

Emerging Role of Immunotherapy in Locally Advanced Non–Small Cell Lung Cancer

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Abstract: Non–small cell lung cancer (NSCLC) accounts for 85% of the cases of lung cancer in the United States, and 70% of patients with NSCLC have locally advanced or metastatic disease at the time of diagnosis. The 5-year overall survival rate for patients with locally advanced NSCLC is 15% to 20%. The traditional treatment paradigm for unresectable locally advanced NSCLC consists of platinum-based chemotherapy with concurrent radiation. Evidence from phase 3 clinical trials has established a role for immunotherapy after chemoradiation, and emerging data continue to elucidate the expanding role of immunotherapy.

Introduction

Non–small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality, accounting for 85% of all lung cancer cases in the United States.¹ Nearly 70% of patients who have NSCLC present with locally advanced or metastatic disease at the time of diagnosis.¹ Curative treatment for stage III or locally advanced NSCLC (LA-NSCLC) varies according to the extent of nodal involvement; combinations of chemotherapy, radiation therapy, and surgery are used.² Patients with unresectable LA-NSCLC often receive platinum-based chemotherapy with concurrent radiation therapy.³ Even with such aggressive management, the 5-year overall survival (OS) rate remains at 15% to 20%.⁴ Treatment modifications, such as the introduction of consolidation or maintenance chemotherapy or escalation of the radiation dose, have not been shown to improve oncologic outcomes in clinical trials.^{5,6} The phase 3 SWOG S0023 trial (Phase III Trial of Maintenance Gefitinib or Placebo After Concurrent Chemoradiotherapy and Docetaxel Consolidation in Inoperable Stage III Non-Small-Cell Lung Cancer) was terminated after the use of gefitinib (Iressa, AstraZeneca), an epidermal growth factor receptor (EGFR) inhibitor, as maintenance therapy following definitive chemoradiation in patients with unresectable stage III NSCLC was found to result in worse survival.⁷ However, recent advances in immunotherapy have led to paradigm changes in the treatment of

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LA-NSCLC that are associated with improvements in survival and disease control.⁸

Early Trials

One of the earliest phase 3 trials that evaluated the role of immunotherapy in LA-NSCLC was START (Cancer Vaccine Study for Unresectable Stage III Non-small Cell Lung Cancer).⁹ Eligible patients for this trial included those with unresectable stage III NSCLC who had stable or reduced disease following concurrent or sequential chemoradiation (CRT). Participants were randomly assigned in a 2:1 ratio to receive tecemotide (L-BLP25) or placebo. The drug tecemotide induces an immune response to mucin 1 (MUC1), a glycoprotein that is abnormally glycosylated in NSCLC. The START trial showed a statistically significant improvement in OS with tecemotide vs placebo in the patients who had previously received concurrent CRT (30.8 vs 20.6 months; $P=.016$), but not in those who had previously received sequential CRT. The rates of pneumonitis did not differ between the study groups. The START trial was not separately powered to detect survival differences in the concurrent CRT cohort as part of the statistical design. Furthermore, uncertainty remains regarding patient selection, and whether the patients who were offered concurrent CRT had a better performance status at the onset of treatment. For such reasons, the apparent benefit of tecemotide did not translate into approval by the US Food and Drug Administration (FDA), and further development was suspended.

Additional immunotherapeutic agents have since been introduced for the treatment of LA-NSCLC. Immune checkpoint inhibitors constitute a novel class of drugs that counteract the mechanisms used by cancer cells to inactivate and evade the immune system.¹⁰ These agents are antibodies against inhibitory receptors that are normally activated by cancer cells.¹¹ By interfering with the tumor-mediated inactivation of T cells, checkpoint inhibitors allow the immune system to mount an adequate response against tumor cells.¹¹

Immunotherapy Agents

The first immune checkpoint inhibitor approved by the FDA was ipilimumab (Yervoy, Bristol-Myers Squibb), an antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), for the treatment of metastatic melanoma.¹² CTLA-4 is a ligand expressed by activated T cells that is homologous in structure to the co-stimulatory molecule cluster of differentiation 28 (CD28).¹³ CTLA-4 competes with CD28 for binding to B7 ligands on antigen-presenting cells (APCs). Whereas CD28/B7 interactions stimulate T-cell activity, CTLA-4/B7 interactions inhibit T-cell activity.¹³ Following FDA approval

of ipilimumab, immune checkpoint inhibitors targeting the programmed death 1 (PD-1) inhibitory pathway were developed.¹⁴ PD-1 expressed on activated T cells interacts with widely expressed programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), thus inhibiting T-cell proliferation and the production of cytokines.¹⁵ Antibodies involving the PD-1 pathway have shown promise in the treatment of multiple cancers, including melanoma, prostate carcinoma, colorectal carcinoma, renal cell carcinoma, and NSCLC, for which they have garnered FDA approvals.^{16,17}

In the last decade, several novel immunotherapeutic agents have demonstrated benefit in the management of LA-NSCLC. This article reviews the role of immunotherapy in the treatment of LA-NSCLC, according to the current evidence. The clinical trials discussed in this review are summarized in the Table.

Role of Immunotherapy After Chemoradiation

Several studies have shown promise for immunotherapy following concurrent CRT in patients with unresectable stage III LA-NSCLC. The PACIFIC trial (A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer) reported encouraging phase 3 data on the use of the anti-PD-L1 antibody durvalumab (Imfinzi, AstraZeneca) in this context.

PACIFIC was one of the first studies to demonstrate improved outcomes in patients with LA-NSCLC who received an immune checkpoint inhibitor.^{18,19} In this phase 3 trial, patients with stage III unresectable NSCLC were randomly assigned in a 2:1 ratio to receive either durvalumab (a PD-L1 inhibitor) or placebo as consolidation therapy every 2 weeks for as long as 1 year. The study population consisted of 713 patients who had received cisplatin-based chemotherapy with concurrent radiation to 66 Gy and had no disease progression following treatment. Progression-free survival (PFS), the primary endpoint, was significantly longer in the durvalumab group than in the placebo group (median PFS, 16.8 vs 5.6 months; $P<.001$). In addition, the co-primary endpoint of OS rate was subsequently found to be significantly higher in the durvalumab group than in the placebo group (24-month OS, 66.3% vs 55.6%; 2-sided $P=.005$). Notably, PFS enhancement was greater when durvalumab was initiated within 2 weeks after radiation (hazard ratio [HR], 0.39; 95% CI, 0.26-0.58) vs more than 2 weeks after radiation (HR, 0.63; 95% CI, 0.49-0.80). In this trial, durvalumab did not appear to increase the incidence of grade 3 or grade 4 pneumonitis; the rates were similar in the 2 study groups (3.4% in the durvalumab group vs 2.6% in the placebo group). A secondary analysis of the PACIFIC trial reported no clinically significant

Table. Summary of Clinical Trials Using Immunotherapy for Stage III NSCLC

Clinical Trial	Phase	IT Agent Used	Disease Stage	Treatment Arms	Results (If Available)
Sequential IT After CRT					
PACIFIC ¹⁸	3	Durvalumab	Stage III unresectable LA-NSCLC	CRT → IT; CRT → placebo	PFS 16.8 mo (IT) vs 5.6 mo (placebo), <i>P</i> < .001
LUN 14-179 ²¹	2	Pembrolizumab	Stage IIIA-B unresectable LA-NSCLC	CRT → IT; CRT → placebo	Primary endpoint not reached
MP-LALC (NCT03379441)	2	Pembrolizumab	Stage IIIA-B unresectable LA-NSCLC	CRT → IT; CRT → observation	
RTOG 3505 ²²	3	Nivolumab	Stage IIIA-B unresectable LA-NSCLC	CRT → IT; CRT → placebo	Terminated
Concurrent IT With CRT					
DETERRED ²³	2	Atezolizumab	Stage III unresectable LA-NSCLC	CRT → IT; CRT + IT → IT	
NICOLAS ²⁵	2	Nivolumab	Stage IIIA-B unresectable LA-NSCLC	CRT + IT → IT (single arm)	
PACIFIC ²⁶	3	Durvalumab	Stage IIIA-B unresectable LA-NSCLC	IT + CRT → IT; placebo + CRT → placebo	
Rutgers Cancer Institute of New Jersey ²⁷	1	Pembrolizumab	Stage II or III unresectable LA-NSCLC	CRT → full- or reduced-dose IT; CRT + full- or reduced-dose IT	Median PFS: 20.3 mo
Neoadjuvant IT					
Alliance (NCT03102242)	2	Atezolizumab	Stage IIIA-B unresectable LA-NSCLC	IT → CRT → IT (single arm)	
IT After CRT With Curative Resection					
Samsung Medical Center ²⁹	2	Pembrolizumab	Stage IIIA-N2 NSCLC	CRT → resection → IT	

CRT, chemoradiation; IT, immunotherapy; LA-NSCLC, locally advanced non-small cell lung cancer; mo, months; PFS, progression-free survival.

differences between patient-reported outcomes in the experimental and placebo groups.²⁰ In subgroup analyses of the PACIFIC trial, patients with PD-L1 expression of less than 25% and those with the *EGFR* mutation did not derive significant benefit from treatment with durvalumab vs placebo.

A similar study conducted by the Hoosier Cancer Research Network, LUN 14-179 (Consolidation Pembrolizumab Following Chemoradiation in Patients With Inoperable/Unresectable Stage III NSCLC), reported phase 2 data on patients who had stage IIIA or IIIB unresectable NSCLC treated with pembrolizumab (Keytruda, Merck) after concurrent CRT.²¹ Following the completion of platinum-based chemotherapy with concurrent radiation to 66 Gy, 93 patients received consolidation pembrolizumab every 3 weeks for up to 1

year. The primary endpoint, time to metastatic disease or death, was not reached. Secondary endpoints included OS rate (1-year OS rate, 80.5%; 2-year OS rate, 68.7%) and PFS (median PFS, 15.4 months). These results appear similar to those observed in the durvalumab arm of the PACIFIC trial. In this study, pneumonitis of grade 2 or higher developed in 17.2% of patients and grade 3 or 4 pneumonitis in 5.4%, with 1 pneumonitis-related death.²¹ A similar multicenter study from Italy, MP-LALC (A Randomized Phase II Study of Pembrolizumab as Maintenance Therapy in Patients With Unresectable Stage III NSCLC Treated With Definitive Chemo-radiotherapy), is underway to evaluate the safety and efficacy of pembrolizumab as maintenance therapy in patients with stage III unresectable LA-NSCLC (NCT03379441).

The Radiation Therapy Oncology Group (RTOG)

3505 study (Cisplatin and Etoposide Plus Radiation Followed by Nivolumab/Placebo for Locally Advanced NSCLC) used the anti-PD-1 antibody nivolumab (Opdivo, Bristol-Myers Squibb).²² This phase 3 trial randomly assigned patients with stage III unresectable NSCLC who had received cisplatin- and etoposide-based chemotherapy with concurrent radiation to 60 Gy to receive either nivolumab or placebo every 2 weeks for up to 1 year. This trial was terminated in January 2019, however, following the results of the PACIFIC trial showing improved outcomes in patients who received immunotherapy after the completion of concurrent chemoradiation.

Role of Concurrent Immunotherapy and Chemoradiation

In light of the promising results of consolidation immunotherapy following CRT, several studies have been initiated to assess the safety and efficacy of concurrent immunotherapy and CRT.

The DETERRED study (MPDL3280A With Chemoradiation for Lung Cancer) was a single-institution phase 2 trial that assessed the safety and feasibility of adding the anti-PD-L1 antibody atezolizumab (Tecentriq, Genentech) to CRT either sequentially or concurrently.^{23,24} In this trial, 10 patients received sequential immunotherapy in which CRT was followed by atezolizumab plus carboplatin/paclitaxel (C/P) for 2 cycles, and 30 patients received concurrent CRT and atezolizumab followed by consolidation atezolizumab plus C/P. Atezolizumab was administered every 3 weeks for up to 1 year after the first dose. Adverse effects of grade 3 or higher were seen in 6 of the 10 patients treated with sequential CRT and atezolizumab; these included pneumonia, dyspnea, arthralgia, and a grade 5 tracheoesophageal fistula. Among the 30 patients treated with concurrent CRT and atezolizumab, followed by consolidation atezolizumab, grade 3 or higher adverse events developed in 17; the most common was pneumonia, followed by dyspnea, fatigue, and heart failure. Atezolizumab was discontinued in 3 of these patients owing to grade 2 or grade 3 radiation pneumonitis. Given the toxicity seen with the concurrent administration of atezolizumab and chemoradiation, other immunotherapy agents are being investigated in this setting.

The NICOLAS trial (Nivolumab Combination With Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Carcinoma) was a phase 2 single-arm study to evaluate the safety and efficacy of concurrent nivolumab and CRT.²⁵ Patients with stage III LA-NSCLC received 3 cycles of platinum-based chemotherapy and concurrent radiation to 66 Gy in 33 fractions. Nivolumab was started concurrently with radiation therapy. The primary outcome was the rate of 6-month post-radiation pneumonitis of grade

3 or higher. In an early analysis involving 21 patients, none was found to have grade 3 or higher pneumonitis. An efficacy evaluation is planned in this cohort given the early safety conclusion of the study.

The PACIFIC2 trial (Study of Durvalumab Given With Chemoradiation Therapy in Patients With Unresectable Non-Small Cell Lung Cancer) is an ongoing phase 3 multi-institutional trial aimed at assessing the efficacy of administering concurrent durvalumab and platinum-based chemotherapy in patients with stage III LA-NSCLC.²⁶ As of February 5, 2020, the study has enrolled 328 participants, who are being randomly assigned in a 2:1 ratio to receive either durvalumab (1500 mg intravenously [IV]) or placebo every 4 weeks with concurrent CRT. At the conclusion of standard-of-care CRT, patients in the experimental arm who have stable disease, a partial response, or a complete response will continue on consolidative durvalumab, and those in the placebo arm will continue on placebo. The primary endpoints of this study are PFS and the OS rate.

Jabbour and colleagues at the Rutgers Cancer Institute of New Jersey designed a prospective multicenter trial to evaluate concurrent pembrolizumab and CRT consisting of weekly C/P with definitive radiation therapy to 60 Gy in 30 fractions.²⁷ In their phase 1 study, 23 subjects with inoperable stage III NSCLC were divided into 5 cohorts based on dose. Cohort 1 (C1) received full-dose pembrolizumab (200 mg IV every 3 weeks) at 2 to 6 weeks after CRT; C2 received reduced-dose pembrolizumab (100 mg IV every 3 weeks) from day 19; C3 received full-dose pembrolizumab from day 29; C4 received reduced-dose pembrolizumab from day 1; and C5 received full-dose pembrolizumab from day 1. The study identified no dose-limiting toxicities in any of these cohorts. Grade 3 or higher immune-related adverse events occurred in 3 patients; these included pneumonitis and interstitial nephritis. Grade 2 toxicities developed in a small number of patients, including pneumonitis (n=4), thyroiditis (n=4), and myositis (n=1), and grade 1 or 2 transaminitis developed in 3 patients. Median PFS in the patients who received at least 2 doses of pembrolizumab (n=18) was 20.3 months.

Role of Neoadjuvant Immunotherapy

The safety and efficacy of neoadjuvant immunotherapy will be evaluated in a phase 2, single-arm Alliance trial that is currently active and recruiting patients (Atezolizumab Immunotherapy in Patients With Advanced NSCLC; NCT03102242). Patients who have stage III LA-NSCLC will be treated with 4 cycles of neoadjuvant atezolizumab at a dose of 1200 mg IV every 21 days and restaged following cycles 2 and 4. Patients with no disease progression will receive weekly chemotherapy

with C/P and concurrent radiation to 60 Gy. They subsequently will receive 2 cycles of consolidative C/P followed by atezolizumab to complete 1 year of treatment. The primary endpoint of this pilot study is the disease control rate after neoadjuvant atezolizumab. Secondary endpoints include the OS rate, PFS, safety, and quality of life according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).

Role of Immunotherapy in Resectable NSCLC

A number of clinical trials are currently investigating the role of immunotherapy in early-stage NSCLC.²⁸ The clinical efficacy of postoperative immunotherapy for stage III NSCLC is being evaluated in a prospective, single-arm phase 2 study.²⁹ In this trial, patients who have stage IIIA-N2 NSCLC and have undergone concurrent CRT (weekly C/P and radiation therapy to 44 Gy in 22 fractions) with curative resection will receive adjuvant pembrolizumab at a fixed dose of 200 mg every 3 weeks for up to 2 years or until disease recurrence. The primary endpoint will be disease-free survival, with a statistical goal of more than 20 months. Thus far, of 37 patients treated in this trial, 14 patients have discontinued treatment owing to disease progression (n=9), adverse events (n=4), or consent withdrawal (n=1). Adverse events have included grade 4 pneumonitis (n=1) and grade 3 autoimmune hepatitis (n=1), which have led to discontinuation, as well as grade 1 or 2 hypothyroidism (n=6), pneumonitis (n=5), and skin rash (n=3).

Immunotherapy vs Systemic Chemotherapy

No studies at the present time support the replacement of systemic chemotherapy with immunotherapy in patients who have LA-NSCLC. However, improved outcomes for immunotherapy vs chemotherapy have been demonstrated in patients with advanced or metastatic NSCLC, particularly in those with high levels of PD-L1 expression. The phase 3 KEYNOTE-024 trial (Study of Pembrolizumab Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer) demonstrated improved OS in patients who had previously untreated advanced NSCLC treated with pembrolizumab vs chemotherapy and whose tumors had PD-L1 expression of greater than 50%.³⁰ The phase 3 KEYNOTE-042 trial (Study of Pembrolizumab Versus Platinum-Based Chemotherapy for Participants With Programmed Cell Death-Ligand 1-Positive Advanced or Metastatic Non-Small Cell Lung Cancer) showed significantly improved OS in patients with previously untreated locally advanced or metastatic NSCLC and PD-L1

expression of 1% or greater treated with pembrolizumab than in those treated with chemotherapy.³¹ The phase 3 IMpower110 study (A Study of Atezolizumab Compared With a Platinum Agent + Pemetrexed or Gemcitabine in Participants With Stage IV Non-Squamous or Squamous Non-Small Cell Lung Cancer) is an active trial that will compare atezolizumab vs chemotherapy in PD-L1-selected, chemotherapy-naïve patients who have advanced NSCLC.³²

The phase 1 ARCHON-1 trial (Accelerated Hypofractionated or Conventionally Fractionated Radiotherapy and Durvalumab in Treating Patients With Stage II-III Non-small Cell Lung Cancer), which is being conducted in patients with stage II/III NSCLC and PD-L1 expression of at least 50%, is currently evaluating the safety of adding durvalumab to 2 schedules of radiation therapy: either a conventional schedule of 60 Gy in 30 fractions or a hypofractionated regimen of 60 Gy in 15 fractions.

Practical Considerations

Immunotherapies show great potential to transform the treatment paradigm of LA-NSCLC. The standard of care for patients with stage III unresectable NSCLC who do not exhibit disease progression after CRT remains durvalumab at 10 mg/kg IV every 2 weeks for up to 12 months.³³ However, the implementation of immunotherapies faces certain challenges.

The aforementioned studies have largely supported the safety and tolerability of various immunotherapies, almost exclusively checkpoint inhibitors targeting PD-1 or PD-L1, and have demonstrated adverse effects comparable with those seen when chemotherapy is used. However, grade 3 or higher pneumonitis is still a pervasive adverse effect across various types of immunotherapy in a small percentage of patients. Because it is difficult to attribute pneumonitis to radiation, immunotherapy, or the combination of the 2 treatment modalities, it is generally acceptable to use the term *pneumonitis*, without specifying the cause.³⁴

Additionally, immunotherapy poses several challenges in patients with pre-existing autoimmune diseases and in transplant recipients on immunosuppressant medications. Such patients have generally been excluded from trials involving immunotherapeutic agents, and retrospective studies have shown that autoimmunity can be exacerbated by the use of immune checkpoint inhibitors.^{35,36} A phase 1 clinical trial is underway to determine the safety of nivolumab in patients who have autoimmune disorders and advanced, metastatic, or unresectable malignancy with known sensitivity to PD-L1 antibodies (Nivolumab in Treating Patients With Immune Disorders or Advanced, Metastatic, or Unresectable Cancer; NCT03816345). Immunotherapy is also challenging

owing to tumor heterogeneity and the potential for the development of resistance to drug treatment.³⁷ This difficulty has been demonstrated in patients with melanoma in whom resistance to pembrolizumab developed.³⁸

In evaluating the future role of immunotherapy in the treatment of LA-NSCLC, it is also critical to consider the importance of value-based oncology. Studies are underway to evaluate this concern. For example, in one systematic review of immune checkpoint inhibitors, it was shown that careful patient selection based on PD-L1 expression might enhance the cost-effectiveness of immunotherapy.³⁹

Disclosures

The authors have no disclosures to report.

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