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Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer

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Summary

The emergence of immune checkpoint inhibitors marked an important advancement in the development of cancer therapeutics. Pembrolizumab is a selective humanized IgG4 kappa monoclonal antibody that inhibits the programmed death-1 (PD-1) receptor, an integral component of immune checkpoint regulation in the tumor microenvironment. The drug is currently approved by the Food and Drug Administration for the treatment of advanced melanoma and metastatic squamous and nonsquamous non-small cell lung cancer (NSCLC). Several published studies demonstrate that single-agent pembrolizumab is safe and has efficacy in patients with NSCLC. Many ongoing protocols are investigating the role of pembrolizumab in combination with other agents in lung cancer and various other cancer types. We review the available data on pembrolizumab in non-small cell lung cancer and examine the role of potential predictive biomarkers of response to therapy.

Keywords

Non-small cell lung cancer; PD-1 inhibitor; anti-PD-1 monoclonal antibody; pembrolizumab; lambrolizumab; MK-3475; SCH 900475

Introduction

Despite the discovery of clinically-actionable driver mutations in genomic subsets of patients, lung cancer remains a leading cause of cancer-related death worldwide for both females and males.^{1,2} Platinum-based chemotherapy remains the preferred first-line treatment for most patients with advanced or metastatic non-small cell lung cancer (NSCLC) without targetable genomic alterations. In comparison to patients with *EGFR*-mutant and *ALK*-rearranged lung cancers where the median survival with targeted therapy is in the order of 2-3 years, in unselected NSCLCs, the one-year survival rate is approximately 30% to 40%, with a median survival of 8 to 10 months. In patients without targetable mutations

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and with a poor performance status, the risk of toxicity with conventional antineoplastics can outweigh the potential benefits of therapy, and prior to the advent of immune checkpoint inhibitors, an alternative treatment with the potential for less toxicity in such patients was not available.^{3,29}

Immune surveillance is essential to both cancer prevention and regulation.⁴ T-cells are a major component of the immune response and are highly regulated by a series of co-stimulatory and inhibitory signals that serve as checkpoints. The interaction between programmed death-1 receptor (PD-1) and programmed death ligand-1 (PD-L1) represents a major checkpoint that regulates immune response. These proteins can be effectively targeted and inhibited by monoclonal antibody therapy with the intent of modulating cancer growth and development (Figure 1).⁵

To date, two such monoclonal antibodies have been approved for use in the United States for the treatment of NSCLC, pembrolizumab and nivolumab, with several more in development. This review will focus on pembrolizumab. These drugs have shown substantial efficacy in both NSCLC and melanoma, tumors which are known to be mutationally complex relative to other malignancies, and are thus perhaps potentially more “visible” to the immune system.³⁰ Smoking-related NSCLC, in particular, can be more complex than NSCLC in never-smokers, with a much higher rate of somatic mutations in the former.³¹

Body of Review

Pembrolizumab (Keytruda®), formerly lambrolizumab, is a selective, humanized IgG4 kappa monoclonal antibody that inhibits the PD-1 receptor. It was first approved in the United States by the Food Drug Administration (FDA) in September of 2014 and in Europe by the European Commission in July of 2015. Accelerated approval was granted by the FDA for the treatment of patients with unresectable or metastatic melanoma with disease progression following ipilimumab, and those with *BRAF*V600 mutation-positive disease following progression on a BRAF inhibitor. Approval for melanoma was based on data from KEYNOTE-001, a Phase 1b multicenter, open-label, randomized, dose-comparative trial of pembrolizumab. Confirmed overall response rate (ORR) was a major efficacy outcome measure of this study. As a condition of accelerated approval, the FDA required that randomized trials be performed to establish the superiority of pembrolizumab over standard therapy. These confirmatory studies are ongoing with survival as the primary endpoint. Pembrolizumab received FDA breakthrough therapy designation in advanced NSCLC in October of 2014 and was later approved in October of 2015 for the treatment of patients with metastatic squamous and non-squamous NSCLC whose tumors express PD-L1 and have progressed on or after platinum-containing chemotherapy or an FDA-approved EGFR or ALK targeted agent if applicable. The FDA-approved dosing for melanoma and NSCLC is 2mg/kg intravenously (IV) over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.⁶

Pharmacodynamics and Pharmacokinetics

Metabolism and Elimination

To our knowledge, a specific process of metabolism and elimination has not been reported for pembrolizumab. It has been suggested that IgG monoclonal antibodies are metabolized via phagocytosis by cells of the reticuloendothelial system.⁷ Although direct evidence is lacking, it is possible that phagocytes break down monoclonal antibodies into low-molecular weight fragments which are then renally eliminated. Patient-specific factors such as antigen concentrations, antigen properties, and protective Fc γ and FcRn receptor expression have been postulated to influence monoclonal antibody pharmacokinetics. The cytochrome P-450 system is not directly involved in the metabolism of IgG monoclonal antibodies.⁷

Pembrolizumab has a long half-life of 26 days with a clearance rate of 0.22 L/day that is unaffected by age or gender. No clinically important differences in drug clearance were found in patients with renal or mild hepatic impairment, and thus dose reduction was not routinely recommended in this setting. However, the drug has not been studied primarily in patients with moderate to severe renal or hepatic dysfunction.⁶

Drug-Drug Interactions

No formal pharmacokinetic drug-drug interaction studies have been conducted with pembrolizumab.⁶ Theoretically, any drug that impairs T-cell function or immune responses may negatively impact pembrolizumab's efficacy and alter its kinetics. For example, immunosuppressants such as methotrexate may downregulate Fc γ receptors, which protect monoclonal antibodies from phagocyte-mediated metabolism. This could potentially affect monoclonal antibody clearance.⁷ Of note, patients on concomitant immunosuppressants, including supraphysiologic doses of steroids, were excluded from many clinical trials. In clinical practice, the use of steroids with pembrolizumab is not expressly prohibited, but the possibility of blunting response to therapy cannot be discounted. Another theoretical concern is that upregulation of T-cell activity may lead to increased cytokine release, and cytokines may impact CYP450 enzymes.⁸ Although drug interaction studies to address this particular concern have not been conducted, it would be prudent to monitor levels and/or signs and symptoms of toxicities of medications that are CYP substrates with narrow therapeutic windows.

Special Populations

While there are currently no labeled contraindications to pembrolizumab, patients with a history of autoimmune disease are likely to be at substantial risk of immune-related adverse events (irAE) and were excluded from the majority of clinical trials. Patients with a history of solid organ transplant may also be at increased risk of graft rejection. In clinical practice, the use of immune checkpoint inhibitor therapy in patients with autoimmune disease is not generally recommended. Pembrolizumab carries a category D pregnancy rating, and the FDA has posted warnings for embryo-fetal toxicity.⁶ IgG crosses the placenta and is excreted in breast milk.⁶ It is possible that fetal exposure to an anti-PD-1 receptor monoclonal antibody in pregnant or breastfeeding patients may increase the risk of fetus or infant developing immune-mediated disorders or altering the normal immune response.⁶

Clinical Efficacy

Biomarker Development

Given that PD-L1 serves as the ligand of the PD-1 receptor, biomarker development has focused on detecting PD-L1 expression on tumor cells via immunohistochemistry (IHC) as a possible predictor of enhanced clinical benefit with pembrolizumab. However, the interpretation and application of data for various PD-1 or PD-L1 inhibitors across clinical trials of different immune checkpoint inhibitors have been challenging due to the lack of standardized methodology, a definition for PD-L1 IHC positivity, and a distinct cut-off value between assays.⁹ The role of PD-L1 expression as a predictive biomarker thus remains highly debated. Data on the prognostic nature of PD-L1 expression remains exploratory due to issues such as small sample size and limited power; however a meta-analysis suggested a correlation between positive PD-L1 expression and poor prognosis in NSCLC patients.³²

While some studies used 1% to 5% as the cutoff for PD-L1 positivity with a separate assay, the KEYNOTE-001 phase I study of pembrolizumab used 50% as the cutoff to define PD-L1 expression positivity.^{10,11} The proportion scores used to correlate with responses in KEYNOTE-001 were based on PD-L1 expression levels of 50%, 1-49%, and <1%. Data on the efficacy of pembrolizumab in PD-L1 negative and PD-L1 positive patients with various levels of expression will be discussed below within the context of specific trials. It is important to highlight that while the FDA approved pembrolizumab for the treatment of advanced NSCLC patients whose tumors test positive for PD-L1 using a specific assay (PD-L1 IHC 22C3 pharmDx, Dako North America Inc., Carpinteria, CA),⁶ the approval for nivolumab does not require PD-L1 positivity despite differences in clinical benefit noted between PD-L1 positive and negative non-squamous NSCLC patients.

Phase I: Monotherapy

The KEYNOTE-001 trial was a phase I study with a complex design and multiple cohorts that included NSCLC patients in addition to patients with a variety of other solid tumors. Garon *et al* published data on the efficacy and safety of pembrolizumab in 495 previously-treated and treatment-naïve patients with advanced NSCLC on this trial. Pembrolizumab was administered intravenously at three different dosing schedules: 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks. Immunohistochemical analysis was employed to examine the expression of PD-L1 in tumor samples. As discussed above, the cutoff for PD-L1 expression positivity was 50%. Response duration, progression-free survival (PFS) and overall survival (OS) were assessed.

The ORR was 19.4% for all patients, 18.0% for 394 previously treated patients, and 24.8% for 101 untreated patients. ORR seemed to correlate with level of PD-L1 expression (ORR 45.2%, 16.5%, and 10.7% respectively for PD-L1 expression categorized by the proportion scores 50%, 1-49%, and <1%). ORR based on histology were 23.5%, 18.7%, and 0% with respect to squamous, nonsquamous, and adenosquamous. The response rates were comparable regardless of the dose or schedule of pembrolizumab. Interestingly, current or former smokers had a response rate of 22.5% versus 10.3% among patients who never smoked. The median duration of response was 12.5 months in all patients: 10.4 months in

previously-treated patients, and 23.3 months in treatment-naïve patients. The median PFS was 3.7 months in all patients: 3 months in previously-treated and 6 months for treatment-naïve patients. The median OS was 12 months for all patients, with 9.3 months in treated and 16.2 months in treatment-naïve patients. Grade 3 or higher adverse events (AEs) were reported in 9.5% of patients. The most common side effects seen in the study were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). The incidence of pneumonitis was 3.6%, and infusion-related reactions were observed in 3% of patients.¹¹

In terms of PD-L1 staining as a biomarker, a validation group of 313 patients was examined (223 previously treated and 90 treatment-naïve patients). Of note, the PD-L1 analyses of previously treated patients were performed on archival samples, which may not have been ideal because PD-L1 expression profile is thought to potentially represent a dynamic marker that can change in response to previous anti-cancer therapies. Response rate was 45.2% in patients with a proportion score of PD-L1 ≥ 50%: 43.9% in previously-treated patients and 50% in treatment-naïve patients. Median PFS in this group (PD-L1 ≥ 50%) was 6.3 months for all patients, 6.1 months for previously treated patients, and 12.5 months for treatment-naïve patients. Median OS was not reached in patients with a PD-L1 expression of ≥ 50%. Among the 1143 screened patients, the prevalence of PD-L1 staining with a proportion score of ≥ 50% was 23.2%, 1% to 49% was 37.6%, and <1% expression was 39.2%. Authors noted that there was no correlation between PD-L1 staining and *EGFR* mutational status; whereby patients with *KRAS* mutations had increased PD-L1 staining. There was an insufficient number of patients with *ALK* rearrangements to draw conclusions.

Updated data from KEYNOTE-001 on PD-L1 as a biomarker of response to pembrolizumab in 101 treatment-naïve PD-L1 positive NSCLC patients were presented by Rizvi *et al* in abstract form at the 2015 ASCO Annual Meeting. In the validation set, which included only 90 patients, with 38 weeks of median follow up, ORR and disease control rate (DCR) were highest and PFS was longest in patients with ≥ 50% PD-L1 tumor cell staining. ORR was 24% in all patients and were 47%, 19%, and 14% in patients with tumors that expressed PD-L1 ≥ 50%, 1%-49%, and <1% respectively. DCR was 68% overall, and were 77%, 71%, and 57% with respect to the three categories of PD-L1 staining. Median PFS rate was 6 months overall and was not reached in patients with tumor that expressed PD-L1 ≥ 50%, 4.4 months (1% - 49%), and 3.4 months (<1%). There was a trend toward longer OS (immature data) as median OS was not reached in tumors with >1% PD-L1+ and was 7.3 months in <1% PD-L1 positive. Eleven percent of patients experienced grade 3 to 5 AEs. The authors concluded that pembrolizumab demonstrated durable antitumor activity and manageable toxicity profile as first-line therapy for PD-L1+ metastatic NSCLC, with greatest efficacy observed in those with PD-L1 positivity ≥ 50% of tumor cells. These data demonstrate that PD-L1 expression in tumor cells may identify NSCLC patients more likely to respond to pembrolizumab, pending confirmation in further studies.¹²

Phase I/II: Combination Therapy

The KEYNOTE-021 trial was a phase I study examining the combination of pembrolizumab with the anti-CTLA4 monoclonal antibody, ipilimumab. Cohort D included advanced NSCLC patients. The results were reported by Patnaik *et al* as an abstract at the 2015

Annual ASCO Meeting. Patients with Stage IIIB/IV disease, an ECOG score of 1, and who received 2 lines of therapy received pembrolizumab and ipilimumab every 3 weeks followed by maintenance pembrolizumab. Doses were reduced from 10 mg/kg to 2 mg/kg for pembrolizumab and 3 mg/kg to 1 mg/kg for ipilimumab due to emerging data from a trial of nivolumab and ipilimumab. The primary endpoint was safety and the incidence of dose-limiting toxicity (DLT) in the first three weeks of therapy. Response was initially assessed at 6 weeks per RECIST 1.1 by investigator review. In a total of 15 patients that were treated, no DLTs were observed, and dose modification was not required. Eleven patients responded to therapy and were included in the analysis. The ORR was 55%, including 1 CR (9%) and 5 PRs (45%). The DCR (CR + PR + SD 6 weeks) was 100%. Ten patients experienced AEs (66%), but none led to discontinuation or death. These included grade 3 rash, grade 2 diarrhea, and grade 2 vomiting (n=2 or 13% for each listed AE). Other AEs were observed, but pneumonitis was not reported. At 26+ weeks, 12 were still on treatment and 3 patients discontinued due to disease progression. The authors concluded that the pembrolizumab and ipilimumab combination has an acceptable toxicity profile and robust activity. Lower doses of pembrolizumab and ipilimumab did not appear to negatively impact efficacy.¹³

Papadimitrakopoulou *et al*/reported the results of cohorts A and C of the KEYNOTE-021 phase I/II trial which evaluated the safety and efficacy pembrolizumab plus platinum-doublet chemotherapy in patients with NSCLC. Treatment-naïve patients with stage IIIB/IV NSCLC were randomized 1:1 to pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks plus carboplatin at an AUC of 6 and paclitaxel at 200 mg/m² (cohort A: any histology) or carboplatin at an AUC 5 and pemetrexed at 500 mg/m² (cohort C: nonsquamous without *EGFR* sensitizing mutation or *ALK* translocation only). Patients received pembrolizumab with carboplatin and paclitaxel for 4 cycles followed by pembrolizumab maintenance in cohort A and pembrolizumab with carboplatin and pemetrexed in cohort C. The DLT window encompassed the first 3 weeks of dosing. This trial included patients with an ECOG of 0-1, measurable disease, and adequate tumor tissue for PD-L1 assessment. Response was assessed via RECIST v1.1 every 6 weeks until disease progression.

The ORR was 30% in cohort A and 58% in cohort C. The best DCR (PR+SD 6 weeks) was 80% for cohort A and 100% for cohort C. A total of 20 patients in cohort A and 24 patients in cohort C were treated. One DLT in cohort C was reported, which required hospitalization due to rash and treatment discontinuation. The grade 3 to 4 treatment-related AE rate was 27% (15% in A, 38% in C). AEs were reversible and included transaminase elevation (n = 3 in C), anemia (n = 1 in A, 2 in C), rash (n = 1 in A, 1 in C), and colitis (n = 2 in C). No grade 3 to 4 febrile neutropenia was observed. This combination is being evaluated in a larger cohort.¹⁴

Efficacy in Brain Metastases

The CNS activity of pembrolizumab is of substantial importance in NSCLC patients who frequently present with brain metastases. A theoretical concern revolves around whether or not the monoclonal antibody is effectively able to penetrate the blood brain barrier with

similar drug levels in all patients. Goldberg *et al*/reported preliminary data of an ongoing phase II trial in NSCLC patients with brain metastasis.¹⁵

Eligibility criteria included the following: one or more brain metastases that were either previously untreated or progressed after prior local therapy, brain metastasis size between 5mm to 20mm, asymptomatic, and not requiring immediate local therapy or corticosteroids. Tumor biopsy demonstrating PD-L1 expression was required. Patients were treated with pembrolizumab 10 mg/kg intravenously every 2 weeks. Response outside the CNS was determined by RECIST 1.1, and brain metastasis response determined by modified RECIST (mRECIST). Brain metastases ≥ 5 mm were considered measurable and up to five target lesions were allowed. The primary endpoint was brain metastasis response rate by mRECIST.

At the time of presentation, 10 NSCLC patients were accrued and nine were evaluable for the study's primary endpoint. The brain metastasis response rate was 44% (4/9 partial responses, 2 unconfirmed due to limited follow-up time); 34% (3/9) had progressive disease (PD) as their best response, and 22% were unable to be evaluated in the brain due to rapid systemic progression. The systemic response rate (response outside the CNS) was 34% (3/9, 1 unconfirmed). Only one patient who responded systemically had PD in the brain. There were no grade ≥ 3 adverse events that were considered treatment-related or attributed to brain metastases. The authors concluded pembrolizumab shows promising clinical activity in the CNS with an intracranial response rate that is comparable to the response rate seen outside the CNS. We await further results of this ongoing prospective effort.

Safety & Tolerability

Pembrolizumab is well tolerated, with most individual grade 3 to 5 adverse events occurring in $\sim 10\%$ of patients. In 495 NSCLC patients treated on the KEYNOTE-001 study, the following adverse events of any grade that were present in more than 5% of patients were noted: fatigue 19%, pruritus 11%, decreased appetite 11%, rash 10%, arthralgia 9%, diarrhea 8%, nausea 8%, and hypothyroidism 7%.¹¹ Infusion-related reactions have been observed but are infrequent.⁶ In general, pembrolizumab may be better tolerated than conventional chemotherapy and may represent a good option even for patients with poor performance status.

Clinicians will need to pay attention to the dose limiting immune-related adverse events (IrAEs). While the frequency of severe IrAEs is low, these can result in substantial morbidity.⁶ IrAEs can happen at any point during the course of treatment and are independent of dosage. Autoimmune endocrinopathies have been noted, including hypophysitis, thyroid disorders, and type 1 diabetes mellitus. Colitis, pneumonitis, hepatitis, and nephritis have also been described. The development of pneumonitis is of special concern in lung cancer patient population given that a substantial proportion of patients may have poor baseline lung function. In the KEYNOTE-001 lung cancer cohort, grade 3-5 pneumonitis was noted in 9 patients (1.8%).¹¹

Other IrAEs (<1% occurrence) include severe dermatitis manifesting in some cases as bullous pemphigoid, myasthenic syndrome, optic neuritis, and rhabdomyolysis. Some of these IrAEs were specifically reported in melanoma patients, but may apply to patients with lung cancer as well. Additionally, a retrospective analysis observed that melanoma patients who developed dermatologic adverse events, hypopigmentation in particular, might have significantly longer PFS compared to patients who did not.³³ While this represents an interesting association, it is not known if this observation will hold true on further prospective testing, or in patients with NSCLC. While toxicity profiles seem to vary slightly depending in various tumor types, clinicians should closely watch for any sign and symptoms of these IrAEs in patients treated with pembrolizumab. The management of the different immune-mediated toxicities has been described in detail elsewhere, and algorithms will need to be clearly delineated moving forward.¹⁶

Conclusion

Pembrolizumab is an effective therapy for patients with advanced NSCLC. Response rates may improve in patients with PD-L1 positive tumors, and in combination with other systemic therapies, but further investigation is required as randomized controlled studies versus chemotherapy are lacking, and survival data is premature. The role of PD-L1 as a predictive biomarker of pembrolizumab efficacy will require additional clinical validation. While the drug is well-tolerated overall, clinicians will need to be vigilant about monitoring for the signs and symptoms of IrAEs and manage them accordingly.

Expert Commentary

For about two and a half decades after cisplatin became widely used in the late 1970s, the therapeutic armamentarium of the medical oncologist for the treatment of NSCLC was limited largely to cytotoxic chemotherapy.¹⁷ The mid-2000s was marked not only by the approval of bevacizumab as a component of first-line therapy,¹⁸ but by an explosion of targeted therapeutic options for genomic subsets of NSCLC sparked by the discovery of sensitizing *EGFR* mutations in 2004.¹⁹ Unfortunately, in the setting of advanced or metastatic disease, the development of therapeutic resistance to both cytotoxic chemotherapy and targeted therapy is universal, and for many patients, disease control can be limited to several months to, at best, a year.²⁰

Immune checkpoint inhibitors such as pembrolizumab and nivolumab are welcome additions to the landscape of NSCLC therapeutics and offer a number of distinct advantages. Pembrolizumab has single-agent activity with a response rate of approximately 20% in previously-treated patients with advanced disease. In early studies, response rates increased in patients with PD-L1 positive disease (approximately 50% in PD-L1-positive patients as defined by a 50% cutoff), and in the setting of combination therapy. Immune checkpoint inhibitor therapy may ultimately represent a treatment of choice after progression on first-line platinum doublet therapy in select patients whose tumors do not harbor targetable driver alterations. It might be offered as an attractive first-line option for patients who are not candidates for conventional chemotherapy (ECOG 2) or who do not qualify for targeted

therapy. Furthermore, the adverse event profile of pembrolizumab as a single agent is favorable, with a relatively low incidence of grade 3 or 4 toxicities.

Beyond response and tolerability, long-term, durable disease control has been observed across various trials in a small proportion of patients with NSCLC. Thus, pembrolizumab may “lift the tail of the curve”, which is a phenomenon similarly observed with advanced, cutaneous melanoma in the era of immunotherapy. Whereby immune checkpoint inhibitor therapy can result in a plateau at the end of a survival curve, non-immunomodulatory strategies usually result in the curve's tail-end returning to zero.

Despite pembrolizumab's promising results in NSCLC, it poses unique challenges in the clinic. In step with the evolution of response assessments on clinical trials that account for pseudoprogression, clinicians would need to exercise judgment to determine if radiologic progression represents true cancer growth versus immune infiltration.²¹ Clinicians will likewise need to be proficient at dealing with immune-related adverse events such as pneumonitis, hepatitis, colitis, and autoimmune endocrinopathies. Trial algorithms for the management of these IrAEs will need to be translated into clear guidelines for physicians in the community setting or any clinicians who are not as familiar with the use of immunotherapeutic agents.^{16,22} Finally, given that both pembrolizumab and nivolumab are FDA-approved for advanced NSCLC patients, physicians will need to decide which agent to use. As efficacy in unselected patients and toxicity are generally comparable between these drugs, routine use may be affected by the FDA requirement for PD-L1 testing for pembrolizumab.

Five-year View

While the efficacy of pembrolizumab as a single-agent for advanced NSCLC after progression on platinum doublet therapy is yet to be confirmed by phase III testing similar to nivolumab, determining whether or not clinical benefit differs or surpasses standard of care in other settings will require further investigation. The efficacy of combination therapy (i.e. pembrolizumab in combination with a second immune checkpoint inhibitor, vaccine therapy, or targeted therapy) deserves further exploration, particularly in distinct patient subsets such as *EGFR*-mutant and *ALK*-rearranged lung cancers, or in patients with a never or former light smoking history.

There are several ongoing trials that are actively recruiting lung cancer patients. KEYNOTE-010 is a phase II/III randomized controlled trial comparing two doses of pembrolizumab (“high” and “low”) versus docetaxel in previously treated patients with NSCLC and PD-L1+ expression.²³ The primary endpoints are OS and PFS. The secondary endpoints are ORR via RECIST criteria, and response duration. KEYNOTE-021 is a phase I/II trial evaluating pembrolizumab in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic NSCLC.²⁴ The primary outcomes are PFS and ORR. OS is a secondary endpoint. KEYNOTE-024 is multicenter phase III trial that randomizes patients to pembrolizumab versus first-line platinum-based chemotherapy in patients with NSCLC whose tumors stain strongly positive for PD-L1 (≥ 50% via IHC).²⁵ KEYNOTE-042 is a phase III trial of similar design to KEYNOTE-024 that includes

treatment-naïve patients whose tumors express strong (staining ≥ 50%) versus weak (staining 1-49%) PD-L1 positivity.²⁶

The role of biomarker-based treatment selection will certainly require rigorous laboratory and clinical validation. Across different assays with different compounds, various approaches to PD-L1 staining have been explored, such as scoring expression on tumor cells and/or infiltrating lymphocytes, and a defined cutoff point for “positivity” will need to be identified.²⁷ The PD-L1 expression cutoff of 50% with pembrolizumab has certainly shown promise, but a methodologic consensus across various assays has not been established. In addition, while response rates were higher in patients with PD-L1-positive tumors, it is difficult to ignore that responses were observed in patients with “PD-L1-negative” tumors (PD-L1 expression 1% to 49%), raising the question of whether or not a biomarker is truly essential for clinical use, given that other factors may be predictive of response. For immune checkpoint inhibitors in general, other potential predictive biomarkers have begun to emerge such as mutational burden, a history of smoking, and the presence of specific tumor neoantigens.^{16,28} A determination of their utility for pembrolizumab in particular will require investigation on prospective trials.²⁸

Regardless of these outcomes, immune checkpoint inhibitors have already begun to reshape our approach to the management of advanced NSCLC.

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Key Issues

- Pembrolizumab is given every three weeks (21-day cycle).
- Monotherapy pembrolizumab offers an overall response rate of approximately 20% in previously-treated patients and up to 50% in treatment-naïve patients with tumors that highly expressed PD-L1 (staining ≥ 50%).
- With a PD-L1 positivity cutoff of 50%, response rates rise in patients with PD-L1 positive disease; however, responses have been reported in patients with lower levels of staining (1% to 49%).
- IrAEs are important and dose-limiting side effects of pembrolizumab. They can be independent of dose and may occur any time during the course of treatment. Pembrolizumab use should be avoided in patients with a previous or active history of autoimmune disease or used with extreme caution.
- Concurrent use of immunosuppressive agents may theoretically decrease pembrolizumab activity.

Figure 1. Overview of the PD-1 and PD-L1 Interaction and the immune checkpoint inhibitor Description

Binding of the PD-L1 ligand found on the surface of tumor cells to the PD-1 receptor on the surface of T-cells (and other immune cells such as NK cells and B-cells) results in a negative regulatory signal that deactivates and downregulates T-cell effector function. PD-1 inhibitors such as pembrolizumab or nivolumab or PD-L1 inhibitors such as atezolizumab abrogate these negative regulatory signals and allow for T-cells to potentially recognize and eliminate tumor cells within the tumor microenvironment. It is worth noting that several other immune checkpoints exist, and that both positive and negative regulatory interactions within the immune milieu are much more complicated than depicted. These are reviewed separately,⁵ and are beyond the scope of this publication.

Abbreviation: TCR, T-cell receptor; APC, antigen presenting cell; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death ligand-1.

Table 1

Summary of published clinical trials

Authors (year)	Drug	NSCLC (Patients #)	ORR RECIST	PFS Median (month)	OS Median (month)
Garon ¹¹ (2015) KEYNOTE-001	Pembrolizumab	Naïve and Relapsed (n= 495)	19.4% (all patients) 45.2% (PD-L1 50%; treated) 50% (PD-L1 50%; naïve)	3.7 (all patients) 6.1 (PD-L1 50%; treated) 12.5 (PD-L1 50%; naïve)	12 (all patients) Not reached (PD-L1 50%; all patients)
Rizvi ¹² (2015) KEYNOTE-001	Pembrolizumab	Naïve; (n = 90)	24% (all patients) 47 % (PD-L1 50%)	6 (all patients) Not reached (PD-L1 50%)	Not reached (all patients)
Pamaik ¹³ (2015) KEYNOTE-021	Pembrolizumab + ipilimumab	Second line (n = 11)	55%	Not reached (at 6 weeks)	Not reported
Papadimitrakopoulou ¹⁴ (2015) KEYNOTE-021	Pembrolizumab + platinum doublet	Naïve (n = 44)	30% (cohort A) 58% (cohort C)	Not reported	Not reported
Goldberg ¹⁵ (2015)	Pembrolizumab	Brain metastasis (n = 9)	44% (CNS) 34% (Systemic)	Not reported	Not reported