Review Article



# The role of immune checkpoint inhibitors in non-small cell lung cancer

**Tiffany L. George[1], Erin M. Bertino[2]**

[1]Divisions of Hematology and Medical Oncology, [2]Division of Medical Oncology, Department of Internal Medicine, Ohio State University Wexner Medical Center, Columbus, OH, USA

*Contributions:* (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Erin M. Bertino, MD. Division of Medical Oncology, Ohio State University Wexner Medical Center, 300 West 10th Avenue, Columbus, OH 43210, USA. Email: erin.bertino@osumc.edu.

**Abstract:** Lung cancer is the leading cause of cancer-related mortality worldwide. Historically, cytotoxic chemotherapy was the primary treatment. Many advances have been made in the treatment of advanced non-small cell lung cancer (NSCLC) over the past decade, including improved targeted therapies and the development of immunotherapy. Immune checkpoint inhibitors have emerged as the primary immunotherapy in NSCLC and have changed the treatment paradigm for advanced disease. These agents are also starting to be utilized in earlier stages of lung cancer. We review the mechanism of action and utilization of immune checkpoint inhibitors in the treatment of locally advanced and advanced NSCLC.

**Keywords:** Non-small cell lung cancer (NSCLC); immunotherapy; checkpoint inhibitors; programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1); cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)

Received: 16 March 2018; Accepted: 10 April 2018; Published: 09 May 2018.
doi: 10.21037/shc.2018.04.06
**View this article at:** http://dx.doi.org/10.21037/shc.2018.04.06

## Introduction

Lung cancer is one of the most common and most deadly malignancies—it accounts for 1.69 million deaths annually worldwide (1). Non-small cell lung cancer (NSCLC) accounts for the majority of these cases (80–85%). Although overall 5-year survival in the United States has changed little over the last 30 years (from 12% to 18%), recent treatment advances may improve this dismal trend (2). Targeted therapies, including vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab and tyrosine kinase inhibitors, were the first major advances for NSCLC. These therapies, however, were limited in scope by either histology (i.e., bevacizumab is only used in non-squamous NSCLC) or tumor mutation status (EGFR, ALK, and BRAF). In contrast, immunotherapy has demonstrated broad applications across all non-small cell histologies as well as multiple lines of therapy. Immunotherapy broadly refers to anti-cancer therapies that utilize a patient's innate immune system to recognize and eliminate malignancy. The success of immunotherapy in NSCLC has centered on the development of immune checkpoint inhibitors.

Immune checkpoint inhibitors constitute a new class of anti-neoplastic agents and have demonstrated promising clinical efficacy. These immune checkpoint inhibitors include programmed death-1 (PD-1) inhibitors such as nivolumab and pembrolizumab, programmed death-ligand 1 (PD-L1) inhibitors such as atezolizumab and durvalumab, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors such as ipilimumab and tremelimumab. This review will discuss the mechanism of action and clinical utility of checkpoint inhibitor immunotherapy in NSCLC.

## Immune checkpoint inhibitors—mechanism of action

Checkpoint inhibitors' mechanism of action impacts the

complex interaction between tumor cells and the native immune system. The mutations that transform normal cells into malignant cells produce neo-antigens that allow the immune system to recognize cancer as abnormal (3). PD-1 is a protein marker expressed on activated T-cells and its ligands—PD-L1 and programmed death-ligand 2 (PD-L2)—are usually expressed on tumor cells. The interaction between the immune cell PD-1 receptor and the tumor PD-L1 ligand inhibits T-cell activation, essentially shielding the tumor from immune surveillance. Although PD-L1 expression occurs in normal cells to regulate autoimmunity and prevent abnormal T-cell activation against normal cells, malignant cells may overexpress PD-L1 as a mechanism to avoid immune detection. Due to this overexpression, the T-cell PD-1 and malignant cell PD-L1 interaction has been identified as a therapeutic target. PD-1/PD-L1 checkpoint inhibitors block this interaction, thus restoring T-cell mediated anti-tumor immune response (4).

Checkpoint inhibitors target both partners in this interaction: PD-1 and PD-L1. There are subtle differences in activity between PD-1 and PD-L1 inhibitors based on the difference in expression as described above. It has been hypothesized that PD-1 interaction with PD-L2 expressed on the parenchymal cells of the heart, lung, and kidney provides negative signaling that prevents autoimmunity (5). PD-1 inhibitors may thus inadvertently lead to enhanced autoimmune toxicities by blocking this interaction, whereas PD-L1 inhibitors may evade some of these immune-mediated effects by leaving the PD-1/PD-L2 pathway intact. Clinically, differences in autoimmune toxicities have not been clearly identified and the drugs are used in similar treatment settings.

PD-L1 expression based on immunohistochemistry (IHC) assays is the most frequently studied biomarker for anti-PD-1/PD-L1 therapies in clinical trials. During early clinical trials, PD-L1 expression was evaluated but generally not required for study enrollment. In addition, different antibodies were utilized: nivolumab trials measured tumor PD-L1 expression with PD-L1 IHC assay clone 28-8 (6-8), pembrolizumab trials evaluated tumor PD-L1 expression using IHC 22C3 assay (9), and atezolizumab trials used SP142 PD-L1 assay on tumor cells and tumor-infiltrating immune cells (10). There are currently several approved assays and current therapeutic thresholds are based upon tumor cell PD-L1 IHC expression. However, there are limitations which may affect result interpretation such as tissue quality, tumor heterogeneity and dynamic expression (11). Other potential biomarkers, such as tumor mutation burden, are being assessed in other clinical trials in hopes of identifying specific populations who may derive clinical benefit from immunotherapy (8).

There are currently four PD-1/PD-L1 inhibitors commercially available for clinical use. The two available PD-1 inhibitors are nivolumab and pembrolizumab which are both humanized immunoglobulin G4 antibodies. The two commercially available PD-L1 inhibitors—atezolizumab and durvalumab—are humanized immunoglobulin G1 monoclonal antibodies.

CTLA-4 is a naturally occurring T-cell regulatory protein. It is expressed on T-cells and is believed to downregulate the immune response by binding to CD80 (B7-1) or CD86 (B7-2) on antigen presenting cells. Inhibition of CTLA-4 enhances T-cell activation, increases T-cell proliferation, and reduces regulatory T-cell mediated immunosuppression (12-14). CTLA-4 inhibitors were the first checkpoint inhibitors available and have been successfully used in the treatment of melanoma. Ipilimumab is approved for use in melanoma in the United States; it is a human immunoglobulin G1 monoclonal antibody which targets CTLA-4. Tremelimumab is an investigational selective human immunoglobulin G2 monoclonal antibody targeting CTLA-4 (13). These agents are not used commercially for NSCLC but are being combined with PD-1/PD-L1 inhibitors in clinical trials.

## Immunotherapy for advanced NSCLC

The evolution of checkpoint inhibitor therapy has led to clinical indications for both untreated (first-line) and previously treated (second-line and later) patients with metastatic NSCLC. Immunotherapies are also being used in locally advanced NSCLC as consolidation therapy following chemoradiation. At this time, anti-PD-1/PD-L1 therapies are only approved as single agents or in combination with cytotoxic chemotherapy for NSCLC (summarized in *Table 1*). Ongoing areas of investigation include combination immunotherapies using anti-PD-1/PD-L1 and anti-CTLA-4 agents together.

### *First-line immunotherapy in metastatic NSCLC*

#### Immunotherapy single agent

Historically, chemotherapy has been the default first-line therapy for metastatic NSCLC, however recent trials have established a role for checkpoint inhibitors in the first-line setting. In contrast to second-line therapy, single agent

 

**Table 1** Summary of United States Federal Drug Administration-approved immunotherapy agents in treatment of non-small cell lung cancer

| Drug | Histology | PD-L1 expression | Dosing/regimen | Clinical trial |
|---|---|---|---|---|
| Stage III NSCLC maintenance after chemoradiation | | | | |
| Durvalumab | Squamous or non-squamous | Any level | Durvalumab 10 mg/kg *vs.* placebo every 2 weeks for up to 12 months | PACIFIC (15) (phase III) |
| Metastatic NSCLC first-line chemotherapy naive | | | | |
| Pembrolizumab | Squamous or non-squamous | ≥50% | Pembrolizumab 200 mg every 3 weeks for 35 cycles *vs.* platinum-based chemotherapy (investigator's choice) for up to 6 cycles with maintenance therapy if indicated | KEYNOTE-024 (8) (phase III) |
| Chemo-immunotherapy; pembrolizumab + chemotherapy | Non-squamous | Any level | Pembrolizumab 200 mg + carboplatin AUC (area under the curve) 5 mg/mL per min + pemetrexed 500 mg/m$^2$ every 3 weeks for 4 cycles, followed by pembrolizumab for 2 years and optional indefinite pemetrexed maintenance therapy | KEYNOTE-021 (12) (phase II) |
| Metastatic NSCLC second-line or later | | | | |
| Nivolumab | Squamous | Any level | Nivolumab 3 mg/kg every 2 weeks *vs.* docetaxel 75 mg/m$^2$ every 3 weeks | CheckMate 017 (16) (phase III) |
| Nivolumab | Non-squamous | Any level | Nivolumab 3 mg/kg every 2 weeks *vs.* docetaxel 75 mg/m$^2$ every 3 weeks | CheckMate 057 (17) (phase III) |
| Pembrolizumab | Squamous or non-squamous | ≥1% | Pembrolizumab 2 mg/kg or 10 mg/kg *vs.* docetaxel 75 mg/m$^2$ every 3 weeks | KEYNOTE-010 (18) (phase II/III) |
| Atezolizumab | Squamous or non-squamous | Any level | Atezolizumab 1,200 mg *vs.* docetaxel 75 mg/m$^2$ every 3 weeks | POPLAR (19) (phase II) |
| Atezolizumab | Squamous or non-squamous | Any level | Atezolizumab 1,200 mg *vs.* docetaxel 75 mg/m$^2$ every 3 weeks | OAK (20) (phase III) |

immune checkpoint inhibitors have demonstrated efficacy in only a select subset of patients. Two similar trials with different outcomes have served to define the current role for single agent immunotherapy: CheckMate 026 (21) and KEYNOTE-024 (22).

The phase III trial, CheckMate 026, compared nivolumab [3 milligram/kilogram (mg/kg) every 2 weeks] with investigator's choice of platinum doublet chemotherapy (up to 6 cycles with maintenance therapy, if indicated) in patients with untreated stage IV or recurrent NSCLC. This trial included both non-squamous and squamous histologies and required positive PD-L1 expression (≥1%). Most patients were non-squamous (76%) and most patients had PD-L1 expression ≥5% (77% were ≥5%; 40% were ≥50%). Among the 423 patients with PD-L1 expression ≥5%, nivolumab did not demonstrate longer progression-free survival (PFS) than chemotherapy [4.2 *vs.* 5.9 months; hazard ratio (HR), 1.15; 95% confidence interval (CI), 0.91–1.45; P=0.25]. Response rate in the nivolumab group was 26% *vs.* 33% in the chemotherapy group. Median overall survival (OS) in the nivolumab and chemotherapy groups was similar (14.4 *vs.* 13.2 months, respectively; HR, 1.02; 95% CI, 0.80–1.30). Grade 3 or 4 treatment-related adverse events (AEs) were less frequent with nivolumab (18%) than with chemotherapy (51%) (8). Based on these negative results, nivolumab is not currently approved as a single agent in untreated patients.

In contrast, the phase III trial (KEYNOTE-024) which compared pembrolizumab (200 mg every 3 weeks) with platinum-based chemotherapy in previously untreated patients with advanced NSCLC and PD-L1 expression in ≥50% of tumor cells (n=305), did demonstrate efficacy for first-line pembrolizumab. The higher PD-L1 cutoff was chosen based on an early phase trial which demonstrated improved efficacy (response rate, PFS, and OS) with pembrolizumab as first-line therapy in patients with PD-L1 expression ≥50% (23,24). Similar to the nivolumab trial, most patients had non-squamous histology (81–82%). In

 

KEYNOTE-024, pembrolizumab resulted in significantly longer median PFS (10.3 *vs.* 6.0 months; HR, 0.50; 95% CI, 0.37–0.68; P<0.001) and OS (HR, 0.60; 95% CI, 0.41–0.89; P=0.005) compared to platinum-based chemotherapy. Response rate was also higher with pembrolizumab than with chemotherapy (44.7% *vs.* 27.8%). Treatment-related AEs of grade 3 or higher occurred less often in the pembrolizumab group than in the chemotherapy group (26.6% *vs.* 53.3%) (22). Based on these results, pembrolizumab has been approved as a single agent in patients with untreated NSCLC and high tumor PD-L1 expression (defined as ≥50%).

Atezolizumab has also been evaluated in first-line therapy, although it is not approved for this indication. BIRCH was a phase II trial with atezolizumab (1,200 mg IV every 3 weeks) in patients with advanced or recurrent NSCLC and PD-L1 expression ≥5%. This study included three cohorts, including first-line therapy (n=142). First-line patients were primarily non-squamous histology (77%) and included a small cohort of EGFR mutant and ALK positive patients (11% and 4%—total of 16 patients). For the first-line cohort, response rate (22%; 95% CI, 15–29), median PFS (5.4 months; 95% CI, 3.0–6.9) and median OS (20.1 months; 95% CI, 20.1 to not estimable) were similar to results observed with nivolumab. The small group of EGFR mutant NSCLC patients demonstrated similar response rates to the non-mutated patients (16).

**Chemo-immunotherapy**

As a follow-up to single agent therapy, chemotherapy and immunotherapy combinations (chemo-immunotherapy) have been investigated. The combination of chemotherapy and pembrolizumab has been approved in the United States; combinations of chemotherapy and nivolumab are currently investigational and not approved for routine clinical use.

The approval of chemo-immunotherapy was based on the KEYNOTE-021 trial. This was a phase II study evaluating carboplatin and pemetrexed with or without pembrolizumab in chemotherapy-naïve, stage IIIB or IV, non-squamous NSCLC patients. In contrast to the single agent pembrolizumab trial, positive PD-L1 expression was not required for enrollment. In the combination therapy arm, 35% had PD-L1 expression <1% and 33% had PD-L1 expression ≥50% (similar in chemotherapy only arm). Median PFS was significantly improved with combination therapy [pembrolizumab plus chemotherapy—13.0 months (95% CI, 8.3 to not reached)] compared with chemotherapy only (8.9 months; 95% CI, 4.4–10.3). Objective response was 55% (33 of 60 patients) with combination therapy compared to 29% (18 of 63 patients) with chemotherapy only. Treatment-related AEs of grade 3 or higher were similar in both groups (39% with pembrolizumab plus chemotherapy and 25% with chemotherapy only) (9). Combination therapy with pembrolizumab and chemotherapy was approved in the United States based on this data. There are ongoing phase III studies to confirm these findings, including KEYNOTE-189 (platinum and pemetrexed with or without pembrolizumab in patients with non-squamous NSCLC) (25) and KEYNOTE-407 (carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab in patients with squamous NSCLC) (18).

Combinations of other checkpoint inhibitors and chemotherapy have also been investigated. A randomized Phase III trial evaluating carboplatin and paclitaxel with or without ipilimumab in chemotherapy-naïve squamous cell lung cancer demonstrated no survival benefit (OS, 13.4 *vs.* 12.4 months; P=0.25) and increased toxicity with the chemo-immunotherapy combination (19). A phase I trial (CheckMate 012) included several cohorts of combination therapy: nivolumab plus either gemcitabine and cisplatin (squamous histology), pemetrexed and cisplatin (non-squamous histology), or paclitaxel and carboplatin (any histology). All patients received 4 cycles, and subsequent nivolumab maintenance therapy until disease progression or unacceptable toxicity. Results demonstrated objective response rate (ORR) of 46%, median PFS of 6.0 months (95% CI, 4.8–8.3), and median OS of 19.2 months (95% CI, 14.1–23.8). ORR and OS were similar irrespective of the level of PD-L1 expression (20). CheckMate 012 also evaluated first-line combination immunotherapy: nivolumab and ipilimumab. Two dosing schedules were evaluated—nivolumab 3 mg/kg every 2 weeks plus either ipilimumab 1 mg/kg every 6 weeks or every 12 weeks. Response rate and PFS were better with the less frequent dosing (47% *vs.* 38% response rate and 8.1 *vs.* 3.9 months PFS—every 12 weeks *vs.* every 6 weeks) (15).

CheckMate 227 was a follow-up phase III trial with over 2,500 patients comparing nivolumab single agent, nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy *vs.* platinum doublet chemotherapy in patients with chemotherapy naïve stage IV or recurrent NSCLC of any histology. The multi-arm trial stratified patients by PD-L1 expression. Part 1a enrolled PD-L1 expressing patients and randomized patients to nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy. Part 1b enrolled PD-L1 negative patients and randomized

 

patients to nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone. In addition to PD-L1 expression, this trial is also evaluating tumor mutation burden as a potential biomarker but these results are not yet available (17). Tumor mutation burden has been previously described as a potential predictor of response (8).

### *Second-line immunotherapy in metastatic NSCLC*

For patients who do not receive immunotherapy as first-line treatment, there are multiple competing options and available drugs including nivolumab, pembrolizumab, and atezolizumab. Several other PD-1/PD-L1 inhibitors have been evaluated but are not currently utilized for metastatic NSCLC (including avelumab and durvalumab). This section will focus on clinical efficacy of nivolumab, pembrolizumab, and atezolizumab in this treatment setting.

There were two separate phase III trials which evaluated second-line nivolumab: CheckMate 017 (7) which evaluated squamous NSCLC and CheckMate 057 (26) which evaluated non-squamous NSCLC. Both trials compared nivolumab (3 mg/kg every 2 weeks) with docetaxel (75 mg/m$^2$ every 3 weeks) in patients with stage IIIB/IV NSCLC who had disease progression during or after one prior platinum-based regimen. In the squamous trial, median OS (9.2 *vs.* 6.0 months), 1-year survival rate (42% *vs.* 24%; HR, 0.59; P<0.001), response rate (20% *vs.* 9%; P=0.008) and median PFS (3.5 *vs.* 2.8 months; HR, 0.62; 95% CI, 0.47–0.81; P<0.001) were significantly better in the nivolumab group (7). The non-squamous trial demonstrated similar positive results favoring nivolumab: median OS (12.2 *vs.* 9.4 months; HR, 0.73; 95% CI, 0.59–0.89; P=0.002) and response rate (19% *vs.* 12%; P=0.02). In the non-squamous study, median PFS favored docetaxel over nivolumab (4.2 *vs.* 2.3 months), but the rate of PFS at 1 year was higher in the nivolumab group than in the docetaxel group (19% *vs.* 8%). In the squamous population, PD-L1 expression was neither prognostic nor predictive of efficacy (7). In contrast, in the non-squamous population, PD-L1 expression was associated with better OS in the nivolumab group suggesting a difference in utility for these patients (6). In both trials, there were less treatment-related toxicities (≥ grade 3) with nivolumab than with docetaxel (6,7).

Pembrolizumab was initially evaluated in a large multi-cohort phase I trial which included previously treated patients (KEYNOTE-001) (24). This trial demonstrated promising results and was followed by the Phase II/III trial, KEYNOTE-010 (27). This study compared pembrolizumab (2 and 10 mg/kg) *vs.* docetaxel (75 mg/m$^2$) every 3 weeks in patients with previously treated NSCLC with tumor cell PD-L1 expression ≥1% (n=1,034). This trial included both squamous (19–22%) and non-squamous (70–71%) histologies in all treatment arms. Across treatment arms, 40–44% of patients were high PD-L1 expressers (≥50%). In the overall population (PD-L1 ≥1%), median PFS was not significantly different between pembrolizumab (2 or 10 mg/kg) and docetaxel (3.9 *vs.* 4.0 months). However, median OS was significantly improved with both doses of pembrolizumab (2 mg/kg—10.4 months; HR, 0.71; 95% CI, 0.58–0.88; P=0.0008; 10 mg/kg—12.7 months; HR, 0.61; 95% CI, 0.49–0.75; P<0.0001) compared with docetaxel (8.5 months) in the total population. In patients with PD-L1 expression of ≥50%, median PFS and OS were significantly longer with pembrolizumab (2 mg/kg—PFS 5.0 months; HR, 0.59; P=0.0001; OS, 14.9 months; HR, 0.54; P=0.0002; 10 mg/kg—PFS 5.2 months; HR, 0.59; P<0.0001; OS, 17.3 months; HR, 0.50; P<0.0001) than with docetaxel (PFS, 4.1 months, OS, 8.2 months). In the overall population (PD-L1 ≥1%), response rate was significantly higher in both pembrolizumab groups than in the docetaxel group (18% *vs.* 9% for both pembrolizumab groups *vs.* docetaxel; 2 mg/kg, P=0.0005; 10 mg/kg, P=0.0002). In patients with PD-L1 expression of ≥50%, response rate was also significant higher in both pembrolizumab groups (30% *vs.* 8% for pembrolizumab 2 mg/kg *vs.* docetaxel and 29% *vs.* 8% for pembrolizumab 10 mg/kg *vs.* docetaxel; P<0.0001 for both) than in the docetaxel group. Treatment-related AEs of grade 3–5 were less frequent in both pembrolizumab groups (13% with 2 mg/kg and 16% with 10 mg/kg) than in the docetaxel group (35%). This data established the use of pembrolizumab (for second-line or later therapy) in patients with previously treated advanced NSCLC with PD-L1 expression ≥1%. This trial also indicated increased benefit of immunotherapy associated with higher PD-L1 expression (27).

Atezolizumab has been evaluated in a series of trials: BIRCH (16), POPLAR (28), and OAK (10). BIRCH was a phase II trial with atezolizumab in patients with stage IIIB/IV or recurrent NSCLC and PD-L1 expression ≥5%. As described above, this multi-cohort trial also included two cohorts for previously treated patients: second-line and third-line or higher. Results essentially demonstrated efficacy and safety with single agent atezolizumab in all lines of therapy in patients with PD-L1 selected advanced NSCLC (16).

POPLAR was a randomized phase II trial which

 

compared atezolizumab (1,200 mg IV) with docetaxel in patients with NSCLC after progression on platinum-based chemotherapy (n=287). This trial also enrolled non-squamous and squamous histologies and stratified patients according to PD-L1 expression (<1%, ≥1% and <5%, ≥5% and < 50%, and ≥50%). OS was significantly improved with atezolizumab compared with docetaxel in the intention-to-treat (ITT) population (12.6 *vs.* 9.7 months; HR, 0.73; 95% CI, 0.53–0.99; P=0.04). Notably, both squamous and non-squamous NSCLC patients achieved improvement in OS with atezolizumab compared with docetaxel. PFS was similar between the atezolizumab and docetaxel groups (2.7 *vs.* 3.0 months; HR, 0.94; 95% CI, 0.72–1.23). ORR was also similar between the two groups, however, median response duration was improved with atezolizumab (14.3 month) compared with docetaxel (7.2 months). As observed with other checkpoint inhibitors, increasing PD-L1 expression correlated with increased OS benefit from atezolizumab. In patients with no PD-L1 expression (<1%), OS was similar between the atezolizumab and docetaxel groups (9.7 months; HR, 1.04; 95% CI, 0.62–1.75). In patients with PD-L1 expression ≥1%, there was a significant improvement in survival, accounting for the overall benefit observed. Grade 3 to 4 treatment-related AEs were less common with atezolizumab compared with docetaxel (11% *vs.* 39%) (28).

OAK was a phase III study to confirm the results of the POPLAR study—the overall design was very similar. This trial also compared atezolizumab with docetaxel in patients with stage IIIB or IV NSCLC who had previously received at least one prior cytotoxic chemotherapy regimens, including ≥1 platinum-based combination therapy (n=850). This trial also stratified patients by PD-L1 expression. Median OS in the ITT population was significantly better with atezolizumab compared with docetaxel (13.8 *vs.* 9.6 months; HR, 0.73; 95% CI, 0.62–0.87; P=0.0003). In contrast to POPLAR, however, there was an improved median OS with atezolizumab compared with docetaxel in patients with PD-L1 expression ≥1% (15.7 *vs.* 10.3 months; HR, 0.74; 95% CI, 0.58–0.93; P=0.0102), as well as PD-L1 expression <1% (12.6 *vs.* 8.9 months; HR, 0.75; 95% CI, 0.59–0.96). Consistent with prior trials, high PD-L1 expression (≥50%) achieved the greatest median OS benefit with atezolizumab (20.5 *vs.* 8.9 months; HR, 0.41; 95% CI, 0.27–0.64; P<0.0001). Median PFS was similar between both groups in the ITT population (2.8 months with atezolizumab and 4.0 months with docetaxel; HR, 0.95; 95% CI, 0.82–1.10). Objective response in the ITT population was also similar between both groups, but the median duration of response in the ITT population was markedly longer in the atezolizumab group compared with the docetaxel group (16.3 *vs.* 6.2 months; HR, 0.34; 95% CI, 0.21–0.55; P<0.0001). Grade 3 or 4 treatment-related AEs were less frequent with atezolizumab than with docetaxel (15% *vs.* 43%) (10).

One notable difference for BIRCH, POPLAR and OAK was the inclusion of patients with EGFR mutations and ALK translocations. These patients are specifically excluded from many immunotherapy trials. For the EGFR-mutant population, BIRCH included 32 patients receiving second-line or later (15%) (16), POPLAR included 19 patients (13% in the atezolizumab arm, 10% in the docetaxel arm) (28), and OAK included 85 patients (10% in each treatment arm) (10). ALK-positive patients were much less common—6 patients in BIRCH (4%) (16), 3 patients in POPLAR (5%) (28), and 2 patients in OAK (<1%) (10). Given the small number of patients, conclusions were limited. A subgroup analysis of EGFR-mutant patients in OAK favored chemotherapy over atezolizumab (HR, 1.24; 95% CI, 0.21–2.18), suggesting a lack of benefit for these patients (10).

## Immunotherapy in stage III NSCLC

The most recent advancement in checkpoint inhibitor therapy is an indication for locally advanced, stage III NSCLC. The current standard of care is combination therapy with chemotherapy and radiation. Concurrent chemoradiation is recommended if tolerable, although sequential therapy is also an option.

PACIFIC was a Phase III trial evaluating durvalumab as maintenance therapy for 1 year after chemoradiation. All patients received at least 2 cycles of concurrent platinum-based chemoradiotherapy. Patients with no disease progression after chemoradiation were randomized to either durvalumab (10 mg/kg IV) or placebo every 2 weeks for up to 12 months (n=709). Durvalumab therapy started within 42 days of completion of chemoradiation. Most patients achieved at least partial response prior to randomization (durvalumab 48.7% and placebo 46.8%). Median PFS was significantly longer with durvalumab than with placebo (16.8 *vs.* 5.6 months; HR, 0.52; 95% CI, 0.42–0.65; P<0.001). Notably, PFS benefit with durvalumab was evident irrespective of PD-L1 expression. Response rate was also significantly better with durvalumab compared with placebo (28.4% *vs.* 16%; P<0.001). Treatment-related AEs of grade 3 or 4 were similar in both the durvalumab and placebo

 

**Table 2** Ongoing clinical trials in immunotherapy for stages I–III non-small cell lung cancer

| Treatment setting | Stage | Trial name |
|---|---|---|
| Concurrent with radiation therapy | I | Phase I/II Study of the Safety, Tolerability, and Efficacy of Stereotactic Body Radiation Therapy (SBRT) Combined With Concurrent and Adjuvant Avelumab for Definitive Management of Early Stage Non-Small Cell Lung Cancer (NSCLC) |
| Concurrent with radiation therapy | I–IIA | Phase II Randomized Clinical Trials Comparing Immunotherapy (nivolumab) Plus Stereotactic Ablative Radiotherapy (I-SABR) Versus SABR Alone for Stage I, Selected Stage IIa or Isolated Lung Parenchymal Recurrent Non-Small Cell Lung Cancer: I-SABR |
| Concurrent with radiation therapy | I | Ablative STEreotactic RadiOtherapy wIth Durvalumab (MEDI4736). An Open Label Randomized Phase II Trial With Durvalumab Following Stereotactic Body Radiotherapy (SBRT) in Patients With Stage I Non-small Cell Lung Cancer (NSCLC) - ASTEROID |
| Adjuvant | IB–III | A Phase III Prospective Double Blind Placebo Controlled Randomized Study of Adjuvant MEDI4736 (durvalumab) In Completely Resected Non-Small Cell Lung Cancer |
| Neoadjuvant | IB–IIIA | Pembrolizumab Prior to Surgery for Stage 1B, 2 or 3A Non-small Cell Lung Cancer (NSCLC): A Phase II Study |
| Neoadjuvant | IIIA | Neoadjuvant Chemo/Immunotherapy for the treatment of resectable stage IIIA Non-Small Cell Lung Cancer (NSCLC): A Phase II Multicenter Exploratory Study |
| Neoadjuvant | IB–IIIA | A Single-arm Phase 2 Study of Atezolizumab as Induction Therapy in Stage IB-IIIA Non N2 Resectable and Untreated Non-small Cell Lung Cancer (NSCLC) |
| Neoadjuvant | IIIA | Neoadjuvant Immunoradiation for Stage IIIA Resectable Non-Small Cell Lung (durvalumab and tremelimumab) |
| Neoadjuvant | IB–IIIA | Neoadjuvant Nivolumab, or Nivolumab in Combination With Ipilimumab, in Resectable Non-Small-Cell Lung Cancer |
| Consolidation therapy | IIIA/IIIB | Phase II Study of Consolidation Immunotherapy With Nivolumab and Ipilimumab or Nivolumab Alone Following Concurrent Chemoradiotherapy for Unresectable Stage IIIA/IIIB Non-small Cell Lung Cancer (NSCLC): BTCRC-LUN16-081 |

groups (29.9% *vs.* 26.1%), although the incidence of pneumonitis was higher with durvalumab (all grades: 33.9% *vs.* 25.2%) (29). Based on these results, durvalumab has been approved for treatment after concurrent chemoradiation in stage III NSCLC in the United States.

## Combination therapies and future directions

Ongoing areas of investigation include combination therapies across multiple lines of therapy. One area of interest is moving immunotherapy into earlier stages of disease. *Table 2* summarizes ongoing clinical trials for neoadjuvant, adjuvant and chemoradiation therapy in early stage NSCLC. These trials include evaluating immunotherapy in combination with stereotactic radiation for unresectable early stage disease, induction therapy for potentially resectable disease, and consolidation therapy for patients receiving chemoradiation for locally advanced disease.

Another area of interest is developing combination therapies to overcome resistance. Although checkpoint inhibitors have demonstrated promising clinical activity, most patients do not achieve durable responses and ultimately die from progressive disease. In addition, as more patients receive checkpoint inhibitors earlier in the course of their disease, options are limited to chemotherapy at progression. Strategies to address this issue have included combination therapies—immunomodulation by addition such as combining PD-1/PD-L1 inhibitors with CTLA-4 inhibitors, adding radiation therapy for abscopal effect, or adding other immune-modulating agents. These trials are still ongoing but may represent the next generation of anti-cancer therapies.

## Conclusions

Checkpoint inhibitor immunotherapy has changed the treatment of NSCLC and improved survival for advanced

 

stage patients. In metastatic NSCLC, checkpoint inhibitor therapy is considered standard of care as first or second-line treatment. As this therapeutic modality continues to evolve, it is likely to impact treatment in early stage disease as well. As we continue to enrich our understanding of mechanisms of resistance and predictive biomarkers through future areas of study, we will further hone our use of these novel agents in the treatment of NSCLC.

## Acknowledgments

*Funding:* None.

## Footnote

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/shc.2018.04.06). Dr. Bertino reports personal fees from Pfizer, null, outside the submitted work. Dr. George has no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



## References

1. World Health Organization. Cancer fact sheet. 2018. Available online: http://www.who.int/mediacentre/factsheets/fs297/en/
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
3. Gubin MM, Zhang X, Schuster H, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. Nature 2014;515:577-81.
4. Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. Nat Rev Drug Discov 2015;14:561-84.
5. Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol 2001;22:265-8.
6. Borghaei H, Brahmer J. Nivolumab in Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2016;374:493-4.
7. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
8. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med 2017;376:2415-26.
9. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-508.
10. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
11. Remon J, Chaput N, Planchard D. Predictive biomarkers for programmed death-1/programmed death ligand immune checkpoint inhibitors in nonsmall cell lung cancer. Curr Opin Oncol 2016;28:122-9.
12. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol 2016;39:98-106.
13. O'Day SJ, Hamid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. Cancer 2007;110:2614-27.
14. Boasberg P, Hamid O, O'Day S. Ipilimumab: unleashing the power of the immune system through CTLA-4 blockade. Semin Oncol 2010;37:440-9.
15. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol 2017;18:31-41.
16. Peters S, Gettinger S, Johnson ML, et al. Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). J Clin Oncol 2017;35:2781-9.
17. Paz-Ares L, Brahmer J, Hellmann MD, et al. CheckMate

 

227: A randomized, open-label phase 3 trial of nivolumab, nivolumab plus ipilimumab, or nivolumab plus chemotherapy versus chemotherapy in hemotherapy-naive patients with advanced non-small cell lung cancer (NSCLC). Annals of Oncology 2017;28:ii28-51.
18. Merck Sharp & Dohme Corp. A Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy With or Without Pembrolizumab (MK-3475) in Adults With First Line Metastatic Squamous Non-small Cell Lung Cancer (MK-3475-407/KEYNOTE-407). 2017. Available online: https://clinicaltrials.gov/ct2/show/NCT02775435
19. Govindan R, Szczesna A, Ahn MJ, et al. Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer. J Clin Oncol 2017;35:3449-57.
20. Juergens RJ, Hellmann MD, Brahmer JR, et al. First-Line Nivolumab plus Platinum-Based Doublet Chemotherapy for Advanced NSCLC: CheckMate 012 3-Year Update. World Conference on Lung Cancer, October 2017; Yokohama, Japan.
21. Gettinger S, Rizvi NA, Chow LQ, et al. Nivolumab Monotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:2980-7.
22. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
23. Hui R, Garon EB, Goldman JW, et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. Ann Oncol 2017;28:874-81.
24. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
25. Hall RD, Gadgeel SM, Garon EB, et al. Phase 3 study of platinum-based chemotherapy with or without pembrolizumab for first-line metastatic, nonsquamous non-small cell lung carcinoma (NSCLC): KEYNOTE-189. J Clin Oncol 2016;3:abstr TPS9104.
26. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
27. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
28. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-46.
29. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:1919-29.

doi: 10.21037/shc.2018.04.06
**Cite this article as:** George TL, Bertino EM. The role of immune checkpoint inhibitors in non-small cell lung cancer. Shanghai Chest 2018;2:35.

 