IJHSR
ijhighschoolresearch.org
RESEARCH ARTICLE

Evaluating Different Anti-PD-1/PD-L1 Immunotherapies for Advanced Non-Small-Cell Lung Cancer

Joey Chow

Raffles Institution, 1 Raffles Institution Ln, Singapore, Singapore, 575954, Singapore; jcchow3@icloud.com
Mentor: Frank Glover

ABSTRACT: Lung cancer is the leading cause of cancer-related death worldwide, with 1-, 3-, and 5-year survival rates that all remain below 50%. Historically, chemotherapy has been the mainstay treatment for advanced non-small cell lung cancer (NSCLC). Recently, significant advances have been made in the field of immune checkpoint inhibitors (ICIs). ICIs targeting the programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) pathway, which inhibits immune responses, have achieved great success over conventional cytotoxic chemotherapy. Specifically, the anti-PD-L1/PD-1 ICIs nivolumab, pembrolizumab, atezolizumab, and durvalumab have demonstrated promising systemic activity in patients with NSCLC. A comprehensive search for studies published in English was conducted using the PubMed database. Studies with the following keywords were assessed: ("advanced" OR "metastatic" OR "recurrent" OR "stage III" OR "stage IV") AND ("non-small cell lung cancer" OR "NSCLC") AND ("nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "durvalumab"). The results of this review paper show that monotherapy with these ICIs, as well as ICIs used alongside chemotherapy, improved overall survival rates for patients with advanced NSCLC. All but durvalumab showed a lower rate of adverse effects compared to chemotherapy. These results are promising and warrant further research into the efficacy of such ICIs in treating advanced NSCLC.

KEYWORDS: Biomedical and Health Sciences, Immunology, Advanced Non-Small-Cell Lung Cancer, Immune Checkpoint Inhibitors, PD-L1/PD-1 Pathway Inhibitors.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with 1-, 3-, and 5-year survival rates that, although showing substantial improvement in recent years, all remain below 50%.[1–3] Roughly 85% of lung cancer cases fall under the category of non-small-cell lung cancer (NSCLC), and the majority of lung cancer patients have advanced, recurrent, or metastatic disease.[4,5]

In the last decade, several immune checkpoint inhibitors (ICIs) have gained approval from the US Food and Drug Administration (FDA) and the European Medicines Agency as standard treatments for advanced NSCLC.[6] Programmed death-ligand 1 (PD-L1) is an immune checkpoint ligand that is broadly expressed in non-small cell lung cancers, both in adenocarcinomas and in squamous cell carcinomas.[7] The PD-1/PD-L1 immune checkpoint pathway involves the programmed death-1 (PD-1) receptor, which is expressed on T cells, binding to the PD-L1 or PD-L2 ligands, which are often upregulated on other cells, including cancer cells. This leads to PD-1 receptors on T cells recruiting the phosphatases SHP-1 and SHP-2, which promote T cell apoptosis by inhibiting co-stimulatory signaling.[8] SHP-2 also prevents signaling in T cells by dephosphorylating T cell antigen receptors, resulting in the inhibition of T cell survival, proliferation, and function (Figure 1, created with BioRender.com).[9,10] Additionally, the binding of PD-1 to PD-L1 can induce differentiation of helper T cells into regulatory T cells, which play a role in suppressing immune responses.

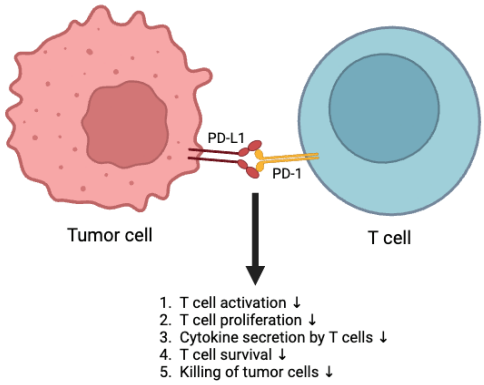

Figure 1: The inhibition of T cell survival, proliferation, and function when the PD-1 receptor on a T cell binds to the PD-L1 ligand on a cancer cell.

Anti-PD-1 and anti-PD-L1 ICIs have shown promising systemic activity in NSCLC patients, although some differ in terms of safety profiles and/or efficacy based on PD-L1 expression levels in patients.[12–15] Numerous studies have found a correlation between PD-L1 expression in tumor tissue and an enhanced response rate to PD-L1 and PD-1 blockade in cancer patients. The prevailing notion is that higher levels of PD-L1 expression on tumor cells indicate that the tumor is actively using the PD-1/PD-L1 immune checkpoint pathway to suppress immune responses against the tumor.[12,16–19] By binding to PD-1 and PD-L1 respectively, anti-PD-1 and anti-PD-L1 ICIs inhibit the binding of PD-1 to PD-L1 (Figure 2, created with BioRender.com), thus preventing SHP-2 recruitment and restoring normal T cell function.[20,21] T cells play a crucial role

DOI: 10.36838/v7i2.78

in the immune response against cancer, particularly within the tumor microenvironment. Restoration of T cell function thus reverses immunosuppression, facilitating tumor destruction through two primary mechanisms: the death ligand pathway and granule exocytosis. In the death ligand pathway, stimulation of the T-cell receptor (TCR) induces cytotoxic T cells to release death ligands, which bind to death receptors on target tumor cells. This binding triggers apoptosis by activating both extrinsic and intrinsic cell death pathways. In the granule exocytosis pathway, TCR activation leads to the mobilization of cytotoxic granules, which contain perforins and granzymes, to the site of contact between T cells and tumor cells. Perforins create pores in the tumor cell membrane, while granzymes enter the tumor cell to cleave essential proteins, inducing tumor cell death.[22–24]

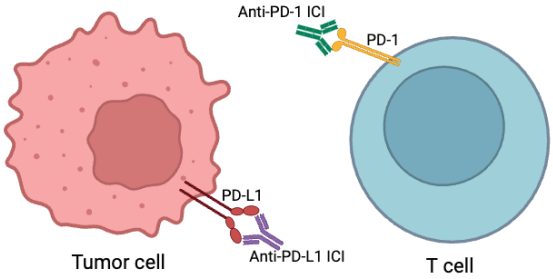

Figure 2: Anti-PD-1 and anti-PD-L1 ICIs inhibiting the binding of the PD-1 receptor on a T cell binds to the PD-L1 ligand on a tumor cell.

Prior to the approval of immunotherapy for NSCLC treatment, third-generation platinum-based chemotherapy doublets were the standard first-line treatment for advanced NSCLC. These doublets combine a platinum compound (cisplatin or carboplatin) with a third-generation chemotherapy agent such as vinorelbine, gemcitabine, or taxanes.[25] The advent of ICIs has transformed the treatment strategy for advanced NSCLC: in recent years, immunotherapy, either as monotherapy or in combination with other therapies, has become the standard front-line treatment for advanced NSCLC in patients who do not have targetable genetic alterations and have no contraindications to PD-1/PD-L1 inhibitors.[26]

Nivolumab, pembrolizumab, atezolizumab, and durvalumab are four widely studied anti-PD-1/PD-L1 ICIs in the treatment of advanced NSCLC. Nivolumab and pembrolizumab were among the first ICIs approved by the FDA for the treatment of NSCLC.[27] Both ICIs are human IgG4 PD-1 immune checkpoint inhibitor antibodies that bind to the PD-1 receptor on T cells with high affinity and specificity, preventing PD-1 from interacting with ligands PD-L1 and PD-L2. This restores the ability of T cells to recognize and attack cancer cells.[13,18]

Following pembrolizumab's approval, the FDA extended treatment options by approving atezolizumab for patients with metastatic NSCLC whose disease had advanced despite prior platinum-based chemotherapy.[28] Atezolizumab and durvalumab are both humanized monoclonal IgG1 antibodies that bind to PD-L1. This blocks the interaction between PD-L1 and the PD-1/B7-1 activation complex, thus allowing T cells to recognize and kill tumor cells.[29–31] Apart from atezolizumab, durvalumab is thus far the only other PD-L1 inhibitor that has been approved by the FDA for the treatment of NSCLC.[32]

Given recent advancements in anti-PD-1/PD-L1 immunotherapy for treating advanced NSCLC, understanding the collective efficacy of these agents is crucial for identifying future directions of treatment development and optimizing treatment strategies. This systematic review thus aims to evaluate the efficacy of the ICIs nivolumab, pembrolizumab, atezolizumab, and durvalumab in the treatment of advanced NSCLC by examining several landmark studies. It will do so by examining overall survival (OS), defined as the time from randomization in a clinical trial to the date of death due to any cause, and progression-free survival (PFS), defined as the time from randomization in a clinical trial to disease progression or death from any cause.[15]

Methods

A comprehensive search for studies published in English was conducted using the PubMed database. Studies were selected using permutations of the following terms: ("advanced" OR "metastatic" OR "recurrent" OR "stage III" OR "stage IV") AND ("non-small cell lung cancer" OR "NSCLC") AND ("nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "durvalumab"), yielding 3,092 results on PubMed. The search results were then filtered to only include those published in 2014 and beyond, bringing the number of results down to 3,086. Finally, the search results were filtered to include only clinical trials and randomized controlled trials, yielding 401 results. From these 401 results, the following were filtered out to yield the 69 articles cited in this article: duplicate articles, articles not primarily focused on the treatment of advanced NSCLC using anti-PD-1/PD-L1 ICIs, articles misclassified as clinical trials, and studies with an impact factor lower than 2.

Discussion

Nivolumab:

- ***Efficacy of nivolumab monotherapy:***

Nivolumab has demonstrated significant survival benefits over docetaxel, a mainstay chemotherapy medication, in treating advanced NSCLC across multiple studies. In the CheckMate 017 study, which specifically assessed the efficacy of nivolumab in treating advanced, previously treated squamous-cell NSCLC, the median OS with nivolumab was 9.2 months compared to 6.0 months with docetaxel, representing a 41% reduction in the risk of death (hazard ratio, 0.59; 95% CI [0.44 to 0.79]; P<0.001).[33] The one-year OS rate was 42% with nivolumab versus 24% with docetaxel. Additionally, the median PFS was 3.5 months for nivolumab compared to 2.8 months for docetaxel (hazard ratio for death or disease progression, 0.62; 95% CI [0.47 to 0.81]; P<0.001). Treatment-related adverse events (TRAEs) of grade 3 or 4 were significantly lower in the nivolumab group (7%) compared to the docetaxel group (55%).

In the CheckMate 057 study, nivolumab also showed superior efficacy in nonsquamous NSCLC.[34] The median OS was

12.2 months with nivolumab compared to 9.4 months with docetaxel (hazard ratio for death, 0.73; 95% CI [0.59 to 0.89]; P=0.002). The one-year OS rate was 51% with nivolumab versus 39% with docetaxel. Although the median PFS did not favor nivolumab (2.3 months vs. 4.2 months with docetaxel), the one-year PFS rate was higher with nivolumab (19% vs. 8%). The efficacy of nivolumab was consistent across different levels of PD-L1 expression.

Nivolumab's efficacy does not appear to be significantly influenced by PD-L1 expression levels. In CheckMate 017, the benefits of nivolumab were observed regardless of PD-L1 expression.[33] Similarly, in CheckMate 057, nivolumab's effectiveness was noted across different PD-L1 expression subgroups (≥1%, ≥5%, and ≥10%).[34]

Long-term follow-up data from both CheckMate 017 and 057 confirm the sustained survival benefits of nivolumab. The two-year OS rates were significantly higher with nivolumab: 23% for squamous NSCLC and 29% for nonsquamous NSCLC, compared to 8% and 16% respectively for docetaxel.[35] Five-year follow-up data from the CheckMate 017 and 057 studies further demonstrated a fivefold increase in OS rates with nivolumab, with some patients experiencing prolonged disease control even after discontinuing treatment.[36] The 5-year follow-up of the CA209-003 study supports these findings, reporting a five-year OS rate of 16% - significantly higher than the historical 5-year OS rates for stage IV NSCLC.[37]

- ***Efficacy of nivolumab + chemotherapy:***

In a four-arm study investigating the safety and efficacy of nivolumab combined with different types of standard chemotherapy in treating advanced NSCLC, it was found that combination therapy with nivolumab and standard chemotherapy enhances the antitumor activity of each monotherapy, with acceptable adverse events observed. The chemotherapy regimens in each arm were nivolumab with gemcitabine/cisplatin (arm A), pemetrexed/cisplatin (arm B), paclitaxel/carboplatin/bevacizumab (arm C), or docetaxel (arm D) respectively. This combination therapy showed enhanced antitumor activity compared to monotherapy, with overall response rates ranging from 50% to 100% in first-line therapy and 16.7% in second-line therapy. Additionally, the median PFS and PFS rates at six and nine months for the first-line arms were superior to those for chemotherapy alone, though OS data was not available.[38]

A five-year follow-up of this study revealed that PFS and OS at five years were observed in arms B and C only. Notably, arm C showed a moderate proportion of patients with five-year PFS (1 out of 6 patients) and OS (4 out of 6 patients). No unexpected severe adverse events or treatment-related deaths occurred, indicating long-term tolerability of nivolumab combined with platinum-based chemotherapy.[39]

- ***Efficacy of dual immunotherapy with nivolumab + ipilimumab:***

Nivolumab combined with ipilimumab has also shown significant efficacy in treating advanced NSCLC, particularly in the CheckMate 227 study.[40] This combination therapy has been associated with a longer OS compared to chemotherapy, regardless of PD-L1 expression levels. For patients with PD-L1 expression levels of 1% or more, the median OS was 17.1 months with nivolumab plus ipilimumab compared to 14.9 months with chemotherapy. The 2-year OS rates were 40.0% and 32.8%, respectively. Even among patients with PD-L1 expression levels below 1%, the median OS was 17.2 months with the combination therapy versus 12.2 months with chemotherapy. The overall population showed a median OS of 17.1 months with nivolumab plus ipilimumab and 13.9 months with chemotherapy, indicating a consistent survival benefit across different PD-L1 expression levels.

The 5-year follow-up data from the CheckMate 227 study further reinforced the long-term benefits of nivolumab plus ipilimumab.[41,42] This combination demonstrated increased 5-year survivorship and a durable clinical benefit regardless of PD-L1 expression. The median OS was 17.1 months for patients with PD-L1 expression ≥1% and 17.4 months for those with PD-L1 expression <1%. The objective response rates (ORR) were similar between nivolumab plus ipilimumab and chemotherapy (33% vs. 28%), but the median duration of response (DOR) was significantly longer with the combination therapy (21.7 months vs. 5.8 months). Notably, 27% of patients had an ongoing response at 5 years with nivolumab plus ipilimumab compared to only 3% with chemotherapy.

However, in a study focusing on patients with advanced, pretreated, immune checkpoint inhibitor-naive squamous NSCLC, the addition of ipilimumab to nivolumab did not improve outcomes.[43] The median OS was 10 months with the combination therapy and 11 months with nivolumab alone, and the objective response rates were similar (18% vs. 17%). The study found no significant differences in OS or PFS between the treatment groups, and grade 3 or higher TRAEs were slightly more frequent with the combination therapy.

Pembrolizumab

- ***Efficacy of pembrolizumab monotherapy:***

Pembrolizumab has demonstrated significant efficacy in treating NSCLC, showing improvements in PFS, OS, ORR, and DOR.

In the KEYNOTE-010 study, pembrolizumab outperformed docetaxel, especially in patients with PD-L1 expression on at least 50% of tumor cells.[30] These patients experienced a median OS of 14.9 months for the 2 mg/kg group and 17.3 months for the 10 mg/kg group, compared to 8.2 months for the docetaxel group. Additionally, the study showed that PFS was significantly longer in patients treated with pembrolizumab, with a median of 5.0 months for the 2 mg/kg group and 5.2 months for the 10 mg/kg group, compared to 4.1 months for the docetaxel group. The ORR was also higher in the pembrolizumab groups, with significant improvements in both efficacy and safety.

In the KEYNOTE-024 study, pembrolizumab demonstrated a median PFS of 10.3 months compared to 6.0 months for chemotherapy.[12] The estimated rate of OS at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group. Pembrolizumab also achieved a higher ORR (44.8% vs. 27.8%) and a longer median DOR (not reached vs. 6.3 months). This study highlighted the significant advantage

DOI: 10.36838/v7i2.78

of pembrolizumab in terms of both efficacy and safety, with fewer TRAEs than chemotherapy.

Prolonged follow-up of KEYNOTE-042 showed that pembrolizumab continued to provide superior OS benefits across various PD-L1 expression levels. In the PD-L1 tumor proportion score (TPS) ≥ 50% population, the median OS was 20.0 months in the pembrolizumab group compared to 12.2 months in the chemotherapy group.[44] Similar benefits were observed in the PD-L1 TPS ≥ 20% and ≥ 1% populations, with median OS of 17.7 months and 16.7 months, respectively, for pembrolizumab, compared to 13.0 months and 12.1 months for chemotherapy. The 5-year follow-up confirmed these long-term benefits, with estimated 5-year OS rates of 21.9% for PD-L1 TPS ≥ 50%, 19.4% for PD-L1 TPS ≥ 20%, and 16.6% for PD-L1 TPS ≥ 1%, compared to 8.5%-10.1% for chemotherapy across these groups.[45]

Despite these benefits, pembrolizumab's efficacy can vary with PD-L1 expression levels. Higher PD-L1 expression correlates with greater benefits in both PFS and OS. For instance, in KEYNOTE-042, patients with PD-L1 TPS ≥ 50% experienced a more pronounced improvement in PFS and OS compared to the overall population.[44] However, pembrolizumab still provided meaningful benefits even in lower PD-L1 expression groups, as seen in the extended follow-up data from KEYNOTE-042.[45]

- ***Efficacy of pembrolizumab + chemotherapy:***

Pembrolizumab combined with chemotherapy has demonstrated significant efficacy in treating advanced NSCLC compared to placebo plus chemotherapy. In a 2018 study focusing on advanced nonsquamous NSCLC (KEYNOTE-189), the OS for patients receiving pembrolizumab plus chemotherapy was 69.2% at 12 months, markedly higher than the 49.4% seen in the placebo group (HR for death, 0.49; 95% CI [0.38, 0.64]; P<0.001). This benefit was consistent across all levels of PD-L1 expression. The median PFS in the pembrolizumab group was 8.8 months versus 4.9 months in the placebo group (HR for disease progression or death, 0.52; 95% CI [0.43,0.64]; P<0.001).[46] These results are supported by a 2022 study investigating the efficacy of pembrolizumab combined with chemotherapy (carboplatin and pemetrexed), which similarly showed a significant improvement in PFS with pembrolizumab plus chemotherapy, with a median PFS of 13.0 months compared to 8.9 months with chemotherapy alone (HR 0.53; 95% CI [0.31,0.91]; p=0.010). However, no significant difference in OS was observed between the two groups (HR 0.90; 95% CI [0.42,1.91]; nominal p=0.39).[47]

In squamous NSCLC, the addition of pembrolizumab to chemotherapy also proved beneficial, with a median OS of 15.9 months compared to 11.3 months in the placebo group (HR for death, 0.64; 95% CI [0.49, 0.85]; P<0.001). The median PFS was 6.4 months in the pembrolizumab group versus 4.8 months in the placebo group (HR for disease progression or death, 0.56; 95% CI [0.45,0.70]; P<0.001).[48] Overall survival benefit was consistent regardless of PD-L1 expression levels.

A retrospective study of elderly patients aged 75 years and older found that pembrolizumab plus chemotherapy showed a significant improvement in PFS and OS compared to chemotherapy alone. The median PFS was 12.5 months versus 5.3 months (P<0.001), and OS was not reached in the pembrolizumab group compared to 21.27 months in the chemotherapy-only group (P=0.037).[49] Subgroup analyses indicated that the benefit was more pronounced in patients with positive PD-L1 expression, stage IV disease, better performance status (ECOG-PS <2), fewer comorbidities, or those who were female. However, treatment discontinuation due to adverse effects was higher in the pembrolizumab group (26%) compared to the chemotherapy-only group (5%).

Atezolizumab

- ***Efficacy of atezolizumab monotherapy:***

Atezolizumab has demonstrated significant efficacy in treating advanced NSCLC. In the POPLAR study (2016), patients treated with atezolizumab had a median OS of 12.6 months compared to 9.7 months for those treated with docetaxel (HR 0.73, 95% CI [0.53,0.99]; p=0.04).[13] Greater OS improvements were associated with higher levels of PD-L1 expression. Similarly, in the OAK study (2017), atezolizumab improved OS to a median of 13.8 months compared to 9.6 months for docetaxel (HR 0.73, 95% CI [0.62,0.87]; p=0.0003).[14] A follow-up of the OAK study showed that after more than two years, atezolizumab continued to provide a durable survival benefit, with 28% of patients surviving longer than 24 months compared to 18% in the docetaxel group.[31]

However, PFS did not show the same level of improvement. In the POPLAR study, PFS was similar between the two groups: 2.7 months for atezolizumab versus 3.0 months for docetaxel (HR 0.94, 95% CI [0.72,1.23]).[13] The OAK study also showed comparable PFS between atezolizumab and docetaxel: 2.8 months versus 4.0 months, respectively (HR 0.95, 95% CI [0.82,1.10]).[14]

The ORR was similar between the two treatments in both studies. In the POPLAR study, 15% of patients in both the atezolizumab and docetaxel groups achieved an objective response. However, the responses with atezolizumab were more durable, with a median DOR of 14.3 months compared to 7.2 months for docetaxel.[13] In the OAK study, the median DOR was notably longer for atezolizumab at 16.3 months compared to 6.2 months for docetaxel.[14]

- ***Efficacy of atezolizumab + chemotherapy***

Atezolizumab combined with chemotherapy further enhanced efficacy. In advanced nonsquamous NSCLC, the IMpower130 study investigated atezolizumab combined with carboplatin plus nab-paclitaxel versus chemotherapy alone. The results showed significant improvements in both OS and PFS.[50] The median OS was 18.6 months (95% CI [16.0,21.2]) in the atezolizumab plus chemotherapy group compared to 13.9 months (95% CI [12.0,18.7]) in the chemotherapy-only group. Similarly, the median PFS was 7.0 months (95% CI [6.2,7.3]) with the combination therapy versus 5.5 months (95% CI [4.4,5.9]) with chemotherapy alone. OS and PFS benefits were observed regardless of PD-L1 expression levels.

The above results are supported by that of the IMpower132 study, which also focused on advanced nonsquamous NSCLC,

and compared atezolizumab plus cisplatin or carboplatin plus pemetrexed (APP) with chemotherapy alone (PP). APP showed a significant improvement in PFS with a median of 7.6 months (HR = 0.60, 95% CI [0.49,0.72]) compared to 5.2 months for PP. Although OS was numerically better for APP, the difference was not statistically significant. OS and PFS benefits were consistent across all levels of PD-L1 expression.[51]

The IMpower131 study, which investigated advanced squamous NSCLC, showed that atezolizumab combined with carboplatin plus nab-paclitaxel (A+CnP) showed a median PFS of 6.3 months (HR = 0.71, 95% CI [0.60–0.85]) compared to 5.6 months with chemotherapy alone (CnP).[52] However, the median OS was similar between the two groups: 14.2 months for A+CnP versus 13.5 months for CnP. The PFS and OS benefits were observed irrespective of PD-L1 expression levels.

Durvalumab/MEDI4736

- ***Efficacy of durvalumab monotherapy:***

The PACIFIC trial was a pivotal phase 3 study evaluating the efficacy of the immune checkpoint inhibitor durvalumab in patients with stage III, unresectable NSCLC who did not exhibit disease progression following concurrent chemoradiotherapy. The trial demonstrated that durvalumab significantly prolonged PFS compared to placebo. Specifically, the median PFS was 16.8 months for the durvalumab group versus 5.6 months for the placebo group (HR for disease progression or death, 0.52; 95% CI [0.42, 0.65]; P<0.001).[15] A separate study found that durvalumab consistently benefited PFS across all prespecified subgroups, including sex and age.[53]

Moreover, durvalumab also showed a significant improvement in OS. The 12-month OS rate was 83.1% in the durvalumab group compared to 75.3% in the placebo group, while the 24-month OS rates were 66.3% versus 55.6%, respectively.[15] The stratified HR for death was 0.68 (99% CI, [0.47,0.997]; P=0.0025), indicating a significant OS benefit with durvalumab across all prespecified subgroups, except for patients with PD-L1 tumor cell expression <1%, where the benefit was uncertain.

A five-year follow-up of the PACIFIC study demonstrated that durvalumab confers long-term benefits on OS and PFS, with estimated 5-year OS rates of 42.9% for the durvalumab group compared to 33.4% for the placebo group, and 5-year PFS rates of 33.1% and 19.0%, respectively.[54]

The safety profile of durvalumab was also assessed, showing that grade 3 or 4 adverse events occurred in 30.5% of patients in the durvalumab group compared to 26.1% in the placebo group. The most common adverse events leading to discontinuation were pneumonitis and radiation pneumonitis, though the incidence of severe events was balanced between the groups (3.4% for durvalumab vs. 2.6% for placebo).[15]

- ***Efficacy of durvalumab + chemotherapy:***

The combination of durvalumab and chemotherapy has also been shown to significantly improve both PFS and OS compared to chemotherapy alone. In the phase III POSEIDON study, the median PFS was 5.5 months with durvalumab plus chemotherapy (D + CT) versus 4.8 months with chemotherapy (CT) alone, and the 24-month OS rates were 29.6% for D + CT versus 22.1% for CT.[55] In a separate non-comparative study (SAKK 16/14), durvalumab combined with neoadjuvant chemotherapy demonstrated notably high OS rates of 91% and 83% at 1 and 2 years respectively. Notably, patients with a PD-L1 expression of ≥25% had a higher rate of pathologic complete response. The study reported that 88% of patients experienced adverse events of grade 3 and above.[56]

Analysis

- ***Nivolumab:***

There exists some contradictory data about the efficacy of nivolumab monotherapy, though it constitutes a small fraction of the clinical studies investigating nivolumab. For instance, nivolumab's efficacy was challenged in the CheckMate 026 study, where patients with a PD-L1 expression level of 5% or more showed a median PFS of 4.2 months with nivolumab versus 5.9 months with chemotherapy, and a median OS of 14.4 months versus 13.2 months (hazard ratio for death, 1.02; 95% CI, [0.80,1.30]).[29] Additionally, TRAEs of any grade were reported in 71% of patients receiving nivolumab, compared to 92% with chemotherapy, with grade 3 or 4 events occurring in 18% and 51% of patients, respectively. These conflicting results may stem from differences in patient populations between this study and other trials, such as variations in genetic factors or immune system function. They may also be a result of external factors that may influence outcomes, including geographic location, healthcare access, and socioeconomic conditions.

Further, the benefit of nivolumab can vary depending on specific patient characteristics. For example, in the CheckMate 057 study, patients with epidermal growth factor receptor (EGFR) mutations derived less benefit from nivolumab compared to those without these mutations, though this finding is limited by the small number of EGFR-positive patients.[34]

Additionally, dual immunotherapy with nivolumab and ipilimumab does not show consistent benefits over nivolumab monotherapy in some studies and leads to higher rates of severe TRAEs compared to nivolumab monotherapy.[43]

- ***Pembrolizumab:***

Despite its efficacy, pembrolizumab has limitations and associated adverse effects. In the KEYNOTE-010 study, while pembrolizumab showed substantial survival benefits, progression-free survival in the total population did not meet statistical significance criteria.[30] Additionally, although pembrolizumab generally has a favorable safety profile compared to chemotherapy, TRAEs still occur. In the KEYNOTE-024 study, TRAEs of any grade occurred in 73.4% of pembrolizumab-treated patients compared to 90.0% in the chemotherapy group, with grade 3, 4, or 5 adverse events occurring in 26.6% versus 53.3%, respectively.[12]

Regarding pembrolizumab combined with chemotherapy, studies conducted on patients with both nonsquamous and squamous NSCLC reported adverse events of grade 3 or higher occurring in a significant proportion of patients—67.2% in the nonsquamous and 69.8% in the squamous groups, respectively.[46,48] Discontinuation rates due to adverse events were

DOI: 10.36838/v7i2.78

notably higher in the pembrolizumab + chemotherapy groups as compared to the placebo + chemotherapy groups.[46,48,49]

- ***Atezolizumab:***

Atezolizumab demonstrated a more favorable safety profile compared to docetaxel. In the POPLAR study, 40% of patients in the atezolizumab group experienced grade 3-4 adverse events, compared to 53% in the docetaxel group.[13] The OAK study also reported fewer TRAEs with atezolizumab, with grade 3-4 events occurring in 15% of patients compared to 43% for docetaxel.[14] The follow-up of the OAK study confirmed that adverse events leading to treatment discontinuation were similar between long-term survivors and non-survivors treated with atezolizumab.[31]

Moreover, despite its promising efficacy, the addition of atezolizumab to chemotherapy is associated with increased adverse effects. In the IMpower130 study, serious TRAEs were reported in 24% of patients receiving atezolizumab plus chemotherapy, compared to 13% in the chemotherapy-only group.[50] Treatment-related deaths occurred in 2% of patients in the atezolizumab group versus less than 1% in the chemotherapy group. The IMpower132 study also indicated higher rates of grade 3 or 4 adverse events in the APP group (54.6%) compared to the PP group (40.1%), with grade 5 events at 3.8% versus 2.9%, respectively.[51] In the IMpower131 study, any-cause adverse events were reported in 99.4% of patients in the A+CnP group and 97.0% in the CnP group.[52]

- ***Durvalumab/MEDI4736:***

Despite the demonstrated efficacy of durvalumab, there are notable limitations and adverse effects associated with its use. One significant limitation is the uncertain benefit in patients with low (<1%) PD-L1 expression. In this subgroup, the hazard ratio for overall survival was greater than 1, suggesting worse outcomes with durvalumab compared to placebo.[15] However, the wide confidence intervals indicate considerable uncertainty around this estimate, preventing definitive conclusions about its efficacy in this population.

Additionally, patients receiving durvalumab experienced a higher percentage of maximum-grade 3 or 4 adverse events compared to those receiving placebo (30.5% vs. 26.1%).[15] Discontinuation of the trial regimen due to adverse events was also more common in the durvalumab group (15.4% vs. 9.8%).

Summary

This review explores the efficacy of four anti-PD-1/PD-L1 immunotherapies for treating advanced NSCLC (summarized in Table 1). Nivolumab, pembrolizumab, and durvalumab demonstrate robust efficacy in improving OS and PFS: nivolumab shows consistent benefits observed across various PD-L1 expression levels and has a favorable safety profile. Dual immunotherapy with nivolumab and ipilimumab also shows promising results, albeit with higher adverse event rates compared to nivolumab monotherapy.

Pembrolizumab similarly has a favorable safety profile but particularly benefits patients with high PD-L1 expression. Durvalumab results in an increased incidence of severe adverse events; its benefit for patients with low PD-L1 expression also remains unclear. Finally, atezolizumab improves OS, especially in patients with higher PD-L1 expression levels, and exhibits a favorable safety profile; however, its efficacy in improving PFS may benefit from further investigation.

Table 1: Summary of studies showing the efficacy of nivolumab, pembrolizumab, atezolizumab, and durvalumab in treating advanced NSCLC.

Name of study	Aim of study	Results
CheckMate 017	Assessing the efficacy of nivolumab in treating advanced, previously treated squamous NSCLC	• Median OS with nivolumab was 9.2 months compared to 6.0 months with docetaxel, representing a 41% reduction in the risk of death.[33] • One-year OS rate was 42% with nivolumab versus 24% with docetaxel. • Median PFS was 3.5 months for nivolumab compared to 2.8 months for docetaxel. • TRAEs of grade 3 or 4 were significantly lower in the nivolumab group (7%) compared to the docetaxel group (55%). • Efficacy of nivolumab was consistent across different levels of PD-L1 expression. • Two-year OS rates were 23% with nivolumab and 8% with docetaxel.[35] • Five-year pooled OS rates (CheckMate 017/057 pooled) were 13.4% versus 2.6% with nivolumab and docetaxel respectively.[36]
CheckMate 057	Assessing the efficacy of nivolumab in treating advanced, previously treated nonsquamous NSCLC	• Median OS was 12.2 months with nivolumab compared to 9.4 months with docetaxel.[34] • One-year OS rate was 51% with nivolumab versus 39% with docetaxel. • Median PFS was 2.3 months with nivolumab versus 4.2 months with docetaxel. • One-year PFS rate was 19% with nivolumab versus 8% with docetaxel. • Efficacy of nivolumab was consistent across different levels of PD-L1 expression. • Two-year OS rates were 29% with nivolumab and 16% with docetaxel.[35] • Five-year pooled OS rates (CheckMate 017/057 pooled) were 13.4% versus 2.6% with nivolumab and docetaxel respectively.[36]
Safety and efficacy of nivolumab and standard chemotherapy drug combination in patients with advanced non-small-cell lung cancer: a four arms phase Ib study	Assessing the safety and efficacy of nivolumab combined with different types of standard chemotherapy in treating advanced NSCLC	• The chemotherapy regimens in each arm were nivolumab with gemcitabine/cisplatin (arm A), pemetrexed/cisplatin (arm B), paclitaxel/carboplatin/bevacizumab (arm C), or docetaxel (arm D) respectively.[38] • Overall response rates were 50%, 50%, 100%, and 16.7% in arms A, B, C, and D respectively. • The median PFS was 6.28 months in arm A, 9.63 months in arm B, not reached in arm C, and 3.15 months in arm D. • PFS rates at 6 months were 60.0%, 83.3%, 83.3%, and 0.0% for arms A, B, C, and D respectively. • PFS rates at 9 months were 40.0%, 83.3%, 83.3%, and 0.0% for arms A, B, C, and D respectively. • 5-year PFS was observed in 0 out of 6, 1 out of 6, 1 out of 6, and 0 out of 6 patients in arms A, B, C, and D, respectively.[39] • 5-year OS was observed in 0 out of 6, 1 out of 6, 4 out of 6, and 0 out of 6 patients in arms A, B, C, and D, respectively. • No unexpected severe AEs or treatment-related deaths occurred.
CheckMate 227	Assessing the efficacy of nivolumab plus ipilimumab in treating advanced NSCLC	• For patients with PD-L1 expression levels of 1% or more, the median OS was 17.1 months with nivolumab plus ipilimumab compared to 14.9 months with chemotherapy.[40] • The 2-year OS rates for patients with PD-L1 expression levels of 1% or more were 40.0% with nivolumab plus ipilimumab and 32.8% with chemotherapy. • For patients with PD-L1 expression levels below 1%, the median OS was 17.2 months with nivolumab plus ipilimumab versus 12.2 months with chemotherapy. • The overall patient population showed a median OS of 17.1 months with nivolumab plus ipilimumab and 13.9 months with chemotherapy. • 5-year median OS was 17.1 months for patients with PD-L1 expression ≥1% and 17.4 months for those with PD-L1 expression <1%.[41] • The ORRs were 33% and 28% for nivolumab plus ipilimumab and chemotherapy respectively. • The median DOR was significantly longer with nivolumab plus ipilimumab (21.7 months) as compared to chemotherapy (5.8 months). • 27% of patients had an ongoing response at 5 years with nivolumab plus ipilimumab compared to only 3% with chemotherapy.

Lung-MAP S1400I	Assessing if the addition of ipilimumab to nivolumab improves survival in patients with advanced, pretreated, immunotherapy-naive squamous NSCLC	• The median OS was 10 months with nivolumab plus ipilimumab and 11 months with nivolumab monotherapy.[43] • ORRs were 18% with nivolumab plus ipilimumab and 17% with nivolumab monotherapy. • OS and PFS were not significantly different between the nivolumab plus ipilimumab and nivolumab monotherapy groups. • Grade 3 or higher TRAEs occurred in 39.5% patients receiving nivolumab plus ipilimumab and 33.3% receiving nivolumab monotherapy.
KEYNOTE-010	Assessing efficacy of pembrolizumab in treating PD-L1-positive, previously treated, advanced NSCLC	• The median OS was 14.9 months for patients given pembrolizumab 2 mg/kg and 17.3 months for patients given pembrolizumab 10 mg/kg, compared to 8.2 months for patients given docetaxel.[30] • PFS was significantly longer in patients treated with pembrolizumab, with a median of 5.0 months for the 2 mg/kg group and 5.2 months for the 10 mg/kg group, compared to 4.1 months for the docetaxel group. • ORRs were 18% in patients given pembrolizumab 2 mg/kg, 18% in those given pembrolizumab 10 mg/kg, and 9% in those given docetaxel. • Grade 3-5 TRAEs occurred in 13% of patients given pembrolizumab 2 mg/kg, 16% of those given pembrolizumab 10 mg/kg, and 35% of those given docetaxel.
KEYNOTE-024	Assessing efficacy of pembrolizumab in treating PD-L1-positive, previously treated, advanced NSCLC	• Pembrolizumab demonstrated a median PFS of 10.3 months compared to 6.0 months for chemotherapy.[12] • The estimated rate of OS at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group. • Pembrolizumab also achieved a higher ORR (44.8% vs. 27.8%) and a longer median DOR (not reached vs. 6.3 months). • TRAEs of any grade occurred in 73.4% vs. 90.0% of patients in the pembrolizumab and chemotherapy groups respectively.
KEYNOTE-042	Assessing efficacy of pembrolizumab in treating PD-L1-expressing, previously untreated, advanced NSCLC	• Median OS was 20.0 months in the pembrolizumab group vs. 12.0 months in the chemotherapy group in the PD-L1 TPS ≥ 50% population, 17.7 months vs. 13.0 months in the PD-L1 TPS ≥ 20% population, and 16.7 months vs. 12.1 months in the PD-L1 TPS ≥ 1% population.[44] • Median PFS was 7.1 months in the pembrolizumab group vs. 6.4 months in the chemotherapy group in the PD-L1 TPS ≥ 50% population, 6.2 months vs. 6.6 months in the PD-L1 TPS ≥ 20% population, and 5.4 months vs. 6.5 months in the PD-L1 TPS ≥ 1% population. • 5-year OS rates with pembrolizumab were 21.9% for PD-L1 TPS ≥ 50%, 19.4% for PD-L1 TPS ≥ 20%, and 16.6% for PD-L1 TPS ≥ 1%. In comparison, 5-year OS rates with chemotherapy were 9.8% for PD-L1 TPS ≥ 50%, 10.1% for PD-L1 TPS ≥ 20%, and 8.5% for PD-L1 TPS ≥ 1%.[45]
KEYNOTE-189	Assessing efficacy of pembrolizumab plus chemotherapy in treating previously untreated, nonsquamous, metastatic NSCLC	• The OS for patients receiving pembrolizumab plus chemotherapy was 69.2% at 12 months, as compared to 49.4% in the placebo group.[46] • This benefit was consistent across all levels of PD-L1 expression. For instance, the OS for patients with PD-L1 TPS < 1% was 61.7% vs. 52.2% in the pembrolizumab plus chemotherapy group and the placebo group respectively. The OS for patients with PD-L1 TPS ≥ 50% was 73.0% vs. 48.1% in the pembrolizumab plus chemotherapy group and the placebo group respectively. • The median PFS in the pembrolizumab group was 8.8 months versus 4.9 months in the placebo group.
Phase 2 cohort of the multicohort study KEYNOTE-021	Assessing if the addition of pembrolizumab to platinum-doublet chemotherapy improves efficacy in patients with advanced nonsquamous NSCLC	• Pembrolizumab demonstrated a median PFS of 13.0 months compared to 8.9 months with chemotherapy alone.[47] • No significant difference in OS was observed between the two groups (HR 0.90; 95% CI 0.42–1.91; nominal p=0.39).
KEYNOTE-407	Assessing if the addition of pembrolizumab to platinum-doublet chemotherapy improves efficacy in patients with advanced squamous NSCLC	• The median OS was 15.9 months in the pembrolizumab plus chemotherapy group, compared to 11.3 months in the placebo group.[48] • The median PFS was 6.4 months in the pembrolizumab plus chemotherapy group versus 4.8 months in the placebo group.
Pembrolizumab Plus Chemotherapy Versus Chemotherapy Monotherapy as a First-Line Treatment in Elderly Patients (≥75 Years Old) With Non-Small-Cell Lung Cancer	Assessing the efficacy and safety of pembrolizumab plus chemotherapy in elderly patients with advanced NSCLC	• The median PFS was 12.5 months in the pembrolizumab plus chemotherapy group versus 5.3 months in the chemotherapy-only group.[49] • OS was not reached in the pembrolizumab plus chemotherapy group compared to 21.27 months in the chemotherapy-only group (P=0.037). • Treatment discontinuation due to adverse effects was higher in the pembrolizumab plus chemotherapy group (26%) compared to the chemotherapy-only group (5%).
POPLAR	Assessing the efficacy and safety of atezolizumab versus docetaxel in previously treated NSCLC	• Patients treated with atezolizumab had a median OS of 12.6 months compared to 9.7 months for those treated with docetaxel.[13] • Greater OS improvements were associated with higher levels of PD-L1 expression. • PFS was similar between the two groups: 2.7 months for atezolizumab versus 3.0 months for docetaxel. • Though 15% of patients in both the atezolizumab and docetaxel groups achieved an objective response, the responses with atezolizumab were more durable, with a median DOR of 14.3 months compared to 7.2 months for docetaxel.[31]
OAK	Assessing the efficacy and safety of atezolizumab versus docetaxel in previously treated NSCLC	• Atezolizumab improved OS to a median of 13.8 months compared to 9.6 months for docetaxel.[14] • PFS was 2.8 months versus 4.0 months with atezolizumab and docetaxel respectively. • The median DOR was notably longer for atezolizumab at 16.3 months compared to 6.2 months for docetaxel. • After more than two years, atezolizumab continued to provide a durable survival benefit, with 28% of patients surviving longer than 24 months compared to 18% in the docetaxel group.
IMpower130	Assessing the efficacy and safety of atezolizumab plus chemotherapy versus chemotherapy alone as first-line therapy for stage IV nonsquamous NSCLC	• The median OS was 18.6 months in the atezolizumab plus chemotherapy group compared to 13.9 months in the chemotherapy-only group.[50] • The median PFS was 7.0 months with atezolizumab plus chemotherapy versus 5.5 months with chemotherapy alone. • OS and PFS benefits were observed regardless of PD-L1 expression levels.
IMpower132	Assessing the efficacy and safety of adding atezolizumab to carboplatin or cisplatin plus pemetrexed for patients with stage IV nonsquamous NSCLC	• Median PFS was 7.6 months with atezolizumab plus cisplatin or carboplatin plus pemetrexed (APP), and 5.2 months with chemotherapy alone (PP).[51] • Median OS was 17.5 months for APP vs. 13.6 months for PP. Although OS was numerically better for APP, the difference was not statistically significant. • OS and PFS benefits were consistent across all levels of PD-L1 expression.
IMpower131	Assessing the efficacy and safety of adding atezolizumab to platinum-based chemotherapy for patients with stage IV squamous NSCLC	• Atezolizumab combined with carboplatin plus nab-paclitaxel (A+CnP) showed a median PFS of 6.3 months compared to 5.6 months with chemotherapy alone (CnP).[52] • The median OS was similar between the two groups: 14.2 months for A+CnP versus 13.5 months for CnP. • PFS and OS benefits were observed irrespective of PD-L1 expression levels.
PACIFIC	Assessing the efficacy and safety of durvalumab in treating stage III NSCLC	• The median PFS was 16.8 months for the durvalumab group versus 5.6 months for the placebo group.[15] • The 12-month OS rate was 83.1% in the durvalumab group compared to 75.3% in the placebo group, while the 24-month OS rates were 66.3% versus 55.6%, respectively. • OS benefits with durvalumab were significant across all prespecified subgroups, except for patients with PD-L1 tumor cell expression <1%, where the benefit was uncertain. • Grade 3 or 4 AEs occurred in 30.5% of patients in the durvalumab group compared to 26.1% in the placebo group. • The incidence of severe events was 3.4% in the durvalumab group vs. 2.6% in the placebo group. • According to a five-year follow-up, estimated 5-year OS rates were 42.9% for the durvalumab group compared to 33.4% for the placebo group, and 5-year PFS rates were 33.1% and 19.0% respectively.[54]
POSEIDON	Assessing the efficacy of durvalumab plus chemotherapy (D + CT) versus chemotherapy alone (CT) in treating metastatic NSCLC	• Median PFS was 5.5 months with D + CT versus 4.8 months with CT alone.[55] • The 24-month OS rates were 29.6% for D + CT versus 22.1% for CT.
SAKK 16/14	Assessing the efficacy and safety of adding perioperative durvalumab to neoadjuvant chemotherapy for stage IIIA NSCLC	• Durvalumab combined with neoadjuvant chemotherapy demonstrated notably high OS rates of 91% and 83% at 1 and 2 years respectively.[56] • Patients with a PD-L1 expression of ≥25% had a higher rate of pathologic complete response. • 88% of patients experienced adverse events of grade 3 and above.

Mechanisms for differential efficacy of the mAbs are still under investigation, and literature on this topic is currently

DOI: 10.36838/v7i2.78

limited. However, a study has found that the epitope region of pembrolizumab has a considerably greater overlap with the PD-L1 binding site than the epitope region of nivolumab.[57] It is possible that for tumors that express high levels of PD-L1, pembrolizumab's stronger binding affinity to the PD-L1 binding site may lead to a more robust anti-tumor immune response compared to nivolumab. This may explain why pembrolizumab is particularly effective in patients with high PD-L1 expression, whereas nivolumab consistently benefits patients regardless of their PD-L1 expression levels.

Cost-effectiveness

A major consideration in access to care regarding cancer therapy is the burden of cost. Each of the ICIs covered demonstrates varying cost-effectiveness and quality-adjusted life year (QALY) improvements across different regions. Nivolumab improved QALYs compared to docetaxel in the US, Canada, and Sweden. For instance, nivolumab increased QALYs by 0.80 and 0.99 in patients with squamous and nonsquamous NSCLC respectively in the US.[58] The incremental cost-effectiveness ratios (ICERs) of nivolumab in the United States (US) were USD 100,776 per QALY in squamous and USD 117,739 per QALY in nonsquamous NSCLC patients. Nivolumab was considered cost-effective at a willingness-to-pay (WTP) threshold of USD 150,000. In Canada, the ICERs were CAN$140,753 per QALY for squamous and CAN$173,804 per QALY for nonsquamous NSCLC, while in Sweden, the ICERs were SEK568,895 per QALY and SEK662,991 per QALY for squamous and nonsquamous NSCLC patients respectively.[59] Despite higher costs, nivolumab remains approved for advanced NSCLC treatment in all three countries due to favorable long-term survival benefits, with Canada and Sweden showing increasingly favorable ICERs based on updated trial data with a minimum follow-up of 5 years.

In a study investigating the cost-effectiveness of pembrolizumab as a first-line advanced NSCLC treatment, patients treated with pembrolizumab gained 1.80 QALYs compared to 1.06 QALYs with chemotherapy.[60] In the United Kingdom (UK), the ICER for pembrolizumab without end-of-life (EoL) adjustments—where a higher WTP threshold is applied for treatments aimed at extending life in terminal patients—is above the UK WTP threshold of GBP 30,000 (USD 42,048), at approximately USD 52,000 per QALY. However, with EoL adjustments, the probability of pembrolizumab being cost-effective in the UK increases from <1% to 97.1%. Pembrolizumab could thus be considered cost-effective in the UK if a higher WTP threshold is implemented. In contrast, in the US, where the WTP threshold ranges from USD 100,000 to USD 150,000, the probabilities of pembrolizumab being cost-effective exceed 97% both with and without EoL adjustments. Finally, in Singapore, the ICER for pembrolizumab is SGD 167,692 per QALY, far exceeding the local WTP threshold of SGD 100,000.[61] This indicates that pembrolizumab is unlikely to be a cost-effective NSCLC treatment in Singapore. Overall, pembrolizumab's use in the clinic is more likely in regions like the US where higher WTP thresholds apply, but its high cost remains a barrier to broader adoption in countries like Singapore and the UK, where its use may be limited unless a higher WTP threshold is applied.

In China, atezolizumab as a first-line treatment for metastatic NSCLC provides an additional 0.42 to 0.91 QALYs in comparison to chemotherapy, depending on PD-L1 expression levels.[62] However, the ICERs for atezolizumab as a first-line treatment for metastatic NSCLC significantly exceed China's WTP threshold of USD 30,828 per QALY, making it unlikely to be cost-effective there. In the US, however, the ICER for atezolizumab as a first-line treatment for metastatic NSCLC patients with high PD-L1 expression is USD 123,424 per QALY, falling within the US WTP threshold range.[63] Lastly, in Canada, atezolizumab as a second-line treatment for advanced NSCLC provides a QALY gain of 0.60 over docetaxel at an ICER of CAD 142,074 per QALY.[64] Docetaxel was more likely to be cost-effective at WTP thresholds below CAD 125,000 per QALY, whereas atezolizumab was more likely to be cost-effective at thresholds above this amount. Since a WTP threshold of CAD 50,000 per QALY is used in Canada, atezolizumab is unlikely to be cost-effective there.[65] Overall, while atezolizumab is more likely to be used in clinics in the US, its high cost limits its use in China and Canada where the WTP threshold is much lower.

Finally, treatment with durvalumab as maintenance therapy in patients with stage III NSCLC provided an additional 0.50 QALYs compared with placebo.[66] The ICER for durvalumab in the US is USD 228,788 per QALY, significantly exceeding the US WTP threshold with only a 7.2% probability of being cost-effective. Similarly, in Brazil and Singapore, the ICERs for durvalumab are USD 141,146 and USD 153,461 per QALY respectively. Both ICERs far exceed local WTP thresholds, with a 0% likelihood of cost-effectiveness in either country. However, in Singapore, a secondary analysis using discounted prices through an industry-sponsored access program improved cost-effectiveness, with the ICER dropping to USD 45,164 per QALY and the probability of durvalumab being cost-effective rising to 74.9%. Overall, while durvalumab is unlikely to be widely used in most countries due to its high cost, reduced pricing in certain regions such as Singapore could increase its viability in clinical practice.

Future directions

This review has found that there is a substantial body of research on the effectiveness of combined immunotherapy with nivolumab and ipilimumab, whereas data on dual immunotherapy involving other anti-PD-1 and anti-PD-L1 ICIs is comparatively sparse. Research evaluating durvalumab in treating advanced NSCLC is limited compared to that evaluating pembrolizumab, nivolumab, and atezolizumab; research investigating the efficacy of durvalumab combined with chemotherapy in treating advanced NSCLC is also lacking. Continued research is essential to maximize the therapeutic potential of all four ICIs in managing advanced NSCLC. Areas that warrant further investigation include the efficacy of dual immunotherapies using ICIs other than nivolumab and the effectiveness of durvalumab, particularly in NSCLC patients with low PD-L1 expression. In addition, studies

on atezolizumab should aim to clarify its role in improving progression-free survival, while research into durvalumab combined with chemotherapy could reveal benefits for advanced NSCLC treatment. Finally, although higher PD-L1 expression levels are generally associated with better overall survival in NSCLC patients treated with anti-PD-1/PD-L1 therapies, further studies are required to confirm PD-L1's value as a prognostic marker, as considerable variability exists in the methods used to assess PD-L1 expression.

Beyond PD-1/PD-L1 inhibition, other immune checkpoint receptors that play a critical role in tumor immune evasion, such as CTLA-4, should be explored further in advanced NSCLC treatment. When CTLA-4 binds to B7, this results in the downregulation of helper T cells, which help activate cytotoxic T cells (Tcs) to kill target tumor cells. This also enhances the activity of regulatory T cells (Tregs), which help the immune system avoid overreacting to antigens by suppressing certain immune responses. Together, these mechanisms contribute to immune suppression, allowing tumors to evade immune detection.[67] The combined inhibition of both the PD-1/PD-L1 and the CTLA-4/B7 axes has already been established as an effective treatment strategy for patients with multiple malignancies.[68] As such, investigating combination therapies targeting multiple immune checkpoints could be a promising approach, as dual inhibition may reduce the likelihood of tumor resistance that can arise when targeting a single immune checkpoint pathway.

Lastly, future research should also prioritize Tregs as a critical target for therapeutic intervention. Tregs play a pivotal role in limiting the therapeutic efficacy of ICIs by suppressing anti-tumor immune responses and promoting immune tolerance within the tumor microenvironment. Their abundance has been associated with poor clinical outcomes, as they inhibit the activation and function of Tcs which are essential for effective tumor eradication.[69] By focusing on strategies to deplete or modulate Tregs, researchers could potentially enhance the effectiveness of ICIs, leading to improved patient outcomes. Investigating combination therapies that target Tregs alongside ICIs may provide a dual approach to overcoming the immunosuppressive barriers posed by Tregs, thereby increasing anti-tumor immunity and improving survival rates for patients with NSCLC.

Limitations

There are limitations to this review that should be noted. Firstly, the exclusion of non-English language studies may limit the generalizability of these findings to different ethnic groups not included in the studies used. Additionally, findings related to PD-L1 expression in tissue are dependent on the accuracy and reliability of the methods used to assess PD-L1 expression levels. Factors such as cutoff values, assays used to assess PD-L1 tumor expression, whether biopsy or excision specimens were used, and whether membranous or cytoplasmic staining was used varied significantly across studies, particularly within studies published before recent attempts to standardize PD-L1 immunochemistry. This may hamper this review's findings regarding the efficacy of various ICIs in patient populations with different PD-L1 expression levels.

■ Conclusion

This review evaluates the effectiveness of four anti-PD-1/PD-L1 immunotherapies—nivolumab, pembrolizumab, durvalumab, and atezolizumab—for advanced NSCLC, with all but atezolizumab showing efficacy in improving PFS, and all but nivolumab demonstrating greater benefits in patients with higher PD-L1 expression levels. Research on dual immunotherapies with other ICIs and the combination of durvalumab with chemotherapy is limited. Continued research is needed to optimize the use of these therapies, particularly regarding the efficacy of dual immunotherapies, the role of PD-L1 expression in predicting outcomes, and the impact of combining durvalumab with chemotherapy.

■ Acknowledgments

I would like to thank Dr. Frank Glover for providing valuable insight and support.

■ References

1. Siegel, R. L.; Miller, K. D.; Fuchs, H. E.; Jemal, A. Cancer Statistics, 2022. *CA. Cancer J. Clin.* **2022**, *72* (1), 7–33. https://doi.org/10.3322/caac.21708.
2. Howlader, N.; Forjaz, G.; Mooradian, M. J.; Meza, R.; Kong, C. Y.; Cronin, K. A.; Mariotto, A. B.; Lowy, D. R.; Feuer, E. J. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. *N. Engl. J. Med.* **2020**, *383* (7), 640–649. https://doi.org/10.1056/NEJMoa1916623.
3. Musika, W.; Kamsa-Ard, S.; Jirapornkul, C.; Santong, C.; Phunmanee, A. Lung Cancer Survival with Current Therapies and New Targeted Treatments: A Comprehensive Update from the Srinagarind Hospital-Based Cancer Registry from (2013 to 2017). *Asian Pac. J. Cancer Prev.* **2021**, *22* (8), 2501–2507. https://doi.org/10.31557/APJCP.2021.22.8.2501.
4. Herbst, R. S.; Morgensztern, D.; Boshoff, C. The Biology and Management of Non-Small Cell Lung Cancer. *Nature* **2018**, *553* (7689), 446–454. https://doi.org/10.1038/nature25183.
5. Chen, S.; Hu, B.; Li, H. A Meta-Analysis of Nivolumab for the Treatment of Advanced Non-Small-Cell Lung Cancer. *OncoTargets Ther.* **2018**, *Volume 11*, 7691–7697. https://doi.org/10.2147/OTT.S171072.
6. Remon, J.; Esteller, L.; Taus, Á. Nivolumab plus Ipilimumab Combination Therapy for the First-Line Treatment NSCLC: Evidence to Date. *Cancer Manag. Res.* **2019**, *Volume 11*, 4893–4904. https://doi.org/10.2147/CMAR.S164935.
7. Johnson, D. B.; Rioth, M. J.; Horn, L. Immune Checkpoint Inhibitors in NSCLC. *Curr. Treat. Options Oncol.* **2014**, *15* (4), 658–669. https://doi.org/10.1007/s11864-014-0305-5.
8. Hudson, K.; Cross, N.; Jordan-Mahy, N.; Leyland, R. The Extrinsic and Intrinsic Roles of PD-L1 and Its Receptor PD-1: Implications for Immunotherapy Treatment. *Front. Immunol.* **2020**, *11*, 568931. https://doi.org/10.3389/fimmu.2020.568931.
9. Fessas, P.; Lee, H.; Ikemizu, S.; Janowitz, T. A Molecular and Preclinical Comparison of the PD-1–Targeted T-Cell Checkpoint Inhibitors Nivolumab and Pembrolizumab. *Semin. Oncol.* **2017**, *44* (2), 136–140. https://doi.org/10.1053/j.seminoncol.2017.06.002.
10. Han, Y.; Liu, D.; Li, L. PD-1/PD-L1 Pathway: Current Researches in Cancer. *Am. J. Cancer Res.* **2020**, *10* (3), 727–742.

DOI: 10.36838/v7i2.78

11. Ai, L.; Xu, A.; Xu, J. Roles of PD-1/PD-L1 Pathway: Signaling, Cancer, and Beyond. In *Regulation of Cancer Immune Checkpoints*; Xu, J., Ed.; Advances in Experimental Medicine and Biology; Springer Singapore: Singapore, 2020; Vol. 1248, pp 33–59. https://doi.org/10.1007/978-981-15-3266-5_3.
12. Reck, M.; Rodríguez-Abreu, D.; Robinson, A. G.; Hui, R.; Csőszi, T.; Fülöp, A.; Gottfried, M.; Peled, N.; Tafreshi, A.; Cuffe, S.; O'Brien, M.; Rao, S.; Hotta, K.; Leiby, M. A.; Lubiniecki, G. M.; Shentu, Y.; Rangwala, R.; Brahmer, J. R. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. *N. Engl. J. Med*. **2016**, *375* (19), 1823–1833. https://doi.org/10.1056/NEJMoa1606774.
13. Fehrenbacher, L.; Spira, A.; Ballinger, M.; Kowanetz, M.; Vansteenkiste, J.; Mazieres, J.; Park, K.; Smith, D.; Artal-Cortes, A.; Lewanski, C.; Braiteh, F.; Waterkamp, D.; He, P.; Zou, W.; Chen, D. S.; Yi, J.; Sandler, A.; Rittmeyer, A. Atezolizumab versus Docetaxel for Patients with Previously Treated Non-Small-Cell Lung Cancer (POPLAR): A Multicentre, Open-Label, Phase 2 Randomised Controlled Trial. *The Lancet* **2016**, *387* (10030), 1837–1846. https://doi.org/10.1016/S0140-6736(16)00587-0.
14. Rittmeyer, A.; Barlesi, F.; Waterkamp, D.; Park, K.; Ciardiello, F.; Von Pawel, J.; Gadgeel, S. M.; Hida, T.; Kowalski, D. M.; Dols, M. C.; Cortinovis, D. L.; Leach, J.; Polikoff, J.; Barrios, C.; Kabbinavar, F.; Frontera, O. A.; De Marinis, F.; Turna, H.; Lee, J.-S.; Ballinger, M.; Kowanetz, M.; He, P.; Chen, D. S.; Sandler, A.; Gandara, D. R. Atezolizumab versus Docetaxel in Patients with Previously Treated Non-Small-Cell Lung Cancer (OAK): A Phase 3, Open-Label, Multicentre Randomised Controlled Trial. *The Lancet* **2017**, *389* (10066), 255–265. https://doi.org/10.1016/S0140-6736(16)32517-X.
15. Antonia, S. J.; Villegas, A.; Daniel, D.; Vicente, D.; Murakami, S.; Hui, R.; Kurata, T.; Chiappori, A.; Lee, K. H.; De Wit, M.; Cho, B. C.; Bourhaba, M.; Quantin, X.; Tokito, T.; Mekhail, T.; Planchard, D.; Kim, Y.-C.; Karapetis, C. S.; Hiret, S.; Ostoros, G.; Kubota, K.; Gray, J. E.; Paz-Ares, L.; De Castro Carpeño, J.; Faivre-Finn, C.; Reck, M.; Vansteenkiste, J.; Spigel, D. R.; Wadsworth, C.; Melillo, G.; Taboada, M.; Dennis, P. A.; Özgüroğlu, M. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N. Engl. J. Med*. **2018**, *379* (24), 2342–2350. https://doi.org/10.1056/NEJMoa1809697.
16. Garon, E. B.; Rizvi, N. A.; Hui, R.; Leighl, N.; Balmanoukian, A. S.; Eder, J. P.; Patnaik, A.; Aggarwal, C.; Gubens, M.; Horn, L.; Carcereny, E.; Ahn, M.-J.; Felip, E.; Lee, J.-S.; Hellmann, M. D.; Hamid, O.; Goldman, J. W.; Soria, J.-C.; Dolled-Filhart, M.; Rutledge, R. Z.; Zhang, J.; Lunceford, J. K.; Rangwala, R.; Lubiniecki, G. M.; Roach, C.; Emancipator, K.; Gandhi, L. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2015**, *372* (21), 2018–2028. https://doi.org/10.1056/NEJMoa1501824.
17. Taube, J. M.; Klein, A.; Brahmer, J. R.; Xu, H.; Pan, X.; Kim, J. H.; Chen, L.; Pardoll, D. M.; Topalian, S. L.; Anders, R. A. Association of PD-1, PD-1 Ligands, and Other Features of the Tumor Immune Microenvironment with Response to Anti–PD-1 Therapy. *Clin. Cancer Res*. **2014**, *20* (19), 5064–5074. https://doi.org/10.1158/1078-0432.CCR-13-3271.
18. Kythreotou, A.; Siddique, A.; Mauri, F. A.; Bower, M.; Pinato, D. J. PD-L1. *J. Clin. Pathol.* **2018**, *71* (3), 189–194. https://doi.org/10.1136/jclinpath-2017-204853.
19. Xu-Monette, Z. Y.; Zhang, M.; Li, J.; Young, K. H. PD-1/PD-L1 Blockade: Have We Found the Key to Unleash the Antitumor Immune Response? *Front. Immunol*. **2017**, *8*, 1597. https://doi.org/10.3389/fimmu.2017.01597.
20. Valecha, G. K.; Vennepureddy, A.; Ibrahim, U.; Safa, F.; Samra, B.; Atallah, J. P. Anti–PD-1/PD-L1 Antibodies in Non-Small Cell Lung Cancer: The Era of Immunotherapy. *Expert Rev. Anticancer Ther.* **2017**, *17* (1), 47–59. https://doi.org/10.1080/14737140.2017.1259574.
21. Tang, Q.; Chen, Y.; Li, X.; Long, S.; Shi, Y.; Yu, Y.; Wu, W.; Han, L.; Wang, S. The Role of PD-1/PD-L1 and Application of Immune-Checkpoint Inhibitors in Human Cancers. *Front. Immunol.* **2022**, *13*, 964442. https://doi.org/10.3389/fimmu.2022.964442.
22. Valecha, G. K.; Vennepureddy, A.; Ibrahim, U.; Safa, F.; Samra, B.; Atallah, J. P. Anti-PD-1/PD-L1 Antibodies in Non-Small Cell Lung Cancer: The Era of Immunotherapy. *Expert Rev. Anticancer Ther*. **2017**, *17* (1), 47–59. https://doi.org/10.1080/14737140.2017.1259574.
23. Martínez-Lostao, L.; Anel, A.; Pardo, J. How Do Cytotoxic Lymphocytes Kill Cancer Cells? *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2015**, *21* (22), 5047–5056. https://doi.org/10.1158/1078-0432.CCR-15-0685.
24. van der Woude, L. L.; Gorris, M. A. J.; Halilovic, A.; Figdor, C. G.; de Vries, I. J. M. Migrating into the Tumor: A Roadmap for T Cells. *Trends Cancer* **2017**, *3* (11), 797–808. https://doi.org/10.1016/j.trecan.2017.09.006.
25. Baxevanos, P.; Mountzios, G. Novel Chemotherapy Regimens for Advanced Lung Cancer: Have We Reached a Plateau? *Ann. Transl. Med*. **2018**, *6* (8), 139. https://doi.org/10.21037/atm.2018.04.04.
26. Alexander, M.; Kim, S. Y.; Cheng, H. Update 2020: Management of Non-Small Cell Lung Cancer. *Lung* **2020**, *198* (6), 897–907. https://doi.org/10.1007/s00408-020-00407-5.
27. Prasad, V.; Kaestner, V. Nivolumab and Pembrolizumab: Monoclonal Antibodies against Programmed Cell Death-1 (PD-1) That Are Interchangeable. *Semin. Oncol.* **2017**, *44* (2), 132–135. https://doi.org/10.1053/j.seminoncol.2017.06.007.
28. U.S. Food & Drug Administration. *Atezolizumab (TECENTRIQ)*. https://www.fda.gov/drugs/resources-information-approved-drugs/atezolizumab-tecentriq (accessed 2024-11-17).
29. Carbone, D. P.; Reck, M.; Paz-Ares, L.; Creelan, B.; Horn, L.; Steins, M.; Felip, E.; Van Den Heuvel, M. M.; Ciuleanu, T.-E.; Badin, F.; Ready, N.; Hiltermann, T. J. N.; Nair, S.; Juergens, R.; Peters, S.; Minenza, E.; Wrangle, J. M.; Rodriguez-Abreu, D.; Borghaei, H.; Blumenschein, G. R.; Villaruz, L. C.; Havel, L.; Krejci, J.; Corral Jaime, J.; Chang, H.; Geese, W. J.; Bhagavatheeswaran, P.; Chen, A. C.; Socinski, M. A. First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2017**, *376* (25), 2415–2426. https://doi.org/10.1056/NEJMoa1613493.
30. Herbst, R. S.; Baas, P.; Kim, D.-W.; Felip, E.; Pérez-Gracia, J. L.; Han, J.-Y.; Molina, J.; Kim, J.-H.; Arvis, C. D.; Ahn, M.-J.; Majem, M.; Fidler, M. J.; De Castro, G.; Garrido, M.; Lubiniecki, G. M.; Shentu, Y.; Im, E.; Dolled-Filhart, M.; Garon, E. B. Pembrolizumab versus Docetaxel for Previously Treated, PD-L1-Positive, Advanced Non-Small-Cell Lung Cancer (KEYNOTE-010): A Randomised Controlled Trial. *The Lancet* **2016**, *387* (10027), 1540–1550. https://doi.org/10.1016/S0140-6736(15)01281-7.
31. Von Pawel, J.; Bordoni, R.; Satouchi, M.; Fehrenbacher, L.; Cobo, M.; Han, J. Y.; Hida, T.; Moro-Sibilot, D.; Conkling, P.; Gandara, D. R.; Rittmeyer, A.; Gandhi, M.; Yu, W.; Matheny, C.; Patel, H.; Sandler, A.; Ballinger, M.; Kowanetz, M.; Park, K. Long-Term Survival in Patients with Advanced Non–Small-Cell Lung Cancer Treated with Atezolizumab versus Docetaxel: Results from the Randomised Phase III OAK Study. *Eur. J. Cancer* **2019**, *107*, 124–132. https://doi.org/10.1016/j.ejca.2018.11.020.

32. Neumann, M.; Murphy, N.; Seetharamu, N. The Evolving Role of PD-L1 Inhibition in Non-Small Cell Lung Cancer: A Review of Durvalumab and Avelumab. *Cancer Med. J.* **2022**, *5* (1), 31–45.
33. Brahmer, J.; Reckamp, K. L.; Baas, P.; Crinò, L.; Eberhardt, W. E. E.; Poddubskaya, E.; Antonia, S.; Pluzanski, A.; Vokes, E. E.; Holgado, E.; Waterhouse, D.; Ready, N.; Gainor, J.; Arén Frontera, O.; Havel, L.; Steins, M.; Garassino, M. C.; Aerts, J. G.; Domine, M.; Paz-Ares, L.; Reck, M.; Baudelet, C.; Harbison, C. T.; Lestini, B.; Spigel, D. R. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2015**, *373* (2), 123–135. https://doi.org/10.1056/NEJMoa1504627.
34. Borghaei, H.; Paz-Ares, L.; Horn, L.; Spigel, D. R.; Steins, M.; Ready, N. E.; Chow, L. Q.; Vokes, E. E.; Felip, E.; Holgado, E.; Barlesi, F.; Kohlhäufl, M.; Arrieta, O.; Burgio, M. A.; Fayette, J.; Lena, H.; Poddubskaya, E.; Gerber, D. E.; Gettinger, S. N.; Rudin, C. M.; Rizvi, N.; Crinò, L.; Blumenschein, G. R.; Antonia, S. J.; Dorange, C.; Harbison, C. T.; Graf Finckenstein, F.; Brahmer, J. R. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2015**, *373* (17), 1627–1639. https://doi.org/10.1056/NEJMoa1507643.
35. Horn, L.; Spigel, D. R.; Vokes, E. E.; Holgado, E.; Ready, N.; Steins, M.; Poddubskaya, E.; Borghaei, H.; Felip, E.; Paz-Ares, L.; Pluzanski, A.; Reckamp, K. L.; Burgio, M. A.; Kohlhäeufl, M.; Waterhouse, D.; Barlesi, F.; Antonia, S.; Arrieta, O.; Fayette, J.; Crinò, L.; Rizvi, N.; Reck, M.; Hellmann, M. D.; Geese, W. J.; Li, A.; Blackwood-Chirchir, A.; Healey, D.; Brahmer, J.; Eberhardt, W. E. E. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *J. Clin. Oncol.* **2017**, *35* (35), 3924–3933. https://doi.org/10.1200/JCO.2017.74.3062.
36. Borghaei, H.; Gettinger, S.; Vokes, E. E.; Chow, L. Q. M.; Burgio, M. A.; De Castro Carpeno, J.; Pluzanski, A.; Arrieta, O.; Frontera, O. A.; Chiari, R.; Butts, C.; Wójcik-Tomaszewska, J.; Coudert, B.; Garassino, M. C.; Ready, N.; Felip, E.; García, M. A.; Waterhouse, D.; Domine, M.; Barlesi, F.; Antonia, S.; Wohlleber, M.; Gerber, D. E.; Czyzewicz, G.; Spigel, D. R.; Crino, L.; Eberhardt, W. E. E.; Li, A.; Marimuthu, S.; Brahmer, J. Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non–Small-Cell Lung Cancer. *J. Clin. Oncol.* **2021**, *39* (7), 723–733. https://doi.org/10.1200/JCO.20.01605.
37. Gettinger, S.; Horn, L.; Jackman, D.; Spigel, D.; Antonia, S.; Hellmann, M.; Powderly, J.; Heist, R.; Sequist, L. V.; Smith, D. C.; Leming, P.; Geese, W. J.; Yoon, D.; Li, A.; Brahmer, J. Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non–Small-Cell Lung Cancer: Results From the CA209-003 Study. *J. Clin. Oncol.* **2018**, *36* (17), 1675–1684. https://doi.org/10.1200/JCO.2017.77.0412.
38. Kanda, S.; Goto, K.; Shiraishi, H.; Kubo, E.; Tanaka, A.; Utsumi, H.; Sunami, K.; Kitazono, S.; Mizugaki, H.; Horinouchi, H.; Fujiwara, Y.; Nokihara, H.; Yamamoto, N.; Hozumi, H.; Tamura, T. Safety and Efficacy of Nivolumab and Standard Chemotherapy Drug Combination in Patients with Advanced Non-Small-Cell Lung Cancer: A Four Arms Phase Ib Study. *Ann. Oncol.* **2016**, *27* (12), 2242–2250. https://doi.org/10.1093/annonc/mdw416.
39. Kanda, S.; Ohe, Y.; Goto, Y.; Horinouchi, H.; Fujiwara, Y.; Nokihara, H.; Yamamoto, N.; Yamamoto, T.; Tamura, T. Five-year Safety and Efficacy Data from a Phase Ib Study of Nivolumab and Chemotherapy in Advanced Non-small-cell Lung Cancer. *Cancer Sci.* **2020**, *111* (6), 1933–1942. https://doi.org/10.1111/cas.14410.
40. Hellmann, M. D.; Paz-Ares, L.; Bernabe Caro, R.; Zurawski, B.; Kim, S.-W.; Carcereny Costa, E.; Park, K.; Alexandru, A.; Lupinacci, L.; De La Mora Jimenez, E.; Sakai, H.; Albert, I.; Vergnenegre, A.; Peters, S.; Syrigos, K.; Barlesi, F.; Reck, M.; Borghaei, H.; Brahmer, J. R.; O'Byrne, K. J.; Geese, W. J.; Bhagavatheeswaran, P.; Rabindran, S. K.; Kasinathan, R. S.; Nathan, F. E.; Ramalingam, S. S. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2019**, *381* (21), 2020–2031. https://doi.org/10.1056/NEJMoa1910231.
41. Brahmer, J. R.; Lee, J.-S.; Ciuleanu, T.-E.; Bernabe Caro, R.; Nishio, M.; Urban, L.; Audigier-Valette, C.; Lupinacci, L.; Sangha, R.; Pluzanski, A.; Burgers, J.; Mahave, M.; Ahmed, S.; Schoenfeld, A. J.; Paz-Ares, L. G.; Reck, M.; Borghaei, H.; O'Byrne, K. J.; Gupta, R. G.; Bushong, J.; Li, L.; Blum, S. I.; Eccles, L. J.; Ramalingam, S. S. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non–Small-Cell Lung Cancer in CheckMate 227. *J. Clin. Oncol.* **2023**, *41* (6), 1200–1212. https://doi.org/10.1200/JCO.22.01503.
42. Borghaei, H.; Ciuleanu, T.-E.; Lee, J.-S.; Pluzanski, A.; Caro, R. B.; Gutierrez, M.; Ohe, Y.; Nishio, M.; Goldman, J.; Ready, N.; Spigel, D. R.; Ramalingam, S. S.; Paz-Ares, L. G.; Gainor, J. F.; Ahmed, S.; Reck, M.; Maio, M.; O'Byrne, K. J.; Memaj, A.; Nathan, F.; Tran, P.; Hellmann, M. D.; Brahmer, J. R. Long-Term Survival with First-Line Nivolumab plus Ipilimumab in Patients with Advanced Non-Small-Cell Lung Cancer: A Pooled Analysis. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2023**, *34* (2), 173–185. https://doi.org/10.1016/j.annonc.2022.11.006.
43. Gettinger, S. N.; Redman, M. W.; Bazhenova, L.; Hirsch, F. R.; Mack, P. C.; Schwartz, L. H.; Bradley, J. D.; Stinchcombe, T. E.; Leighl, N. B.; Ramalingam, S. S.; Tavernier, S. S.; Yu, H.; Unger, J. M.; Minichiello, K.; Highleyman, L.; Papadimitrakopoulou, V. A.; Kelly, K.; Gandara, D. R.; Herbst, R. S. Nivolumab Plus Ipilimumab vs Nivolumab for Previously Treated Patients With Stage IV Squamous Cell Lung Cancer: The Lung-MAP S1400I Phase 3 Randomized Clinical Trial. *JAMA Oncol.* **2021**, *7* (9), 1368. https://doi.org/10.1001/jamaoncol.2021.2209.
44. Mok, T. S. K.; Wu, Y.-L.; Kudaba, I.; Kowalski, D. M.; Cho, B. C.; Turna, H. Z.; Castro, G.; Srimuninnimit, V.; Laktionov, K. K.; Bondarenko, I.; Kubota, K.; Lubiniecki, G. M.; Zhang, J.; Kush, D.; Lopes, G.; Adamchuk, G.; Ahn, M.-J.; Alexandru, A.; Altundag, O.; Alyasova, A.; Andrusenko, O.; Aoe, K.; Araujo, A.; Aren, O.; Arrieta Rodriguez, O.; Ativitavas, T.; Avendano, O.; Barata, F.; Barrios, C. H.; Beato, C.; Bergstrom, P.; Betticher, D.; Bolotina, L.; Bondarenko, I.; Botha, M.; Buddu, S.; Caglevic, C.; Cardona, A.; Castro, G.; Castro, H.; Cay Senler, F.; Cerny, C. A. S.; Cesas, A.; Chan, G.-C.; Chang, J.; Chen, G.; Chen, X.; Cheng, S.; Cheng, Y.; Cherciu, N.; Chiu, C.-H.; Cho, B. C.; Cicenas, S.; Ciurescu, D.; Cohen, G.; Costa, M. A.; Danchaivijitr, P.; De Angelis, F.; De Azevedo, S. J.; Dediu, M.; Deliverski, T.; De Marchi, P. R. M.; De The Bustamante Valles, F.; Ding, Z.; Doganov, B.; Dreosti, L.; Duarte, R.; Edusma-Dy, R.; Emelyanov, S.; Erman, M.; Fan, Y.; Fein, L.; Feng, J.; Fenton, D.; Fernandes, G.; Ferreira, C.; Franke, F. A.; Freitas, H.; Fujisaka, Y.; Galindo, H.; Galvez, C.; Ganea, D.; Gil, N.; Girotto, G.; Goker, E.; Goksel, T.; Gomez Aubin, G.; Gomez Wolff, L.; Griph, H.; Gumus, M.; Hall, J.; Hart, G.; Havel, L.; He, J.; He, Y.; Hernandez Hernandez, C.; Hespanhol, V.; Hirashima, T.; Ho, C. M. J.; Horiike, A.; Hosomi, Y.; Hotta, K.; Hou, M.; How, S. H.; Hsia, T.-C.; Hu, Y.; Ichiki, M.; Imamura, F.; Ivashchuk, O.; Iwamoto, Y.; Jaal, J.; Jassem, J.; Jordaan, C.; Juergens, R. A.; Kaen, D.; Kalinka-Warzocha, E.; Karaseva, N.; Karaszewska, B.; Kazarnowicz, A.; Kasahara, K.; Katakami, N.; Kato, T.; Kawaguchi, T.; Kim, J. H.; Kishi, K.; Kolek, V.; Koleva, M.; Kolman, P.; Koubkova, L.; Kowalyszyn, R.; Kowalski, D.; Koynov, K.; Ksienski, D.; Kubota, K.; Kudaba, I.; Kurata, T.; Kuusk, G.; Kuzina, L.;

DOI: 10.36838/v7i2.78

Laczo, I.; Ladrera, G. E. I.; Laktionov, K.; Landers, G.; Lazarev, S.; Lerzo, G.; Lesniewski Kmak, K.; Li, W.; Liam, C. K.; Lifirenko, I.; Lipatov, O.; Liu, X.; Liu, Z.; Lo, S. H.; Lopes, V.; Lopez, K.; Lu, S.; Martinengo, G.; Mas, L.; Matrosova, M.; Micheva, R.; Milanova, Z.; Miron, L.; Mok, T.; Molina, M.; Murakami, S.; Nakahara, Y.; Nguyen, T. Q.; Nishimura, T.; Ochsenbein, A.; Ohira, T.; Ohman, R.; Ong, C. K.; Ostoros, G.; Ouyang, X.; Ovchinnikova, E.; Ozyilkan, O.; Petruzelka, L.; Pham, X. D.; Picon, P.; Piko, B.; Poltoratsky, A.; Ponomarova, O.; Popelkova, P.; Purkalne, G.; Qin, S.; Ramlau, R.; Rappaport, B.; Rey, F.; Richardet, E.; Roubec, J.; Ruff, P.; Rusyn, A.; Saka, H.; Salas, J.; Sandoval, M.; Santos, L.; Sawa, T.; Seetalarom, K.; Seker, M.; Seki, N.; Seolwane, F.; Shepherd, L.; Shevnya, S.; Shimada, A. K.; Shparyk, Y.; Sinielnikov, I.; Sirbu, D.; Smaletz, O.; Soares, J. P. H.; Sookprasert, A.; Speranza, G.; Srimuninnimit, V.; Sriuranpong, V.; Stara, Z.; Su, W.-C.; Sugawara, S.; Szpak, W.; Takahashi, K.; Takigawa, N.; Tanaka, H.; Tan Chun Bing, J.; Tang, Q.; Taranov, P.; Tejada, H.; Tho, L. M.; Torii, Y.; Trukhyn, D.; Turdean, M.; Turna, H.; Ursol, G.; Vanasek, J.; Varela, M.; Vallejo, M.; Vera, L.; Victorino, A.-P.; Vlasek, T.; Vynnychenko, I.; Wang, B.; Wang, J.; Wang, K.; Wu, Y.; Yamada, K.; Yang, C.-H.; Yokoyama, T.; Yokoyama, T.; Yoshioka, H.; Yumuk, F.; Zambrano, A.; Zarba, J. J.; Zarubenkov, O.; Zemaitis, M.; Zhang, L.; Zhang, L.; Zhang, X.; Zhao, J.; Zhou, C.; Zhou, J.; Zhou, Q.; Zippelius, A. Pembrolizumab versus Chemotherapy for Previously Untreated, PD-L1-Expressing, Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomised, Open-Label, Controlled, Phase 3 Trial. *The Lancet* **2019**, *393* (10183), 1819–1830. https://doi.org/10.1016/S0140-6736(18)32409-7.

45. de Castro, G.; Kudaba, I.; Wu, Y.-L.; Lopes, G.; Kowalski, D. M.; Turna, H. Z.; Caglevic, C.; Zhang, L.; Karaszewska, B.; Laktionov, K. K.; Srimuninnimit, V.; Bondarenko, I.; Kubota, K.; Mukherjee, R.; Lin, J.; Souza, F.; Mok, T. S. K.; Cho, B. C. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non–Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score ≥ 1% in the KEYNOTE-042 Study. *J. Clin. Oncol*. **2023**, *41* (11), 1986–1991. https://doi.org/10.1200/JCO.21.02885.
46. Gandhi, L.; Rodríguez-Abreu, D.; Gadgeel, S.; Esteban, E.; Felip, E.; De Angelis, F.; Domine, M.; Clingan, P.; Hochmair, M. J.; Powell, S. F.; Cheng, S. Y.-S.; Bischoff, H. G.; Peled, N.; Grossi, F.; Jennens, R. R.; Reck, M.; Hui, R.; Garon, E. B.; Boyer, M.; Rubio-Viqueira, B.; Novello, S.; Kurata, T.; Gray, J. E.; Vida, J.; Wei, Z.; Yang, J.; Raftopoulos, H.; Pietanza, M. C.; Garassino, M. C. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. *N. Engl. J. Med*. **2018**, *378* (22), 2078–2092. https://doi.org/10.1056/NEJMoa1801005.
47. Langer, C. J.; Gadgeel, S. M.; Borghaei, H.; Papadimitrakopoulou, V. A.; Patnaik, A.; Powell, S. F.; Gentzler, R. D.; Martins, R. G.; Stevenson, J. P.; Jalal, S. I.; Panwalkar, A.; Yang, J. C.-H.; Gubens, M.; Sequist, L. V.; Awad, M. M.; Fiore, J.; Ge, Y.; Raftopoulos, H.; Gandhi, L. 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* (11), 1497–1508. https://doi.org/10.1016/S1470-2045(16)30498-3.
48. Paz-Ares, L.; Luft, A.; Vicente, D.; Tafreshi, A.; Gümüş, M.; Mazières, J.; Hermes, B.; Çay Şenler, F.; Csőszi, T.; Fülöp, A.; Rodríguez-Cid, J.; Wilson, J.; Sugawara, S.; Kato, T.; Lee, K. H.; Cheng, Y.; Novello, S.; Halmos, B.; Li, X.; Lubiniecki, G. M.; Piperdi, B.; Kowalski, D. M. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. *N. Engl. J. Med*. **2018**, *379* (21), 2040–2051. https://doi.org/10.1056/NEJMoa1810865.
49. Yang, Z.; Chen, Y.; Wang, Y.; Hu, M.; Qian, F.; Zhang, Y.; Zhang, B.; Zhang, W.; Han, B. Pembrolizumab Plus Chemotherapy Versus Chemotherapy Monotherapy as a First-Line Treatment in Elderly Patients (≥75 Years Old) With Non-Small-Cell Lung Cancer. *Front. Immunol*. **2022**, *13*, 807575. https://doi.org/10.3389/fimmu.2022.807575.
50. West, H.; McCleod, M.; Hussein, M.; Morabito, A.; Rittmeyer, A.; Conter, H. J.; Kopp, H.-G.; Daniel, D.; McCune, S.; Mekhail, T.; Zer, A.; Reinmuth, N.; Sadiq, A.; Sandler, A.; Lin, W.; Ochi Lohmann, T.; Archer, V.; Wang, L.; Kowanetz, M.; Cappuzzo, F. Atezolizumab in Combination with Carboplatin plus Nab-Paclitaxel Chemotherapy Compared with Chemotherapy Alone as First-Line Treatment for Metastatic Non-Squamous Non-Small-Cell Lung Cancer (IMpower130): A Multicentre, Randomised, Open-Label, Phase 3 Trial. *Lancet Oncol.* **2019**, *20* (7), 924–937. https://doi.org/10.1016/S1470-2045(19)30167-6.
51. Nishio, M.; Barlesi, F.; West, H.; Ball, S.; Bordoni, R.; Cobo, M.; Longeras, P. D.; Goldschmidt, J.; Novello, S.; Orlandi, F.; Sanborn, R. E.; Szalai, Z.; Ursol, G.; Mendus, D.; Wang, L.; Wen, X.; McCleland, M.; Hoang, T.; Phan, S.; Socinski, M. A. Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results From the Randomized Phase 3 IMpower132 Trial. *J. Thorac. Oncol.* **2021**, *16* (4), 653–664. https://doi.org/10.1016/j.jtho.2020.11.025.
52. Jotte, R.; Cappuzzo, F.; Vynnychenko, I.; Stroyakovskiy, D.; Rodríguez-Abreu, D.; Hussein, M.; Soo, R.; Conter, H. J.; Kozuki, T.; Huang, K.-C.; Graupner, V.; Sun, S. W.; Hoang, T.; Jessop, H.; McCleland, M.; Ballinger, M.; Sandler, A.; Socinski, M. A. Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results From a Randomized Phase III Trial. *J. Thorac. Oncol*. **2020**, *15* (8), 1351–1360. https://doi.org/10.1016/j.jtho.2020.03.028.
53. Antonia, S. J.; Villegas, A.; Daniel, D.; Vicente, D.; Murakami, S.; Hui, R.; Yokoi, T.; Chiappori, A.; Lee, K. H.; De Wit, M.; Cho, B. C.; Bourhaba, M.; Quantin, X.; Tokito, T.; Mekhail, T.; Planchard, D.; Kim, Y.-C.; Karapetis, C. S.; Hiret, S.; Ostoros, G.; Kubota, K.; Gray, J. E.; Paz-Ares, L.; De Castro Carpeño, J.; Wadsworth, C.; Melillo, G.; Jiang, H.; Huang, Y.; Dennis, P. A.; Özgüroğlu, M. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2017**, *377* (20), 1919–1929. https://doi.org/10.1056/NEJMoa1709937.
54. Spigel, D. R.; Faivre-Finn, C.; Gray, J. E.; Vicente, D.; Planchard, D.; Paz-Ares, L.; Vansteenkiste, J. F.; Garassino, M. C.; Hui, R.; Quantin, X.; Rimner, A.; Wu, Y.-L.; Özgüroğlu, M.; Lee, K. H.; Kato, T.; De Wit, M.; Kurata, T.; Reck, M.; Cho, B. C.; Senan, S.; Naidoo, J.; Mann, H.; Newton, M.; Thiyagarajah, P.; Antonia, S. J. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. *J. Clin. Oncol.* **2022**, *40* (12), 1301–1311. https://doi.org/10.1200/JCO.21.01308.
55. Johnson, M. L.; Cho, B. C.; Luft, A.; Alatorre-Alexander, J.; Geater, S. L.; Laktionov, K.; Kim, S.-W.; Ursol, G.; Hussein, M.; Lim, F. L.; Yang, C.-T.; Araujo, L. H.; Saito, H.; Reinmuth, N.; Shi, X.; Poole, L.; Peters, S.; Garon, E. B.; Mok, T.; for the POSEIDON investigators. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study. *J. Clin. Oncol*. **2023**, *41* (6), 1213–1227. https://doi.org/10.1200/JCO.22.00975.
56. Rothschild, S. I.; Zippelius, A.; Eboulet, E. I.; Savic Prince, S.; Betticher, D.; Bettini, A.; Früh, M.; Joerger, M.; Lardinois, D.; Gelpke, H.; Mauti, L. A.; Britschgi, C.; Weder, W.; Peters, S.; Mark, M.; Cathomas, R.; Ochsenbein, A. F.; Janthur, W.-D.; Waibel, C.;

Mach, N.; Froesch, P.; Buess, M.; Bohanes, P.; Godar, G.; Rusterholz, C.; Gonzalez, M.; Pless, M.; for the Swiss Group for Clinical Cancer Research (SAKK). SAKK 16/14: Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients With Stage IIIA(N2) Non–Small-Cell Lung Cancer—A Multicenter Single-Arm Phase II Trial. *J. Clin. Oncol.* **2021**, *39* (26), 2872–2880. https://doi.org/10.1200/JCO.21.00276.
57. Fessas, P.; Lee, H.; Ikemizu, S.; Janowitz, T. A Molecular and Preclinical Comparison of the PD-1-Targeted T-Cell Checkpoint Inhibitors Nivolumab and Pembrolizumab. *Semin. Oncol.* **2017**, *44* (2), 136–140. https://doi.org/10.1053/j.seminoncol.2017.06.002.
58. Chaudhary, M. A.; Lubinga, S. J.; Smare, C.; Hertel, N.; Penrod, J. R. Cost-Effectiveness of Nivolumab in Patients with NSCLC in the United States. *Am. J. Manag. Care* **2021**, *27* (8), e254–e260. https://doi.org/10.37765/ajmc.2021.88726.
59. Chaudhary, M. A.; Holmberg, C.; Lakhdari, K.; Smare, C.; Theriou, C.; Dale, P.; Penrod, J. R. Cost-Effectiveness of Nivolumab in Squamous and Non-Squamous Non-Small Cell Lung Cancer in Canada and Sweden: An Update with 5-Year Data. *J. Med. Econ*. **2021**, *24* (1), 607–619. https://doi.org/10.1080/13696998.2021.1917139.
60. Georgieva, M.; da Silveira Nogueira Lima, J. P.; Aguiar, P.; de Lima Lopes, G.; Haaland, B. Cost-Effectiveness of Pembrolizumab as First-Line Therapy for Advanced Non-Small Cell Lung Cancer. *Lung Cancer Amst. Neth.* **2018**, *124*, 248–254. https://doi.org/10.1016/j.lungcan.2018.08.018.
61. Aziz, M. I. A.; Tan, L. E.; Tan, W. H. G.; Toh, C.-K.; Loke, L. P. Y.; Pearce, F.; Ng, K. Cost-Effectiveness Analysis of Pembrolizumab Monotherapy versus Chemotherapy for Previously Untreated Advanced Non-Small Cell Lung Cancer. *J. Med. Econ*. **2020**, *23* (9), 952–960. https://doi.org/10.1080/13696998.2020.1775620.
62. Liu, G.; Kang, S.; Wang, X.; Shang, F. Cost-Effectiveness Analysis of Atezolizumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer With Different PD-L1 Expression Status. *Front. Oncol*. **2021**, *11*, 669195. https://doi.org/10.3389/fonc.2021.669195.
63. Cheng, S.; Pei, R.; Li, J.; Li, B.; Tang, L.; Yin, T.; Liu, S. Atezolizumab Compared to Chemotherapy for First-Line Treatment in Non-Small Cell Lung Cancer with High PD-L1 Expression: A Cost-Effectiveness Analysis from US and Chinese Perspectives. *Ann. Transl. Med.* **2021**, *9* (18), 1481. https://doi.org/10.21037/atm-21-4294.
64. Ondhia, U.; Conter, H. J.; Owen, S.; Zhou, A.; Nam, J.; Singh, S.; Abdulla, A.; Chu, P.; Felizzi, F.; Paracha, N.; Sangha, R. Cost-Effectiveness of Second-Line Atezolizumab in Canada for Advanced Non-Small Cell Lung Cancer (NSCLC). *J. Med. Econ.* **2019**, *22* (7), 625–637. https://doi.org/10.1080/13696998.2019.1590842.
65. Balijepalli, C.; Gullapalli, L.; Joshy, J.; Rawson, N. S. The Impact of Willingness-to-Pay Threshold on Price Reduction Recommendations for Oncology Drugs: A Review of Assessments Conducted by the Canadian Agency for Drugs and Technologies in Health. *J. Comp. Eff. Res. 13* (5), e230178. https://doi.org/10.57264/cer-2023-0178.
66. Kareff, S. A.; Han, S.; Haaland, B.; Jani, C. J.; Kohli, R.; Aguiar, P. N.; Huang, Y.; Soo, R. A.; Rodríguez-Perez, Á.; García-Foncillas, J.; Dómine, M.; de Lima Lopes, G. International Cost-Effectiveness Analysis of Durvalumab in Stage III Non-Small Cell Lung Cancer. *JAMA Netw. Open* **2024**, *7* (5), e2413938. https://doi.org/10.1001/jamanetworkopen.2024.13938.
67. Topalian, S. L.; Taube, J. M.; Anders, R. A.; Pardoll, D. M. Mechanism-Driven Biomarkers to Guide Immune Checkpoint Blockade in Cancer Therapy. *Nat. Rev. Cancer* **2016**, *16* (5), 275–287. https://doi.org/10.1038/nrc.2016.36.
68. Postow, M. A.; Callahan, M. K.; Wolchok, J. D. Immune Checkpoint Blockade in Cancer Therapy. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol*. **2015**, *33* (17), 1974–1982. https://doi.org/10.1200/JCO.2014.59.4358.
69. Principe, D. R.; Chiec, L.; Mohindra, N. A.; Munshi, H. G. Regulatory T-Cells as an Emerging Barrier to Immune Checkpoint Inhibition in Lung Cancer. *Front. Oncol.* **2021**, *11*, 684098. https://doi.org/10.3389/fonc.2021.684098.

Authors

Joey Chow is a recent high school graduate from Singapore with a keen interest in immunology and immunotherapy. She aspires to deepen her understanding of complex biological systems during university studies and beyond, with the ultimate goal of contributing to advancements in medical therapies and treatments.

DOI: 10.36838/v7i2.78