

Immune Checkpoint Inhibitors in Advanced Non–Small Cell Lung Cancer

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The emergence of immune checkpoint inhibitors for the treatment of cancer has led to major changes to the therapeutic landscape of lung cancer. Improvements in overall survival relative to standard chemotherapy have been observed in the first-line and second-line therapy settings for patients with advanced non–small cell lung cancer (NSCLC) who are treated with immune checkpoint inhibitors. Consequently, every patient with advanced-stage NSCLC is now a candidate for immune checkpoint inhibitor therapy. However, it is clear that the benefit from therapy is not universal, and identification of biomarkers to select therapy has assumed importance. In addition to programmed cell death receptor ligand 1 expression, both tissue-based and blood-based markers are under evaluation to select patients. In an era of increasing costs of care and potential for toxicities related to immune checkpoint inhibition, proper patient selection is critical to the optimal use of this new class of agents. In addition, development of novel combination approaches has also emerged as an important way to improve the efficacy of immune checkpoint inhibition. Studies in earlier stages of NSCLC are already underway with the hope of improving the cure rate. In this article, the authors review the current landscape of immune checkpoint inhibitors in the treatment of advanced NSCLC. *Cancer* 2018;124:248–61. © 2017 American Cancer Society.

KEYWORDS: biomarkers, checkpoint inhibitors, immunotherapy, non–small cell lung cancer (NSCLC), programmed cell death receptor ligand 1 (PD-L1).

INTRODUCTION

During the past decade, the management of non–small cell lung cancer (NSCLC) has evolved enormously. Multiple treatment modalities, including surgery, chemotherapy, targeted therapy, and radiotherapy, have all led to robust improvements in outcomes for this disease. Systemic therapy is essential for nearly all stages of NSCLC given the high propensity for micrometastasis even in patients with early stage disease. Platinum-based chemotherapy has been the standard of care for the treatment of advanced, unresectable NSCLC, in which cisplatin or carboplatin is combined with other chemotherapeutic agents, such as taxanes, pemetrexed, or gemcitabine, as frontline treatment. However, response rates for such regimens range between 20% and 40% of patients, with limited options in case of cancer recurrence.¹ Indeed, studies and clinical practice have demonstrated that the median progression-free survival (PFS) and the median overall survival (OS) for such regimens reach 6 months and 12 months, respectively.² Targeted therapies against epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) gene rearrangements have improved the survival of a small proportion of patients whose tumors express these molecular abnormalities.^{3,4} Throughout the last century, observations of cancer remission after infections have stimulated the scientific community's interest to further evaluate the link between cancer and the immune system. This approach has come to fruition in recent years, with the emergence of immune checkpoint inhibition as another important treatment approach for patients with advanced-stage disease.⁵

CHECKPOINT INHIBITORS

The tumor environment is characterized by a state of immune tolerance maintained by various mechanisms, which include the recruitment of regulatory immune cells, the release of immunosuppressive molecules, and the expression of inhibitory receptors on tumor-infiltrating T cells that dampen immune responses.^{6,7} Inhibitory receptors expressed on T cells are also called *checkpoint molecules* because of their physiologic role in controlling T-cell activation to prevent excessive inflammation and pathology.⁸ Checkpoint inhibitors constitute a novel class of agents that block inhibitory receptors and thus harness the immune system to mount effective antitumor responses. The approval of checkpoint inhibitors by the US Food and Drug Administration (FDA) has led to substantial improvement in the management of various tumors, including NSCLC.⁹

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The first checkpoint inhibitor approved by the FDA for the treatment of patients with advanced cancer was a blocking antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) (ipilimumab).¹⁰ CTLA-4 is expressed on activated T cells and is structurally similar and homologous to cluster of differentiation 28 (CD28), a key T-cell–costimulatory molecule. CTLA-4 competes with CD28 by binding to the same ligands B7-1 (CD80) and B7-2 (CD86), but with higher affinity and avidity. In addition to reducing CD28/B7 interactions, CTLA-4 ligation may transmit intracellular inhibitory signals that reduce T-cell activation.¹¹ CTLA-4 blockade also promotes immune responses through extrinsic effects by inhibiting regulatory CD4 T cells (Tregs).¹² CTLA-4 is highly expressed by Tregs, and it has been demonstrated that the efficacy of anti-CTLA-4 antibodies in tumor models relies on Treg cell depletion at the tumor site.^{13–15} During T-cell interactions with antigen-presenting cells (APCs), it has also been reported that CTLA-4 can reduce the expression of B7 molecules on APCs, resulting in APCs with attenuated priming ability.^{16,17} Thus in animal models, different mechanisms have been proposed to explain how CTLA-4 checkpoint inhibition functions to elicit enhanced T-cell responses. In humans, the precise mechanism whereby CTLA-4 blockade is able to induce effective antitumor responses is still not completely understood. To date, ipilimumab has been approved for the management of advanced melanoma, and the clinical benefit of CTLA-4 checkpoint inhibitors (ipilimumab and tremelimumab) as monotherapy or in combination with other therapies is still under investigation for other cancers types.

After the approval of ipilimumab, promising data from checkpoint inhibitors targeting the programmed cell death 1 (PD-1)-inhibitory pathway were reported from clinical trials in patients with diverse cancer types.^{10,18–20} In T cells, PD-1 expression is induced and maintained by T-cell receptor (TCR) signaling. PD-1 engagement hampers T-cell activation by the inhibition of downstream TCR/CD3 signaling and CD28 dephosphorylation.^{21,22} Sustained and high PD-1 expression is a hallmark of exhausted T cells, which became progressively dysfunctional because of chronic antigenic stimulation.²³ In animal models of chronic viral infection and tumor, blockade of PD-1 interactions with its ligands leads to expansion and functional rescue of exhausted PD-1–positive CD8 T cells, resulting in control of viral load or tumor burden.^{24–26}

PD-1 has 2 ligands: PD-L1 and PD-L2. PD-L2 appears to be restricted to fewer cell types and certain microenvironmental cues,^{27,28} and its functional role has

been overshadowed by the importance of PD-1:PD-L1 interactions. PD-L1 expression is ubiquitous and can be identified in both hematopoietic and nonhematopoietic cells (including many tumor cells). Cytokines regulate the expression of PD-1 ligands^{29–31}; and, in particular, interferon gamma (IFN- γ) enhancement of PD-L1 expression in the tumor microenvironment is an important component of immune escape (adaptive immune resistance).³² In addition, PD-L1 expression in tumor cells can be driven by mutations in tumor-suppressor genes, oncogenic pathways, and gene duplications.^{33–35} In accordance with previous studies,³⁶ recent data indicate that PD-L1 expression on both tumor cells and hematopoietic cells can inhibit T-cell responses in tumor models.^{37–39} In summary, the PD-1 inhibitory pathway restricts the initiation and amplification of T-cell responses by hematopoietic cells, and it also inhibits T-cell function directly at target tumor sites.

Currently, 2 antibodies against PD-1 (nivolumab and pembrolizumab) and 1 antibody against PD-L1 (atezolizumab) have been approved by the FDA for the management of NSCLC—and each therapy is approved for specific indications. Two other antibodies against PD-L1 (durvalumab and avelumab) are under evaluation. More important, several clinical trials are currently evaluating an expansion of the indication for PD-1 checkpoint inhibition as monotherapy or in combinations with other treatments. Herein, we review data from randomized clinical trials assessing immune checkpoint inhibitors for the treatment of NSCLC as both first-line and salvage therapy, and we discuss the development of biomarkers to optimize patient selection and management.

Biomarkers of Response

Although PD-1 checkpoint inhibition has changed the landscape of lung cancer treatment, objective response rates still range from 20% to 30% for patients with advanced NSCLC who receive monotherapy, and complete responses are rare.² The identification of predictive biomarkers is a major research priority and is essential not only to optimize patient selection and treatment efficacy, but also to develop alternative approaches to treat those with an unfavorable biomarker profile and to reduce the cost of care. Because checkpoint inhibition strategies aim to unleash the suppressive mechanisms that restrain tumor-specific T cells, it has become increasingly clear that pre-existing T-cell responses to tumor antigens determine the success of checkpoint inhibition. Pre-existing antitumor responses have been assessed by high CD8 T-cell tumor infiltration and were correlated with clinical

responses to PD-1 checkpoint inhibition.^{32,40} Tumors have been classified as “inflamed” or “cold,” according to high or low immune-cell infiltration.⁴¹ In addition to quantity, we propose that the quality of T cells and APCs in the tumor also affects the outcome of checkpoint inhibition (Fig. 1). T-cell exhaustion is a dynamic process, and not all PD-1-expressing CD8 T cells are similar.⁴² In mice, PD-1-positive CD8 T cells that proliferate after blockade of the PD-1 pathway have stem cell-like features.^{43,44} Stem cell-like, PD-1-positive CD8 T cells have reduced coexpression of other inhibitory receptors (eg, they are negative for T-cell immunoglobulin mucin protein 3 [TIM-3]) and increased expression of costimulatory molecules (eg, CD28) compared with terminally differentiated, effector-like, PD-1-positive CD8 T cells, which fail to expand after blockade of PD-1 signals.⁴³

In both chronic infection and tumor models, we previously demonstrated that CD28 signaling is required for CD8 T-cell rescue after PD-1 blockade.⁴⁵ However, many CD8 T cells that infiltrate NSCLC tumors are CD28-negative and thus may be unresponsive to PD-1 checkpoint inhibition. According to this hypothesis, we demonstrated that PD-1-positive CD8 T cells that proliferate in peripheral blood after PD-1-targeted checkpoint inhibition in patients with NSCLC were mostly positive for CD28 (Fig. 1A).⁴⁵ The selective proliferation of CD28-positive, PD-1-positive CD8 T cells is consistent with the findings in mouse models, in which only a subset of PD-1-positive CD8 T cells expands after blockade of PD-1-inhibitory signals. Further studies in patients with cancer are needed to characterize T cells that respond to checkpoint inhibition. Furthermore, our data suggest that productive T-cell responses are contingent on the presence of APCs that express B7 molecules and thus promote CD28 signaling (Fig. 1A,B). Thus, as characterization of the immune infiltrate in tumors progresses, it will be important to assess the quality of T cells and APCs to improve predictions of clinical response.

Several studies have demonstrated that PD-L1 expression in the tumor microenvironment may increase the likelihood of clinical benefit.⁴⁶ PD-L1 in tumor biopsies is now used as a biomarker to select patients with advanced NSCLC for pembrolizumab as first-line therapy.^{47,48} In many situations, PD-L1 expression is strongly associated with CD8 T-cell infiltration and IFN- γ messenger RNA. Because IFN- γ increases PD-L1 expression, PD-L1 may be a surrogate biomarker for pre-existing T-cell responses. Studies assessing PD-L1 expression and characterizing tumor immune infiltrate will help elucidate how best to evaluate the quality of pre-existing immune

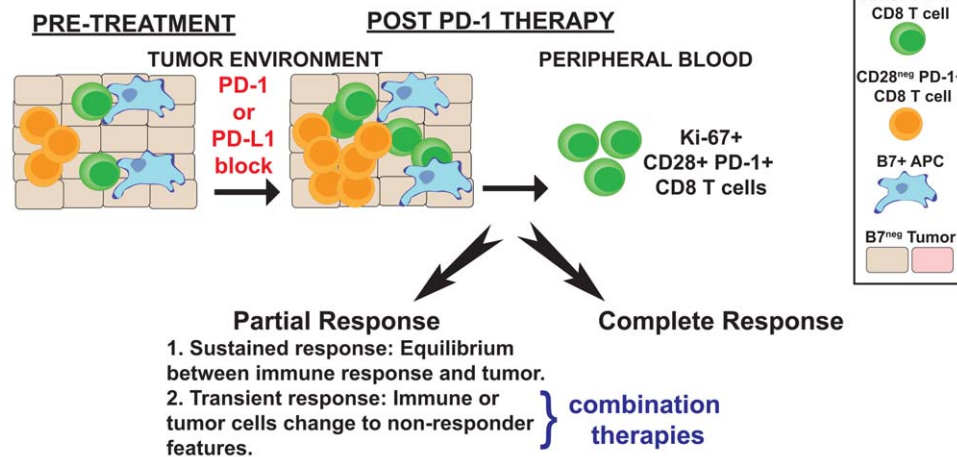
responses and establish more reliable biomarkers for predicting responses to checkpoint inhibition.

Genetic features of the tumor also affect response to checkpoint inhibition. Consistent with the T-cell-mediated mechanism of action of checkpoint inhibition, tumors with mutations that affect antigen presentation, sensitivity to IFN- γ signaling, or T-cell infiltration are resistant to immunotherapy (Fig. 1B).^{40,49,50} In addition, the efficacy of PD-1 checkpoint inhibition for NSCLC has been correlated with smoking history, tumor mutational load, and neoantigen burden; and it has become increasingly clear that T cells recognizing unique neoantigens expressed on tumor cells drive the clinical activity of immunotherapies.^{51,52} In accordance with these observations and confirmation by clinical trials,^{53,54} pembrolizumab was approved in 2017 for the treatment of unresectable or metastatic solid tumors characterized by high microsatellite instability or mismatch-repair deficiency. This unprecedented approval was based on genetic defects rather than the tissue origin of the tumor. Further genetic tests on tumor cells that may predict resistance or susceptibility to immunotherapy have yet to be developed.

Associations between pretreatment tumor features and clinical response are not definitive, and responder and nonresponder groups exhibit high overlap for most biomarkers. Immunologic assessments are not static, thus sampling and timing are certainly issues. Furthermore, features beyond the tumor microenvironment may also affect responses to checkpoint inhibition. For example, it is still not understood how draining lymph nodes contribute to antitumor immune responses. Additional factors that affect the immune status of individuals likely also impact immunotherapy outcomes, such as host genetics, age, microbiome, nutrition, and other environmental factors.⁴¹

In contrast to pretreatment assessments, CD8 T-cell infiltration in tumor biopsies from patients who are receiving treatment is strongly associated with clinical benefit from PD-1 checkpoint inhibition.^{32,40,55} After PD-1 therapy, CD8 T-cell responses can also be monitored in peripheral blood.⁵⁶⁻⁵⁸ In particular, in a small cohort of patients with advanced NSCLC, we have demonstrated that 80% of those who attained a partial clinical response had initially presented with a proliferation of peripheral blood CD8 T cells that expressed PD-1 within 4 weeks of treatment initiation. In contrast, 70% of patients who had disease progression had either delayed or absent peripheral blood PD-1-positive CD8 T-cell responses.⁵⁸ Although these observations need to be

A. Responder to PD-1 therapy:



B. Non-Responder to PD-1 therapy:

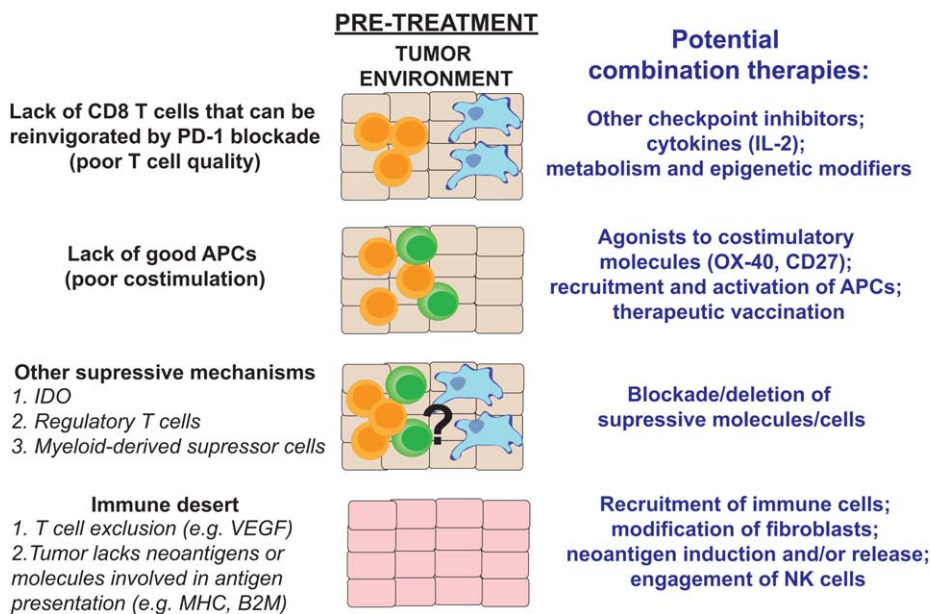


Figure 1. Response to programmed cell death 1 (PD-1) checkpoint inhibition is illustrated, linking biomarkers to therapies. (A) Tumors that respond to PD-1 checkpoint inhibition have pre-existing T-cell responses that are suppressed by the PD-1 pathway. Blockade of PD-1-inhibitory signals promotes proliferation of a subset of PD-1-positive CD8 T cells that express CD28 positivity and have unique stem cell-like features (in green). Proliferating CD28-positive/PD-1-positive CD8 T cells can be transiently detected in peripheral blood. Stem cell-like, PD-1-positive CD8 T cells expand to self-renew and also differentiate to generate a large number of PD-1-positive, terminally differentiated CD8 T cells that exert effector cytotoxic function (in orange) to reduce tumor load. (B) Not all tumors respond to PD-1 checkpoint inhibition. The mechanisms of resistance to PD-1 checkpoint inhibition are multifaceted and, in 1 individual, may involve 1 or more specific features of immune cells, stroma, or tumor cells. Features of immune cells that may confer resistance include poor quality of T cells, antigen-presenting cells (APCs), or other immune-suppressive mechanisms. Intrinsic features of tumor cells that may confer resistance include lack of antigens specific to tumor cells (eg, neoantigens), mutations on molecules involved in antigen presentation or sensitivity to interferon gamma (IFN- γ), and mutations that promote T-cell exclusion or suppression (eg, β -catenin, phosphatase and tension homolog [PTEN]). Other factors produced by tumor and/or stroma cells can mediate T-cell exclusion and suppression (eg, vascular endothelial growth factor [VEGF]). Combination therapies should be tailored to specific conditions of resistance in a personalized cancer therapy approach. B2M indicates β 2-microglobulin; B7, a family of peripheral membrane proteins on activated antigen-presenting cells; IDO, indoleamine 2,3-dioxygenase; IL-2, interleukin-2; MHC, major histocompatibility complex; NK, natural killer; OX-40, tumor necrosis factor receptor superfamily, member 4 (also known as cluster of differentiation 134 [CD134]); PD-L1, programmed cell death ligand 1.

confirmed in larger studies, our data support the possibility that a further detailed analysis of CD8 T cells in peripheral blood from patients who are receiving checkpoint inhibition may provide important insights about clinical responses. If these results are confirmed and expanded, then peripheral blood monitoring during immunotherapy could aid in the management of patients. In summary, we envisaged the possibility that integrative approaches incorporating distinct features of tumor cells and immune infiltrate in pretreatment biopsies may determine patient selection for checkpoint inhibition, and subsequent immune monitoring in peripheral blood may further guide personalized treatment decisions.

PD-1/PD-L1 Inhibition as Monotherapy

Initial evidence of the anticancer effects of PD-1 inhibition in NSCLC were provided by phase 1 studies in which expansion cohorts, consisting of patients with advanced-stage NSCLC, were included. A phase 1/2 study of nivolumab in 296 patients who had different types of malignancies included 122 heavily pretreated patients with advanced NSCLC.¹⁸ In that study, the objective response rate ranged from 6% to 32% across various dose cohorts,¹⁸ with comparable results for patients who had squamous and nonsquamous cell histology.⁵⁹ Approximately 41% of patients with NSCLC experienced an adverse event, most commonly skin, gastrointestinal, and pulmonary events.⁵⁹

Pembrolizumab also demonstrated promising results in a cohort of patients with advanced-stage NSCLC. In a study of 495 such patients, the overall response rate was 19% (18% in previously treated patients and 25% in untreated patients).⁶⁰ Higher response rates were observed among ever-smokers compared with non-smokers (22.5% and 10.3%, respectively). Better outcomes were reported for patients who had tumors with a PD-L1 expression score of at least 50% (median PFS, 6.3 months; median OS, not reached).⁶⁰ Adverse events were observed in 70.9% of patients, with no differences related to dose or schedule, and 9.5% of adverse events were grade 3 or higher.⁶⁰ Similar results were observed with durvalumab and avelumab (inhibitors of PD-L1) in patients with advanced NSCLC,⁶¹ and the overall response rates for the 2 agents were 14% and 12%, respectively, in an unselected cohort of patients with NSCLC.^{61,62} Across these studies, long-term survival was noted in a subset of patients, increasing the enthusiasm to study them in randomized clinical trials against existing standards of care for advanced NSCLC.

Immune Checkpoint Inhibition Versus Salvage Chemotherapy

Nivolumab has demonstrated efficacy in a cohort of patients (N = 117) with advanced-stage squamous cell lung cancer (CheckMate 063).⁶³ In that trial, the response rate was 14.5%, and the disease stabilization rate was 26%. Long-term survival was observed in a subset of patients, as noted by the 2-year survival rate of 27%.⁶⁴ Given the relatively limited treatment options for patients who have tumors with advanced squamous cell histology after progressing on platinum-based chemotherapy, these results suggested a potential role for nivolumab in this patient population.

The observations from CheckMate 063 were confirmed by a phase 3 study that compared nivolumab versus docetaxel in patients with advanced-stage squamous cell cancer of the lung (CheckMate 017).⁶⁵ In total, 272 patients were randomized to receive either nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/m² every 3 weeks after progression on platinum-based chemotherapy. There was a clear improvement in the median OS with nivolumab (9.2 vs 6 months), and the 1-year survival rates were 41% and 24% for the nivolumab and docetaxel arms, respectively. Response rates were not correlated with PD-L1 expression.⁶⁵ The tolerability profile also was more favorable with nivolumab, as evidenced by the lower incidence of grades 3 and 4 adverse events (7% vs 55%, respectively).

Similar results were observed in a phase 3 study in patients with nonsquamous histology (CheckMate 057).⁶⁶ Patients (N = 582) were randomized to receive either nivolumab or docetaxel. Both the OS (12.2 vs 9.4 months) and the 1-year survival rate (51% vs 39%) were superior with nivolumab. The median duration of response was 17.2 months in the nivolumab arm compared with 5.6 months in the docetaxel arm, suggesting that objective responses were more durable with immune checkpoint inhibition.⁶⁶ Another important observation in that study was related to the higher efficacy results in patients who had tumors that expressed higher levels of PD-L1, as assessed by immunohistochemistry. Indeed, the differences in efficacy were relatively modest in patients who had tumors with low PD-L1 levels, and their survival curves were comparable to those in patients who had PD-L1–negative tumors. Nevertheless, those 2 phase 3 trials resulted in FDA approval of nivolumab as salvage therapy for advanced NSCLC regardless of PD-L1 status.

The development of pembrolizumab in advanced NSCLC has also proceeded at a rapid pace. In a phase 3 study (KEYNOTE 010), patients with advanced-stage

NSCLC were randomly assigned to receive pembrolizumab or docetaxel.⁶⁷ Patients who had $\geq 1\%$ PD-L1 expression in their archived tumor tissue were eligible for the study. The median survival was 10.5 months with pembrolizumab at its approved dose and 8.6 months with docetaxel, and the 1-year survival rate was 43% and 35%, respectively.⁶⁷ For the subset of patients who had PD-L1 tumor expression $\geq 50\%$, the hazard ratio for survival in the pembrolizumab group was approximately 0.50, suggesting a stronger therapeutic effect among patients who had higher PD-L1 expression. The median PFS was also significantly better with pembrolizumab compared with docetaxel in patients who had PD-L1 expression $\geq 50\%$ (hazard ratio, 0.59). The most common pembrolizumab-related adverse events included hypothyroidism, hyperthyroidism, and pneumonitis. These results led to FDA approval of pembrolizumab as salvage therapy for patients with advanced NSCLC who harbor tumors with $\geq 1\%$ PD-L1 expression.

Atezolizumab has also received approval by the FDA as salvage therapy for advanced NSCLC. The “OAK” trial randomized patients (N = 1225) with advanced NSCLC after 1 or 2 lines of prior therapy to receive either atezolizumab or docetaxel. There was a significant improvement in OS with atezolizumab (13.8 vs 9.6 months; hazard ratio, 0.73).⁶⁸ The improved OS was observed regardless of age, PD-L1 expression level, or smoking status; however, a slightly better OS was observed in patients who had tumors with nonsquamous histology.⁶⁸ The adverse event profile of atezolizumab was more favorable than that of docetaxel. A stronger correlation between PD-L1 expression and the efficacy of atezolizumab also was observed in this trial. The biomarker used for atezolizumab evaluated PD-L1 expression individually in tumor tissue and in infiltrating cells, but the antibody (SP-142) appears to have lower sensitivity for detecting PD-L1 expression compared with the 22C3 assay of the 28-8 antibodies used with pembrolizumab and nivolumab, respectively.⁶⁹

Taken together, the results from these randomized studies changed the therapeutic landscape of advanced NSCLC in the salvage therapy setting. Immune checkpoint inhibition emerged as the standard approach after progression on platinum-based combination chemotherapy. Although clinical benefit was observed regardless of PD-L1 expression level, patients with higher expression appeared to derive a greater degree of efficacy improvement. In all of these trials, immune checkpoint inhibition was better tolerated than docetaxel, which also contributed to the adoption of this class of agents for routine

clinical practice in the United States. There do not appear to be any clinically significant differences in the efficacy or safety profile between the 3 immune checkpoint inhibitors that have been approved for salvage therapy. A notable finding across trials is that patients with EGFR mutations did not derive a benefit with checkpoint inhibition; indeed, docetaxel was associated with a more favorable outcome.⁷⁰ Therefore, it is important for patients who have driver mutations to receive treatment with the appropriate targeted therapy first to achieve the best results.

Given the proclivity to develop autoimmune adverse events, it is important for clinicians to recognize and treat them early. Autoimmune endocrinopathies can be detected early by routine clinical monitoring of hormone status, particularly the thyroid functions; and pneumonitis is detected primarily based on symptoms. In the event of severe autoimmune toxicities, the use of corticosteroids and discontinuation of checkpoint inhibition are warranted. There appears to be a high risk of recurrence of toxicities with the re-introduction of checkpoint inhibitors. Therefore, discontinuation of therapy followed by close monitoring of disease status and symptoms appears to be a safer approach.

In the pivotal clinical trials, immune checkpoint inhibitors are administered for at least 2 years or until patients develop disease progression or toxicity. The optimal duration of therapy to achieve the most favorable clinical outcomes has not been defined. A recent study with nivolumab suggested that continuation of therapy until disease progression was associated with a more favorable outcome compared with treatment for 12 months.⁷¹ Although this is an interesting observation, the study had several limitations and did not have the required statistical design to address the clinical question. Appropriately designed clinical trials are necessary to address this important clinical question, which has tremendous implications for toxicity, patient convenience, and cost.

Immune Checkpoint Inhibition Versus Platinum-Based Chemotherapy in the First-Line Setting

For decades, platinum-based chemotherapy has remained the mainstay of treatment for patients with advanced NSCLC in the first-line therapy setting. This paradigm has recently undergone a major change, with the approval of pembrolizumab as first-line therapy for advanced NSCLC by the FDA. This change was a result of 2 randomized clinical trials that demonstrated efficacy for pembrolizumab.

The KEYNOTE-024 study randomized patients (N = 305) with previously untreated NSCLC to receive either pembrolizumab or platinum-based combination therapy.⁴⁸ The study selected patients based on PD-L1 expression $\geq 50\%$ in archived tumor tissue. Of the patients who were screened, approximately 25% met the biomarker threshold for enrolment to the study. There was a significant improvement in response rate (45% vs 28%), median PFS (10.3 vs 6 months), and OS for the patients who received pembrolizumab; and the 1-year survival rate was 80% with pembrolizumab versus 54% with chemotherapy.⁴⁸ It is noteworthy that a survival benefit was observed with pembrolizumab, despite the high degree of crossover of patients from chemotherapy to pembrolizumab upon disease progression. The tolerability of pembrolizumab also was more favorable compared with chemotherapy. On the basis of the results from this trial, pembrolizumab is currently approved for use as first-line therapy for patients who have metastatic lung cancer with high PDL-1 expression. However, 2 other clinical trials with a similar design have failed to improve outcomes with nivolumab and durvalumab. The Bristol-Myers Squibb (BMS)-026 study compared nivolumab versus chemotherapy in advanced NSCLC. There was no improvement in survival for patients who had tumors that met a PD-L1 expression threshold of $\geq 5\%$.⁷² A similar trial with durvalumab versus chemotherapy in patients with PD-L1 expression $>25\%$ failed to improve PFS over platinum-based chemotherapy.⁷³ These conflicting results are difficult to attribute to differences in pharmacologic and biologic properties between the immune checkpoint inhibitors, because these agents have a similar mechanism of action and were not expected to produce variable clinical results. It is noteworthy that, in patients with head and neck cancers, nivolumab has demonstrated superiority over chemotherapy, whereas pembrolizumab failed to do so.^{74,75} This further reinforces the likelihood that variable outcomes between trials of these agents are more likely related to patient selection, biomarker threshold, unrecognized patient variables, and study design. However, the results from a confirmatory study of pembrolizumab versus chemotherapy (KEYNOTE 42) in the first-line setting are likely to shed more light on the utility of checkpoint inhibition as first-line therapy for advanced NSCLC and to provide validation of this paradigm. Notably, the study has a sample size of 1240 patients and has the ability to report on outcomes based on different biomarker thresholds with statistical rigor.

Combination of Checkpoint Inhibition With Chemotherapy

There are relatively limited data on chemotherapy combined with checkpoint inhibition in NSCLC. Nevertheless, pembrolizumab has received FDA approval in this setting based on a randomized phase 2 study (KEYNOTE 021G). Patients (N = 123) with advanced nonsquamous NSCLC were randomized to receive carboplatin and pemetrexed with or without pembrolizumab. Patients with known activating mutations in EGFR or translocation of ALK were not eligible.⁷⁶ The primary endpoint was a comparison of the response rate between the 2 regimens. The objective response rate was 57% in the pembrolizumab arm compared with 30% in the chemotherapy-alone arm. This resulted in a significant improvement in PFS with a hazard ratio of 0.50 for the pembrolizumab-chemotherapy combination.⁷⁶ There was a favorable trend in OS with the pembrolizumab-chemotherapy regimen, but it did not meet statistical significance. Toxicity was more common with the 3-drug combination and included higher incidence of nausea, vomiting, diarrhea, fatigue, rash, elevation of liver enzymes, and certain autoimmune events.⁷⁶ The correlation between PD-L1 expression level and benefit from the combination approach has not been fully addressed. The beneficial results from the phase 2 study may have been driven entirely by the efficacy of pembrolizumab in the high PD-L1-expressing patient population. Confirmatory trials with larger sample sizes will likely shed additional light on this important issue. Until then, the use of chemotherapy in combination with pembrolizumab should be based on discussions at the individual patient level.

Combination Immune-Therapy Strategies

Successful targeting of the PD-1 pathway has prompted the investigation of combinations with agents that modulate other relevant immune checkpoints. Given the important role played by the CTLA-4 pathway in determining antitumor responses, combined inhibition of both PD-1 and CTLA-4 has been studied with success in melanoma. A similar approach is under investigation in lung cancer with the combination of ipilimumab and nivolumab. The CheckMate 012 trial enrolled 148 patients with NSCLC to 4 different dosing regimens of nivolumab and ipilimumab.⁷⁷ The overall response rate ranged from 13% to 49% with the combination approach. However, there was also a higher incidence of grade 3 and 4 adverse events (range, 29%-37%). The safety and tolerability of this combination was improved with less frequent

ipilimumab dosing every 6 weeks. This modified dosing regimen of lower dose of ipilimumab, given less frequently in combination with the standard dose and schedule of nivolumab, is currently being studied in a phase 3 clinical trial. A phase 3 trial using a similar concept that evaluated durvalumab and tremelimumab failed to detect an improvement in PFS over platinum-based chemotherapy (the MYSTIC trial).⁷³ The results from that study have not been presented, and the survival results are immature. Taken together, the path forward for this combination will depend on the identification of biomarkers to select patient populations, maximize efficacy, and minimize toxicity.

Immune Checkpoint Inhibition in Earlier Stages of NSCLC

The ability to achieve long-term survival in a subset of patients with immune checkpoint inhibitors provides the rationale to evaluate these agents in curative settings. Indeed, a recent phase 3 study of durvalumab demonstrated improved PFS for patients with surgically unresectable, locally advanced, stage III NSCLC. The study randomized patients who had completed concurrent chemoradiotherapy to receive treatment for 1 year with either durvalumab or placebo. The median PFS was substantially improved in the durvalumab arm, with a hazard ratio of 0.52 (16.8 vs 5.6 months).⁷⁸ It is noteworthy that there was no undue toxicity with the receipt of checkpoint inhibition in this setting. Although the OS data are not mature, the robust improvement in PFS denotes an important step forward for stage III NSCLC, in which no significant advance has been achieved in more than 2 decades. This is also likely to increase enthusiasm for ongoing clinical trials in patients with surgically resected, early stage NSCLC in the adjuvant therapy setting after the receipt of platinum-based regimens. Promising results were recently reported with the use of nivolumab as neoadjuvant therapy in a phase 2 trial for patients with early stage NSCLC, with major pathologic responses observed in the majority of patients who had a relatively short duration of therapy.⁷⁹ Phase 3 studies of checkpoint inhibitors have been initiated in the neoadjuvant therapy setting. Currently, the clinical significance of major pathologic response as an endpoint for neoadjuvant studies is not known for patients with lung cancer. The enthusiasm for this approach should be balanced by the relatively limited data that are presently available. Table 1^{18,48,60-62,64-68,72,80-84} and Table 2^{76,77,85-90} summarize single-agent and combination immunotherapy trials in NSCLC, respectively; and Table 3 includes ongoing studies. In

addition, Table 4 lists the common checkpoint inhibitors and their characteristics.^{19,91-94}

FUTURE PERSPECTIVES

The integration of immune checkpoint inhibition into clinical practice has resulted in significant improvements in outcomes for patients with advanced NSCLC. The role of checkpoint inhibitors in combination with targeted agents for patients with oncogene-addicted NSCLC is unclear, and early reports have indicated higher toxicity. Strategies that reduce tumor size may improve outcomes from immunotherapies, because high antigen burden is a major driver of T-cell dysfunction.^{42,57} However, there are many other mechanisms by which targeted therapies and traditional cancer treatments modulate immune responses to cancer cells, from release of antigens (because of tumor cell death)⁹⁵ to direct effects on immune cells.^{96,97} Further mechanistic understanding of how different therapies affect antitumor immunity should guide combinations with immune checkpoint inhibitors to improve synergy.

The biologic rationale for combinations of different checkpoint inhibitors to improve clinical outcomes is strong. T cells infiltrating tumors can co-express several potentially inhibitory molecules (CTLA-4, TIM-3, LAG-3 [lymphocyte-activation gene 3], TIGIT [T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains]), and these appear to provide a cumulative inhibitory effect to PD-1.^{98,99} Although the downstream signaling events for many of these molecules is still undefined, in preclinical models, combination treatments produce improved tumor control.¹⁰⁰ Synergy between checkpoint inhibitors can be the result of targeting different cells/signaling pathways. It is interesting to point out that the upregulation of CTLA-4 is observed in CD8 T cells that proliferate in the blood of patients with NSCLC after PD-1 checkpoint inhibition.⁵⁸ Reciprocal PD-L1 upregulation has been observed in tumors that were resistant to CTLA-4 and radiation therapy; and optimal responses were achieved with a combination of radiation, anti-CTLA4, and anti-PD-L1/PD-1.¹⁰¹ These data demonstrate that, because checkpoint molecules are usually upregulated during T-cell activation, blockade of 1 checkpoint molecule may promote other inhibitory pathways, providing a rationale for combination therapies. Mechanistic studies and clinical trials should reveal the most favorable combinations for increased efficacy and reduced toxicity.

Nearly 900 clinical trials are listed in the clinicaltrials.gov website that involve novel immunotherapy

TABLE 1. Trials of Immunotherapy for Treatment of Advanced Non-small cell Lung Cancer

Drug Name	Study Design	Patient Population	Treatment	Outcomes
First line Nivolumab	CheckMate 012 (phase 1; Gettinger 2016 ⁸⁰) CheckMate 026 (phase 3; Carbone 2017 ⁷²)	Advanced NSCLC (n = 52) Metastatic or recurrent, PD-L1–positive NSCLC (n = 541)	Nivolumab 3 mg/kg q2w Arm A: Nivolumab 3 mg/kg q2w Arm B: PT-DC q3w (up to 6 cycles) Pembrolizumab at 2 mg/kg or 10 mg/kg q3w or 10 mg/kg q2w Arm A: Pembrolizumab 200 mg q3w (35 cycles) Arm B: Platinum-based chemotherapy Avelumab 10 mg/kg q2w Durvalumab 10 mg/kg q2w (up to 12 mo)	ORR, 23% Arm A: PFS, 4.2 mo; OS, 14.4 mo Arm B: PFS, 5.9 mo; OS, 13.2 mo ORR, 24.8% Arm A: PFS, 10.3 mo; ORR, 45% Arm B: PFS, 6 mo; ORR, 28% ORR, 22.4% ORR, 25%
Pembrolizumab	KEYNOTE 001 (phase 1; Garon 2015 ⁶⁰) KEYNOTE 024 (phase 3; Reck 2016 ⁴⁸)	Locally advanced or metastatic NSCLC (n = 495 with 94 treatment naive) NSCLC with high PD-L1 expression (n = 305)	Nivolumab at escalating doses of 1, 3, and 10 mg/kg q2w Nivolumab 3 mg/kg q2w Arm A: Nivolumab 3 mg/kg q2w (n = 287) Arm B: Docetaxel 75 mg/m ² q3w (n = 268) Arm A: Nivolumab 3 mg/kg q2w (n = 135)	ORR, 6%, 32%, and 18%, respectively, with the 3 escalating doses ORR, 14.5%; median OS, 8.2 mo; median PFS, 1.9 mo Arm A: ORR, 19%; OS, 12.2 mo; PFS, 2.3 mo Arm B: ORR, 12%; OS, 9.4 mo; PFS, 4.2 mo Arm A: ORR, 20%; OS, 9.2 mo; PFS, 3.5 mo
Avelumab Durvalumab Salvage therapy Nivolumab	JAVELIN (phase 1; Jerusalem 2016 ⁸¹) Phase 1/2 (Antonia 2016 ⁸²) Phase 1/2 trial (Topalian 2012 ¹⁸) CheckMate 063 (phase 2; Ramalingam 2016 ⁸⁴) CheckMate 057 (phase 3; Borghaei 2015 ⁸⁶) CheckMate 017 (phase 3; Brahmer 2015 ⁶⁵)	Advanced NSCLC (n = 156) Treatment-naïve NSCLC Heavily pretreated, advanced NSCLC (n = 122) Advanced, refractory squamous cell NSCLC (n = 117) Advanced, nonsquamous cell NSCLC (n = 582) Advanced squamous cell NSCLC, regardless of PD-L1 expression (n = 272)	Nivolumab 3 mg/kg q2w Arm A: Pembrolizumab 2 mg/kg (n = 344) Arm B: Pembrolizumab 10 mg/kg (n = 346) Arm C: Docetaxel (n = 343) 10 mg/kg q2w Avelumab 10 mg/kg q2w Arm A: Atezolizumab 1200 mg q3w Arm B: Docetaxel 75 mg/m ² q3w Arm A: No prior therapy Arm B: One prior therapy Arm C: At least 2 prior therapies Arm A: Atezolizumab 1200 mg q3w Arm B: Docetaxel 75 mg/m ² q3w	ORR, 12%; PFS, 2.7 mo Arm A: ORR, 33%; OS, 12.6 mo Arm B: ORR, 13%; OS, 9.7 mo Arm A: ORR, 26% (high PD-L1) and 19% (medium-high PD-L1) Arm B: ORR 24% (high PD-L1) and 17% (medium-high PD-L1) Arm C: ORR, 27% (high PD-L1) and 17% (medium-high PD-L1) Arm A: Median OS, 13.8 mo Arm B: Median OS, 9.6 mo
Pembrolizumab	KEYNOTE 001 (phase 1; Garon 2015 ⁶⁰) KEYNOTE 010 (phase 1/2; Herbst 2016 ⁶⁷)	Advanced-stage NSCLC (n = 495; 401 previously treated) Advanced, previously treated NSCLC with ≥1% PD-L1 expression (n = 991)	Arm A: Pembrolizumab 2 mg/kg (n = 344) Arm B: Docetaxel 75 mg/m ² q3w (n = 137) Pembrolizumab 2 mg/kg or 10 mg/kg q3w or 10 mg/kg q2w	ORR, 18% Arm B: ORR, 9%; OS, 6 mo; PFS, 2.8 mo ORR, 18%
Durvalumab	Phase 1/2 (Rizvi 2015 ⁶¹)	Patients with various solid tumors, including NSCLC (n = 149)	Arm A: Pembrolizumab 2 mg/kg (n = 344) Arm B: Pembrolizumab 10 mg/kg (n = 346) Arm C: Docetaxel (n = 343) 10 mg/kg q2w	ORR, 14%
Avelumab	Phase 1b (Guillely 2015 ⁸²)	Advanced NSCLC as second-line therapy (n = 184)	Avelumab 10 mg/kg q2w	ORR, 12%; PFS, 2.7 mo
Atezolizumab	POPLAR study (phase 2; Fehrenbacher 2016 ⁸⁵) The BIRCH study (phase 2; Besse 2015 ⁸⁴)	Previously treated NSCLC (n = 287) PDL-1–positive, advanced NSCLC (n = 667)	Arm A: Atezolizumab 1200 mg q3w Arm B: Docetaxel 75 mg/m ² q3w Arm A: No prior therapy Arm B: One prior therapy Arm C: At least 2 prior therapies Arm A: Atezolizumab 1200 mg q3w Arm B: Docetaxel 75 mg/m ² q3w	ORR, 12%; PFS, 2.7 mo Arm A: ORR, 33%; OS, 12.6 mo Arm B: ORR, 13%; OS, 9.7 mo Arm A: ORR, 26% (high PD-L1) and 19% (medium-high PD-L1) Arm B: ORR 24% (high PD-L1) and 17% (medium-high PD-L1) Arm C: ORR, 27% (high PD-L1) and 17% (medium-high PD-L1) Arm A: Median OS, 13.8 mo Arm B: Median OS, 9.6 mo
The OAK study (phase 3; Gadgeel 2017 ⁶⁸)	Advanced NSCLC (n = 1225)	Advanced NSCLC (n = 1225)	Arm A: Atezolizumab 1200 mg q3w Arm B: Docetaxel 75 mg/m ² q3w	ORR, 12%; PFS, 2.7 mo Arm A: ORR, 33%; OS, 12.6 mo Arm B: ORR, 13%; OS, 9.7 mo Arm A: ORR, 26% (high PD-L1) and 19% (medium-high PD-L1) Arm B: ORR 24% (high PD-L1) and 17% (medium-high PD-L1) Arm C: ORR, 27% (high PD-L1) and 17% (medium-high PD-L1) Arm A: Median OS, 13.8 mo Arm B: Median OS, 9.6 mo

Abbreviations: NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PT-DC, platinum-based doublet chemotherapy; q2w, once every 2 weeks; q3w, once every 3 weeks.

TABLE 2. Trials of Combination Treatments for Advanced Non-small cell Lung Cancer

Drug Name	Study Design	Patient Population	Treatment	Outcomes
First line Nivolumab + 3 standard PT-DC regimens	CA 209-012 trial (phase 1; Kanda 2016 ⁶⁵)	Newly diagnosed NSCLC (n = 56)	Arm A: Four cycles of Nivolumab 10 mg/kg + cisplatin-gemcitabine, then nivolumab 10 mg/kg q3w (n = 12) Arm B: Nivolumab 10 mg/kg + cisplatin-pemetrexed, then nivolumab 10 mg/kg q3w (n = 15) Arm C: Nivolumab 10 mg/kg + carboplatin-paclitaxel then nivolumab 10 mg/kg q3w (n = 15) Arm D: Nivolumab 5 mg/kg + carboplatin-paclitaxel, followed by nivolumab 10 mg/kg q3w (n = 14) Arm A: Carboplatin with pemetrexed	Arm A: OS, 50.5 mo; ORR, 33% Arm B: OS, 83.4 mo; ORR, 47% Arm C: OS, 64.9 mo; ORR, 47% Arm D: OS, not reached; ORR, 43% Arm A: ORR, 30%
Pembrolizumab with chemotherapy	KEYNOTE 021G (phase 2; Langer 2016 ⁷⁶)	Treatment-naïve, advanced nonsquamous cell NSCLC (n = 123)	Arm B: Carboplatin/pemetrexed with pembrolizumab Arm A: Chemotherapy alone (paclitaxel + carboplatin)	Arm B: ORR, 57% Arm A: PFS, 4.2 mo; ORR, 14%
Chemotherapy alone (pacli- taxel + carboplatin), che- motherapy with concurrent or chemotherapy with phased ipilimumab	Phase 2 (Lynch 2012 ⁶⁶)	Treatment-naïve NSCLC (n = 204)	Arm B: Chemotherapy with concurrent ipilimumab (10 mg/kg for 4 cycles) Arm C: Chemotherapy with phased ipilimumab (10 mg/kg from cycle 3 to 6) Arm A: Atezolizumab with carboplatin/paclitaxel	Arm B: PFS, 4.1 mo; ORR, 21% Arm C: PFS, 5.1 mo; ORR, 32% Arm A: RR, 50%
Atezolizumab with PT-DC	Phase 1b (Giaccone 2015 ⁶⁷)	Chemotherapy-naïve, locally advanced and metastatic NSCLC (N = 58)	Arm B: Atezolizumab with carboplatin/pemetrexed Arm C: Atezolizumab with carboplatin/Nab-paclitaxel Arm A: Nivolumab 1 mg/kg and ipilimumab 1 mg/kg q3w	Arm B: RR, 77% Arm C: RR, 56% Arm A: ORR, 13%
Nivolumab and ipilimumab	CheckMate 012 (phase 1; Hellmann 2017 ⁷⁷)	NSCLC patients (n = 148)	Arm B: Nivolumab 1 mg/kg q3w and ipilimumab 1 mg/kg q6w Arm C: Nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q12w Arm D: Nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w Nivolumab 3 mg/kg every 2 weeks + erlotinib 150 mg PO daily	Arm B: ORR, 25% Arm C: ORR, 47% Arm D: ORR, 33% ORR was 19%; 24-wk PFS rate was 47%
Nivolumab + erlotinib	Phase 1 (Gettinger 2014 ⁶⁸)	Stage IIIB/IV, EGFR-mutated, chemotherapy-naïve NSCLC (N = 21)	Arm A: Durvalumab 10 mg/kg with gefitinib 250 mg daily	Arm A: ORR, 77.8%
Durvalumab with gefitinib	Phase 1 (Gibbons 2016 ⁶⁹)	Tyrosine kinase-naïve, EGFR-mutant NSCLC (N = 20)	Arm B: Gefitinib for 4 wk, then concurrent durvalumab + gefitinib	Arm B: ORR, 80%
Salvage Therapy Durvalumab with osimertinib	TATTON study (phase 1b; Ahn 2016 ⁹⁰)	EGFR mutant NSCLC	Part A-dose escalation: Osimertinib 80 mg daily + durvalumab 3 mg/kg or 10 mg/kg q2w (N = 23) Part B-dose expansion: Osimertinib 80 mg daily + durvalumab 10 mg/kg (N = 11)	Arm A: PR, 57%; SD, 42.9% Arm B: PR, 80%; SD, 20%

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; Nab-paclitaxel, nanoparticle albumin-bound paclitaxel; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PO, orally; PR, partial response; PT-DC, platinum-based doublet chemotherapy; RR, response rate; q2w, once every 2 weeks; q3w, once every 3 weeks; q6w, once every 6 weeks; q12w, once every 12 weeks; SD, stable disease.

TABLE 3. Ongoing Trials of Immunotherapy as Treatment for Advanced Non-small cell Lung Cancer

Study/Design	Treatment	Patient Population	Primary Endpoint
Phase 1 (NCT01998126)	Nivolumab or ipilimumab + erlotinib (EGFR mutant) or crizotinib (ALK mutant)	Stage IV NSCLC, failed prior platinum-based therapy	Toxicity profile
CheckMate 568, phase 2 (NCT02659059)	Nivolumab + ipilimumab	Treatment-naïve, metastatic NSCLC	ORR
CheckMate 227, phase 3 (NCT02477826)	Nivolumab vs nivolumab/ipilimumab, nivolumab/platinum-based doublet and platinum-based doublet	Treatment-naïve, metastatic or recurrent NSCLC	PFS and OS
KEYNOTE-011, phase 1 (NCT01840579)	Pembrolizumab in combination with PT-DC or ipilimumab	Advanced NSCLC (stage IIIB/IV)	No. of participants experiencing dose-limiting toxicities
Phase 1b/2 (NCT02538510)	Pembrolizumab + vorinostat	Stage IV NSCLC progressed on at least 1 prior therapy	Maximum-tolerated dose and ORR
KEYNOTE 042, phase3 (NCT02220894)	Pembrolizumab vs platinum-based chemotherapy	PD-L1-positive, treatment-naïve, advanced or metastatic nonsquamous cell NSCLC	OS
KEYNOTE 189, phase 3, (NCT02578680)	Platinum/pemetrexed with or without pembrolizumab	Metastatic, treatment-naïve, nonsquamous cell NSCLC	PFS
KEYNOTE 407 (NCT02775435)	Carboplatin-paclitaxel/Nab-paclitaxel chemotherapy with or without pembrolizumab	Metastatic, squamous cell NSCLC (first line)	PFS and OS
PEARLS, phase 3 (NCT02504372)	Pembrolizumab vs placebo	Early stage NSCLC after resection and completion of standard adjuvant therapy	DFS
Phase 3 (NCT02279732)	Paclitaxel/carboplatin with or without ipilimumab	Treatment-naïve, squamous cell NSCLC	OS
Phase 3 (NCT02366143)	Atezolizumab with PT-DC therapy with or without bevacizumab vs platinum-based chemotherapy with bevacizumab	Treatment-naïve NSCLC, nonsquamous cell histology	PFS
IMpower 111, phase 3 (NCT02409355)	Atezolizumab vs gemcitabine with cisplatin or carboplatin	Treatment-naïve, stage IV, PDL-1-positive NSCLC, squamous cell histology	PFS
IMpower 132 (NCT02657434)	Atezolizumab in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed	Chemotherapy-naïve, stage IV, nonsquamous cell NSCLC	PFS and OS
JAVELIN lung 100, phase 3 (NCT02576574)	Avelumab vs docetaxel	Treatment-naïve, nonsquamous cell, PDL-1-positive NSCLC	PFS
JAVELIN lung 200, phase 3 (NCT02395172)	Avelumab vs PT-DC	NSCLC progressing after platinum-based therapy	OS
MYSTIC, phase 3 (NCT02453282)	Durvalumab with or without tremelimumab vs standard-of-care PT-DC	Treatment-naïve, stage IV NSCLC	PFS and OS
NEPTUNE, phase 3 (NCT02542293)	Durvalumab + tremelimumab vs standard-of-care PT-DC	Treatment-naïve, stage IV NSCLC	OS

Abbreviations: ALK, anaplastic lymphoma kinase; DFS, disease-free survival; EGFR, epidermal growth factor receptor; NCT, National Clinical Trials Identifier (clinicaltrials.gov); NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; Nab-paclitaxel, nanoparticle albumin-bound paclitaxel; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PT-DC, platinum-based doublet chemotherapy.

TABLE 4. Checkpoint Inhibitors

Medication	Type of Immunoglobulin	Half-Life
Nivolumab (Guo 2017 ⁹¹)	Human immunoglobulin G4 κ (IgG4κ) against programmed cell death receptor-1 (PD-1)	Approximately 20 d
Pembrolizumab (Lindauer 2017 ⁹²)	Humanized IgG4κ monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2	23 d
Avelumab (Hamid 2013 ¹⁹)	Humanized IgG1 anti-PD-L1	6 d
Durvalumab (WHO 2014 ⁹³)	Humanized IgG1κ monoclonal antibody against PD-L1	12 d
Ipilimumab (Leach 1996 ⁹⁴)	Monoclonal antibody against CTLA4	Approximately 15 d

Abbreviations: CTLA4, cytotoxic T lymphocyte antigen-4; WHO, World Health Organization.

combinations, and many of those trials involve patients with NSCLC.⁴¹ Combinations with other strategies targeting the immune system, such as agonists for costimulatory molecules (eg, OX40 [tumor necrosis factor receptor superfamily, member 4], CD27) or inhibitors of alternative suppressive mechanisms, such as indoleamine 2,3-dioxygenase or vascular endothelial growth factor, are in advanced stages of clinical investigation. Therefore, as new regimens are developed, efforts to identify predictive biomarkers as companion diagnostic tests need to be a major thrust of ongoing research efforts to achieve personalized cancer treatments that will result in more effective responses (Fig. 1B).

In conclusion, immunotherapy has emerged as an important therapeutic option for patients with advanced-stage NSCLC. The definition and use of biomarkers to identify patients who are more likely to benefit from immunotherapeutic agents remain fundamental issues and will lead to personalized treatment approaches. Furthermore, treatment monitoring using blood-based biomarkers could further help the early identification of therapy failure and the underlying reasons for inefficacy to enable tailored subsequent treatments.

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