Review Article on Lung Cancer Immunotherapy

# Results of clinical trials with anti-programmed death 1/ programmed death ligand 1 inhibitors in lung cancer

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**Abstract:** One of the main hallmarks of cancer is the capability of evading immune destruction. In order to drive tumor progression, malignant cells are able to promote immunosuppressive mechanisms avoiding recognition and elimination. Increasing knowledge of the mechanisms of immune tolerance has led to the identification of several membrane receptors strongly implicated in this cancer feature: the immune checkpoints. Among them, programmed death 1 (PD-1) receptors and their ligands have been identified as potential targets for a new anti-cancer therapeutic approach: the use of immune-modulatory monoclonal antibodies designed to interrupt the immune escape activated by the interaction of PD-1 receptors and their ligands. Five of these antibodies are now in their late stages of clinical development and this review will summarize their up-to-date efficacy and toxicity data.

**Keywords:** Lung cancer; nivolumab; pembrolizumab; programmed death 1 (PD-1); programmed death ligand 1 (PD-L1)

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## Introduction

Immune destruction escape is one of the main features that allow cancer cells to survive, proliferate and eventually kill our patients. In order to drive tumor progression, malignant cells acquire the ability to promote immunosuppressive mechanisms to their own benefit, avoiding recognition and elimination by the host immune system. Most solid tumors are able to establish potent immunosuppressive networks that operate locally (within the tumor mass) and systemically (in the circulation and bone marrow). The immune checkpoints are different families of membrane receptors and their ligands that are strongly implicated in this cancer feature. Among them, programmed death 1 (PD-1) receptors and their ligands have been identified as potential targets for a new anti-cancer therapeutic approach.

PD-1 are immunosuppressive receptors expressed on the surface of activated T lymphocytes or natural killer cells or their ligands that are meant to control the physiological extinction of immune responses and the maintenance of peripheral tolerance. Interaction of PD-1 with its ligands, programmed death ligands 1 and 2 (PD-L1 and PD-L2), dampens T-cell receptor signaling, leading to downregulation of T-cell activation, proliferation, and T-cell-mediated antitumor immune response (1-3). The PD-1 pathway represents one of the immune checkpoints used by tumors to suppress antitumor immunity (4). Moreover, potential tumor-reactive lymphocytes are often kept in check by PD-1 transduced signals, reflecting the ability of many cancers to express increased levels of their ligands.

Immunomodulatory monoclonal antibodies inhibit safeguard systems that are harnessed by cancer cells to establish immunological tolerance (5,6). These molecules represent a promising means to induce robust and durable

responses when employed as single agents (7,8) but also hold promise to significantly boost the efficacy of several anticancer chemo-, radio- or other targeted treatments.

The safety and efficacy of immunomodulatory monoclonal antibodies have been assessed in numerous cohorts of patients with non-small cell lung cancer (NSCLC) or other pulmonary neoplasms, as well as in virtually every other major tumor type. This review summarizes up-to-date efficacy and toxicity data of the main five PD-1/PD-L1 antibodies that are in their late stages of clinical development nowadays.

## Efficacy of agents targeting PD-1

At this moment there are two main different compounds targeting PD-1: nivolumab (Opdivo) and pembrolizumab (Keytruda) are anti-PD1 monoclonal antibodies and have recently received approval from the Food and Drug Administration (FDA) in second line treatment for NSLC patients.

Nivolumab is a genetically engineered, fully human immunoglobulin G4 monoclonal antibody specific for the human PD-1 receptor. Nivolumab binds PD-1 with high affinity on activated immune cells, preventing its interaction with PD-L1 and PD-L2 ligands, therefore reducing the inhibitory signals and augmenting the host antitumor response.

First six NSCLC patients to be treated with nivolumab were enrolled in a phase I trial that was conducted in the USA from October 2006 through June 2009 (9). This phase I study sought to determine the safety and tolerability of anti-PD-1 blockade in patients with treatment-refractory solid tumors and to preliminarily assess antitumor activity, pharmacodynamics, and immunologic correlates. The trial included a total of 39 patients with different cancer types including melanoma and renal cell carcinoma among others. Patients received a single intravenous infusion of nivolumab in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg. Patients with evidence of clinical benefit at 3 months were eligible for repeated therapy. Six patients in total were included in the subset of NSCLC patients and from those, one patient had a significant lesional regression not reaching partial response criteria as it was defined per protocol with the dose of 1 mg/kg.

These results encouraged further development in NSCLC so a second phase I trial with specific tumor-type pre-planned expansion cohorts was conducted between November 2008 and January 2012 (10). The objective of the trial was to evaluate the safety, anti-tumor activity, and pharmacokinetics of nivolumab. One hundred and twenty-nine patients with heavily pre-treated advanced NSCLC were enrolled to receive 1.0, 3.0 or 10.0 mg per kilogram of body weight every 2 weeks. Response was assessed after each 8-week treatment cycle. Patients received up to 12 cycles until disease progression or a complete response occurred.

In this trial objective response rate (ORR) to nivolumab monotherapy was 17% (22/129 patients), lasting for a median of 17.0 months across all doses. Eleven responses (50%) were documented at the first 8-week tumor assessment in contrast with the extended idea that immune therapies are slower to show objective lesional reductions than cytotoxic treatments. However, a subset of patients achieved delayed responses and the mechanism of this is yet to be better understood.

No differences in ORR were found regarding histological subtype, 17% and 18% in squamous *vs.* non-squamous. An additional exploratory analysis of response by smoking exposure in 80 evaluable patients found ORR was higher in patients with a smoking history of more than 5 pack-years (30%; n=66) than in those with a history of 5 pack-years or less (no responses; n=14).

Median progression-free survival (PFS) across doses was only 2.3 months but interestingly PFS rates at 6 months, 1 year, and 2 years of 33%, 22%, and 9%, respectively. In fact, median PFS of the 22 responders was 20.6 months, an unprecedented long interval for heavily pre-treated NSCLC patients. Specially intriguing is the fact that among 18 responders who discontinued nivolumab therapy for reasons other than disease progression, 50% (nine) had responses for more than 9 months after the end of therapy.

Median overall survival (OS) was 9.9 months for all 129 patients with NSCLC but in 37 patients receiving nivolumab 3 mg/kg, the dose currently being used for phase III trials, median OS was 14.9 months. Again, there were no differences in median OS and survival rates in patients with squamous and non-squamous histology.

At that point nivolumab had not only showed a good safety profile but also an impressive potential to change lung cancer natural history prolonging significantly the PFS and OS of a subset of patients. These results were also observed in melanoma and renal cell carcinoma patients so an ambitious development program named CheckMate was started. CheckMate program includes several trials meant to evaluate nivolumab treatment in different tumors, settings and combinations.

CheckMate 017 was conducted from October 2012 through December 2013 and randomly assigned 272 squamous cell lung carcinoma patients to receive nivolumab, at a dose of 3 mg/kg every 2 weeks, *vs.* docetaxel, at a dose of 75 mg/m$^2$ every 3 weeks (11). PD-L1 protein expression was evaluated retrospectively in pre-treatment (archival or recent) tumor-biopsy specimens.

The rate of confirmed objective response was significantly higher with nivolumab than with docetaxel (20% *vs.* 9%; P=0.008). The median PFS was 3.5 months in the nivolumab group and 2.8 months in the docetaxel group, slightly disappointing, but again, those patients that achieved responses obtained long-term PFS and OS benefits. The rate of PFS at 1 year was 21% in the nivolumab group and only 6% in the docetaxel group. The median OS was 9.2 months in the nivolumab group as compared with 6.0 months in the docetaxel group with the risk of death 41% lower with nivolumab (hazard ratio, 0.59). The OS rate at 1 year was 42% in the nivolumab group *vs.* 24% in the docetaxel group. The hazard ratios for death in the analysis of OS were favorable to nivolumab in almost all subgroups but not in those patients who were 75 years of age or older.

CheckMate 063 was conducted between November 2012 and July 2013, designed as a phase II open label, multinational and multicenter single arm trial in 117 patients (12). In this trial nivolumab was given to squamous cell lung cancer patients who had progressed at least to two lines of chemotherapy including a platinum containing doublet. Again, patients were included regardless of PD-L1 status. ORR assessed by an independent radiology review committee was 14.5% (17 patients) and median duration of response was not reached (95% CI, 8.31–not applicable); as much as 13 (76%) of 17 of responses were ongoing more than 6 months. Twenty-six percent of patients had stable disease with a median duration of 6 months. Median PFS was 1.9 months, with PFS of 20.0% at 1 year. Median OS was 8.2 months and OS at 1 year was 40.8%.

Nivolumab was FDA approved on March 2015 to treat metastatic squamous NSCLC with progression on or after treatment with platinum-based chemotherapy based on combined data from CheckMate-017 and -063.

The most recently published trial has been CheckMate 057 that was conducted from November 2012 through December 2013 to confirm if the results observed in squamous-cell lung cancer were also reproducible in the non-squamous histology subset (13). It was a phase III trial that randomized 582 patients with advanced non-squamous NSCLC after failing platinum doublet chemotherapy to nivolumab at 3 mg/kg intravenously every 2 weeks (n=292) or docetaxel (n=290). The response rate was 19% with nivolumab *vs.* 12% with docetaxel (P=0.02). Although PFS did not favor nivolumab over docetaxel (median, 2.3 months and 4.2 months, respectively), the rate of PFS at 1 year was higher with nivolumab than with docetaxel (19% and 8%, respectively) consistently with the long lasting responses that have been previously observed. In this trial conversely of what was observed in the squamous-cell lung cancer population, nivolumab was associated with even greater efficacy than docetaxel across all end points in subgroups defined according to pre-specified levels of tumor-membrane expression (≥1%, ≥5%, and ≥10%) of the PD-1 ligand.

The median OS was 12.2 months in the nivolumab group and 9.4 months in the docetaxel group (hazard ratio for death, 0.73). The OS rate at 18 months was 39% with nivolumab *vs.* 23% with docetaxel.

On October 2015 the FDA expanded the approval of nivolumab to include patients with non-squamous NSCLC on or after progression with platinum-based chemotherapy with the data from CheckMate-057.

Currently there are several key nivolumab trials ongoing to address important questions as the activity of nivolumab on different clinical settings and in combinations. Results from a phase III trial, CheckMate 026, comparing nivolumab *vs.* chemotherapy in the first line setting for PD-L1 positive NSCLC patients are pending (NCT02041533).

Preliminary results of a phase I trial of nivolumab in combination with platinum-based doublet chemotherapy have been reported (14). In this trial 56 chemotherapy-naïve patients with advanced NSCLC were assigned into four different cohorts according to histology to receive different chemotherapy regimens with nivolumab (at 5 mg/kg or 10 mg/kg doses) every 3 weeks. Treatment was given for four cycles, with continued nivolumab alone until progression or unacceptable toxicity. ORR was similar in the four cohorts and ranged from 33% to 47%. An astounding OS rate of 86% at 18 months was reported in the nivolumab combined with carboplatin and paclitaxel arm for patients of either histology (squamous and non-squamous).

Other CheckMate trials ongoing are: CheckMate 012 (NCT01454102), a phase I trial with multiple arms using combinations of nivolumab with chemotherapy, bevacizumab, Ipilimumab or erlotinib; CheckMate 227 (NCT02477826), a phase III trial to test the combination

 

of nivolumab plus Ipilimumab *vs.* chemotherapy in the first line setting and CheckMate 331(NCT02481830), a phase III trial for small cell lung cancer (SCLC) patients that will test nivolumab *vs.* topotecan in the second line setting.

Pembrolizumab (Keytruda) is a highly selective IgG4-κ humanized monoclonal antibody directed against human cell surface receptor PD-1 (15). Its mechanism of action is similar to nivolumab, binding PD-1 with high affinity on activated immune cells to prevent its interaction with PD-L1 and PD-L2 ligands.

The first-in-human phase 1 trial to evaluate pembrolizumab in the clinical setting was called KEYNOTE-001, and it was a large, international, multicohort study for the treatment of patients with advanced solid tumors (15,16).

Between April 27, 2011, and August 1, 2012, 32 patients were enrolled in the dose escalation, part A of the trial, in which seven NSCLC patients were included (15). Two of them showed tumor shrinkage that did not meet RECIST v1.1 objective response criteria: one patient treated with 10 mg/kg every 2 weeks (initial tumor reduction of 9.7%, followed by progression in subsequent imaging performed 8 weeks later) and one patient treated with 1 mg/kg every 2 weeks (initial 25% decrease in target lesion, followed by progression in a subsequent imaging performed 8 weeks later). Two more NSCLC patients achieved disease stabilization. Data from this part of the trial provided the basis for enrolling patients in multiple NSCLC expansion cohorts of KEYNOTE-001 part B.

From May 2012 through February 2014, a total of 495 patients received at least one dose of pembrolizumab in several cohorts in which two doses were tested: intravenous pembrolizumab at a dose of 2 mg or 10 mg per kilogram every 2 weeks over a 30-min period.

One of the main differences with the CheckMate program used to develop nivolumab was that in KEYNOTE-001 a contemporaneous biopsy sample was required to determine the PD-L1 status for eligibility.

The overall response rate was 19.4% which included a response rate of 18.0% in the 394 previously treated patients and 24.8% in the 101 previously untreated patients. The response rate was similar regardless of dose, schedule, and histologic analysis. Current or former smokers had a response rate of 22.5%, as compared with 10.3% among patients who had never smoked cigarettes, a consistent observation through anti-PD1 trials that needs further exploration.

The median duration of response was 12.5 months in all patients, 10.4 months in previously treated patients, and 23.3 months in previously untreated patients. Median PFS was 3.7 months for all the patients, 3.0 months for previously treated patients, and 6.0 months for previously untreated patients. Median OS was 12.0 months for all the patients, 9.3 months for previously treated patients, and 16.2 months for previously untreated patients.

Pembrolizumab was FDA approved in metastatic NSCLC expressing PD-L1, as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy based on data from KEYNOTE-001.

Currently pembrolizumab is being tested in different clinical settings in the context of the KEYNOTE program specially focusing on the issue of PD-L1 expression.

KEYNOTE-010 (NCT01905657) is a phase II/III trial in advanced PD-L1 positive NSCLC comparing two different doses of pembrolizumab. KEYNOTE-42 (NCT02220894) is a phase III trial comparing first line pembrolizumab (200 mg every 3 weeks) for up to 35 treatments with platinum-based doublet chemotherapy in PD-L1 positive NSCLC patients. Very similar is the KEYNOTE-24 (NCT02142738) trial that shares the same design but enrolls only PD-L1 strong positive patients. KEYNOTE-021 (NCT02039674) is a phase I/II trial in PD-L1 positive NSCLC exploring the combinations of pembrolizumab with Ipilimumab or chemotherapy.

Outside KEYNOTE program, Hoosier Cancer Research Network is conducting LUN14-179 (NCT02343952) a phase II trial of adjuvant pembrolizumab after chemo-radiotherapy for stage III NSCLC patients.

Data in SCLC patients were presented in May 2015 as preliminary results of KEYNOTE-028 (NCT02054806) an ongoing multi-cohort, phase Ib study of pembrolizumab in patients with PD-L1+ advanced solid tumors. The SCLC cohort had an ORR of 35% with durable responses (17). Another ongoing phase II trial is testing pembrolizumab in patients with extensive stage SCLC after completion of combination chemotherapy (NCT02359019).

## Efficacy of agents targeting PD-L1

Atezolizumab, durvalumab and avelumab are the three main anti PD-L1 monoclonal antibodies that are being quickly developed and will soon have phase III data in different clinical settings. Until now there are no published articles of these compounds, but preliminary results have been reported in form of abstract at American Society of Clinical Oncology (ASCO) or European Society for Medical

 

Oncology (ESMO) meetings.

Two studies reported at the European Cancer Congress held in September 2015 in Vienna showed positive results for atezolizumab (18). In the single-arm, phase II, BIRCH study, 667 patients with advanced NSCLC and high levels of PD-L1 were treated with atezolizumab. The ORR was 19% when atezolizumab was a first-line therapy and 17% when it was a second-line or subsequent therapy. The drug seemed to work best in patients with the highest levels of PD-L1. The second study of atezolizumab, the phase II POPLAR trial, involved 287 patients with NSCLC who had already received chemotherapy. Patients were treated with either atezolizumab or docetaxel, a standard second-line treatment for NSCLC. OS was 12.6 months in patients who received atezolizumab, compared with 9.7 months in those who received docetaxel. As in the BIRCH study, atezolizumab appeared to be most effective in patients with the highest levels of PD-L1.

The FIR trial (NCT01846416), a phase II study using atezolizumab in PD-L1 positive NSCLC patients is expected to be completed in June 2016 while several phase III trials are ongoing to test different doses and settings.

Durvalumab preliminary results of a phase I trial in patients with different solid tumor types including NSCLC reported clinical benefit and durable disease control with no dose limiting toxicities or grade 3–4 toxicities (19). Objective response was seen in 23% of patients with pretreated NSCLC (12 out of 53 evaluable patients) in the phase II trial (19).

Preliminary results from an ongoing study with 346 patients with solid tumors, of whom 143 had NSCLC, used durvalumab at 10 mg/kg every 2 weeks for 1 year. The median treatment duration was 8 weeks, and activity was seen as early as 6 weeks. After finishing active therapy, ORR in NSCLC was 13% (20).

JAVELIN clinical trial program is an extensive international program exploring the use of PD-L1 inhibition with avelumab to treat multiple types of cancer. The JAVELIN clinical trial program includes a phase III open-label, multicenter trial to investigate avelumab *vs.* docetaxel in patients with stage IIIb/IV or recurrent NSCLC that has progressed after platinum-based chemotherapy (JAVELIN Lung 200).

A phase Ib in advanced NSCLC patients progressing after platinum-based chemotherapy (NCT01772004) preliminary pre-specified analyses of 184 patients with ≥3 months follow-up was performed and reported at ASCO 2015 and updated at European Cancer Conference (ECC) 2015. Objective responses were observed in 25 (13.6%) patients. Nineteen responses were ongoing at data cutoff. Stable disease was observed in 68 patients (37.0%). Median PFS was 11.6 weeks and the PFS rate at 48 weeks was 18.1%. Median OS was 8.4 months.

## Safety of anti-PD-1/PD-L1 agents

A thorough review of adverse reactions reported in trials and abstracts with anti PD-1 or PD-L1 antibodies show a very similar profile of toxicity in all five compounds described in this article. Up to 80% of patients treated with immunomodulatory antibodies experienced treatment-related adverse events of any grade, while most of them were low grade reactions.

Common low grade reactions were fatigue, asthenia, fever, chills, myalgias, headaches, dyspnea, cough, decreased appetite, nausea, and constipation (13,16).

Immune-related adverse events (irAEs) were of special interest because of the presumed mechanism of action of immunomodulatory antibodies and prior experience with anti-CTLA-4 (21,22). IrAEs included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis. Treatment of severe reactions consists of withdrawal of the drug and, if required, prednisone 1 to 2 mg/kg daily should be given until the patient is back at baseline and then tapered over a month (23).

Severe adverse events (grade 3 or 4) were unfrequently seen ranging from 6–30% and treatment withdrawal rates were also low.

Few treatment-related deaths have been described, but pneumonitis was involved in most of them (12,24). Notably, this side effect was more frequent in lung cancer patients (regardless histology) that tumors from other primary origins, suggesting that the toxicity profile might be related with the localization of the disease, probably due to a local inflammatory effect. No clear relationships between the occurrence of pneumonitis and dose level or treatment duration were noted (24).

Combination of these drugs with other agents my rise the frequency and severity of side effects, and needs to be prospectively investigated. For example, when combining Ipilimumab with PD-1 inhibitors like nivolumab in melanoma, drug-related adverse events of grade 3 or 4 were reported in 53% of patients compared with 18% of patients who received Ipilimumab monotherapy (25,26). Grade 3 or 4 adverse events, regardless of attribution, were observed in 72% of patients, and grade 3 or 4 treatment-related

events were noted in 53%, with the most common events being elevated levels of lipase (in 13% of patients), aspartate aminotransferase (in 13%), and alanine aminotransferase (in 11%).

## Immunologic biomarkers

PD-L1 expression in cancer cells or in tumor infiltrating lymphocytes measured by immunohistochemistry (IHC) has been postulated as a potential predictive biomarker for anti PD-1/PD-L1 antibodies (27). Interpretation of its usefulness is difficult due to the different approaches that have been used with every antibody (different techniques, cut-off points and the use of archival *vs.* contemporaneous biopsy).

One of the caveats is the fact that expression of PD-L1 may dynamically change during tumor evolution, probably in response to treatments or even as one of the mechanisms for tumor immune response escape (24).

The cut-off for PD-L1 positivity, is another important factor for the interpretation of results. For example, 1% of cut-off has been used in studies with pembrolizumab and tumors were classified in three categories: negative, light positive or strong positive. Following this classification there is a reported 30% of strong positive PD-L1 NSCLC patients (15). In the studies with nivolumab, a 5% of membrane staining of tumor cells was considered as positive. About 33-48% of tumor samples were PD-L1 positive in those trials (12). In the studies with atezolizumab, PD-L1 positivity criteria included 5% of IHC staining on tumor in infiltrating lymphocytes and tumor cells. According to these criteria, 25% of NSCLC samples were positive for PD-L1 expression (28).

Further studies are required to demonstrate if PD-L1 expression by IHC correlates with a higher response rate when tumor cells are positive for staining. Median response rates oscillate from 38% in PD-L1 positive patients (ranging from 23% to 83%) to 7% (ranging from 0% to 15%) in PD-L1 negative patients depending on the trial.

KEYNOTE 001, has shown improved ORR in patients with positivity for PD-L1 expression. Results of PD-L1 expression were reported as the percentage of neoplastic cells with PD-L1 membrane staining; objective responses among all patients was 19.4%, and the median duration of response was 12.5 months. The median PFS was 3.7 months, and median OS was 12.0 months. Intriguingly a response rate of 45.2% was seen among patients with a proportion score of at least 50% and median PFS was 6.3 months while median OS was not reached. Garon *et al.* (16) reported higher response rate and longer survival for PD-L1 positive cases.

## Conclusions

Lung cancer had been traditionally considered immune resistant but nivolumab and pembrolizumab approval by FDA in 2015 pave the way for a new era in which precise immune manipulation will be essential for cancer treatment. Atezolizumab, durvalumab and avelumab will join soon the immune armamentarium but they will need to find their niche in the clinical setting. Immune modulatory antibodies favorable toxicity profile in comparison to chemotherapy is a major advantage, although much needs to be better understood in order to avoid severe autoimmune related adverse events that can spoil their clinical benefits. The presence of long lasting responses holds new hopes for physicians and patients but the tools to predict what patients are going to achieve them remain in urgent need.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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