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Lung Cancer (HA Wakelee, Section Editor)

Immune Checkpoint Inhibitors in NSCLC

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Opinion statement

Lung cancer is the leading cause of cancer-related mortality worldwide. Cytotoxic chemotherapy and tyrosine kinase inhibitors provide palliation and prolong survival, however, the median survival for patients with metastatic disease remains poor and more effective therapies are needed. Immune checkpoint inhibitors have shown promising results in phase I trials and are being evaluated in ongoing clinical trials in both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) patients. These include agents targeting the programmed cell death-1 receptor and its ligand (PD-1/PD-L1; notably nivolumab, pembrolizumab, MPDL3280A, and MEDI-4736) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; ipilimumab and tremelimumab); these agents induce antitumor responses by inhibiting critical negative T cell regulators. In particular, the anti-PD-1/PD-L1 therapies administered as single agent therapy in chemotherapy refractory patients have produced objective response rates ranging from 15 %–25 %, the majority of which were rapid and ongoing 1 year after starting therapy. Furthermore, the toxicity profile for these agents differs from that of cytotoxic chemotherapy but generally is much better tolerated. Promising biomarkers, particularly tumor expression of PD-L1 and tumor infiltrating lymphocytes, may aid in treatment selection and stratification. Ongoing evaluation is needed to define the most appropriate timing and patient population that will benefit from therapy with an immune checkpoint inhibitors and the role of combining these agents with existing therapies including systemic therapy and radiation.

Introduction

Lung cancer has been the leading cause of cancer-related death for the past 50 years for American men and the last 25 years for women [1]. During this time, platinum-based chemotherapy has become the standard treatment for advanced non-small cell lung cancer (NSCLC) in unselected patient populations. Although combination platinum-based regimens have been associated with improved survival compared with best supportive care, the median overall survival remains less than one year and almost no patients are alive at 5 years [2–4]. Moreover, these therapies induce neuropathy, renal dysfunction, and cytopenias, which limit their use in patients with medical comorbidities. In a subset of patients, small molecule inhibitors targeting oncogenic driver alterations such as EGFR and ALK may induce dramatic (albeit temporary) tumor regression [5, 6]. Although the development of these agents has represented a major advance for patients with EGFR mutations and ALK fusions, the majority of NSCLC patients lack genetic alterations, which may be targeted by approved agents at this time. More effective therapies are clearly needed.

Newly developed immune checkpoint inhibitors are challenging current treatment paradigms. Building on successful clinical trials in other tumor types, drugs targeting the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the programmed cell death receptor-1 (PD-1) and its ligand (PD-L1) are currently being evaluated in patients with advanced stage lung cancer. These new therapeutics exert their antitumor effects not by conventional cytotoxic mechanisms, but rather by unleashing suppressed immune responses, thereby preventing cancer from evading immune-mediated destruction. In contrast to chemotherapy and therapeutics targeting molecular alterations, some patients experience durable remissions without evidence of tumor resistance or relapse. This class of agents has generated tremendous excitement both in the oncology community and in the lay press even prior to widespread availability.

Immune checkpoint inhibitors function by modulating the interactions of T cells and either antigen presenting cells (APCs) or tumor cells. Ipilimumab blocks the negative T cell regulator cytotoxic T-lymphocyte antigen-4 (CTLA-4), thereby unleashing suppressed immune responses primarily at the level of the APC-T cell interaction, and potentially depleting regulatory T cells in the tumor microenvironment [7, 8]. Although inducing tumor-specific immune responses is the goal of therapy, autoimmune toxicities may occur as a consequence of non-specific T cell activation. Newer antibodies target PD-1 and PD-L1 at the interface between T cells and malignant cells. In early trial results, these agents appear to have more tumor-specific activity across malignancies and produce fewer immune-related adverse events as compared with anti-CTLA-4 therapy. In contrast to conventional chemotherapy, these agents appear to have potential for effecting durable responses and possibly long-term survival. In this article, we review the mechanism of action, clinical efficacy, and toxicity of CTLA-4 inhibitors and agents targeting the PD-1/PD-L1 axis.

CTLA-4 Inhibition

CTLA-4 inhibitors were among the first immune checkpoint inhibitors to be developed clinically and have been the best characterized to date [9–11]. Cytotoxic T cell activation requires not only the engagement of the T cell receptor with an MHC molecule but also an additional costimulatory signal mediated through CD28 and B7 binding. The CTLA-4 protein is expressed on the surface of T-cells and competes with CD28, thereby, functioning as a repressor of T-cell activation. Antibodies to CTLA-4 inhibit this critical negative regulator of T cell activation with a goal of inducing antitumor activity. This immune activation causes a distinct toxicity profile of autoimmune adverse events that has created new challenges in the clinic, including colitis, dermatitis,

hepatitis, endocrinopathies, and neuropathy. Ipilimumab was approved for the treatment of metastatic melanoma in 2011; this was also the first immune checkpoint inhibitor to be evaluated in NSCLC patients.

Ipilimumab

- Pharmacology: ipilimumab (Yervoy) is a fully humanized monoclonal antibody directed at CTLA-4 and functions to prevent receptor binding to cognate ligands [12]. The half-life of ipilimumab is 15.4 days. Although different schedules and doses of administration have been previously assessed in lung cancer and other tumor types, the approved dose in melanoma is 3 mg/kg.
- A randomized phase II clinical trial evaluated ipilimumab with chemotherapy in patients with both NSCLC and SCLC [13, 14•]. Two hundred and four chemotherapy-naïve patients were treated with carboplatin (area under curve=6) and paclitaxel (175 mg/m2) for six cycles, and either placebo, "concurrent" ipilimumab, or "phased" ipilimumab [14•]. In the concurrent regimen, ipilimumab was administered with chemotherapy for cycles one through four, followed by chemotherapy and placebo for cycles five and six. The phased regimen consisted of chemotherapy and placebo for cycles one and two followed by ipilimumab and chemotherapy for cycles three through six. In this study, ipilimumab was dosed at 10 mg/kg every 3 weeks (higher than the now-approved dose for melanoma). Notably, corticosteroid premedications were administered prior to chemotherapy infusion in all study arms. Following induction chemotherapy in both the concurrent and phased treatment groups, ipilimumab was administered every 12 weeks as a maintenance therapy in patients with acceptable side effects who had not demonstrated disease progression.
- The primary endpoint was immune relate progression free survival (irPFS). This endpoint was chosen to better capture the unique pattern of response to immune therapy including regression of index lesions in the face of new lesions and initial progression followed by tumor stabilization or regression [15, 16•].
- In this study, irPFS was improved in the phased ipilimumab arm compared with chemotherapy alone (median 5.7 vs 4.6 months, HR 0.72; $P=0.05$); no improvement in irPFS was observed in the concurrent arm compared with chemotherapy (median 5.5 vs 4.6 months HR=0.81, $P=0.13$). Best overall response rate (BORR), as measured by immune-related response criteria (irRC) appeared higher in patients who received ipilimumab (32 % and 21 % in the phased and concurrent arms, respectively, vs 18 % with chemotherapy alone) although these were not formally compared. No statistically significant

improvement in overall survival (OS) in either of the ipilimumab arms compared with placebo; however, in the phased arm the median survival appeared to be higher than for the chemotherapy alone arm (12.2 months vs 8.3 months, log rank $P=0.23$).

- An unplanned subset analysis of histologic subgroups revealed that both PFS and OS were improved in the phased ipilimumab group for patients with squamous histology (HR for progression 0.40 [95 % CI, 0.18–0.87], HR for death 0.48 [95 % CI, 0.22–1.03]).
- Grade 3/4 adverse events occurred with similar frequency across arms (control, 37 %; concurrent, 41 %; phased, 39 %) although grade 4 events appeared more frequent in the ipilimumab arms [10]. Serious immune mediated events including rash (4 %), colitis (10 %), and hypophysitis (1 case) occurred with similar frequency as in previous studies with ipilimumab.
- Of note, a study with similar design was conducted in 103 patients with extensive-stage SCLC who were randomized to carboplatin and paclitaxel plus either placebo, phased ipilimumab, or concurrent ipilimumab [13]. Phased, but not concurrent ipilimumab, improved irPFS compared with chemotherapy alone (median irPFS 6.4 vs 5.2 months; HR 0.67, $P=0.03$ for phased ipilimumab vs chemotherapy alone). No statistically significant improvement in OS or PFS (as measured by RECIST) was demonstrated for either arm.
- Based on this data a phase III trial is ongoing comparing chemotherapy alone to chemotherapy with phased ipilimumab in patients with squamous histology NSCLC (NCT01285609). The estimated data collection completion date for this trial is April 2015. However, with the ascendance of PD-1 directed therapies, CLTA-4 as an immune checkpoint inhibitor has fallen somewhat out of favor for NSCLC. Whether ipilimumab will play a role in combined immune checkpoint inhibition in conjunction with PD-1 therapy remains an unanswered question as discussed below.

Tremelimumab

- Tremelimumab is a fully humanized IgG2 monoclonal antibody to CTLA-4. In contrast to ipilimumab, a large phase III trial in melanoma did not demonstrate improved PFS or OS compared with cytotoxic chemotherapy although durable responses were observed in some patients [17].
- A phase II trial enrolled 87 patients with advanced NSCLC and administered tremelimumab as maintenance therapy following four cycles of chemotherapy [18]. There was no improvement in PFS in this study (20.9 % vs 14.3 % progression free at 3 months). Approximately 20 % of patients on the tremelimumab arm experienced a grade 3/4 adverse event the most common being colitis (9.1 %). Studies with

tremelimumab in combination with anti-PD-L1 therapy and gefitinib in patients with NSCLC are ongoing (NCT02000947; NCT02040064).

PD-1/PD-L1 Directed Therapies

Anti-PD-1 in NSCLC

PD-L1 (B7-H1) is broadly expressed in non-small cell lung cancers, both in adenocarcinomas and in squamous cell carcinomas (approximately 50 % in each subtype), and may be associated with a poor prognosis [19]. The frequent expression of this immune-suppressive ligand coupled with high levels of tumor infiltrating lymphocytes suggests that exhausted and ineffective antitumor T cell responses may serve as a critical mechanism of lung cancer progression and immune evasion. Anti-PD-1 directed agents block the interaction of PD-1 to its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), activating previously functionally exhausted immune responses. Moreover, PD-L1 expression is largely confined to the tumor microenvironment (although normal lung tissue does have low levels of expression), potentially promoting tumor-specific immune responses and limiting widespread T cell activation [20]. Tumor expression of PD-L1 by immunohistochemistry (IHC) is a promising predictive biomarker of response to anti-PD-1/PD-L1 (see below) although its role in treatment decision making is still being clarified. The dynamic nature of PD-L1 expression may limit its use. Additionally, at least three distinct PD-L1 antibodies have been developed as potential companion diagnostics to each agent (nivolumab, pembrolizumab, and MPDL3280A), each with its own performance specifications and thresholds for positivity. The definition of "positive" PD-L1 expression, therefore, is variable across studies and may impact on trial results.

Nivolumab (BMS-936558; MDX-1106)

- Nivolumab is a human IgG4 monoclonal antibody to PD-1. A large, phase I trial was conducted, primarily with large expansion cohorts of patients with NSCLC, melanoma, and renal cell carcinoma (RCC) [21••].
- In this trial, 129 patients with NSCLC received nivolumab (1 mg/kg, 3 mg/kg or 10 mg/kg IV every 2 weeks); >95 % had performance status of 0–1, 54 % had received≥three prior systemic therapies. Across dosing levels, the ORR was 17.1 % and appeared similar between squamous (16.7 %; nine of 54) and nonsquamous histology (17.6 %; 13 of 74). A difference in response rate between different dose levels was observed; 3 % for the 1 mg/kg cohort compared with 24.3 % and 20.3 % for the 3 mg/kg and 10 mg/kg cohort respectively. Based on these results the 3 mg/kg dose was selected for further study. The median PFS and OS were 2.3 months and 9.6 months, respectively. One year after starting therapy, 42 % of patients were alive [2]. Durable responses were common with a median duration of response of

74 months. See Table 1 for summary of response rates in NSCLC to anti-PD-1/PD-L1 directed therapies.

- Nivolumab was well-tolerated; 14 % of patients had grade 3/4 drug-related adverse events that were immune-mediated in 6 % and reversible with corticosteroid administration. Pneumonitis has emerged as the most concerning toxicity of nivolumab but was only observed in nine patients; three of which resulted in deaths (two in NSCLC and one in colorectal cancer).
- In patients enrolled in the phase I trial with tumor samples available for assessment, PD-L1 expression by immunohistochemistry was associated with a response to therapy, while no responses were observed in patients with tumors that were PD-L1 negative. A subsequent study in melanoma showed that although PD-L1 does correlate with response, PD-L1 negative patients can respond to nivolumab albeit at low rates [23]. Technical aspects of PD-L1 staining and tumor heterogeneity may complicate this analysis. Furthermore, expression appears dynamic and may vary over time.
- The significance of oncogenic driver mutations and other clinical factors on response to nivolumab remains uncertain. The response rate in EGFR-mutant NSCLC appeared similar to EGFR wild type (17 % vs 19 %). KRAS mutation may predict for lower responses (14 % vs 25 %) although larger numbers are needed. In addition, the prognostic impact of former/current smoking status, a possible predictor of response for MPDL3280A (discussed below), has not been defined.
- A single arm phase II trial of nivolumab in unselected squamous cell NSCLC patients (NCT01721759) and two large phase III trials of nivolumab as second line therapy in both squamous and nonsquamous NSCLC patients have completed accrual and results are anticipated (NCT01642004;NCT01673867). A randomized phase III trial comparing first-line nivolumab to chemotherapy in patients with tumors that are positive for expression of PD-L1 is ongoing (NCT02041533). Studies combining nivolumab with chemotherapy, tyrosine kinase inhibitors (ie, erlotinib), and bevacizumab are ongoing or planned (NCT01454102).
- Early results from two of these studies were presented at ASCO 2014. The combination of nivolumab and investigator's choice of platinum doublet was assessed in 46 patients [24]. Across arms, 45 % of patients experienced an objective response to therapy and OS at 1 year ranged from 59 %–87 %. Grade 3/4 adverse events were higher than what has previously been reported for either chemotherapy or nivolumab alone, with an AE reported in 45 % of patients. These included pneumonitis (7 %), acute kidney injury (5 %), and fatigue (5 %). In a separate study, 21 patients with EGFR-mutant NSCLC received nivolumab and erlotinib [25]. Of the 20 patients with acquired resistance to erlotinib three patients experienced a PR (15 %) and nine patients had stable disease (45 %). Grade 3/4 adverse events

Table 1. Response rate to anti-PD-1/PD-L1 overall and by PD-L1 expression status

Agent	Nivolumab	Pembrolizumab	MPDL3280A
Overall response rate	17.1 % (22 of 128)	19 % (28 of 146)	23 % (12 of 53)
PD-L1 staining threshold	≥5 % cells staining	≥50 % cells (strong) 1–49 % cells (weak)	IHC 3+ (strong) IHC 1–2+ (weak)
PD-L1 (+) response rate	36 % (9 of 25)[a]	23 %[b]	86 % (5 of 6; strongly +) 15 % (3 of 20; weakly +)
PD-L1 (-) response rate	0 % (0 of 17)	9 %	20 % (4 of 20)

IHC immunohistochemistry, PD-L1 programmed cell death ligand.
[a]Includes tumors of all histologies in the phase I trial.
[b]Response rate by irRC.

occurred in four patients including three with elevations in liver function tests.

Pembrolizumab (MK-3475)

- Pembrolizumab is a humanized IgG4 monoclonal antibody to PD-1. A phase I study included 450 patients with NSCLC who had received prior chemotherapy, 305 patients (67.7 %) were eligible for therapy based on PD-L1 tumor expression. Strong PD-L1 expression was defined as staining ≥50 % of tumor cells, weak PD-L1 expression was 1 %–49 % of tumor cells. Approximately 25 % of samples were classified as strong staining [26].
- Pembrolizumab was administered as 10 mg/kg IV every 2 weeks or every 3 weeks. In preliminary data reported on the 159 patients with tumors that were positive for expression of PD-L1, the response rate was 23 %, median time to response was 9 weeks, and duration of response was 31 weeks. The RR was similar for Q2W dosing (26 %) or Q3W dosing (21 %) prompting an expansion of enrollment of an additional cohort of patients with Q3W dosing. In 35 patients with tumors that were PD-L1 (-) the response rate was 9 %, median time to response was longer at 14 weeks and duration has not been reported [27]. Among all patients, current/former smokers appeared to have a higher response rate compared with never smokers (26 % vs 8 %).
- Drug-related adverse events were reported in 64 % of patients, most commonly grade 1–2 toxicities were fatigue (24 %), decreased appetite (10 %), arthralgia (9 %), diarrhea (8 %), pruritus, nausea, and pyrexia (7 %). There were four cases of drug-related grade 3/4 pneumonitis [25].
- A subset of this trial included 84 treatment-naïve NSCLC patients, 73 with tumors evaluable for expression of PD-L1, of which 57 (78 %) were positive and enrolled on trial. This number is higher than the

62 % reported in the cohort treated with prior chemotherapy. In the 42 patients evaluable for response, the RR was 26 % with median PFS of 27.0 weeks by central review [28]. Responses by RECIST criteria were observed in 20 % at the 10 mg/kg Q3W regimen and 31 % with Q2W dosing (46 % and 41 %, respectively, with irRC).

- Several studies are ongoing or planned for pembrolizumab all requiring biopsies and enrolling patients with tumors that are positive for expression of PD-L1, including a single arm monotherapy trial (NCT01295827), and a phase III trial comparing docetaxel with pembrolizumab in previously treated patients (NCT01905657). A phase I/II trial in unselected patients is evaluating in pembrolizumab in combination with chemotherapy, bevacizumab, tyrosine kinase inhibitors, or ipilimumab (NCT02039674). A first-line trial compared with standard, platinum-based chemotherapy is also planned.

Anti-PD-L1

Several agents that target PD-L1, the ligand for PD-1, are also in development. These agents block the interaction of PD-L1 with PD-1 and with B7.1. The effects of these agents are predicted to be similar to anti-PD-1, although distinct immune checkpoint interactions are suppressed by each class of drugs, which may produce differing anti-tumor and toxicity profiles. At this point, it is not clear which approach is superior. Pneumonitis seems to be less frequent in patients treated with anti-PD-L1 directed agents.

MPDL3280A

- MPDL3280A is a human IgG1 monoclonal antibody to PD-L1. A phase I study was conducted in advanced solid tumors. Activity was observed in NSCLC, melanoma, RCC, gastric cancer, and head and neck squamous cell carcinoma.
- Among 53 patients with NSCLC included, the ORR was 23 % per RECIST 1.1 criteria [29]. Preliminary data reported the response rate was higher in tumors that were IHC3 positive (83 %), defined as 10 % of tumors staining positive for expression of PD-L1 and in former and current smokers (11 of 43) compared with never smokers (1 of 10). There was no significant difference in response between EGFR wild type and mutant or KRAS wild type and mutant NSCLC patients.
- Treatment related adverse events occurred in 66 % of patients, of which 11 % were grade 3/4 including fatigue, nausea, dyspnea, and emesis. No cases of pneumonitis were observed and only one grade 3 immune related adverse event occurred (diabetes mellitus).
- Ongoing clinical trials include a single agent study in patients with PD-L1 positive tumors (NCT02031458) comparing MDPL3280A with chemotherapy (NCT02008227), in combination with erlotinib in

EGFR mutant NSCLC (NCT02013219), and combined with chemotherapy and/or bevacizumab in solid tumor patients (NCT01633970).

Other anti-PD-L1 Agents

- BMS-936559 was the first PD-L1 antibody to be assessed in NSCLC patients. A response rate of 10 % was observed in 49 patients enrolled in a phase I trial evaluating multiple different dose levels with no significant difference between squamous and nonsquamous NSCLC patients [30]. Clinical development of this agent has been suspended at this time.
- MEDI-4736 – An ongoing dose escalation trial is being conducted in patients with NSCLC and other malignancies. Among patients treated to date response and toxicities appear consistent with other anti-PD-L1 directed agents. In early results, three of 13 heavily pretreated patients experienced confirmed partial responses [31].

Nivolumab and Ipilimumab

- Combining anti-PD-1/PD-L1 directed agents with CTLA-4 antibodies is also being explored in clinical trials. These agents activate the immune response at different stages of immune activation, potentially offering a complementary approach.
- A phase I trial including 52 patients with advanced melanoma reported a 40 % response rate across multiple dosing levels; and was particularly high in the nivolumab 1 mg/kg and ipilimumab 3 mg/kg arm (53 % ORR, nine of 17 patients) [32•]. Furthermore, responses were rapid and dramatic; all nine patients with responses on the above dosing arm had >80 % reduction in tumor size by 12 weeks after starting therapy. This combination was associated with a higher rate of adverse events compared with either regimen alone. Serious treatment related adverse events (grade 3/4) occurred in 49 % of patients and most frequently included elevated liver function tests (15 %), gastrointestinal toxicity (9 %), and renal insufficiency (6 %). Grade 3/4 pneumonitis occurred in one patient.
- In contrast to trials of anti-PD-1 or ipilimumab monotherapy, PD-L1 expression did not correlate with response rate. The ORR was 46 % (six of 13 patients) in those with PD-L1 (+) tumors and 41 % (9 of 22) in PD-L1 (-) patients.
- Early results from a phase I study combining nivolumab with ipilimumab in NSCLC were presented at ASCO 2014 [33]. Forty-six chemotherapy-naive patients were treated with either nivolumab 3 mg/kg and ipilimumab 1 mg/kg or nivolumab 1 mg/kg and ipilimumab 3 mg/kg.

The confirmed and unconfirmed ORR was 22 % in these patients with an additional 33 % experiencing stable disease. Responses occurred in patients with squamous (four of 15 patients, 27 %), and nonsquamous (six of 31, 19 %) histologies, and in PD-L1 (+) (three of 16, 19 %) and PD-L1 (-) tumors (three of 22, 14 %). Of note, grade 3/4 treatment related adverse events occurred in 48 % of patients and three patients died of therapy related complications (respiratory failure, bronchopulmonary hemorrhage, and toxic epidermal necrolysis). This trial is ongoing (NCT01454102).

- An early phase trial is ongoing in SCLC patients combining nivolumab with ipilimumab (as well other tumor types; NCT01928394). Additionally, early phase I trials are being planned with tremelimumab (anti-CTLA-4) and MEDI-4736 (anti-PD-L1). In addition, there is interest in combining PD-1/PD-L1 directed agents with other immune checkpoint modulators (eg, OX40, LAG-3, etc.).

Conclusions

Immune checkpoint inhibitors, particularly agents targeting the PD-1/PD-L1 axis are clinically active in advanced NSCLC and represent a major step forward in lung cancer therapeutics. These novel therapies will likely play a major role in NSCLC given the potential for rapid, durable responses and their favorable toxicity profiles. Their role in the treatment of patients with SCLC remains to be defined. Recently presented studies show the feasibility of combining these agents with other clinically active therapies for NSCLC as well as with CTLA-4 inhibitors, with higher reported response rates but also higher rates of grade 3/4 adverse events. Further defining patients who benefit from immune checkpoint monotherapy and patients who require potentially more active albeit more toxic combination regimens will be a critical need moving forward. The effect of targeted therapy and chemotherapy on expression of PD-L1 remains to be determined and is being evaluated in ongoing trials. PD-L1 expression by the tumor and a history of smoking appear to be predictors of response in early data, although confirmation in ongoing studies is needed. In addition the efficacy of these agents in select molecular cohorts remains to be defined. Many of these questions may be answered in ongoing and proposed trials.

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Compliance with Ethics Guidelines

Conflict of Interest
Douglas B. Johnson, Matthew J. Rioth, and Leora Horn declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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