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# Checkpoint Inhibitors in Nonsmall Cell Lung Cancer

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Karen G. Zeman, Joseph E. Zeman,  
Christina E. Brzezniak and Corey A. Carter

Additional information is available at the end of the chapter

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## Abstract

Lung cancer remains the leading cause of cancer-related deaths worldwide. The majority of NSCLC patients present with advanced stage disease. Lung cancer was once thought of as a low antigenicity cancer unlikely to benefit from immunotherapy, but has recently been found to have a high level of antigenicity. Moreover, a large body of research now exists to support both the safety and efficacy of immunotherapy in advanced stage NSCLC. The checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab are now approved by the U.S. Federal Drug Administration for second-line treatment in advanced stage NSCLC. In addition to being efficacious, checkpoint inhibitors have a superior safety profile compared to previous standard of care, chemotherapy. Further trials are needed to investigate the checkpoint inhibitors' role in combination treatment, first-line treatment, and early stage disease.

**Keywords:** PD-1, PD-L1, checkpoint inhibitors, NSCLC, nivolumab, pembrolizumab, atezolizumab, mutational load, PD-L1 expression, immunotherapy

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## 1. Introduction

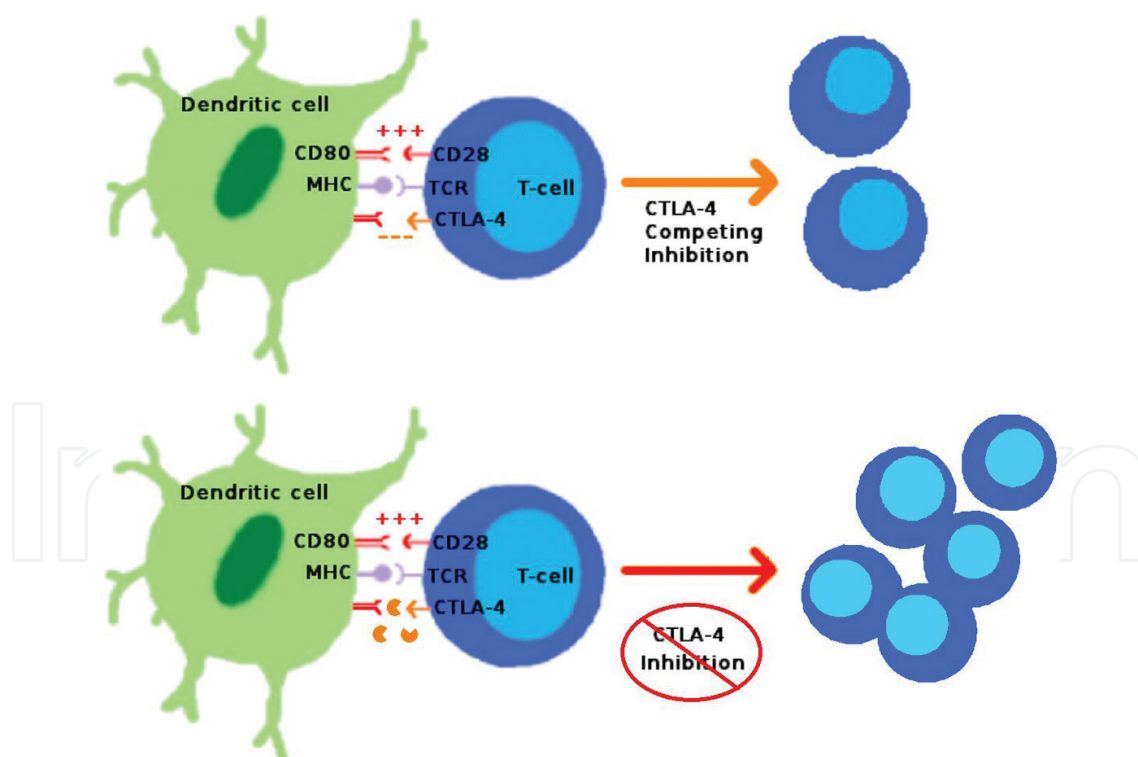
Lung cancer is the second most common cancer in both men and women; approximately 14% of all new cancers diagnosed are lung cancer. Lung cancer is the leading cause of cancer death among both men and women; one in four cancer deaths in the United States is due to lung cancer and worldwide it accounts for 1.59 million deaths annually [1, 2]. The survival rates for nonsmall cell lung cancer (NSCLC) remain low with 49% of Stage IA patients, 14% of Stage IIIA, and 1% of Stage IV patients alive at 5 years. The majority of NSCLC patients present with advanced stage disease [3]. Despite years of research in treatment strategies for NSCLC, few significant improvements on outcomes with available cytotoxic chemotherapy have been made. In addition, a large portion of patients with advanced disease are not treated with aggressive cytotoxic therapy due to performance status or other comorbidities [4]. Major

inroads have been made for patients with targetable driver mutations who make up a minority of NSCLC patients but for the vast majority of patients further innovative treatments are needed. In the last half decade, there has been an explosion of evidence demonstrating lung cancer's antigenicity and clinical response to immune therapy.

## 2. Lung cancer and the immune system

One of the primary functions of our immune system is the ability to detect and destroy abnormal cells, which includes malignant cells. In lymphoid tissue, T cells are activated by the antigen presenting cells (APCs) carrying antigen from the tumor. T cells are then activated by the APCs and migrate to the peripheral tissues where they search and destroy antigen-expressing tumor cells. The human immune system maintains regulatory mechanisms to prevent autoimmunity or more specifically the immune system from attacking self.

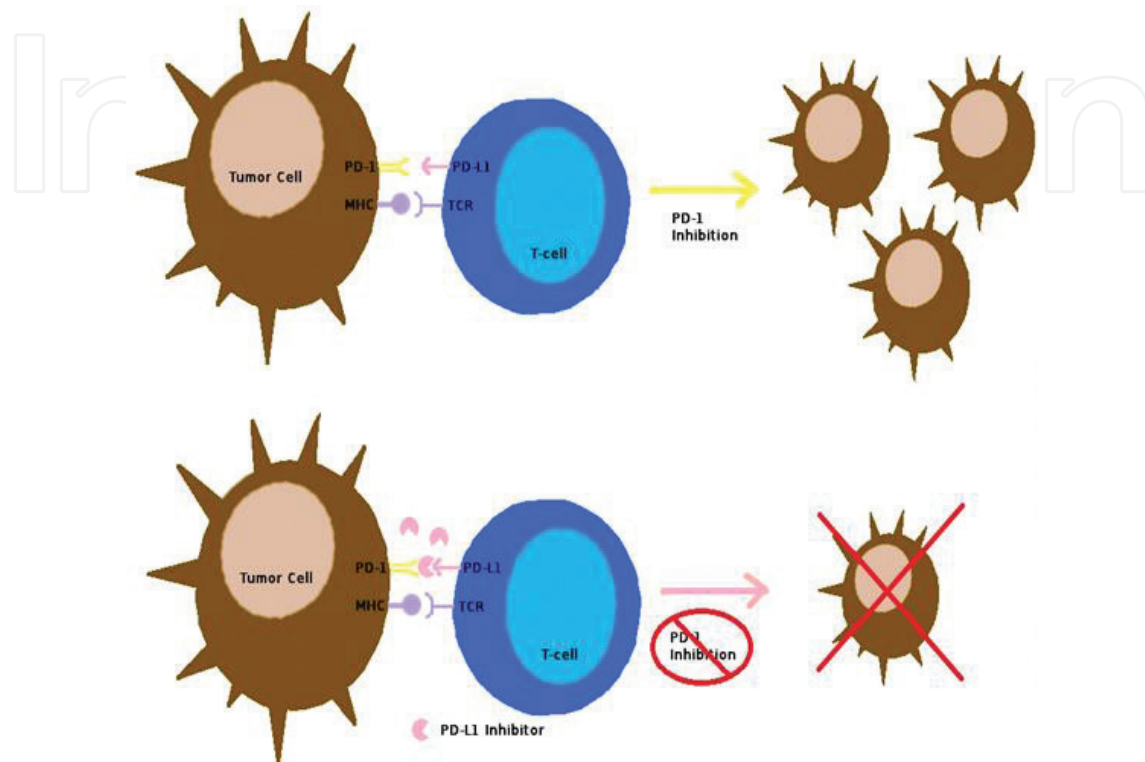
In lymphatic tissue, expression of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) negatively regulates the early stages of T-cell activation by competing with the T-cell costimulatory receptor CD28 for binding with CD80 and CD86 expressed on the APC (**Figure 1**) [3, 5]. Antibody blockade of CTLA-4 has been shown to increase antitumor immunity in clinical settings, and this has been well described in the melanoma therapy [6, 7].



**Figure 1.** Immune system activation and inhibition in the lymphoid tissue. MHC, major histocompatibility complex; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; TCR, T-cell receptor.

In the peripheral tissues, the adaptive immune system is negatively regulated in part through binding of the programmed cell death protein 1 (PD-1) expressed on activated T cells with the

programmed death ligand 1 (PD-L1) and/or programmed death ligand 2 (PD-L2). Tumor cells can evade the immune response through upregulation of expression of PD-L1, resulting in decreased T-cell response and immune resistance (**Figure 2**). PD-1 and PD-L1 inhibitors can take the breaks off the T-cell activity in peripheral tissues by blocking PD-1 binding to PD-L1.



**Figure 2.** Immune system activation and inhibition in the peripheral tissue. MHC, major histocompatibility complex; TCR, T-cell receptor; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand.

It has been a previously accepted belief that lung tumors have a very low antigenicity and approaching lung cancer with immunotherapy would have little hope of causing any significant benefit. However, through thoughtful translational research, immunotherapy is now being seen as promising therapeutic agents with a significant potential to affect NSCLC. Smokers' tumors are now understood to have some of the most complex and extensive genetic mutations seen in solid malignancies, and consequentially they have some of the highest antigenicity [8, 9].

In 2015, the benefits of checkpoint inhibition in the treatment of NSCLC went from theoretical to breaking news with new agents such as pembrolizumab, nivolumab, and atezolizumab receiving breakthrough drug designation and later approval by the U.S. Federal Drug Administration (FDA) for treatment of advanced stage NSCLC in the second-line setting after progression on or after platinum containing chemotherapy [10–12]. In the case of pembrolizumab, treatment was indicated only for patients with tumors expressing PD-L1 greater than 50% by the Dako assay. Nivolumab was approved without the need for PD-L1 testing. Here is a review of the key trials that brought immunotherapy into standard of care treatment for NSCLC. Summarization of key clinical trials in checkpoint inhibition is presented in **Table 1**.

Clinical trial	Phase trial	Line of treatment	Histology	Patients	Treatment regimen	OS (months)	PFS (months)	Median DOR (months)
CheckMate 063	2	Third	Squamous	117	Nivolumab 3 mg/kg every 2 weeks	8.2	1.9	NR
CheckMate 017	3	Second line	Squamous	272	Nivolumab 3 mg/kg every 2 weeks	9.2	3.5	NR
					Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	6.0	2.8	8.4
CheckMate 057	3	Second line	Nonsquamous	582	Nivolumab 3 mg/kg every 2 weeks	12.2	2.3	17.6
					Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	9.4	4.2	5.6
Keynote-001	1	First to fifth	All histologies	495	Pembrolizumab efficacy reported for all doses	12.0	3.7	12.5
Keynote-010	2/3	Second line	All histologies	1034	Pembrolizumab 2 mg/kg every 3 weeks	10.4	5.0	NR
					Pembrolizumab 10 mg/kg every 3 weeks	12.7	5.2	NR
					Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	8.5	4.1	6.0
CheckMate 012 Gettinger et al.	1	First line	All histologies	52	Nivolumab 3 mg/kg every 2 weeks	19.4	3.6	NR
CheckMate 012 Rizvi et al.	1	First line	All histologies	56	Nivolumab 10 mg/kg + gemcitabine-cisplatin (squamous)	11.6	5.7	10.3
					Nivolumab 10 mg/kg + pemetrexed-cisplatin (nonsquamous)	19.2	6.8	5.8
					Nivolumab 5 mg/kg + paclitaxel-carboplatin (all histologies)	NR	7.1	19.6
					Nivolumab 10 mg/kg + paclitaxel-carboplatin (all histologies)	14.9	4.8	5.5

Clinical trial	Phase trial	Line of treatment	Histology	Patients	Treatment regimen	OS (months)	PFS (months)	Median DOR (months)
CheckMate 012 Hellman et al.	1	First line	All histologies	148	Nivolumab 3 mg/kg every 2 weeks + Ipilimumab 1 mg/kg every 12 weeks Nivolumab 3 mg/kg every 2 weeks + Ipilimumab 1 mg/kg every 6 weeks Nivolumab 3 mg/kg every 2 weeks	n/a	8.1 3.9 3.6	NR NR NR
POPLAR	2	Second line	All histologies	287	Atezolizumab 1200 mg every 3 weeks Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	12.6 9.7	2.7 3	NR 7.8
OS, overall survival; PFS, progression-free survival; DOR, duration of response; NR, not reached; n/a, not available.								

**Table 1.** Summary of key checkpoint inhibitor trials efficacy data.

### 3. Key trials in checkpoint inhibition therapy of NSCLC

#### 3.1. Checkpoint inhibitor trials: pembrolizumab second line and beyond

##### 3.1.1. *Keynote-001*

Keynote-001 was a phase I study assessing safety and efficacy of treatment with pembrolizumab of advanced NSCLC [13]. The primary objectives were to investigate safety, side effect profile, and efficacy of pembrolizumab. Treatment-related adverse events were 70.9% and grade 3 or higher severe adverse events were 9.5%. With regards to efficacy, overall response rate was 19.4%: 18% in previously treated patients and 24.8% in treatment naïve patients. There was no significant difference noted between treatment dose and dose interval. Current smokers had an increased response rate at 22.3% and never smokers had a 10.3% response rate. Median duration of response was 12.5 months and median progression-free survival was 3.7 months with an overall median survival of 12 months. Additionally, the study sought to evaluate PD-L1 as a biomarker and evaluated tissue obtained within 6 months of treatment for PD-L1 expression. They concluded that a percentage of 50% PD-L1 tumor cell expression was associated with a higher response rate and longer progression-free survival (PFS) and overall survival (OS).

Keynote-001 was a phase I study that established safety and efficacy of pembrolizumab in heavily treated patients with NSCLC. Furthermore, it used the DAKO PD-L1 expression assay with 22C3 antibody clone for patient selection to solidify this as the chosen PD-L1 assay [13].

##### 3.1.2. *Keynote-010*

Keynote-010 was a randomized phase II/III study assessing pembrolizumab versus docetaxel in PD-L1 positive advanced NSCLC [14]. Eligible patients had advanced NSCLC that had progressed despite two or more cycles of platinum doublet chemotherapy or appropriate tyrosine kinase inhibitor (TKI) therapy, a fresh tumor sample showing PD-L1 expression of at least 1% was required. The primary endpoints were overall survival and progression-free survival both in the total population and in patients with PD-L1 expression  $\geq 50\%$ . Secondary endpoints were safety/toxicity, response rate, and duration of response.

In patients with a PD-L1 tumor proportion score of 50% or greater, median overall survival was 14.9 months for pembrolizumab 2 mg/kg, 17.3 months for pembrolizumab 10 mg/kg, and 8.2 months for the docetaxel group. In the total population, median overall survival was 10.4 months for pembrolizumab 2 mg/kg, 12.7 months for pembrolizumab 10 mg/kg, and 8.5 months for the docetaxel group. Pembrolizumab demonstrated improvement in progression-free survival in patients with tumor proportion score of  $\geq 50\%$  but progression-free survival was not significantly different in the total population. Neither pembrolizumab dosage reached the median duration of response for patients with tumor proportion score of  $\geq 50\%$  or



all patients. The docetaxel group duration of response was 8 months in the tumor proportion score of  $\geq 50\%$  or all patients and 6 months in all patients.

With regards to toxicity, treatment-related adverse events were 13% for pembrolizumab 2 mg/kg, 16% for pembrolizumab 10 mg/kg, and 35% for docetaxel. Severe adverse events, grade 3 or higher, were reported as 63% for pembrolizumab 2 mg/kg, 66% for pembrolizumab 10 mg/kg, and 81% for docetaxel.

Based on these two landmark clinical trials, pembrolizumab was approved by the FDA for metastatic NSCLC in patients with PD-L1 expressing tumors who have progression on platinum doublet chemotherapy and tyrosine kinase inhibitor therapy for EGFR or ALK mutant tumors [12–14].

### **3.2. Checkpoint inhibitor trials: nivolumab second line and beyond**

#### *3.2.1. CheckMate 017*

Previous phase I and II studies, CheckMate 003 and CheckMate 063, respectively, demonstrated both safety and efficacy of nivolumab in heavily pretreated NSCLC patients. CheckMate 003 defined treatment dose at 3 mg/kg every 2 weeks. CheckMate 063 demonstrated efficacy endpoints of OS of 8.2 months and overall response rate (ORR) of 14.5% with an adverse event rate of 74% with 17% grade 3–4 [15, 16].

Checkmate 017 was a phase 3, randomized, study investigating nivolumab as compared to docetaxel in the second-line setting for treatment of advanced squamous cell NSCLC in 272 patients [17]. Eligible patients had advanced squamous cell NSCLC and progression after one prior platinum containing regimen, prior treatment with EGFR TKI therapy was allowed. The primary endpoint was overall survival. Secondary endpoints were ORR, PFS, patient-reported outcomes, efficacy by PD-L1 expression, and safety.

The median overall survival was 9.2 months in the nivolumab group, which is significantly higher compared to 6 months in the docetaxel treatment group. The ORR was 20% with nivolumab and 9% with docetaxel. The median duration of response was not reached in the nivolumab treatment group (2.9–20.5+ months) compared to the docetaxel treatment group 8.4 months (1.4–15.2). The median PFS for nivolumab and docetaxel treatment groups was 3.5 and 2.8 months, respectively. PD-L1 expression in this study was neither predictive nor prognostic of any efficacy endpoints.

With regards to toxicity, treatment-related adverse events were less frequent in the nivolumab treatment group. The nivolumab and docetaxel treatment groups demonstrated 58% and 86% of patients with any adverse event (AE), respectively. Furthermore, only 7% of the nivolumab treatment group demonstrated grade 3 or 4 events and no grade 5 events. Docetaxel had a 55% grade 3 or 4 event rate and 2% of patients had events of grade 5. Docetaxel demonstrated higher rates of treatment-related serious adverse events mainly attributable to hematologic toxic events and infections.



This study demonstrated improved overall survival and safety profile with nivolumab treatment over standard of care second-line therapy in squamous-cell NSCLC. Additionally, PD-L1 expression was not found to be predictive or prognostic of any efficacy endpoints.

### 3.2.2. *CheckMate 057*

Checkmate 057 expanded on the results of checkmate 017 and evaluated nivolumab versus docetaxel in advanced nonsquamous NSCLC. This study was a randomized phase 3 trial specifically looking at nivolumab versus docetaxel in the second-line setting for nonsquamous histology NSCLC [18]. A total of 582 patients with advanced nonsquamous cell NSCLC, progression after one prior platinum containing regimen, prior treatment with EGFR TKI therapy were enrolled. Patients were treated until disease progression or discontinuation of treatment due to toxic side effects or other reasons. The primary endpoint was overall survival. Secondary endpoints included safety, confirmed objective response, PFS, patient-reported outcomes, and efficacy by PD-L1 expression.

With regards to efficacy, the median overall survival was 12.2 months in the nivolumab group and was significantly higher compared to 9.4 months in the docetaxel treatment group. The ORR was 19% with nivolumab and 12% with docetaxel. The median duration of response in the nivolumab treatment group was 17.2 months compared to the docetaxel treatment group 5.6 months. The median PFS for nivolumab and docetaxel treatment groups were 2.3 and 4.2 months, respectively.

Treatment-related adverse events were less frequent in the nivolumab treatment group. The nivolumab and docetaxel treatment groups demonstrated 69% and 88% of patients with any AE. Furthermore, only 10% of the nivolumab treatment group demonstrated grade 3 or 4 events compared to docetaxel, which had a 54% grade 3 or 4 event rate. Docetaxel demonstrated higher rates of treatment-related serious adverse events as seen in prior study.

PD-L1 expression demonstrated a strong predictive association between increased PD-L1 expression and clinical outcomes. Improved clinical outcomes was noted in this study but the magnitude of improvement across all efficacy endpoints was greater with tumors expressing PD-L1 compared to those who did not. Patients whose tumors expressed PD-L1 demonstrated a nearly doubled median overall survival compared to docetaxel. Patients whose tumors did not demonstrate PD-L1 expression, defined as <1%, demonstrated similar overall survival. This finding differed compared to Checkmate 017 where PD-L1 expression was not predictive or prognostic for all comers.

This study demonstrated improved overall survival and safety profile with nivolumab treatment over standard of care second-line therapy in nonsquamous cell NSCLC. It also found no significant difference in overall survival in patients whose tumors did not express PD-L1 although safety profile and durability of response remain compelling arguments of the use of checkpoint inhibitors over chemotherapy.

These two studies resulted in the FDA approving nivolumab for the treatment of NSCLC in both squamous and nonsquamous after progression on a platinum containing doublet and TKI if applicable [11]. Nivolumab's approval and indication are not contingent on PD-L1

expression. This difference has greatly impacted medical oncology's use of both drugs as pembrolizumab requires the tissue be assessed for PD-L1 expression with varying costs and the availability of testing available in addition to the wait time for testing results, whereas nivolumab is approved regardless of expression level.

### 3.3. Checkpoint inhibitor clinical trials of nivolumab first line

#### 3.3.1. CheckMate 012: nivolumab as monotherapy in first-line advanced NSCLC

The purpose of Checkmate 012 was to determine if in a phase I, multicohort study, there was clinical benefit of nivolumab as monotherapy or combined with current standard therapies in first-line advanced NSCLC [19]. Eligibility criteria for this study was Stage IIIB or IV NSCLC of any histology who had no prior chemotherapy for advanced disease. Prior adjuvant or neo-adjuvant chemotherapy was allowed. Additionally, prior radiotherapy or TKI therapy was permitted if completed at least 2 weeks before treatment on study. Patients were treated with nivolumab until disease progression, discontinuation due to toxicity, withdrawal of consent, or loss to follow up. The primary objective of this study was to investigate safety and tolerability of nivolumab monotherapy. Secondary study objectives were ORR and PFS with OS included as an exploratory efficacy endpoint.

The study found an ORR of 23% with four patients with ongoing complete responses. Stable disease was seen in 27% of patients with a median DOR was not reached, range 4.2–25.8 months+, and 75% was achieved by the first tumor assessment at week 11. Median OS was 19.4 months, 16.8 months for squamous and not reached for nonsquamous histology. Median PFS was 3.6 months. The primary endpoint was to assess safety and tolerability, and the study demonstrated a 71% AE rate and 19% of grade 3 and 4 with treatment-related adverse events led to discontinuation in 12% of patients.

Additionally, Checkmate 012 investigated several variables for correlation with clinical response to include PD-L1 expression, KRAS, and EGFR mutation status. Tumors specimens were evaluable in 88% of the patients for PD-L1 expression, finding 70% of patients had  $\geq 1\%$  and 30%  $< 1\%$ . Clinical activity was observed regardless of PD-L1 expression across all expression levels although higher response rates correlated with higher expression levels. Confirmed ORR was 28 and 14% in tumors with  $\geq 1\%$  or  $< 1\%$ . This study did not demonstrate a relationship between PFS and OS and baseline PD-L1 expression. ORRs and disease control rates were higher among patients with a history of smoking. Additionally, median PFS was longer in current smokers compared to former smokers although the study was not powered to assess this. Median PFS was lower for patients with EGFR-mutant tumors vs. EGFR-wild-type. In contrast, median PFS was longer in KRAS mutant tumors compared to wild-type.

This study demonstrated good tolerance compared to standard first-line therapy in addition to demonstrating promising DOR and survival. It is important to note that this trial was not randomized, had a selected patient population with good performance status, and no standard of care comparison arm. Of note, four patients had durable complete clinical responses which are unlikely in chemotherapy treatment of NSCLC. Two phase III clinical trials will further assist answering the question is nivolumab monotherapy superior to current standard of care or is

indicated first line in a select patient population? CheckMate 026, NCT02041533, is investigating nivolumab in the first-line setting compared to standard of care therapy, platinum doublet chemotherapy, in advanced NSCLC patients with PD-L1 expressing tumors [20]. CheckMate 227, NCT02477826, is a multiarm study comparing nivolumab vs. nivolumab+ipilimumab vs. standard of care therapy platinum doublet chemotherapy  $\pm$  nivolumab [21].

Checkmate 012 established safety and efficacy of nivolumab monotherapy in the first-line setting of NSCLC. There are ongoing clinical trials comparing nivolumab to standard of care and in combination.

### 3.3.2. CheckMate 012: nivolumab in combination with platinum-based doublet

Another cohort of Checkpoint 012 was released studying nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced NSCLC. Patients were assigned by histology to receive nivolumab 10 mg/kg plus gemcitabine-cisplatin (squamous) or pemetrexed-cisplatin (nonsquamous) or nivolumab 5 or 10 mg/kg plus paclitaxel-carboplatin (all histologies) followed by nivolumab monotherapy [22]. In this study, nivolumab was administered every 3 weeks to coincide with chemotherapy administration. Eligibility criteria included patients with newly diagnosed advanced NSCLC with no prior treatment. The primary objective of this study was to assess safety and tolerability of immunotherapy and platinum doublet chemotherapy. Secondary objective was antitumor activity measured by PFS and ORR. A total of 56 patients were enrolled in this study.

For patients treated with 10 mg/kg nivolumab plus platinum based chemotherapy adverse events of any grade occurred at 93% and grade 3 or 4 occurred in 50%. In the overall population, 95% of patients experienced any grade adverse event and 45% of patients experienced graded 3 or 4 treatment-related events. Median PFS time ranging from 4.8 to 7.1 months and median OS in the 10 mg/kg nivolumab plus platinum-based chemotherapy ranged from 11.6 to 19.2 but was not reached in the nivolumab 5 mg/kg plus paclitaxel/carboplatin arm. PD-L1 expression was able to be quantified for 79% of patients in the study, no association was found between PD-L1 expression and PFS or OS. No difference in ORR or PFS was noted between histologies although median DOR was longer in the squamous histology subset. Median OS was longer with nonsquamous versus squamous NSCLC.

Treatment-related adverse events resulted in 21% of patients discontinuing the clinical trial. No treatment related deaths were reported in this study.

Based on these results, it is not clear if there is an OS benefit to combination therapy of nivolumab plus platinum-based chemotherapy. There was an increase in adverse events although no patient-related deaths were reported with combination therapy.

### 3.3.3. CheckMate 012: safety and efficacy of first-line nivolumab and ipilimumab in advanced NSCLC

CheckMate 012 recently presented an abstract at ASCO 2016 on another cohort-investigating nivolumab and ipilimumab in advanced NSCLC in their phase I clinical trial [23]. This study

extrapolated from efficacy in nivolumab and ipilimumab combination therapy in melanoma and monotherapy efficacy and safety in NSCLC. The trial enrolled 148 patients with all NSCLC histologies and distributed patients between four cohorts varying in nivolumab and ipilimumab drug dosing. Primary endpoints investigated were safety and secondary endpoints were ORR and PFS. Exploratory endpoints included overall survival and efficacy by tumor PD-L1 expression. The primary endpoint demonstrated adverse events in 69–77% of patients across cohorts and 28–35% grade 3–4 toxicities. Treatment-related adverse events resulting in discontinuation of therapy was reported at 10% similar to nivolumab monotherapy trials. Efficacy endpoints, ORR, and PFS were improved at the higher dosing of nivolumab 3 mg/kg compared to 1 mg/kg. Recommended dosing for further testing is nivolumab 3 mg/kg q2 weeks and ipilimumab 1 mg/kg q6 weeks. PD-L1 expression corresponded with higher efficacy response rates.

This data helped to establish safety of dual complimentary checkpoint inhibition although final publication is pending. CheckMate 227 trial, NCT02477826, will further evaluate dual checkpoint inhibition with nivolumab 3 mg/kg and ipilimumab 1 mg/kg compared to standard of care therapy [21].

### **3.4. Checkpoint inhibitor clinical trials of pembrolizumab first line**

#### **3.4.1. KEYNOTE 024**

KEYNOTE 024 was an open-label phase 3 randomized controlled trial investigating pembrolizumab versus platinum-based doublet chemotherapy in first-line setting. Inclusion criteria included patients with stage IV NSCLC, no sensitizing EGFR mutations or ALK translocations, no previous chemotherapy for metastatic disease, and PD-L1 expression of 50% or greater. The patients were assigned either pembrolizumab 200 mg every 3 weeks for 35 cycles or the investigators choice of one of five platinum-based chemotherapy regimens for 4–6 cycles. The primary endpoint was progression-free survival. Secondary endpoints include overall survival, objective response rate, and safety. A total of 305 patients were enrolled in this study [24].

The estimated percentage of patients alive at 6 months was 80.2% in the pembrolizumab group and 72.4% in the chemotherapy group. The ORR was 44.8% with pembrolizumab and 27.8% in the chemotherapy group. The median duration of response was not reached in the pembrolizumab treatment group (1.9 to 14.5+ months) compared to the chemotherapy treatment group of 6.3 months (2.1–12.6). The median PFS for pembrolizumab and docetaxel treatment groups was 10.3 and 6.0 months, respectively.

The pembrolizumab and chemotherapy treatment groups demonstrated 73.4% and 90% of patients with any adverse event (AE), respectively. The pembrolizumab treatment group demonstrated 26.6% of patients with grade 3 or 4 events and no grade 5 events. The chemotherapy arm had twice the incidence of grade 3, 4, or 5 events at 53.3%.

This trial was a landmark for demonstrating superiority of checkpoint inhibition therapy with pembrolizumab over that of standard of care platinum-based chemotherapy. An important



feature is that this population was selected for patients with at least 50% PD-L1 expression. Also of recurring significance, checkpoint inhibition therapy was better tolerated with less overall adverse events and significantly decreased severe adverse events.

### 3.5. Checkpoint inhibitor clinical trials with PD-L1 inhibitors

#### 3.5.1. POPLAR study

POPLAR was an open label phase 2 randomized controlled trial investigation of atezolizumab vs. docetaxel in 287 patients with advanced NSCLC with progression on platinum-based therapies [25]. Atezolizumab is currently the only approved anti-PD-L1 inhibitor approved by the U.S. FDA for the second-line treatment of bladder cancer. It is not approved for the treatment of lung cancer. The primary endpoint for the POPLAR trial was overall survival and secondary endpoints were ORR, PFS, and DOR. Of note, in addition to testing PD-L1 expression on tumor cells it also investigated PD-L1 expression on tumor-infiltrating lymphocytes.

Atezolizumab demonstrated a trend toward improvement in overall survival of 12.6 months compared to the 9.7 months with docetaxel. PFS was similar between groups, 2.7 months with atezolizumab vs. 3.0 months with docetaxel. Median DOR for atezolizumab and docetaxel respectively was 14.3 months compared with 7.2 months. The survival benefit with atezolizumab correlated with increasing PD-L1 expression on tumor cells and tumor infiltrating cells. Survival in patients with minimal PD-L1 expression was similar to that of the docetaxel treatment group.

Treatment-related adverse events were less frequent in the atezolizumab treatment group. The atezolizumab and docetaxel treatment groups demonstrated 67% and 88% of patients with any AE. Atezolizumab treatment group demonstrated a 40% grade 3 or 4 events rate and docetaxel had a 53% grade 3 or 4 event rate. Docetaxel demonstrated higher rates of treatment-related serious adverse events as previously demonstrated in PD-1 checkpoint inhibitor second-line trials.

POPLAR was the first study of a PD-L1 checkpoint inhibitor in a randomized clinical trial of patients with previously treated NSCLC. Atezolizumab showed a superior overall survival compared with docetaxel in patients with advanced NSCLC similar to those findings in CheckMate 017 and 057. A trend toward increased efficacy was appreciated with increased PD-L1 tumor expression. Patients with the lowest PD-L1 expression group demonstrated similar overall survival to the docetaxel treatment group.

At the European Society for Medical Oncology Conference held on October 2016, the OAK, NCT02008227, phase 3 randomized clinical trial comparing atezolizumab to docetaxel in locally advanced disease or metastatic NSCLC who have failed platinum therapy was presented. OAK demonstrated increased overall survival with atezolizumab, 13.8 months, vs. docetaxel, 9.6 months [26]. On October 18, 2016, the FDA approved atezolizumab for the treatment of patients with metastatic NSCLC in the second-line setting based on the findings of the POPLAR and OAK clinical trials [10].

#### 4. Adverse events in checkpoint inhibition

Checkpoint inhibitors confer a unique toxicity profile compared to chemotherapy as a result of activation of the patient's immune system. Immune-related adverse events (irAEs) are a direct result of immune system's stimulation resulting in both activation against tumor and against self. irAEs include but are not limited to colitis, pneumonitis, hepatitis, dermatitis, neuropathies, nephritis, and endocrinopathies [4, 27]. Of note, these irAEs were first appreciated with a different checkpoint inhibitor, ipilimumab, designed to affect CTLA-4. Additionally, irAEs from anti-PD-1 and anti-PD-L1 treatment occur at a lower rate than from anti-CTLA-4 [28].

Ipilimumab's side effect profile is well studied in the treatment of melanoma. Gastrointestinal and dermatologic immune-mediated toxicities were the most common. Moreover, they frequently appear in predictable time courses with dermatologic toxicities typically appearing in the first 2 weeks of therapy and gastrointestinal manifestations emerging after week 6 of therapy. Endocrinopathies are typically seen after longer duration of therapy although it is important to note that toxicities can occur at any time and even after cessation of therapy [29].

Anti-PD-1 and anti-PD-L1 treatment as mentioned above has a superior side effect profile compared to CTLA-4 inhibitions. The most common irAEs are rash, diarrhea, and colitis. These typically present at grade 1 or 2 and do not require discontinuation of therapy. Endocrinopathies include hypothyroidism as the most common, thyroiditis, hyperthyroidism, hypophysitis, and adrenal insufficiency [4, 13, 16]. Pneumonitis is a rare irAE but can be life threatening and occurs more often in lung cancer patients [3, 28].

PD-L1 inhibition was previously theorized to result in fewer irAEs as a result of targeting the tumor cell ligand and sparing PD-L2 which is more prevalent in healthy tissue, notably lung cells. Unfortunately, the POPLAR study did not demonstrate reduced irAE with PD-L1 inhibition compared to other trials that reported adverse event rates of PD-1 inhibitors [25].

The first and foremost purpose of checkpoint inhibitors is to determine efficacy either in monotherapy or in a combination regimen. One common thread in the clinical trials reviewed and markedly apparent in clinical trials comparing checkpoint inhibitors to docetaxel is that in subpopulations with the lowest rate of response to checkpoint inhibitors treatment efficacy is similar but adverse events are reduced compared to chemotherapy as well as grade 3 or 4 severe adverse events (**Table 2**) [18]. Therefore, if in the case of CheckMate 017, CheckMate 057, and POPLAR, we review the results for patients with minimal PD-L1 expression, EGFR mutants, and never smokers and observe similar efficacy but reduced adverse events. This argues in favor of checkpoint inhibition therapy secondary to its improved safety profile [17, 18, 25].

Treatment of grade 3 or 4 irAE typically requires discontinuation of therapy and systemic immunosuppression with high dose corticosteroids as the first-line therapy. Immune modulators such as infliximab can be used for patients that are steroid refractory. Grade 1 and 2 toxicities can be managed with supportive care alone and may not require discontinuation of checkpoint inhibition [30].



Clinical trial	Line of treatment	Treatment	All adverse events (AE) %	Grade 3 or 4 AE %
CheckMate 017	3	Nivolumab 3 mg/kg every 2 weeks Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	58 86	7 55
CheckMate 057	3	Nivolumab 3 mg/kg every 2 weeks Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	69 88	10 54
Keynote-010	2/3	Pembrolizumab 2 mg/kg every 3 weeks Pembrolizumab 10 mg/kg every 3 weeks Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	63 66 81	13* 16* 35*
POPLAR	2	Atezolizumab 1200 mg every 3 weeks Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	67 88	40 53

AE, adverse events.

\*Annotates data including grade 3, 4, and 5.

**Table 2.** Summary of adverse events in trials for checkpoint therapy in second line setting compared to docetaxel therapy.

## 5. PD-L1 expression

PD-L1 expression has been looked at extensively to identify patients who will confer benefit from checkpoint inhibitor therapy. Most studies to date have demonstrated increased PD-L1 expression as a positive prognostic indicator of response but there is substantial debate in its appropriateness for patient selection for therapy. In KEYNOTE 001 and KEYNOTE 010, PD-L1 expression was utilized as inclusion criteria for enrollment where patients demonstrating at least 1% expression were eligible for the trial and divided into cohorts of 1–49% expression and ≥50% expression [13, 14]. The FDA-approved pembrolizumab for second-line therapy of advanced NSCLC for PD-L1 expressing patients only, defined as patients with ≥50% PD-L1 expression on tumor cells. In CHECKMATE 017, PD-L1 was neither significantly prognostic nor predictive of efficacy although this study was not powered for this subset analysis [17]. In CHECKMATE 057, PD-L1 expression was strongly correlated with ORR and predictive of OS [18]. POPLAR interestingly investigated both tumor cell and immune cell expression of PD-L1 and found both were prognostic of response to PD-L1 inhibition with significant improvement in OS with increased expression. OS in patient with TC0 and IC0 was consistent with that of the docetaxel treatment group (**Table 3** for comparison of studies) [25].

While several studies have supported the finding of PD-L1 as a prognostic and predictive factor there is debate on how to use this information if at all. First, PD-L1 expression assays have varied across studies to include usage of Dako 28-8, Dako 22C3, Ventana SP142, and Ventana SP263 [31]. Second, the cut-off expression percentage has varied throughout published trials

Clinical trial	Treatment regimen	Phase trial	Histology	PD-L1 expression	PD-L1 assay	ORR PD-L1+ vs. PDL1-	Overall survival
Checkmate 063	Nivolumab	2	Squamous	59% ≥ 1% 33% ≥ 5% 33% ≥ 10%	Dako 28-8	20% vs. 13% 24% vs. 14% 24% vs. 14%	NR
Checkmate 017	Nivolumab vs. docetaxel	3	Squamous	47% ≥ 1% 31% ≥ 5% 27% ≥ 10%	Dako 28-8	17% vs. 17% 21% vs. 15% 19% vs. 16%	HR 0.69 vs. 0.58 HR 0.53 vs. 0.70 HR 0.50 vs. 0.70
Checkmate 057	Nivolumab vs. docetaxel	3	Nonsquamous	53% ≥ 1% 41% ≥ 5% 37% ≥ 10%	Dako 28-8	31% vs. 9% 36% vs. 10% 37% vs. 11%	HR 0.67 vs. 0.56 HR 0.54 vs. 0.75 HR 0.58 vs. 0.70
KEYNOTE-001	Pembrolizumab	1	All	23% < 1% 38% ≥ 1% and < 50% 34% ≥ 50%	Dako 22C3	10.7% vs. NR 16.5% vs. NR 45.2% vs. NR	10.4 mo vs. NR 10.6 mo vs. NR NR vs. NR
KEYNOTE-010	Pembrolizumab vs. docetaxel	1	All	43% ≥ 50%	Dako 22C3	30% vs. NR	2 mg/kg: 14.9 mo vs. NR 10 mg/kg: 17.3 mo vs. NR
CheckMate 012 Gettinger et al	Nivolumab	1	All	70% ≥ 1% 57% ≥ 5%	Dako 28-8	28% vs. 14% 31% vs. 15%	1 yr OS: 69% vs. 70% 1 yr OS: 73% vs. 70%
CheckMate 012 Rizvi et al	Nivolumab + PD-CT	1	All	52% ≥ 1%	Dako 28-8	48% vs. 43%	1 yr OS: 70% vs. 76% 20.2 mo vs. 19.2 mo
CheckMate 012 Hellman et al	Nivolumab + ipilimumab	1	All	77% ≥ 1%* 23% ≥ 50%*	Dako 28-8	57% vs. 0% 86% vs. 30%	1 yr OS: 83% vs. NR 1 yr OS: 100% vs. NR
POPLAR	Atezolizumab vs. docetaxel	2	All	32% TC-IC 0 < 1% 68% TC-IC 1/2/3 ≥ 1% 37% TC-IC 2/3 ≥ 5% 16% TC3 ≥ 50% or IC3 ≥ 10%	Ventana SP142	NR	1.04 vs. NR 0.59 vs. NR 0.54 vs. NR 0.49 vs. NR

OS, overall survival; ORR, objective response rate; NR, not reported; PD-1L, programmed cell death-1 ligand; mo, month.

\*Annotates reported nivolumab 3 mg/kg q2 week + ipilimumab 1 mg/kg q6 week data only.

**Table 3.** PD-L1 expression and clinical benefit.

and includes exclusion of a small proportion of responders. Finally, PD-L1's expression is dynamic calling into question the reliability in its use as a biomarker if expression varies by time accessioned, recent treatment, and variability in expression between sites biopsied [31–33]. To answer some of these questions, the “Blueprint Project” was established to formulate the cross-platform standards for PD-L1 positivity [34]. Ultimately, we hope to either validate one assay or demonstrate consistent reliability between assays of PD-L1 expression. As we continue to learn the complex symphony of the tumor microenvironment it is likely PD-L1 expression will be one of many prognostic tests utilized to tailor individual treatment.

## 6. Genomics and predicting clinical efficacy to checkpoint inhibition

While checkpoint inhibition appears promising at this time, it confers improvement of overall survival in only a minority of patients. Yet, many patients that do respond to checkpoint inhibition demonstrate durable response to therapy making patient selection and identifying predictive and prognostic factors necessary for future clinical decision-making. Despite the numerous studies that have found PD-L1 expression to correspond with disease response, PD-L1 expression is not without its own shortcomings with the most significant being its validity and its negative predictive value. There is a large variability in mutation burden within tumor types ranging from tens to thousands of mutations. This heterogeneity is appreciated in NSCLC secondary to the variability within the disease compared to smokers, nonsmokers, and patients with driver mutations such as EGFR-mutant [35]. In the studies reviewed here, smoking has been found to correspond to clinical efficacy while decreased clinical efficacy was found in checkpoint inhibitor therapy with EGFR-mutant patients and nonsmokers [3]. Significant research is currently underway evaluating molecular determinants of clinical benefit to include evaluating for mutational load, mismatch-repair deficiency, and isolating specific somatic neoepitopes [36, 37]. Rizvi et al. [35] found using whole-exome sequencing of NSCLC patients treated with pembrolizumab that higher nonsynonymous mutation burden in tumors was associated with improved objective response, durable clinical benefit, and PFS. In a recently published genetic analysis of clinical response to anti-CTLA-4 in melanoma tumors, evaluating neoantigens was assessed in patients with clinical response. They found the presence of the neoepitope signature peptides correlated strongly with survival. They also found a correlation with high mutational load. Although this was not statistically significant in their study to support clinical benefit, the mutational load seen in many lung cancer patients make this an interesting topic for future research [36].

## 7. Conclusion

Lung cancer remains the leading cause of cancer-related mortality worldwide with the majority of NSCLC patients presenting with advanced stage disease. We now have robust literature demonstrating both efficacy and increased safety using checkpoint inhibition compared to standard of care chemotherapy in advanced stage disease. Still, immunotherapy and its efficacy in treatment of NSCLC as well as our understanding of how to best utilize this therapy remains in its infancy. We currently have data to support improved efficacy with

advanced stage disease with checkpoint inhibition in the first and second line. CheckMate 026, NCT02041533, is investigating nivolumab in the first-line setting compared to standard of care therapy, platinum doublet chemotherapy, in advanced NSCLC patients with PD-L1 expressing tumors [20]. CheckMate 227, NCT02477826, is a multiarm study comparing nivolumab vs. nivolumab+ipilimumab vs. standard of care therapy platinum doublet chemotherapy  $\pm$  nivolumab in the first-line setting [21]. KEYNOTE 042, NCT02220894, is an ongoing clinical trials investigating pembrolizumab in the first-line setting in PD-L1 expressing tumors [38, 39]. Atezolizumab is the first FDA-approved PD-L1 inhibitor approved in the second-line setting. As more studies mature, we look to further understand checkpoint inhibition in combination therapy, the sequence of therapy, and defining the appropriate population.

An additional question which remains unanswered is the efficacy of checkpoint inhibitors in early stage disease. Also, which patients benefit the most from checkpoint inhibition is still to be determined. It is generally accepted that patients who are smokers, have squamous histology, high expression of PD-L1, and a high mutational load are more likely to respond to checkpoint inhibition, whereas patients who are nonsmokers, EGFR-mutant, minimal or no PD-L1 expression, and low mutational load are less likely to respond to checkpoint inhibition. Future investigation will help delineate which of these factors can reliably predict response to therapy. The ability for us to define mechanisms by which tumors evade our immune system complemented with our ability to predict response will hold the key to successful incorporation of immunotherapy in a wide population of patients with lung cancer.

## Author details

Karen G. Zeman<sup>1\*</sup>, Joseph E. Zeman<sup>2</sup>, Christina E. Brzezniak<sup>3</sup> and Corey A. Carter<sup>1</sup>

\*Address all correspondence to: [karengmayr@gmail.com](mailto:karengmayr@gmail.com)

1 Department of Hematology Oncology, Walter Reed National Military Medical Center, Bethesda, Maryland, USA

2 Department of Pulmonary and Critical Care Medicine, Walter Reed National Military Medical Center, Bethesda, Maryland, USA

3 Thoracic Oncology and Immuno-Oncology, Walter Reed National Military Medical Center, Bethesda, Maryland, USA

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