



Review Article

# Immune checkpoint inhibitors for nonsmall cell lung cancer treatment

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## Abstract

Immune checkpoint inhibition with blocking antibodies that target cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the programmed cell death protein 1 (PD-1) pathway [PD-1/programmed death-ligand 1 (PD-L1)] have demonstrated promise in a variety of malignancies. While ipilimumab has been approved as a CTLA-4 blocking antibody by the US Food and Drug Administration for the treatment of advanced melanoma, it is still not approved for lung cancer treatment. In contrast, nivolumab and pembrolizumab, both PD-1 blocking antibodies, have been approved for second-line treatment of nonsmall cell lung cancer in 2015 because of their high potency and long-lasting effects in some patient subgroups. Other PD-1 and PD-L1 monoclonal antibodies are also in active development phase. Treatment with such immune checkpoint inhibitors is associated with a unique pattern of immune-related adverse events or side effects. Combination approaches involving CTLA-4 and PD-1/PD-L1 blockade or checkpoint inhibitors with chemotherapy or radiotherapy are being investigated to determine whether they may enhance the efficacy of treatment. Despite many challenges ahead, immunotherapy with checkpoint inhibitors has already become a new and important treatment modality for lung cancer in the last decade following the discovery of targeted therapy.

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**Keywords:** adenocarcinoma; checkpoint inhibitor; immunotherapy; lung cancer; lymphocytes

## 1. Introduction

Lung cancer is the leading cause of cancer-related deaths in Taiwan and other developed countries in the world. The 5-year survival rate was only 15.9%, with a median survival of 13.2 months, in Taiwan between 2002 and 2008.<sup>1</sup>

There are two arms of the immune system, the innate and the adaptive, which protect the body from foreign agents. The innate immune system includes physical epithelial barriers, phagocytes, natural killer cells, and circulating complement proteins. The innate immune system is the first line of defense

against pathogens. In contrast, the adaptive arm of the immune system is dormant until it is primed by the presence of a pathogen that has evaded or overwhelmed the innate immunity. Components of the adaptive immune system include both B cells and T cells. Naïve B cells are activated to produce antigen-recognizing antibodies when they are presented with antigens from a pathogen. When foreign antigens are presented to naïve T cells, they mature into one of two types of effector T cells: CD4<sup>+</sup> helper T cells that facilitate antibody production, and CD8<sup>+</sup> cytotoxic T cells that directly kill cells recognized as foreign (such as viral infected cells or tumor cells); this process is called cell-mediated immunity. The adaptive immune response is initiated when tumor cell antigens released by innate immunity are taken up by dendritic cells. These dendritic cells then migrate to the draining lymph nodes, where they present these tumor antigens to T cells, causing them to mature into cytotoxic T cells to destroy tumor cells (Fig. 1).

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Although the immune system plays an important role in recognizing, controlling, and eradicating cancer, cancer induces immunosuppression through several mechanisms that may suppress effective antitumor immunity, including but not limited to: (1) secretion of immunosuppressive cytokines; (2) loss of major histocompatibility complex antigen expression; (3) and programmed cell death protein 1/programmed cell death protein 1 ligand (PD-1/PD-L1) interaction of tumor cells with immune cells.<sup>2–6</sup> In the past, immunotherapy has had minimal success in lung cancer treatment, which was attributed in part to the belief that lung cancer is non-immunogenic.<sup>7–11</sup> Most patients present with advanced disease and are immunosuppressed, as documented by decreased lymphocyte counts and cytotoxic function seen in this patient population.<sup>8,11–13</sup> Regulatory T-cells (CD4<sup>+</sup> Treg) are a subpopulation of lymphocytes that play an important role in suppressing tumor immune surveillance, and have been found to have higher levels in peripheral blood and tumor microenvironment of lung cancer patients compared with other T-cell subpopulations.<sup>14</sup> CD4<sup>+</sup> Treg suppress cytotoxic T-cell functions that are responsible for killing tumor cells. We previously also showed that double signal stimulation is needed for these immunosuppressed lymphocytes to recover their cytotoxic function against tumor cells.<sup>9,15–18</sup>

It was recently found that cancer cells can prevent themselves from immune surveillance and killing through adaptive immune resistance, causing the disabling of tumor-specific T cells (Fig. 2).<sup>19,20</sup> Many types of cancers have been found to express PD-L1 on their tumor cell surfaces, which is a known ligand of the PD-1 receptor on T cells. This pathway of interaction between PD-1 and PD-L1 causes T-cell

downregulation and functional inhibition.<sup>5,6</sup> There are two immune checkpoint inhibitory pathways that involve signaling through CTLA-4 or PD-1 with their ligands (Figs. 1 and 2). Antibody therapies against these negative immunologic regulators have demonstrated significant success in lung cancer treatment in recent years. This review focuses on antibodies that block the CTLA-4 and PD-1/PD-L1 pathways. We discuss the preclinical rationale and clinical experience with these antibodies in nonsmall cell lung cancer (NSCLC) treatment.

## 2. Cytotoxic T-lymphocyte antigen-4 pathway

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a receptor that is expressed on the T-cell surface during the T-cell activation phase. Activation of the T-cell requires both antigen presentation in the context of a major histocompatibility complex molecule and a costimulatory signal stimulation by B7 from an antigen-presenting cell to interact with CD28 on the T-cell. Early after T-cell activation, CTLA-4 is translocated to the plasma membrane of the T-cell. CTLA-4 binds members of the B7 family with a much higher affinity than CD28, where it downregulates the function of activated T-cells (Fig. 1). CTLA-4 downregulates activated T-cell function not only through preventing costimulation by outcompeting CD28 for its ligand, B7, but also by inducing T-cell cycle arrest.<sup>21–24</sup> Through these mechanisms, CTLA-4 has an essential role in maintaining normal immunologic homeostasis, as evidenced by the fact that mice deficient in CTLA-4 died from fatal lymphoproliferative disease.<sup>25</sup>

CTLA-4 also regulates tumor immunity via Treg that expresses high levels of surface CTLA-4. CTLA-4-expressing

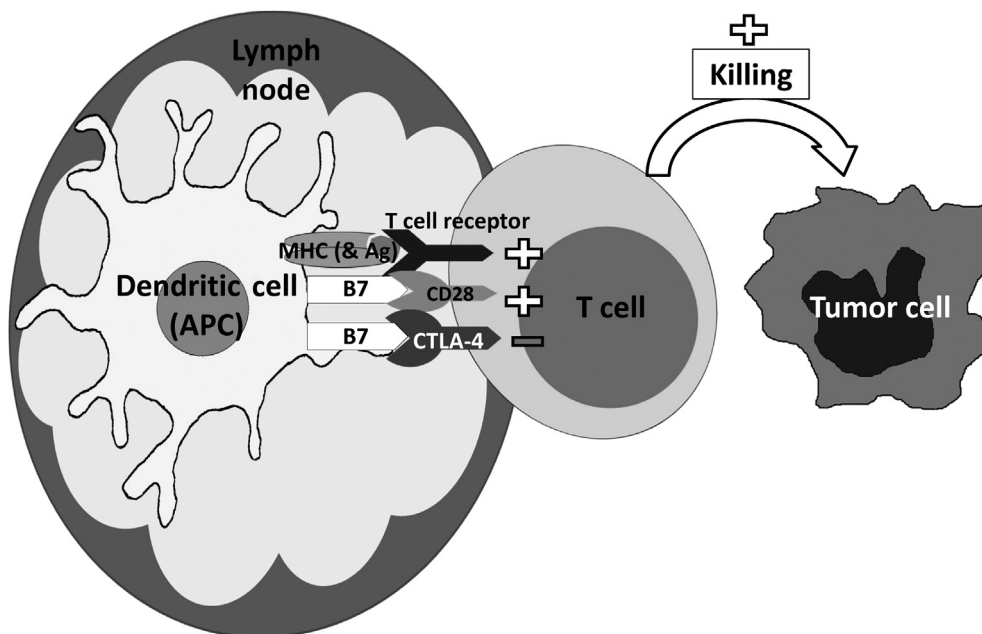


Fig. 1. T-cell activation phase and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) immunologic checkpoint. T-cell activation requires antigen presentation in the context of a major histocompatibility complex (MHC) molecule in addition to the costimulatory signal stimulation when B7 on an antigen-presenting cell interacts with CD28 on a T cell. Soon after activation, CTLA-4 is translocated to the plasma membrane where it downregulates the function of T cells to maintain immunologic homeostasis.

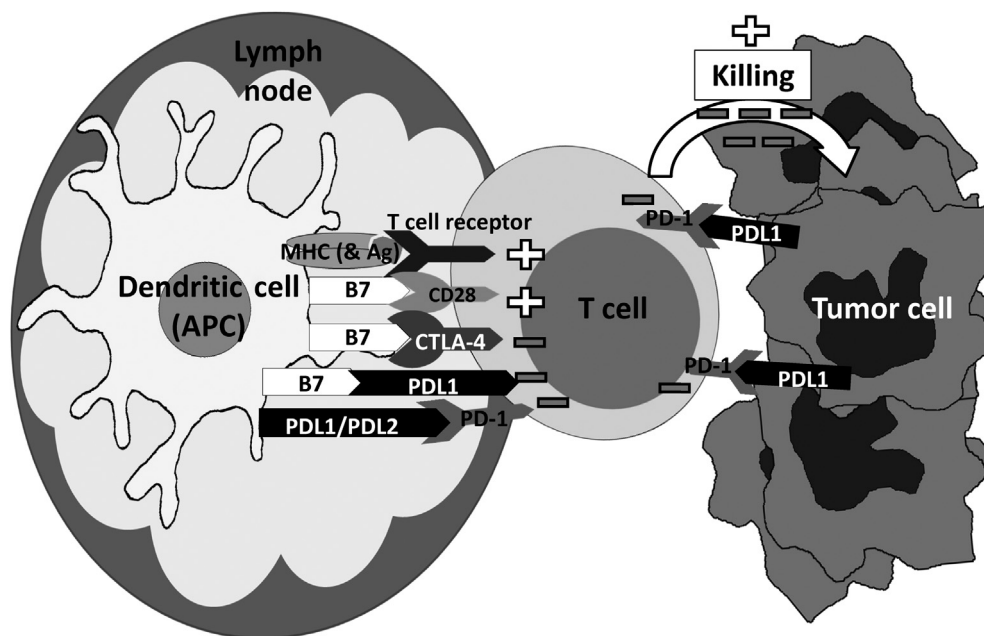


Fig. 2. T-cell effector phase and the programmed cell death protein 1 (PD-1) immunologic checkpoint. PD-1 is expressed on activated T cells. Interactions between PD-1 and its ligands, programmed death-ligand (PD-L)1 and PD-L2, are complex and occur at many steps of an immune response. An interaction soon after activation in the lymph node where PD-L1 or PD-L2 on an antigen-presenting cell negatively regulates T-cell activity through PD-1 and through an interaction between B7 and PD-L1. The PD-1 pathway is important in the tumor microenvironment, where PD-L1 expressed by tumors interacts with PD-1 on T cells to suppress T-cell effector function.

Tregs may facilitate nonresponsiveness of the immune system to tumor antigens.<sup>26</sup> Tregs have been shown to be present in tumors and coexist with primed effector T cells. Thus, blocking Treg function through anti-CTLA-4 antibodies may have the potential to remove Treg suppression and enhance antitumor immunity.

Based on preclinical studies that demonstrated antibody blockades of CTLA-4 could result in antitumor immunity,<sup>27,28</sup> two antibodies targeting CTLA-4, ipilimumab (Bristol-Myers Squibb, Princeton, NJ, USA) and tremelimumab (MedImmune/AstraZeneca, Wilmington, DE, USA) entered clinical development. Early reports on both agents showed durable clinical responses in some patients, particularly melanoma patients.<sup>29–31</sup> Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody that is now approved for the treatment of melanoma.<sup>32</sup>

The rationale for the combined use of anti-CTLA-4 antibody with chemotherapy is based on the assumption that tumor-specific antigens will be released during chemotherapy-induced tumor necrosis and that will augment tumor-specific immune reactions. Ipilimumab plus chemotherapy showed promising results in a phase II CA184-041 study that randomized previously untreated advanced NSCLC patients to receive paclitaxel plus carboplatin, alone or in association with concurrent ipilimumab (10 mg/kg from Cycle 1 to Cycle 4) or with phased ipilimumab (10 mg/kg from Cycle 3 to Cycle 6).<sup>33</sup> There were 204 patients included in this study. Response was assessed by using immune-related response criteria and modified World Health Organization criteria.<sup>34,35</sup> This study met its primary end point of improved immune-related

progression-free survival (PFS) for phased ipilimumab versus the control [hazard ratio (HR) = 0.72,  $p = 0.05$ ], but not for concurrent ipilimumab (HR = 0.81,  $p = 0.13$ ). For the phased arm, concurrent arm, and control arm, the median immune-related PFSs were 5.7 months, 5.5 months, and 4.6 months, respectively; median PFSs of 5.1 months, 4.1 months, and 4.2 months, respectively; immune-related best overall response rates of 32%, 21%, and 18%, respectively; and best overall response rates of 32%, 21%, and 14%, respectively.

A phase III study of paclitaxel/carboplatin with or without ipilimumab in treatment-naïve squamous NSCLC is ongoing.

Another CTLA-4-blocking antibody, tremelimumab (CP-675,206) is a fully human immunoglobulin G (IgG)-2 monoclonal antibody. Tremelimumab has induced durable tumor responses in patients with melanoma in a phase I/II clinical trial.<sup>36</sup> However, a phase III trial was discontinued after review of interim data showed that the trial would not demonstrate superiority to conventional standard chemotherapy.<sup>37</sup> Tremelimumab has shown promising responses in patients with malignant mesothelioma.<sup>38</sup>

### 3. PD-1/PD-L1 pathway

Successful treatment targeting CTLA-4 has created enthusiasm for approaches targeting other immunologic checkpoints. Among them, the PD-1/PD-L1 axis has been most actively studied (Figure 2). PD-1 is a negative regulator of T-cell activity that limits the activity of T cells, especially in the effector phase, when it interacts with its two ligands PD-L1 and PD-L2.<sup>5,39,40</sup> When engaged by the ligand, PD-1

inhibits kinase signaling pathways that normally lead to T-cell activation.<sup>5</sup> Mice that are deficient in PD-1 have a different and distinct autoimmune phenotype from mice deficient in CTLA-4.<sup>41,42</sup> PD-1 is expressed on many types of lymphocytes, including B cells and natural killer cells.<sup>40,43</sup>

There are several antibodies that disrupt the PD-1 axis that have entered clinical development; two of them (nivolumab, Bristol-Myers Squibb, New York, NY, USA; pembrolizumab, Merck, Whitehouse Station, NJ, USA) have Food and Drug Administration (FDA) approval for second-line treatment of NSCLC (Table 1). These antibodies can be classified into two main categories: those that target PD-1 and those that target PD-L1.

### 3.1. Nivolumab

Nivolumab (ONO-4538, BMS-936558) is a human IgG4 monoclonal antibody that targets the PD-1 receptor.<sup>44–47</sup> A report of the long-term follow-up of 129 patients with heavily pretreated NSCLC who entered a phase I dose-escalation cohort expansion trial of nivolumab 1 mg/kg, 3 mg/kg, or 10 mg/kg intravenously (IV) once every 2 weeks revealed that 1-, 2-, and 3-year overall survival (OS) rates were 42%, 24%, and 18%, respectively, across doses, and were 56%, 42%, and 27%, respectively, at the 3 mg/kg dose ( $n = 37$ ) chosen for further clinical development.<sup>45</sup> Response rates were similar in squamous (16.7%) and nonsquamous (17.6%) NSCLC. A phase II trial of squamous type NSCLC was performed in France, Germany, Italy, and the USA. Patients with squamous NSCLC who had received two or more previous treatments received IV nivolumab (3 mg/kg) every 2 weeks until progression or unacceptable toxic effects. Between 2012 and 2013, 117 patients were enrolled.<sup>44</sup> Seventeen (14.5%) of 117 patients had an objective response. The response rate was 14% in patients with tumor PD-L1 expression < 5% and 24% in those with expression  $\geq 5\%$ . A phase III trial was done on 272 squamous NSCLC patients who had disease progression during or after first line chemotherapy (CheckMate 017).<sup>46</sup> Patients were randomized to receive nivolumab 3 mg/kg every 2 weeks, or docetaxel 75 mg/m<sup>2</sup> every 3 weeks. The median OS was 9.2 months with nivolumab versus 6.0 months with docetaxel (HR = 0.59,  $p < 0.001$ ). One-year survival rate was 42% with nivolumab versus 24% with docetaxel. The response

rate was 20% with nivolumab versus 9% with docetaxel ( $p = 0.008$ ). The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR = 0.62,  $p < 0.001$ ). The expression of the PD-L1 was neither prognostic nor predictive of treatment benefit. The US FDA granted approval to nivolumab for the treatment of metastatic squamous NSCLC patients with progression on or after platinum-based chemotherapy in 2015.

In CheckMate 057, patients with nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy were randomized to receive nivolumab or docetaxel.<sup>47</sup> The median OS was 12.2 months among 292 patients in the nivolumab arm and 9.4 months among 290 patients in the docetaxel arm (HR = 0.73,  $p = 0.002$ ). One-year survival rate was 51% with nivolumab versus 39% with docetaxel. The response rate was 19% with nivolumab versus 12% with docetaxel ( $p = 0.02$ ). Based on these data, the FDA approved nivolumab for the treatment of metastatic NSCLC patients with progression on or after platinum-based chemotherapy recently. This approval expands the indication for nivolumab in NSCLC to include nonsquamous histologies.

A phase I study evaluating the efficacy and safety of nivolumab monotherapy in patients with chemotherapy naïve advanced NSCLC was reported recently.<sup>48</sup> There were 52 advanced NSCLC patients who received nivolumab 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity. Preliminary results showed that the response rate (RR) was 21% (11/52). Objective RRs for subgroups were 23% (9/39) in nonsquamous and 15% (2/13) in squamous NSCLC. Objective responses were 31% (8/26) in PD-L1 positive patients and 10% (2/21) in PD-L1 negative patients.

Nivolumab has been combined with platinum-based chemotherapy or anti-CTLA4 immunotherapy as first-line treatment for advanced NSCLC, or with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor targeted therapy for EGFR-tyrosine kinase inhibitor acquired resistance.<sup>49–51</sup> The data are too premature to be discussed.

### 3.2. Pembrolizumab

Pembrolizumab (MK-3475, lambrolizumab, Keytruda, Kenilworth, NJ, USA) is an IgG4-engineered humanized antibody that targets the PD-1 receptor. A recently published paper

Table 1  
Immune checkpoint inhibitors in development for nonsmall cell lung cancer.

Inhibitor	Target	Monoclonal antibody type	Company	Development phase
Nivolumab (ONO-4538, BMS-936558)	PD-1	Fully human IgG4	Ono Pharmaceutical/Bristol-Myers Squibb	FDA-approved
Pembrolizumab (MK-3475)	PD-1	Humanized IgG4	Merck Sharp & Dohme	FDA-approved
Atezolizumab (MPDL3280A)	PD-L1	Human IgG1	Genentech/Roche	III
Durvalumab (MEDI-4736)	PD-L1	Fully human IgG1	MedImmune/Astra-Zeneca	III
Avelumab (MSB0010718C)	PD-L1	Fully human IgG1	Merck/Pfizer	III
Ipilimumab	CTLA-4	Fully human IgG1	Bristol-Myers Squibb	III
Tremelimumab (CP-675,206)	CTLA-4	Fully human IgG2	MedImmune/Pfizer	III

CTLA-4 = cytotoxic T-lymphocyte antigen-4; FDA = Food and Drug Administration; IgG = immunoglobulin G; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death-ligand 1

included 495 NSCLC patients who received pembrolizumab (at a dose of either 2 mg/kg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks) as part of the international phase 1 KEYNOTE-001 trial.<sup>52</sup> Among all the NSCLC patients, the objective RR was 19.4%, and the median duration of response was 12.5 months. The median duration of OS was 12.0 months. Among patients with a PD-L1 proportion score of at least 50%, the RR was 45.2% in the validation group. Among all the patients with a proportion score of at least 50%, median PFS was 6.3 months. The US FDA granted accelerated approval to pembrolizumab for metastatic NSCLC treatment in patients whose tumors expressed PD-L1, as determined by an FDA-approved test, with disease progression during or after platinum-containing chemotherapy in 2015.<sup>53</sup>

The KEYNOTE-021 trial evaluated the safety, tolerability, and clinical activity of pembrolizumab plus platinum-based doublet chemotherapy for treatment-naïve patients with advanced NSCLC.<sup>54</sup> Patients were randomized 1:1 to pembrolizumab 2 or 10 mg/kg every 3 weeks plus carboplatin and paclitaxel (Cohort A; any histology) or carboplatin plus pemetrexed (Cohort C; nonsquamous without *EGFR* sensitizing mutation nor *anaplastic lymphoma kinase* translocation). Patients received pembrolizumab plus chemotherapy for four cycles followed by pembrolizumab maintenance therapy in Cohort A and pembrolizumab plus pemetrexed maintenance therapy in Cohort C. As of December 2014, 44 patients were treated. Preliminary RR was 30% in Cohort A and 58% in Cohort C.

Since combined anti-PD-1 and anti-CTLA-4 treatment has shown robust efficacy and manageable toxicity in patients with melanoma, a phase 1 study evaluating pembrolizumab plus ipilimumab was performed in NSCLC patients.<sup>55</sup> Patients with NSCLC that recurred after no more than two prior regimens received pembrolizumab plus ipilimumab every 3 weeks for four cycles followed by maintenance pembrolizumab therapy. The preliminary data demonstrated an acceptable toxicity profile and robust antitumor activity for pembrolizumab plus ipilimumab in patients with recurrent NSCLC.

Regarding immunotherapy in NSCLC patients with brain metastases, a preliminary report of phase II pembrolizumab on patients with at least one brain metastasis that was previously untreated or progressing after prior local therapy showed promising results, with four of an initial nine patients who had brain metastatic lesion showing partial response to the treatment.<sup>56</sup> The study is still ongoing.

### 3.3. Atezolizumab

Atezolizumab (MPDL3280A) is a humanized, engineered monoclonal antibody of IgG1 against PD-L1. Preliminary results of two phase II trials in NSCLC were reported recently. One of the studies (POPLAR,  $n = 287$ ) was a randomized trial with docetaxel as the control arm; the data showed that atezolizumab significantly improved OS.<sup>57</sup> In this study, previously treated NSCLC patients were randomized to receive atezolizumab 1200 mg IV every 3 weeks or docetaxel 75 mg/m<sup>2</sup> IV every 3 weeks. PD-L1 expression was evaluated using

the SP142 antibody assay. Patients were grouped as tumor cell PD-L1 staining (TC) 0, 1, 2, or 3 and immune cell PD-L1 staining (IC) 0, 1, 2, or 3. Improved efficacy was found with increasing PD-L1 expression (OS: HR = 0.47; PFS: HR = 0.56; RR = 38% vs. 13% in TC3 or IC3 patients comparing atezolizumab with docetaxel), while patients with the lowest PD-L1 levels (TC0 and IC0) did not appear to benefit from atezolizumab (OS: HR = 1.22).<sup>58</sup> Median OS was 12.6 months with atezolizumab versus 9.7 months with docetaxel (HR = 0.73,  $p = 0.04$ ). However, there was no difference between atezolizumab and docetaxel (median OS of 9.7 months in both arms) in patients with little or no expression of PD-L1. The other study (known as BIRCH) was a single-arm study in which atezolizumab was used in patients with PDL1-positive advanced NSCLC.<sup>59</sup> PD-L1 expression was assessed in the same way as in the POPLAR study. Patients were divided into three cohorts: Cohort 1 had no prior therapy, Cohort 2 had received one prior chemotherapy, and Cohort 3 had received at least two prior systemic therapies. The primary endpoint was RR, which was 26%, 24%, and 27%, respectively, for the three cohorts of patients who had a high expression of PD-L1. The response rates were 19%, 17%, and 17%, respectively, for patients who had a medium to high expression of PDL1. Another phase II study of atezolizumab (FIR) in stage IIIB/IV NSCLC patients based on PD-L1 expression was also reported recently.<sup>60</sup> Cohort 1 included chemo-naïve patients, Cohort 2 included patients who had received no less than two lines of systemic treatment without brain metastasis, and Cohort 3 included patients who had received no less than two lines of systemic treatment and were with treated asymptomatic brain metastasis. Atezolizumab dose and PD-L1 expression and scoring system were the same as in POPLAR and BIRCH. Patients with PD-L1 TC 2/3 and/or IC 2/3 tumors were enrolled. Of the 138 patients enrolled, the response rates were 29%, 17%, and 17% in Cohort 1, Cohort 2, and Cohort 3, respectively, while the highest response rates were seen in patients with PD-L1 TC3 or IC3 tumors (29%, 26%, and 25%, respectively). It seems that atezolizumab had a remarkable activity in NSCLC patients with high PD-L1 expression regardless of the line of treatment.

A phase Ib study that evaluated atezolizumab in combination with carboplatin plus either paclitaxel (Arm C), pemetrexed (Arm D) or weekly nab-paclitaxel (Arm E) was done in chemo-naïve locally advanced or metastatic NSCLC, and preliminary results are available.<sup>61</sup> Patients received atezolizumab every 3 weeks with a standard chemotherapy dosing for four to six cycles followed by atezolizumab maintenance therapy until disease progression. Across all arms, the RR was 67% (20 of 30), including 60% in Arm C (three of five), 75% in Arm D (eight of 12), and 62% in Arm E (eight of 13). Phase III studies are ongoing.

### 3.4. Durvalumab

Durvalumab (MEDI-4736) is a human IgG1 monoclonal antibody targeting PD-L1. Preliminary results of an ongoing

Table 2  
Summary of programmed cell death-ligand 1 immunohistochemistry in nonsmall cell lung cancer (NSCLC) clinical trials.

Drug	Marker antibody	Treatment line	Definition of "positive", %	No. positive, %	Positive predictive outcome	RR%, overall	RR% IHC positive cases	RR% IHC negative cases	Ref.
Nivolumab	Dako 28-8	≥ 2 <sup>nd</sup> , squamous	≥ 10, ≥ 5, ≥ 1 in > 100 cells	83 for ≥ 1	No	20	19, 21, 18	16, 15, 17	46
Nivolumab	Dako 28-8	≥ 2 <sup>nd</sup> , nonsquamous	≥ 10, ≥ 5, ≥ 1 in > 100 cells	78 for ≥ 1	Yes	19	37, 36, 31	11, 10, 9	47
Pembrolizumab	Dako 22C3	Any line	≥ 50	23.2	Yes	19.4	45.2	NR	52
Atezolizumab (MPDL3280A)	Roche Ventana, SPI42	2 <sup>nd</sup> or 3 <sup>rd</sup> , NSCLC	Tumor cell: ≥ 50, ≥ 5, ≥ 1 or immune cell: ≥ 10, ≥ 5, ≥ 1	68 for ≥ 1	Yes	15	38, 22, 18	8	57, 58
Durvalumab (MedJ-4736)	Roche Ventana, SPI42	1 <sup>st</sup> (1L), 2 <sup>nd</sup> (2L), or ≥ 3 <sup>rd</sup> (3L+), NSCLC	Tumor cell: ≥ 50, ≥ 5 or Immune cell: ≥ 10, ≥ 5	Nil	Yes	1L: 19, 2L: 17, 3L+: 17	1L: 19, 2L: 17, 3L+: 17	Nil	59
Avelumab (MSB0010718C)	Roche Ventana, SP263	Any line, NSCLC	≥ 25% of tumor cell at any intensity	48	Yes	16	27	5	62
	Dako, clone: not reported	PD after 1 line of platinum -containing doublet c/t, NSCLC	≥ 1% of tumor cells at any intensity	66.3	Yes	13.6	15.6	10	63

IHC = immunohistochemistry; PD = programmed death; RR = response rate.

phase I/II, multicenter study of durvalumab evaluating the safety and clinical activity of durvalumab in patients with multiple solid tumor types including NSCLC were reported recently.<sup>62</sup> Durvalumab was administered at 10 mg/kg IV every 2 weeks until unacceptable toxicity, disease progression, or 12 months was reached. Tumor PD-L1 expression was assessed using Ventana PD-L1 IHC (SP263). As of October 31, 2014, 198 patients had been treated. There were 149 patients evaluable for response, and RR was 14% (23% in tumor PD-L1 positive patients). The response rate was higher in squamous (21%) than in nonsquamous patients (10%). Durvalumab has been accelerated into phase III clinical development in NSCLC at present.

### 3.5. Avelumab

Avelumab (MSB0010718C) is a fully human anti-PD-L1 IgG1 monoclonal antibody. By retaining a native Fc-region, avelumab is also able to induce antibody-dependent cell-mediated cytotoxicity.

There was a preliminary report of a phase Ib expansion trial evaluating safety and clinical activity in patients with advanced NSCLC progressing after platinum-based chemotherapy.<sup>63</sup> Patients were treated with avelumab at 10 mg/kg every 2 weeks until disease progression, confirmed complete response, or intolerable toxicity. A follow-up analysis of 184 patients was performed. Objective responses were observed in 22 (12%) patients. Median PFS was 2.7 months. The RR in PD-L1 positive patients ( $n = 118$ ) was 14.4% and 10.0% in PD-L1 negative patients ( $n = 20$ ).

## 4. Surrogate marker

Among predictors for checkpoint inhibitor therapy, tumor PD-L1 immunohistochemical staining is the most frequently used predictor for anti-PD-1 and anti-PD-L1 immunotherapy.<sup>64,65</sup> There are at least four kinds of kits or platforms for detection of tumor PD-L1 expression. Some studies also count PD-L1 expression in immune cells and correlate both tumor and immune cell PD-L1 expression with treatment response. Most studies assess PD-L1 expression in tumor cells and regard membrane staining as most significant.<sup>46,47,52,64</sup> In general, there is a trend of higher response rates in the PD-L1 expression positive patients compared with the PD-L1 expression negative patients, although in some studies this difference was not significant (Table 2). Up to now, PD-L1 expression is not a perfect biomarker, since most studies also report significant response rates (3–20%) in PD-L1 expression negative patients.<sup>65</sup> Other proposed methodologies include examination of mutational burden by genomics.<sup>66</sup>

In conclusion, with the approval of both nivolumab and pembrolizumab in the treatment of second-line NSCLC treatment, the use of immune checkpoint inhibitors for the treatment of NSCLC is firmly established. The ongoing plethora of phase III studies of PD-1 and PD-L1 inhibitors, either alone or in combination with chemotherapy, targeted

therapy, radiotherapy, or immunotherapy in different stages of NSCLC, will serve to clarify and likely expand their use in NSCLC treatment. However, there are still many challenges ahead for oncologists, including determining the optimal time for integration of immunotherapy into the lifetime course of NSCLC patient treatment. Despite these challenges, immunotherapy with checkpoint inhibitor has already become the newest, most important, and most novel treatment modality during the decade following the discovery of targeted therapy.

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