PD-1 and PD-L1 Inhibitors in Advanced Non-small Cell Lung Cancer—Promising Agents and Evolving Questions

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Abstract

There exists increasing evidence that PD-1 and PD-L1 inhibitors may be effective in the treatment of non-small cell lung cancer (NSCLC)—an unforeseen finding given the early failure of several immuno- and vaccine-based therapies in this field. This suggests that NSCLC is a more immunogenic tumor than initially appreciated and that it may manipulate various immune checkpoints in order to blunt a potential anti-tumor immune response. NSCLC has subsequently been shown to commonly overexpress PD-L1 as a means of suppressing such cell-mediated immune response through PD-1-mediated signaling. Numerous PD-1 and PD-L1 inhibitors are currently in development as well as various combinations of these inhibitors with chemotherapy, kinase inhibitors, and other immune checkpoint inhibitors. Although these treatments have demonstrated clinical activity in early phase clinical trials, reliable data on the impact of these agents on clinically meaningful endpoints in advanced NSCLC remains scarce. Important questions remain unanswered regarding the appropriate use of PD-L1 expression as a predictive biomarker for the use of these agents as well as the ability of the aforementioned drug combinations to achieve durable disease control.

Keywords

NSCLC, immunotherapy, PD-1, PD-L1

The use of immunotherapy in advanced non-small cell lung cancer (NSCLC) has long been investigated in advanced NSCLC. The frequent presence of tumor infiltrating lymphocytes (TILs) noted in numerous tumor types provided early evidence of the potential immunogenicity of several cancers including NSCLC.1-3 However, initial attempts to exploit this therapeutically through tumor vaccines, interleukin (IL)-2, interferon, and similar immunotherapies were generally met with limited success.3,4 The significant clinical benefit from cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoint inhibitors found in melanoma led to clinical trials of ipilimumab attempting to demonstrate similar benefit in NSCLC.5 Although modest activity was demonstrated with both ipilimumab and certain vaccine-based therapeutic strategies and some clinical trials are still ongoing,5-11 there has been pessimism in the field regarding the utility of immunotherapy in NSCLC.

The development of programmed cell death protein 1 (PD-1) and programmed cell death-ligand protein 1 (PD-L1) inhibitors and their observed clinical activity in advanced NSCLC reinvigorated the study of immunotherapy in this tumor type and suggested NSCLC must utilize powerful mechanisms to evade and dampen the immune response in order to proliferate despite potential immunogenic features. The PD-1/PD-L1 signaling pathway represents a key immune checkpoint that allows NSCLC to evade immune surveillance and whose activation, in concert with other mechanisms, may explain the lackluster performance of early attempts at immunotherapy. The PD-1/PD-L1 pathway represents a promising therapeutic target under active investigation in NSCLC and a foundation upon which to build multidrug immunotherapy strategies.

Immunogenicity and Mechanisms of Immune Escape in NSCLC

The tumor stroma consists of a complex infiltrate of various cell types including both inflammatory cells and TILs.2 The presence of this immune infiltrate provided early evidence of the potential relationship between the immune system and several tumor types including NSCLC. The composition of the immune infiltrate associated with NSCLC exhibits variability between patients. An increased proportion of TILs relative to other inflammatory cells in the tumor stroma have been associated with improved prognosis in both the prospective and retrospective cohorts of patients with advanced...
NSCLC. Conversely, an increased proportion of T regulatory cells (TREGs) relative to cytotoxic T lymphocytes (CTLs) has been associated with a poorer prognosis in advanced NSCLC. The secretion of specific chemokines has been suggested to directly recruit TREGs to the tumor microenvironment with subsequent blunting of any potential anti-tumor immune response. These findings suggest an important interaction between the progression of advanced NSCLC and these TILs—potentially reflecting an underlying adaptive anti-tumor immune response and supporting the assertion of tumor immunogenicity in NSCLC.

The interaction between the TIL population and the tumor cells themselves constitutes an extremely complex interplay of co-stimulatory and co-inhibitory immune signals. This directly affects both the composition of the inflammatory infiltrate and TIL population as well as the associated T-cell-mediated immune response. Many tumor types can manipulate specific immune checkpoints associated with self-tolerance in order to downregulate and evade T-cell-mediated anti-tumor response. Several of the receptors associated with these immune checkpoints have been characterized and therapeutically targeted in NSCLC including CTLA-4, killer cell immunoglobulin-like receptor (KIR), T cell immunoglobulin mucin 3 (TIM-3), and the PD-1 pathway. The PD-1 pathway has emerged as a killer cell immunoglobulin-like receptor (KIR), T cell immunoglobulin mucin specific immune checkpoints associated with self-tolerance in order to T-cell-mediated immune response. Many tumor types can manipulate specific immune checkpoints associated with self-tolerance in order to downregulate and evade T-cell-mediated anti-tumor response. Several of the receptors associated with these immune checkpoints have been characterized and therapeutically targeted in NSCLC including CTLA-4, killer cell immunoglobulin-like receptor (KIR), T cell immunoglobulin mucin 3 (TIM-3), and the PD-1 pathway. The PD-1 pathway has emerged as a key checkpoint of interest in NSCLC due to both the frequency of PD-1 expression in this tumor type well as early evidence suggesting significant clinical activity using PD-1 pathway inhibitors.

**PD-L1 Overexpression and Evasion of the T-cell-mediated Immune Response in NSCLC**

PD-L1 is expressed on the surface of activated T cells and serves primarily to dampen the effector function of T cells through interaction with its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC). Interaction of PD-1 with its ligand results in downregulation of T-cell-mediated cell killing, altered cytokine production, and, ultimately, apoptosis. PD-L1 is expressed in various normal tissues in response to inflammatory cytokine signaling in order to maintain self-tolerance. This same mechanism is co-opted by tumor cells in order to avoid an acquired immune response to tumor-associated antigens.

The overexpression of PD-L1 by tumor cells in NSCLC has been demonstrated in several large retrospective studies. The largest of these studies examined archived tumor tissue from 458 patients with stage I–IV NSCLC across all histologies using quantitative immunofluorescence (QIF) to detect PD-L1 expression on the tumor cell surface. This revealed that 32 % of these samples expressed elevated PD-L1. Similar smaller retrospective studies in NSCLC using both QIF and immunohistochemistry (IHC) have reported rates of PD-L1 expression by tumor cells ranging from 27 to 58 %. Several of these studies report an increased inflammatory infiltrate associated with PD-L1 overexpression. The expression of PD-L1 by tumor cells may also be mediated by the activation of specific oncogenes associated with NSCLC including epidermal growth factor receptor (EGFR) and KRAS although the relationship with the latter remains controversial. Smoking status has also been correlated with elevated PD-L1 expression. However, association between overall survival (OS) and PD-L1 expression remains controversial with reports of both an associated improvement and decrease in OS.

PD-L1 overexpression and associated activation of the PD-1 pathway thus appears to be broadly exploited by tumor cells in NSCLC as a means to evade T-cell-mediated anti-tumor activity. The observed high rate of PD-L1 overexpression in NSCLC occurs across both disease stage and histology. In particular, high rates of overexpression have been reported in both squamous cell and sarcomatoid lung cancer.

**Therapeutic Inhibition of the PD-1/PD-L1 Immune Checkpoint**

The therapeutic targeting of the PD-1 pathway using immune checkpoint inhibitors represents a potentially important new treatment modality for various NSCLC histologies including less-common tumor types for which a paucity of effective treatments exist. Numerous PD-1 and PD-L1 blocking antibodies are currently in clinical development—each aiming to facilitate a vigorous and sustained anti-tumor immune response in patients with advanced NSCLC.

A major challenge in understanding the efficacy and properties of the multiple PD-1 and PD-L1 inhibitors currently in development is the paucity of published data associated with these agents. With the exception of nivolumab and MPDL3280A, the majority of agents in this drug class do not have published early phase data in NSCLC. As such, distinguishing...
Lung Cancer

Table 2: Ongoing Phase II and III Clinical Trials

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<tr>
<th>Agent</th>
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<th>Phase</th>
<th>Line of Therapy</th>
<th>Histology</th>
<th>Primary Endpoint</th>
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DFS = disease-free survival; NCT = National Clinical Trial; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

between these various agents is challenging with respect to both clinical activity and toxicity. We will review the current agents that have entered into later phase clinical trials including preliminary data on their activity and toxicity (see Table 1). However, we would caution against drawing any major distinction between the activity and toxicity of these agents until more published data is available.

Nivolumab (BMS-936558, Opdivo)
The clinical activity of PD-1 immune checkpoint inhibitors was first demonstrated in a phase I clinical trial of nivolumab (BMS-936558)—a fully human immunoglobulin (Ig)-G4 monoclonal PD-1 blocking antibody. A cohort of 296 heavily pretreated advanced cancer patients, including 76 patients with advanced NSCLC, were treated with escalating doses of nivolumab administered intravenously every 2 weeks to a maximum of 12 cycles.1 A response rate of 18 % (14 of 76 patients) was noted among the advanced NSCLC patients despite being heavily pretreated with 47 % of patients having received three or more previous lines of therapy. These responses were durable with a reported progression-free survival (PFS) rate of 26 % at 24 weeks among advanced NSCLC patients. The grade 3/4 adverse event rate reported was a modest 14 % albeit with three deaths secondary to pulmonary toxicity (two with NSCLC). Of note, no objective responses were seen among the patients that did not have evidence of PD-L1 overexpression in their pretreatment biopsy specimens although only 42 patients in the overall study underwent testing.

The noted clinical activity of this agent in this study was remarkable given the heavily pretreated nature of the initial study population. The pertinent toxicities noted with nivolumab included rare but fatal episodes of pneumonitis as well as grade 3–4 diarrhea (1 %), hepatotoxicity (1 %) and occasional infusion reactions (1 %). However, early data indicates that this agent is generally well tolerated. The updated results of the expanded phase I study of nivolumab in advanced NSCLC revealed significant and durable activity of this agent among 129 heavily pretreated patients. An objective response rate of 17 % was reported across all dose cohorts with a median response duration of 17 months.1 A similar overall response rate (ORR) was noted between PD-L1 negative and PD-L1 positive patients, using a 5 % threshold for determining positive expression.

These initial early phase data were the first to clearly demonstrate the promise of this class of agents and their acceptable toxicity profile. The tantalizing possibility that these agents may yield durable treatment responses with minimal toxicity even in heavily pretreated patients has led to the rapid proliferation of multiple PD-1 and PD-L1 inhibitors. Several phase II and III studies of nivolumab in advanced NSCLC have been initiated since the completion of the aforementioned phase I study (see Table 2). The makers of nivolumab have announced that the CheckMate 017 phase III trial of nivolumab versus docetaxel in the second-line treatment of advanced squamous cell lung cancer has been stopped early due to significant OS benefit in the nivolumab arm.43 Nivolumab has received approval for use in metastatic melanoma refractory to ipilimumab in Japan.44

Pembrolizumab (MK-3475, Keytruda)
Pembrolizumab is a humanized IgG4 monoclonal antibody against PD-1. It is currently being examined in both multiple phase I trials as well as...
later phase studies. Preliminary data presented from a phase I trial of pembrolizumab in advanced NSCLC patients revealed a comparable degree of clinical activity toxicity to nivolumab. Among 217 advanced NSCLC patients having received at least one previous line of therapy, pembrolizumab against chemotherapy as well as novel combination studies in NSCLC. Pembrolizumab has also recently received US Food and Drug Administration (FDA) approval for use in metastatic melanoma refractory to ipilimumab irrespective of tumor PD-L1 status.42 Interestingly, the same phase I trial that demonstrated a promising ORR to pembrolizumab irrespective of PD-L1 status in melanoma was the same that found an increased ORR among high PD-L1 expressing patients with NSCLC.44,45

**MPDL3280A**

MPDL3280A is a human Fc optimized monoclonal antibody directed against PD-L1. Early data from a phase I study of MPDL3280A in advanced cancers demonstrated an ORR of 23 % among 53 evaluable NSCLC patients.42 A significantly higher ORR of 83 % was demonstrated among the subgroup of patients with high PD-L1 IHC expression on tumor-infiltrating immune cells. By contrast, the ORR was not significantly

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**Table 3: Combination Trials in NSCLC**

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|                | EGFR = epidermal growth factor receptor; NCT = National Clinical Trial; NHL = non-Hodgkin lymphoma; NSCLC = non-small cell lung cancer; ORR = overall response rate; PFS = progression-free survival.
increased at 38% among patients with high PD-L1 IHC expression on tumor cell. Interestingly, no episodes of grade 3–5 pneumonitis were reported with this agent, which may be theoretical benefit of directing therapy against PD-L1. The overall grade 3–4 adverse event rate regardless of attribution was 13% including dyspnea, fatigue, nausea, vomiting, anemia, laboratory abnormalities, and rare instances of tumor lysis syndrome and cardiac tamponade. These promising early results have led to the development of two phase II studies evaluating MPDL3280A in any line of treatment as well as a phase II and recent phase III study evaluating the efficacy of MPDL3280A versus standard docetaxel chemotherapy in the second-line setting (see Table 2).

MEDI4736
MEDI4736 is a human IgG1k monoclonal antibody directed against PD-L1. Similar to previous agents, preliminary phase I trial data demonstrate an ORR of 16% among 58 evaluable pretreated advanced NSCLC patients. This rate was higher among PD-L1 positive tumors at 25% (5/20) compared with 3% (1/29). Toxicity was evaluable in 155 patients revealing a 3% grade 3–4 adverse event rate secondary to autoimmune endocrinopathy and arthralgia/myalgia but no episodes of high-grade pneumonitis.

**Rationale for Combination Therapy and Ongoing Trials**
Early data indicating significant clinical activity and manageable toxicity associated with PD-1 and PD-L1 inhibitors has led not only to rapid proliferation of single-agent later-phase trials, but a multitude of trials evaluating the combination of these inhibitors with various other agents. Broady, these combinations fall into several main classes including combined immune checkpoint blockades, tyrosine kinase inhibitor (TKI) combinations, and combinations with chemotherapy.

**Combined Immune Checkpoint Blockade**
This strategy utilizes the biologic rationale that multiple mechanisms may be exploited simultaneously by tumor cells in order to evade anti-tumor immune activity. As such, it has been proposed that combining PD-1 or PD-L1 inhibitors with antibodies directed against other immune checkpoints including CTLA4, KIR, lymphocyte activation gene-3 protein (LAG-3), or TIM-3 may enhance T lymphocyte and NK cell-mediated anti-tumor activity. The combination of PD-1 and CTLA4 inhibitors has demonstrated promising activity in metastatic melanoma. However, the increased toxicity of this combination and limited single-agent activity of ipilimumab in advanced NSCLC in contrast to melanoma makes the combination still of uncertain benefit in NSCLC. The more novel combination of PD-1 inhibitors and anti-KIR, anti-LAG3, and anti-IDO antibodies has also entered early clinical development (see Table 3).

**PD-1/PD-L1 Inhibition and Tyrosine Kinase Inhibitor**
The combined inhibition of both the PD-1/PD-L1 immune checkpoint as well as aberrant cell signaling secondary to an underlying driver mutation is a particularly promising treatment approach in advanced NSCLC. Several targetable oncogenic driver mutations have been identified in lung adenocarcinoma including EGFR mutations, ALK rearrangements, ROS1 rearrangements, and BRAF mutations. An increasing number of TKIs have been developed that are able to specifically target these mutations with significant clinical activity. Further, emerging preclinical data suggests a potential interplay between PD-L1 overexpression and normal EGFR signaling. It has thus been theorized that significant synergy may exist between PD-1/PD-L1 inhibitors and various TKIs whereby significant responses induced by TKIs may facilitate immunologic priming by inducing tumor cell lysis. The combination of PD-1/PD-L1 inhibitors with TKI therapy in patients with known targetable mutations is thus postulated to hold significant therapeutic synergy potential. As such, various combinations of these inhibitors with kinase inhibitors targeting both EGFR and MEK signaling in mutant selected populations are currently underway (see Table 3) with trials of combined therapy with ALK inhibitors in the planning stages as well.

**PD-1/PD-L1 Inhibition and Chemotherapy**
The use of standard chemotherapy combined with PD-1/PD-L1 inhibition has been proposed as a potential means of enhancing therapeutic efficacy. The combination of these agents has been postulated to allow for both nonspecific cytotoxic reduction of tumor burden followed by immune-mediated tumor cell killing. Additional enhancement of the activity of PD-1/PD-L1 inhibitors may also occur secondary to immunologic priming occurring as a result of chemotherapy-induced tumor cell lysis. Several of these combinations have entered early phase clinical trials in advanced NSCLC (see Table 3).

**Key Questions in the Use of PD-1/PD-L1 Inhibitors**
Perhaps the most controversial matter surrounding the development of PD-1 and PD-L1 inhibitors has been the use of PD-L1 expression as a predictive biomarker. It follows logically that PD-L1 expression levels on the surface of tumor cells would predict the activity of these inhibitors based on the biology that we have previously outlined. However, early studies of the activity of these agents across all four major commercial drugs in development in NSCLC indicate a variable degree of association between PD-L1 expression and clinical activity of these agents.

Even in trials where increased expression does correlate with increased activity, a modest rate of treatment response is also seen in PD-L1-
negative patients. The use of multiple antibodies to detect PD-L1 as well as variable definitions of the IHC threshold that constitutes PD-L1 positivity further complicates this matter. This is illustrated by the reported finding in the early-phase study of pembrolizumab in advanced NSCLC, which reported increasing ORR at high thresholds of PD-L1 positivity (>50%). In this study, long-term outcomes of patients with 0% expression was similar to those with 1–49% expression. PD-L1 expression may thus represent a continuum where higher levels correlate with clinical response as opposed to a binary phenomenon. This may explain the lack of difference in ORR between PD-L1 negative and positive patients seen in early studies of nivolumab where the cut-off for PD-L1 positivity was set at 5% and determined using a different antibody. The relationship between PD-L1 expression and response to these agents is further complicated by the poorly understood dynamic nature of PD-L1 expression particularly in response to previous treatment as well as potential tumor heterogeneity in expression levels. This may have also contributed to the aforementioned differences as the 50% cut-off used in the pembrolizumab study required fresh tumor biopsies for PD-L1 expression evaluation whereas nivolumab studies and others have used primarily archival tissue for this testing.

Although PD-L1 is an important integrated biomarker for any study of this class of agents, there are many unanswered questions about how best to use it as a predictive biomarker. Even in the pembrolizumab study where a high cut-off was utilized and only fresh biopsies analyzed, the response rate in PD-L1 positive patients was only 37%. The recent study demonstrating that high PD-L1 expression on tumor-infiltrating immune cells is a superior predictor of response to MPDL3280A in NSCLC introduces a new dimension of complexity to the use of PD-L1 as a biomarker. Further study of other aspects of the anti-tumor immune response including TILs, PD-L1 expression in other cellular compartments, and serum biomarkers may better elucidate the complex factors that predict response to these agents.

Use of Immune Response Criteria

Another major area of controversy in the development of clinical trials for these agents has been the use of strict RECIST 1.1 criteria for the interpretation of ORR. Early phase trials of these agents have suggested that a subset of patients may experience initial increases in tumor size secondary to anti-tumor immune activity, which ultimately leads to subsequent tumor regression or long-term disease stability (pseudoprogression). The re-biopsy of such pseudoprogressed lesions has been reported to yield predominantly inflammatory material consistent with a robust anti-tumor immune response. The time period over which these agents act may thus complicate the interpretation of strict ORR using established RECIST 1.1 criteria. Efforts to utilize immune-related response criteria provide an important method to better understand this phenomenon and many current trials have allowed continued treatment beyond RECIST-defined progression (see Table 4). More exact rules regarding the interpretation of response and appropriate treatment discontinuation guidelines for these agents will be required should they transition to use outside of the research context in the future. The need for such consensus criteria is particularly urgent given the recent FDA approval of pembrolizumab for use in metastatic melanoma—a situation that may lead to its premature off-label use in NSCLC.

Summary

The development of PD-1 and PD-L1 inhibitors has generated significant enthusiasm and unprecedentedly rapid design of later phase trials of these agents and combination drug studies. The potential for these agents to provide clinical benefit to NSCLC patients with manageable toxicity is considerable—particularly among cancers lacking oncogenic drivers and squamous cell lung cancers where few good treatment options exist. Early results from phase I clinical trials indicate potential clinical activity even in heavily pretreated advanced NSCLC with rare but serious incidences of pneumonitis. However, extremely limited data exist on the potential survival benefit of these agents either alone or in combination with other drug classes. The role of PD-L1 expression as a predictive biomarker for these agents remains controversial. The potential of these agents to achieve long-term disease control when combined with other immune checkpoint or kinase inhibitors remains a tantalizing possibility. We await the outcome of the aforementioned studies in order to definitely answer these pending questions regarding the real benefit of these agents and the appropriate biomarker selected population in which they should be employed.

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