillance could be harnessed to prevent relapse in earlier-stage NSCLC patients (21).

CURRENT TREATMENT STRATEGIES FOR EARLY-STAGE NON–SMALL CELL LUNG CANCER

When feasible, surgical resection with curative intent is the standard of care for earlier-stage (stages I–IIIA) NSCLC, although definitive (curative intent) chemoradiation may be employed, depending on surgical candidacy and medical comorbidities. The treatment of stage IIIA disease is complex and varies depending on the extent of tumor invasion and lymph node involvement; a multidisciplinary evaluation is crucial for treatment strategy development. Adjuvant or neoadjuvant platinum-based chemotherapy is recommended for stage II–IIIA disease. This is supported by the LACE meta-analysis which demonstrated an absolute decreased risk of death of 5.4% at five years with adjuvant cisplatin-based chemotherapy versus observation in resected NSCLC (22). But, as stated above, relapse rates are high, and novel treatment strategies have so far been largely unsuccessful. An important consideration, however, is the relatively high rate of toxicity seen with perioperative chemotherapy, with high-grade toxicity rates of >60% (23).

The most recent phase III adjuvant trial, E1505, demonstrated no survival benefit with the addition of bevacizumab to adjuvant platinum-based chemotherapy (23). Targeted therapies, while attractive options in metastatic disease found to harbor an activating driver mutation such as *EGFR* or *ALK* translocation, have so far failed to demonstrate an overall survival benefit in earlier-stage patients. The NCIC CTG BR19 study demonstrated no benefit of adjuvant gefitinib compared to placebo in patients with completely resected stage IB, II, or IIIA NSCLC (24). Furthermore, the RADIANT trial failed to identify a disease-free survival benefit of adjuvant erlotinib over placebo in stage IB–IIIA patients expressing *EGFR* (25). Last, antigen-specific immunotherapy in the form of vaccine trials, despite encouraging results in early studies with a favorable side effect profile, has yet to translate into clinical benefit in large-scale clinical trials (26, 27).

CURRENT USE OF ADJUVANT IMMUNE CHECKPOINT BLOCKADE

Although antigen-specific immunotherapy has yet to translate into meaningful clinical benefit in the adjuvant setting, immune checkpoint therapy has become a mainstay in the adjuvant treatment paradigm in several malignancies. In melanoma, the cancer in which immunotherapy was first shown to demonstrate significant response, ipilimumab was approved as adjuvant therapy in stage III disease based on a significant increase in recurrence-free survival compared with placebo in the EORTC 18071 trial (28). More recently, when nivolumab was compared head-to-head with ipilimumab as adjuvant treatment in patients with resected stage III–IV disease as part of CHECKMATE 238, nivolumab demonstrated significantly increased recurrence-free survival with significantly less toxicity compared to ipilimumab and has become the standard of care for adjuvant treatment in this population (29).

In unresectable stage III NSCLC, concurrent chemoradiation is the standard of care. However, long-term outcomes with definitive concurrent chemoradiation alone are poor, with five-year

survival of ~15% (30). The PACIFIC trial studied the addition of consolidation anti-PD-L1 therapy with durvalumab compared with placebo in unresectable stage III NSCLC patients treated with definitive concurrent chemoradiation (31). Results demonstrated a median progression-free survival of 16.8 months with durvalumab versus 5.6 months with placebo, as well as a near doubling in the time to death or distant metastases from 14.6 months with placebo to 23.2 months with durvalumab. Based on these results, durvalumab is now approved as consolidation therapy following standard concurrent chemoradiation in unresectable stage III NSCLC.

RATIONALE FOR NEOADJUVANT IMMUNOTHERAPY

While adjuvant immune checkpoint therapy has demonstrated efficacy in multiple malignancies, the neoadjuvant approach also shows exciting promise. Using a murine model of triple-negative breast cancer, Liu and colleagues compared neoadjuvant and adjuvant administration of anti-PD-1/anti-CD137 combination therapy (32). Neoadjuvant therapy resulted in 40% long-term survival compared with 0% in adjuvant-treated mice. Furthermore, mice treated with neoadjuvant therapy showed an increase in tumor-specific $CD8^+$ T cells that was not observed in adjuvant-treated mice. Interestingly, the increase in peripheral $CD8^+$ T cells was shown to correlate with survival, suggesting a potential biomarker for response.

Conceptually, neoadjuvant immune checkpoint blockade has the advantage of utilizing the intact primary tumor and its cognate neoantigens (protein products of somatic mutations in the tumor) as a source for antigen-specific T cell immunity spurred by PD-(L)1 blockade. Additionally, the removal of the treated tumor and lymph nodes at the time of surgery allows an early efficacy assessment and potential development of a surrogate endpoint such as pathologic complete response (pCR) for regulatory purposes (33).

Early clinical reports of neoadjuvant immune checkpoint blockade in solid tumors other than lung cancer have been promising. In the phase I OpACIN trial, neoadjuvant nivolumab with ipilimumab was administered to 10 melanoma patients with stage III disease (34). Eight of these patients experienced reduction in tumor burden, including three pCRs, and at a median follow-up of 45 weeks no relapses had occurred. Immune checkpoint blockade is also being investigated in the neoadjuvant paradigm for breast cancer. The ongoing KEYNOTE-173 study is examining the neoadjuvant combination of pembrolizumab with chemotherapy in triple-negative breast cancer patients, and early data suggest the combination is safe and feasible with encouraging response rates (35). The I-SPY phase II trial is investigating the addition of pembrolizumab to chemotherapy in the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2)-negative breast cancer. In both the hormone-receptor-positive and triple-negative groups, early data suggest that the addition of pembrolizumab to chemotherapy improves pCR rates (36). Neoadjuvant immune therapy with ipilimumab has been studied in urothelial cancer, and early results suggest its use is safe and feasible (37).

NEOADJUVANT IMMUNE CHECKPOINT BLOCKADE IN NON–SMALL CELL LUNG CANCER

The earliest experiences with preoperative use of PD-(L)1 antibodies have included patients with metastatic lung cancer who had prolonged courses of immunotherapy and eventually underwent surgical resection for residual primary cancers or isolated progression. In a case study of five patients, Chaft and colleagues described the surgical experience of lung resection after immunotherapy (38). Only one of the patients in this study had stage III NSCLC while the rest had metastatic disease; however, findings at surgery were notable for an apparent discrepancy between radiologic and pathologic findings, as well as the presence of dense nodal fibrosis in some cases.

Neoadjuvant Nivolumab in Non–Small Cell Lung Cancer

A recently published clinical trial aimed to evaluate the safety and feasibility of using two doses of nivolumab over four weeks prior to surgical resection in stage I–IIIA NSCLC (39). This prospective study enrolled 21 patients with surgically-resectable tumors. Its goal was to detail the immune response to therapy in both the periphery and tumor, while developing potential predictive genomic and immune biomarkers of response to therapy.

Importantly, neoadjuvant administration of nivolumab was well tolerated and did not cause any delays to planned surgery. Any-grade toxicity was noted in 5 of the 21 patients, with only one grade 3 toxicity (of pneumonia). Twenty of the 21 patients underwent complete resection of their lung cancer, a figure comparable to historical data with neoadjuvant chemotherapy. Major pathologic response has been reported in ~20% of NSCLC tumors after neoadjuvant chemotherapy and is associated with long-term efficacy outcomes, including disease-free survival (40). Among the 20 tumors fully resected after neoadjuvant nivolumab, 9 (45%) demonstrated a major pathologic response, including 3 patients whose primary tumors had a pCR. Sixteen of the 20 patients were without recurrence at a median of 12 months after surgery, and long-term follow-up is continuing.

Pathologic Analyses

Evaluation of pretreatment tumor biopsies and post-treatment resection specimens from this study demonstrated that major pathologic responses occurred in both PD-L1-positive and -negative tumors and that PD-L1 expression in this cohort did not predict the degree of pathologic response (39). This is in contrast to what has been observed in advanced NSCLC, where PD-L1 expression has been a positive predictive factor for benefit from PD-(L)1 antibody therapy. This finding requires confirmation in larger studies that are ongoing. In-depth analyses of the post-treatment resection specimens from this study have also been reported and proposals put forward for immune-related pathologic response criteria (41).

Genomic Analyses

Whole-exome sequencing of tumor and normal tissue revealed a close relationship between somatic tumor mutation burden in the pretreatment tumors and percent pathologic regression. Similarly, a correlation was observed between the predicted neoantigen burden (based on algorithmic predictions of likely host immune response to protein products of mutations in the tumor) and the pathologic response. These findings are consistent with prior mutation burden and neoantigen analyses in advanced NSCLC (42, 43).

Immunologic Analyses

T cell receptor sequencing was performed on T cells isolated from peripheral blood before, during, and after nivolumab therapy and also on T cells from pretreatment biopsies and post-treatment resection specimens. It was demonstrated that T cell clones found in both tumor and blood prior to treatment increased exponentially with nivolumab and declined after resection of the tumor, suggesting stimulation of a preexisting immune response.

In conjunction with neoantigen predictions formulated from whole-exome sequencing of tumor and normal tissue, a functional evaluation of T cell reactivity was performed using a novel technique known as MANAFEST (mutation-associated neoantigen functional expansion of specific T cells) (44). In-depth analysis of tumor and blood from a patient whose primary tumor

underwent pCR demonstrated expansion of tumor neoantigen-specific T cells in peripheral blood after anti-PD-1. This T cell population declined, though it remained detectable, after surgical resection of the tumor, suggesting the potential for long-lived antitumor immunity.

Ongoing Projects Examining Neoadjuvant Checkpoint Blockade

Several clinical trials are currently ongoing to evaluate the safety, feasibility, and efficacy of neoadjuvant checkpoint blockade for earlier-stage NSCLC (**Table 1**).

COMBINATION NEOADJUVANT CHEMOTHERAPY PLUS PD-(L)1 ANTIBODY THERAPY

Given that neoadjuvant chemotherapy is already an accepted treatment approach for early-stage NSCLC, and emerging data suggest synergy between chemotherapy and PD-(L)1 antibodies in metastatic lung cancer, an important question is whether the addition of checkpoint inhibitors to chemotherapy would add further therapeutic benefit. Several trials have been designed to assess the role of checkpoint inhibition in this setting.

An ongoing phase II study explores the combination of neoadjuvant atezolizumab (anti-PD-L1) with chemotherapy for stage IB–IIIA resectable NSCLC (45). Results from 14 patients were recently presented. Patients were treated with four cycles of atezolizumab plus nab-paclitaxel and carboplatin, followed by surgery. Radiologic partial response was reported in 57% of the patients; 7 of the 14 tumors had a major pathologic response, including 3 with a pCR.

Ongoing studies include a phase II trial of the anti-PD-L1 antibody durvalumab, administered sequentially after chemotherapy for neoadjuvant treatment of stage IIIA (N2) disease (46). In this study, patients are treated with three cycles of chemotherapy (cisplatin and docetaxel) followed by two cycles of durvalumab, and durvalumab will be continued in the adjuvant setting every two weeks for 12 months.

Interim results from the ongoing phase II NADIM study have been reported. Patients with stage IIIA (N2) NSCLC received neoadjuvant chemotherapy plus nivolumab followed by resection and subsequent adjuvant nivolumab for one year (47). Results thus far are impressive, with 69.2% of cases showing pCR and an overall pathologic response rate (comprising complete and major pathologic responses) of 84.6%.

Placebo-controlled studies may be valuable in assessing the potential added efficacy of neoadjuvant immunotherapy. KEYNOTE-671 (NCT03425643) is a current double-blind phase III study evaluating perioperative pembrolizumab in combination with neoadjuvant platinum-based chemotherapy for resectable stage IIB or IIIA NSCLC. The treatment group received neoadjuvant chemotherapy (cisplatin with gemcitabine or pemetrexed) combined with four cycles of pembrolizumab prior to surgery, followed by adjuvant pembrolizumab for 13 additional cycles. Patients are randomized 1:1, and investigators plan to enroll 786 participants.

Neoadjuvant Checkpoint Inhibitor Monotherapy

Additional studies evaluating PD-1 blockade in the neoadjuvant setting are ongoing. The LCMC3 study, examining neoadjuvant atezolizumab in resectable NSCLC, recently reported initial data on 21 of the 180 planned patients (48). Among the 19 patients who underwent pathologic response assessment, 21% of tumors achieved a major pathologic response. There were no treatment-related delays to surgery.

Table 1 Neoadjuvant clinical trials: ongoing clinical trials to evaluate the safety, feasibility, and efficacy of neoadjuvant checkpoint blockade for earlier-stage non–small cell lung cancer (NSCLC)

NCT number	Phase	Clinical goal	Country	Primary endpoint
NCT03366766	II	Evaluate neoadjuvant nivolumab + chemotherapy in resectable NSCLC	United States	Major pathologic response
NCT03110978	II	Compare immunotherapy + stereotactic ablative radiotherapy (I-SABR) versus SABR alone for stage I NSCLC	United States	Event-free survival, secondary malignancy and death
NCT02998528	III	Determine the safety and effectiveness of nivolumab + ipilimumab or nivolumab + chemotherapy compared to chemotherapy alone in the adjuvant treatment of resected NSCLC	United States	Event-free survival, pathologic response
NCT03158129	II	Compare nivolumab alone to nivolumab + ipilimumab when given to patients with NSCLC that can be surgically treated	United States	Major pathologic response
NCT03081689	II	Assess the feasibility, safety, and efficacy of combined neoadjuvant chemotherapy and immunotherapy with carboplatin + paclitaxel + nivolumab followed by adjuvant immunotherapy with nivolumab for patients with resectable stage IIIA N2-NSCLC	Spain	Progression-free survival
NCT02259621	II	Evaluate the safety and feasibility of preoperative administration of nivolumab +/– ipilimumab in patients with high-risk resectable NSCLC	United States	Safety
NCT03237377	II	Evaluate durvalumab or durvalumab + tremelimumab with standard thoracic radiation for patients with stage IIIA NSCLC	United States	Safety
NCT03425643	III	Evaluate standard neoadjuvant chemotherapy with perioperative pembrolizumab or placebo in early-stage NSCLC	United States	Event-free survival, overall survival
NCT02927301	All resectable	Evaluate neoadjuvant atezolizumab in resectable NSCLC	United States	Major pathologic response
NCT02716038	II	Evaluate neoadjuvant atezolizumab + chemotherapy in resectable NSCLC	United States	Major pathologic response
NCT02572843	II	Evaluate durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA (N2) NSCLC	Switzerland	Event-free survival at 12 months
NCT02994576	II	Evaluate atezolizumab as induction therapy in stage IB–IIIA non-N2 resectable and untreated NSCLC	France	Rate of patients without major toxicities or morbidities

Neoadjuvant Immunoradiation

Preclinical research has shown that radiation in combination with PD-1 inhibitors may have synergistic antitumor immunity leading to upregulation of PD-L1 expression in the tumor (49). In the clinical setting, retrospective analyses suggest improved progression-free survival and overall survival in patients receiving the anti-PD-L1 antibody pembrolizumab, who had prior exposure

to radiotherapy (50). Several ongoing trials are assessing the safety and efficacy of combination radiotherapy and checkpoint inhibition for treatment of metastatic NSCLC (51).

Given promising early data in metastatic lung cancer, the scope of this potential synergistic relationship between radiation and the immune system is being examined further in the neoadjuvant treatment of early stage disease. A phase I/II clinical trial is comparing stereotactic ablative radiotherapy (SABR) plus nivolumab with SABR alone for stage I and IIA disease (NCT03110978). Recruitment is under way with planned enrollment of 140 patients. Primary endpoints for the study include event-free survival, secondary malignancy, and death. In a pilot study ongoing at Johns Hopkins University, neoadjuvant immunoradiation (the anti-PD-L1 antibody durvalumab with concurrent standard thoracic radiotherapy) is administered prior to surgery for patients with resectable stage IIIA NSCLC (NCT03237377).

Neoadjuvant Combination Immune Checkpoint Inhibition

Within the realm of neoadjuvant therapy, the role of combination checkpoint inhibition is an active area of research. Several trials are ongoing (**Table 1**), focusing primarily on the potential synergy of combination nivolumab with ipilimumab. These studies will ultimately help answer questions regarding safety as well as efficacy outcome measurements including pathologic response. Further subgroup analysis may help establish useful biomarkers to better select patients for combination therapy.

ADJUVANT PD-(L)1 BLOCKADE

Several large phase III clinical trials are exploring the use of adjuvant PD-(L)1 blockade after surgical resection of NSCLC (**Table 2**). These include the US cooperative group ANVIL study (NCT02595944) examining one year of nivolumab therapy versus observation; the National Cancer Institute of Canada study (NCT02273375) that evaluates durvalumab versus placebo; and the PEARLS study of adjuvant pembrolizumab active in Europe (NCT02504372). Primary endpoint results from these studies will take several years to mature but have the potential to be practice changing for many patients with earlier-stage NSCLC.

Table 2 Adjuvant clinical trials: ongoing clinical trials to evaluate the safety, feasibility, and efficacy of adjuvant checkpoint blockade for earlier-stage non–small cell lung cancer (NSCLC)

NCT number	Phase	Clinical goal	Country	Primary endpoint
NCT02595944	III	Evaluate nivolumab after surgery and chemotherapy in patients with stage IB–IIIA NSCLC	United States	Overall survival, disease-free survival
NCT02486718	III	Compare the efficacy and safety of atezolizumab treatment compared with best supportive care in participants with stage IB–IIIA NSCLC following resection and adjuvant chemotherapy	Not reported	Disease-free survival
NCT02504372	III	Investigate whether adjuvant treatment with pembrolizumab after completion of radical surgery and standard adjuvant chemotherapy is appropriate for stage IB–IIIA NSCLC patients	Multinational (Europe)	Disease-free survival
NCT02273375	III	Evaluate efficacy of durvalumab versus placebo in completely resected NSCLC	Canada	Disease-free survival

FUTURE DIRECTIONS

Over a period of less than ten years, treatment for metastatic lung cancer has evolved to the point that a previously universally fatal disease now has the potential of being considered a chronic illness for a minority of patients. Despite these advances, most patients with metastatic lung cancer still die from their cancer within 2–3 years of diagnosis. Therapies that intercept relapse of earlier-stage lung cancer and prevent the morbidity and mortality of advanced disease are urgently needed.

Early results from clinical trials of neoadjuvant PD-1 blockade show promise, and the neoadjuvant design offers the potential for broad-based translational scientific analyses evaluating the antitumor immune response. The development and validation of surrogate endpoints such as pCR are ongoing and offer the potential for early incorporation of PD-1 blockade into standard clinical practice on a provisional basis pending long-term survival data. Finally, the use of the neoadjuvant setting as a platform for investigation of novel combination therapies is an untapped resource that offers many potential advantages, not least the opportunity for pathologic response to serve as an early efficacy measure.

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