Advances in Immunotherapy for Non–Small Cell Lung Cancer

Karen L. Reckamp, MD

Dr Reckamp is an associate professor in the Department of Medical Oncology and Therapeutics Research at the City of Hope Comprehensive Cancer Center in Duarte, California.

Corresponding author:
Karen L. Reckamp, MD
1500 E. Duarte Road, Bldg 51
Duarte, CA 91010
Tel: (626) 256-4673, ext 68218
E-mail: kreckamp@coh.org

Abstract: In most patients, lung cancer presents as advanced disease with metastases to lymph nodes and/or distant organs, and survival is poor. Lung cancer is also a highly immune-suppressing malignancy with numerous methods to evade antitumor immune responses, including deficiencies in antigen processing and presentation, release of immunomodulatory cytokines, and inhibition of T-cell activation. Advances in understanding the complex interactions of the immune system and cancer have led to novel therapies that promote T-cell activation at the tumor site, resulting in prolonged clinical benefit. Immune checkpoint inhibitors, specifically programmed death receptor 1 pathway antibodies, have demonstrated impressively durable responses and improved survival in patients with non–small cell lung cancer. This article will review the recent progress made in immunotherapy for lung cancer with data from trials evaluating programmed death receptor 1 and cytotoxic T-lymphocyte–associated protein 4 monoclonal antibodies in addition to cancer vaccines. The review will focus on studies that have been published and the latest randomized trials exploring immune therapy in lung cancer. These results form the framework for a new direction in the treatment of lung cancer toward immunotherapy.

Keywords
Cancer vaccines, cytotoxic T-lymphocyte–associated protein 4, immune therapy, lung cancer, programmed death receptor 1

Introduction

Cancer immunosurveillance is the principle that the immune system can identify precancerous and cancerous cells and kill these cells before they become clinically relevant, which has been demonstrated in immunodeficient mouse models.[1] Innate and adaptive immune responses work together to either promote or inhibit cancer growth, and evasion of immune destruction is an emerging hallmark of cancer.[2] Historically, methods of immune stimulation were not effective for lung cancer patients in the clinic.[3,4] Deficiencies in tumor antigen expression and presentation on antigen presenting cells (APCs),

Table 1. Randomized Trials Investigating Checkpoint Inhibition in NSCLC

Author	Phase	N	Checkpoint Inhibitor	Comparator	Outcome	Histology
Lynch[23]	2	204	Ipilimumab (with carboplatin/paclitaxel)	Carboplatin/ paclitaxel	irPFS, 5.7 vs 4.6 mo (HR, 0.72)	All
Brahmer[26]	3	272	Nivolumab	Docetaxel	OS, 9.2 vs 6.0 mo (HR, 0.59)	SCC
Borghaei[27]	3	582	Nivolumab	Docetaxel	OS, 12.2 vs 9.4 mo (HR, 0.73)	Non-SCC
Spira[33]	2	287	Atezolizumab	Docetaxel	OS, 11.4 vs 9.5 mo (HR, 0.11)	All

HR, hazard ratio; irPFS, immune-related progression-free survival; mo, months; NSCLC, non–small cell carcinoma; OS, overall survival; PD-L1, programmed death ligand 1; SCC, squamous cell carcinoma.

infiltration of immunosuppressive cells and cytokines, and ineffective T-cell activation lead to immunosuppression at the tumor site.[5] Advances in our understanding of cancer and the immune system have led to effective therapies that activate antitumor responses, even in tumors that have highly developed methods of immune evasion, such as lung cancer.[6]

Lung cancer is the leading cause of cancer-related death in the United States and is responsible for more than 1 million deaths worldwide annually.[7,8] Most patients present with advanced disease and require systemic therapy. Targeted therapy for oncogene-driven lung cancers has led to improved outcomes for a subgroup of patients with non–small cell lung cancer (NSCLC) tumors that harbor genetic alterations.[9-11] Despite the advances, the 5-year survival rate remains less than 20%, and most patients develop resistance to therapy. Immune therapy offers potential advantages over cytotoxic and targeted therapy, but lung cancer is poorly immunogenic. Lung cancers express tumor antigens, but they are ineffective as APCs.[12] In addition, lung cancers lack costimulatory molecules while producing inhibitory factors, which promotes a state of specific T-cell anergy.[13] Therapeutic options that incorporate the tumor, the tumor microenvironment, and novel mechanisms to activate the immune system can produce antitumor effects and represent a shift in the treatment of lung cancer.

The Immune System in Lung Cancer

The adaptive immune response is activated by immature dendritic cells (DCs) that process tumor antigens. DCs then mature and migrate to lymph nodes where they present tumor antigens to T cells, resulting in activation and an antitumor immune response.[14] Interactions between T-cell receptors and major histocompatibility complex molecules on APCs, in addition to costimulatory molecules, are necessary to induce an effective T-cell response to the tumor. $CD4^+CD25^+$ regulatory T cells (Tregs) are activated in an antigen-specific manner and inhibit T cells and natural killer cells nonspecifically by producing immunosuppressive cytokines and signals. An increase in the $CD4^+CD25^+$ Treg population, which blocks T-cell proliferation and leads to inhibition of the antitumor T cell response, has been shown at the tumor site in NSCLC patients.[15] Myeloid-derived suppressor cells (MDSCs) also create an immunosuppressive environment in cancer by inhibiting $CD4^+$ and $CD8^+$ T-cell antitumor immune responses. MDSCs are associated with increased tumor burden in patients with advanced NSCLC.[16]

Immune checkpoints that regulate T-cell activation were identified approximately 30 years ago. Among these checkpoints are programmed death receptor 1 (PD-1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4). The receptors are expressed on tumor cells and immune cells within the tumor microenvironment, including Tregs.[17] CTLA-4 is expressed on T cells, regulates early T-cell activation, and provides an inhibitory counterpart to the costimulatory receptor, CD28, found on T cells. CTLA-4 and CD28 share the ligands CD80 (B7.1) and CD86 (B7.2), and CTLA-4 is able to block the interaction of the ligands with CD28, thereby inhibiting T-cell activation. CTLA-4 antibodies demonstrated early responses in melanoma, but were not effective as monotherapy in nonimmunogenic tumors.[18] The CTLA-4 antibody ipilimumab (Yervoy, Bristol-Myers Squibb) was the first checkpoint inhibitor to demonstrate survival benefit in melanoma,[19] which led to investigations in other tumors, including NSCLC.

PD-1 dampens T-cell activity during inflammatory responses, resulting in immunosuppression within the tumor microenvironment.[20] PD-1 interacts with ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), and expression can be induced within tissue and tumors to mitigate effector T-cell activity. PD-L1 is upregulated on the tumor cells of multiple cancer types, including lung cancer,[21] and myeloid cells in the tumor microenvironment. The clinical development of PD-1 inhibitors has utilized expression of PD-L1 on tumor and immune cells in various combinations to provide insight into responses to the therapy. The first phase 1 trials evaluating PD-1 and PD-L1 inhibition in the clinic demonstrated responses across multiple tumors that proved to be durable.[6,22] Randomized trials evaluating the efficacy of checkpoint inhibitor therapy in NSCLC are presented in Table 1.

Checkpoint Inhibitors in NSCLC

Ipilimumab

Ipilimumab is a monoclonal antibody that inhibits CTLA-4 by binding and blocking its interaction with its ligands. A phase 2 trial of ipilimumab plus carboplatin and paclitaxel vs carboplatin and paclitaxel alone was conducted in 204 patients with chemotherapy-naive advanced NSCLC.[23] Patients were randomly assigned in a 1:1:1 ratio to receive carboplatin and paclitaxel with placebo, with concurrent ipilimumab, or with phased ipilimumab following 2 cycles of chemotherapy. Immune-related response criteria were used in patient assessments. The immune-related progression-free survival (irPFS) was improved for the phased group vs the control group (5.7 vs 4.6 months; hazard ratio [HR], 0.72; *P*=.05). The concurrent ipilimumab group had a median irPFS of 5.5 months, which did not reach statistical significance compared with the control group (HR, 0.81; *P*=.13). Treatment-related grade 3/4 adverse events were similar across the 3 arms. In the ipilimumab arms, there was a trend toward increased rash, pruritus, and diarrhea. Immune-related adverse events also were higher in both ipilimumab arms. Clinical benefit was more pronounced in patients with squamous cell histology, and a phase 3 trial is ongoing for patients with squamous cell NSCLC (NCT02279732).

Nivolumab

Nivolumab (Opdivo, Bristol-Myers Squibb) was the first PD-1 inhibitor in clinical development and is a fully human immunoglobulin G4 monoclonal antibody directed against PD-1. The phase 1 trial conducted across multiple tumor types showed early responses in NSCLC, in addition to melanoma and renal cell carcinoma.[6] Long-term safety and follow-up in 129 patients with heavily pretreated NSCLC reported a median overall survival (OS) of 9.9 months (95% CI, 7.8-12.4 months) and an overall response rate (ORR) of 17%. Similar results were found in nonsquamous and squamous cell histologies.[24] A subsequent phase 2 trial showed activity in patients with previously treated NSCLC with squamous histology. The study enrolled 117 patients, and the median OS was 8.2 months with an ORR of 15%. Nivolumab was generally well tolerated, and the most common grade 3/4 toxicities included fatigue, pneumonitis, and diarrhea.[25]

Recent randomized phase 3 trials in previously treated patients compared nivolumab vs docetaxel in both squamous[26] and nonsquamous[27] histologies. The phase 3 study in squamous cell histology randomly assigned 272 patients to either nivolumab or docetaxel, and showed an improvement in OS of 9.2 months vs 6 months, respectively, (HR, 0.59; 95% CI, 0.43-0.81; *P*=.00025) at the time of interim analysis. The ORR was 20% with nivolumab and 9% with docetaxel, and PFS was improved with nivolumab (3.5 vs 2.8 months, *P*=.004). Patients were not required to undergo fresh biopsy, but archival or fresh tissue was available for evaluation of PD-L1 expression in 83% of patients. PD-L1 expression was analyzed by cutoff points of 1%, 5%, and 10%, but expression was not prognostic or predictive of patient outcome at any level. Treatment-related adverse events were less frequent in patients who received nivolumab (7% had serious events) compared with docetaxel (24% had serious events). The most frequent adverse events were hypothyroidism, diarrhea, pneumonitis, increased creatinine, and rash. The results of this phase 3 trial led to the US Food and Drug Administration (FDA) approval of nivolumab for previously treated squamous cell NSCLC in March 2015.

The open-label phase 3 trial in patients with previously treated nonsquamous histology randomly assigned 582 patients to nivolumab or docetaxel.[27] The primary endpoint was OS, and the median OS was significantly improved in the nivolumab group vs the docetaxel group (12.2 months vs 9.4 months, respectively; HR, 0.73; 95% CI, 0.59-0.89; *P*=.0016). The ORR also was improved with nivolumab vs docetaxel (19% vs 12%, respectively), but there was no statistically significant difference in PFS (2.3 months vs 4.2 months, respectively). In this group with nonsquamous histology, archival or fresh biopsy tissue was evaluable for PD-L1 expression in 78% of patients. PD-L1 expression was predictive of clinical benefit at each cutoff point (1%, 5%, and 10%), and OS was similar in both arms when PD-L1 was not expressed (nivolumab, 10.4 months; docetaxel, 10.1 months). The safety profile of nivolumab was consistent with previous studies; 10% of patients experienced grade 3/4 events in the nivolumab arm, and 54% of patients experienced grade 3/4 events in the docetaxel arm. The most common treatment-related events with nivolumab were fatigue, nausea, decreased appetite, asthenia, and diarrhea. This study resulted in the approval of nivolumab by the FDA for previously treated nonsquamous cell NSCLC in October 2015.

Pembrolizumab

Pembrolizumab (Keytruda, Merck) is a highly selective, humanized monoclonal immunoglobulin G-kappa isotype antibody against PD-1. The exceptional durable responses seen in the phase 1 trial in melanoma patients led to FDA approval of pembrolizumab for patients with advanced melanoma following ipilimumab.[28] A follow-up, randomized, phase 3 trial evaluating pembrolizumab vs ipilimumab demonstrated superior PFS and OS with pembrolizumab in advanced melanoma.[29] The early promise of benefit across tumor types led to a single-arm

trial of 495 patients with NSCLC that assessed PD-L1 expression and correlated that expression with response to treatment.[30] The study evaluated chemotherapy-naive and previously treated patients with multiple dosing schedules, and required a newly obtained tumor sample for PD-L1 staining as part of eligibility. Patients were enrolled into a training group (n=182) or validation cohort (n=313), and the percentage of tumor cells with membranous PD-L1 was examined for association with tumor response. The overall response rate was significantly improved in increasing quartiles of PD-L1 expression, and those with a score of 50% or greater had an ORR of 45%, which was similar for treatment-naive and previously treated patients. The median PFS in this group was 6.3 months. This was the first study to demonstrate the correlation between response and PD-L1 expression on tumor cells in NSCLC. The most common toxicities found in this study were fatigue, pruritus, and decreased appetite. A phase 2/3 randomized trial of pembrolizumab vs docetaxel in previously treated patients with advanced NSCLC is complete and results should be available soon (NCT01905657). These data caused the FDA to grant accelerated approval to pembrolizumab for patients with metastatic NSCLC whose tumors express PD-L1 and who experience progression after first-line therapy.

The level of tumor antigen expression also may provide valuable information regarding tumor response to PD-1 inhibition. Data from the Cancer Genome Atlas Research Network demonstrate a high mutation rate in squamous cell lung cancer, and early studies associated squamous histology with response to checkpoint inhibitors.[22] Rizvi and colleagues used whole-exome sequencing of patients with NSCLC who received pembrolizumab to associate mutation rate with clinical benefit.[31] They found that a higher somatic nonsynonymous mutation burden was associated with clinical benefit in a discovery (n=16) and validation cohort (n=18). These patients experienced improved durable clinical benefit, defined as partial or stable response lasting greater than 6 months, in addition to better ORR and PFS. These data are consistent with the theory that somatic mutations and associated neoantigens are integral for PD-1 efficacy. The work examining PD-L1 expression in tumor and immune cells and somatic mutation rate may provide guidance for the use of these inhibitors in NSCLC and other tumors to enrich for a population that will have greater benefit, and thus result in a significant impact on outcomes.

MPDL3280A (Atezolizumab)

MPDL3280A (atezolizumab) is a monoclonal antibody against PD-L1 that prevents the binding of PD-L1 to PD-1 and CD80, in addition to preserving the interaction between PD-L2 and PD-1, which may decrease systemic toxicity because PD-L2 is more highly expressed in normal tissue, such as the lung.[32] Analysis from a phase 1 trial with atezolizumab in multiple tumor types showed an association between tumor PD-L1 expression and tumor response. Furthermore, the study found that the correlation with response was more prominent when tumor-infiltrating immune cells expressed PD-L1.[33]

Atezolizumab has demonstrated efficacy when compared with docetaxel in NSCLC in a recently presented trial. In the randomized phase 2 study, 287 patients with metastatic NSCLC (both squamous and nonsquamous histology) who had received prior therapy were randomly assigned to receive atezolizumab or docetaxel.[34] Patients were required to have tissue for the assessment of PD-L1 expression in both tumor cells (TC) and immune cells (IC). In the intent-to-treat population, there was a trend toward increased OS with atezolizumab compared with docetaxel at the interim analysis (11.4 months vs 9.5 months, respectively; HR, 0.77; 95% CI, 0.55-1.06; *P*=.11). Across all PD-L1–positive tumors (those with TC and/or IC 1-3 scores) the OS was significantly improved with atezolizumab (HR, 0.63; 95% CI, 0.42-0.94, *P*=.024), despite similar PFS and ORRs in both arms. Those with the highest TC and/or IC levels appeared to have the most benefit, whereas patients without PD-L1 expression did not experience improvement in survival. Patients who received atezolizumab had significantly fewer grade 3/4 adverse events than those receiving docetaxel (12% vs 39% treatment-related adverse events, respectively). The most common adverse events for atezolizumab were decreased appetite, dyspnea, nausea, diarrhea, and arthralgia. A randomized phase 3 trial with atezolizumab vs docetaxel in advanced NSCLC has completed accrual and results are anticipated (NCT02008227).

Immune-Related Toxicities

Activation of the immune system to produce antitumor responses leads to distinct toxicities related to immune stimulation. Immune-related adverse events (irAEs) include pneumonitis, colitis, dermatitis, hepatitis, nephritis, endocrinopathies, and neuropathy. These side effects are autoimmune manifestations that lead to new challenges in management of the toxicities. In clinical trials and practice, the incidence and severity of irAEs are greater with CTLA-4 inhibition as compared with anti–PD-1 and anti–PD-L1 agents, but all may result in life-threatening toxicities.

Analyses of irAE data with ipilimumab in melanoma are the most robust at this time. Gastrointestinal and dermatologic toxicities were the most common, but other significant irAEs included endocrine, hepatic, and neurologic toxicities. Endocrine toxicity may manifest as hypothyroidism, hyperthyroidism, hypophysitis, and

Table 2. Correlation of PD-L1 Expression With PD-1/PD-L1 Efficacy in NSCLC

Agent	Target	Antibody	Cutpoints	Correlation
Nivolumab[26] (squamous histology)	PD-1	Dako 28-8	1%, 5%, 10%	None
Nivolumab[27] (nonsquamous histology)	PD-1	Dako 28-8	1%, 5%, 10%	Increased OS with increasing % positive
Pembrolizumab[30]	PD-1	Dako 22C3	<1%, 1%-49%, ≥50%	Increased OS with ≥50%
Atezolizumab[34]	PD-L1	Roche Ventana, SP142	TC score, 1/2/3 IC score, 1/2/3	Increased OS with TC/IC 1-3 scores

IC, immune cell; OS, overall survival; PD, programmed death; PD-L1, programmed death ligand 1; TC, tumor cell.

adrenal insufficiency. Ipilimumab demonstrates a predictable kinetic profile with regard to toxicity, with timing of onset depending on the organ system involved.[35] Dermatologic irAEs tend to appear in the first 2 to 3 weeks of treatment, followed by gastrointestinal irAEs after 6 to 7 weeks, and endocrine irAEs occurring later.[35] However, such guidelines are not absolute; late toxicity even after treatment discontinuation also has been reported.[36]

Toxicities related to anti–PD-1 and anti–PD-L1 agents are usually milder and less common, but life-threatening presentations can occur. Frequently reported irAEs include dermatologic AEs (rash, pruritus) and gastrointestinal AEs (diarrhea, colitis), which are usually grade 1 or 2. Additional unique irAEs include hepatitis, hypophysitis, thyroiditis, and vitiligo.[6,22,25] Endocrine toxicity may be insidious, and monitoring of thyroid function during treatment is recommended. Pneumonitis, although rare, is an irAE of specific concern to lung cancer patients, and may be associated more with anti–PD-1 agents than anti–PD-L1 therapies.[37] Most low-grade irAEs can be addressed with supportive measures and may not require therapy cessation. Management of grade 3/4 irAEs typically requires therapy discontinuation and use of high-dose intravenous corticosteroids. A prolonged corticosteroid taper after symptom resolution (up to 1 month) generally is advised.[38]

Tumor Vaccines

Researchers have tried a number of approaches using vaccines to stimulate specific antitumor responses to tumor-associated antigens. Most have had disappointing results thus far, but may find a role in the therapy of lung cancer in combination with checkpoint inhibition. Below is a summary of tumor vaccines that have been studied extensively in NSCLC.

Belagenpumatucel-L

Belagenpumatucel-L is an allogeneic tumor cell vaccine consisting of 4 irradiated NSCLC cell lines and modified with a transformed growth factory β2 antisense plasmid. A randomized phase 2 trial enrolled 75 patients with stage II to IV NSCLC to one of 3 doses of vaccine.[39] The 2 highest-dose cohorts had improvement in OS compared with the low-dose cohort, which led to further study. A randomized, phase 3 study enrolled 532 patients with stage IIIA to IV NSCLC following front-line therapy to belagenpumatucel-L or placebo.[40] The study did not meet its primary endpoint of improvement in OS. A subgroup of patients with stage IIIB and IV disease experienced a median survival of 20.7 months with the vaccine compared with 13.4 months with placebo, although this result was not statistically significant. An analysis of patients with nonadenocarcinoma histology and stage IIIB or IV disease did demonstrate an improved OS, and the drug remains in development.

MAGE-A3

The melanoma-associated antigen-A3 (MAGE-A3) is an antigen mainly expressed in nonmalignant cells, and in about 20% to 50% of patients with NSCLC. It has been associated with poor prognosis and advanced disease in NSCLC.[41] A phase 2 trial evaluated the efficacy of a recombinant MAGE-A3 protein vaccine following surgical resection in 182 patients with stage IB or II NSCLC, but did not demonstrate a statistically significant improvement in PFS or OS.[42] The study revealed a trend that the vaccine enhanced the disease-free survival interval, and a subsequent phase 3 trial in the adjuvant setting in patients with stage IB to IIIA resected NSCLC and MAGE-A3 protein expression was completed. The study did not meet its primary endpoint, which was to demonstrate an improvement in disease-free survival.

Tecemotide (Liposomal BLP25)

Tecemotide (L-BLP25) is a liposome-based vaccine made from the tandem repeat region of MUC1. MUC1 expression occurs in NSCLC and was shown to be associated with poor survival in patients.[43] A phase 3 trial randomly assigned 1513 patients in a 2:1 ratio with stage III NSCLC

who experienced objective response or stable disease following definitive chemoradiation (either sequential or concurrent) to receive tecemotide or placebo. The trial did not achieve an improvement in OS for tecemotide, but a subgroup analysis demonstrated increased OS in patients who received concurrent chemoradiation with tecemotide over placebo (median OS, 30.8 months vs 20.6 months, respectively; HR, 0.78; *P*=.016).[44]

Future Directions

Immunotherapy has clear benefit for patients NSCLC and treatment with PD-1/PD-L1 inhibition has changed the landscape of lung cancer therapy. The optimal setting for use (frontline, refractory, adjuvant, consolidation, maintenance) and the duration of therapy are not optimally defined. The development of effective biomarkers to predict response is a high priority and several have shown promise (Table 2). Tumor expression of PD-L1 has been studied in most trials, although results are not comparable across studies owing to lack of consistency of antibody and differing thresholds for positive expression. Tumor-infiltrating immune cell assessment of PD-L1 also shows significant association with response, but has been studied with one agent to date. Whole-exome sequencing is not practical for all patients with NSCLC in the current practice setting, although mutation burden may be another predictor for response to PD-1 inhibition. Furthermore, the phase III trials using nivolumab demonstrated a significant increase in survival over second-line chemotherapy regardless of PD-L1 expression. Additional investigation to define a predictive biomarker is needed to characterize the patients who will derive the most benefit from therapy.

Introducing a new therapeutic class of drugs for lung cancer requires learning unique side effects that patients may experience. Immune-related toxicities are less common with PD-1/PD-L1 inhibitors than with CTLA-4 antibodies, but life-threatening events do occur. Most adverse events can be treated with supportive measures and corticosteroids, but vigilance is needed in the assessment of potential toxicities.

Owing to the survival benefit and durable responses seen with immunotherapy, current studies are evaluating combinations with chemotherapy, targeted therapy, immune-modulating therapy, and vaccine therapy to enhance the antitumor effects with the goal of long-term survival gains. The advances must consider impact and cost as we implement immune-based treatments into the standard of care for lung cancer.

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