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PD-1 and PDL-1 Immune Checkpoint Inhibitors: Emerging Hope for the Future of Lung Cancer Immunotherapy

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Abstract

Background: Lung cancer is the leading cause of cancer-related deaths worldwide, with Non-Small Cell Lung Cancer (NSCLC) being the most common type. Despite advances in treatment, the prognosis remains poor. Immune checkpoint inhibitors targeting PD-1 and PD-L1 have emerged as a promising first-line treatment approach in combating cancer. **Objectives:** This literature review aims to evaluate the effectiveness of PD-1 and PD-L1 immune checkpoint inhibitors in the treatment of NSCLC. It also explores the potential of these inhibitors to improve patient survival rates compared to conventional therapies. **Methods:** A systematic literature search was conducted using databases such as PubMed, Google Scholar, ScienceDirect, and NCBI, with keywords including "PD-1," "PD-L1," "NSCLC," "lung cancer," and "immunotherapy." **Results:** All four inhibitors significantly improve survival rates compared to traditional chemotherapy. Atezolizumab and pembrolizumab show high effectiveness in patients with high PD-L1 expression. Durvalumab, when combined with chemotherapy, overcomes resistance mechanisms. Nivolumab, enhancing survival rates. **Conclusion:** PD-1 and PD-L1 inhibitors provide substantial benefits in the treatment of NSCLC, including increased survival rates and reduced need for aggressive therapies. Further research should focus on optimizing combination therapies to expand the therapeutic benefits of these inhibitors.

Keywords: *PD-1, PDL-1, Lung Cancer, NSCLC, Immunotherapy*

Introduction

Cancer is still the most feared disease today, not only because of its very little and expensive treatment but also the high number of mortality. Cancer is a condition in which there is an abnormal and uncontrolled growth that can invade and spread to surrounding tissue structures. Cancer can occur in almost all parts of the human body. And under normal circumstances, cells in the human body can grow and divide to form new cells according to the needs required by the body[1,2]. However, when cancer develops, this process is disrupted. Cell growth becomes increasingly abnormal, characterized by disruption of the cell regeneration process such as damaged cells that should have died surviving, the growth of new cells that are not needed which will lead to excess cells and accumulate to form a condition called a tumor[3].

There are many types of cancer and one of the most frightening is Lung Cancer. Lung Cancer is the deadliest cancer with 1.76 million deaths from lung cancer expected in 2018 (18.4% of all cancer fatalities). The prognosis for lung cancer is often dismal; only 18.6% of patients will survive for five years. Smoking is thought to be the cause of 80% of lung cancer cases, whereas never smokers account for 10% to 25% of instances. The other significant reasons are exposure to environmental carcinogens such radon gas, asbestos, or other pollutants[4].

Lung cancer cases and mortality keeps increasing every year, The global data in 2022 which covers 185 countries and 36 types of cancers show that Lung cancer accounted for 2.5 million new cases globally, or 12.4% of all new cases, making it the most common cancer. Moreover, The most common cause of cancer-related deaths (1.8 million, or 18.7% of all cancer-related deaths) was lung cancer. Although there are differences in cancer incidence and mortality by sex, the most frequent disease diagnosed and the primary cause of cancer-related death was lung cancer for men, while for women it was second in terms of cases and death[5].

The World Health Organization (WHO) classifies lung tumors into two main groups: non-small cell lung cancer (NSCLC), which accounts for 80–85% of all instances of lung cancer, and small cell lung cancer (SCLC), which accounts for the remaining 15% of cases. Large cell carcinoma (LCC), squamous cell carcinoma (LUSC), and adenocarcinoma (LUAD) are further subtypes of non-small cell lung cancer[6].

Despite advances in therapeutic strategies, the overall survival rates have not significantly improved over the past decades. The high mortality rate, coupled with the growing burden of lung cancer cases, underscores the pressing need for innovative treatment approaches.

Actually, our body already has an immune system to fight cancer cells. However, what makes cancer so frightening is its ability to evade our body's immune system, one way being by expressing checkpoint inhibitors that can kill our own cells. Immune checkpoint inhibitors targeting PD-1 and PD-L1 have recently emerged as transformative therapies, offering a novel mechanism to empower the immune system to combat cancer. This paradigm shift represents a beacon of hope for patients with advanced NSCLC, promising not only improved survival rates but also a better quality of life compared to traditional therapies.

The use of immunotherapy, in particular the suppression of different checkpoints that regulate host T cell activation, represents a paradigm change in the treatment of cancer. Interaction between Programmed cell death 1 (PD-1) and its ligand PD-L1 has become a popular method for cancer cells to avoid being attacked by the host's immune system[3]. When activated, PD-1 is expressed on B cells, natural killer cells, and CD8+ T cells in the context of persistent antigen exposure. On host tissues, the interaction of PD-1 with either PD-L1 or PD-L2 results in the T cell proliferation restricted by the suppression of TCR signaling and CD28 costimulation contacts with the target cells, which finally causes them to become inactive and lose ability to proliferate.

Localized factors stimulate PDL-1 expression in which it represents the implementation of the cancer cell to protect themself from T cell mediated response. As a result of this novel approach to cancer treatment, therapeutic monoclonal antibodies that block PD-1 or PD-L1 are now in clinical development. While atezolizumab, and durvalumab inhibit PD-L1, pembrolizumab and nivolumab target PD-1. When taken as a whole, these drugs have approval for the treatment of numerous cancers, such as head and neck squamous cell cancer, renal cell carcinoma (RCC), urothelial carcinoma, Merkel cell carcinoma, gastric carcinoma, and hepatocellular carcinomas, as well as non-small-cell lung cancer (NSCLC)[7].

This literature review will focus on a few examples of immune checkpoint inhibitors, aims to investigate how PD-1 and PD-L1 inhibitors compare to conventional therapies in improving survival outcomes for NSCLC patients. It seeks to evaluate the specific benefits and limitations associated with each inhibitor, including atezolizumab, pembrolizumab, durvalumab, and nivolumab. Furthermore, the research explores the potential of combination therapies involving

these inhibitors to enhance therapeutic efficacy while addressing the challenges of resistance mechanisms and finally aims to bridge existing gaps in understanding the efficacy and optimization of these therapies, emphasizing their role in clinical practice.

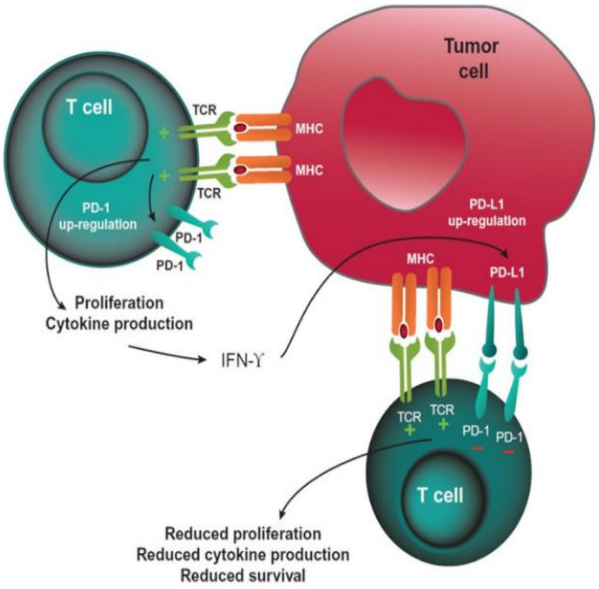


Figure 1. PD-1 and PDL-1 interaction result in inhibition of T-cell proliferation and survival[8].

Materials and Methods

This literature review is based on a literature study method by collecting various valid references from English-language journals or other literature regarding the effectiveness of PD-1 and PDL-1 immune checkpoint inhibitors as a primary treatment effort for lung cancer. In the search for literature sources or available data, the author used various journals from PubMed, Google Scholar, and Science Direct with the keywords "PD-1", "PDL-1", "Lung Cancer", "NSCLC", and "immunotherapy". The author conducted a scanning process to exclude journals that did not meet the desired criteria and included journals relevant to the author's criteria, with the inclusion criteria that consists of references that were drawn from English-language journals or other scientific literature and with a publication date within the last 10 years. The literature that met the inclusion criteria were analyzed systematically and the results of the analysis were presented in the form of articles, tables, and diagrams as appropriate to facilitate understanding of immune checkpoint inhibitor in the management of lung cancer.

Study Design

The research employs a systematic literature review design to evaluate the efficacy of PD-1 and PD-L1 immune checkpoint inhibitors as primary treatments for NSCLC. This approach allows for a comprehensive synthesis of existing evidence, providing critical insights into their clinical applicability.

Sample

A total of 174 journal articles were initially identified through systematic searches in PubMed, Google Scholar, and ScienceDirect. After a rigorous screening process, 19 articles were selected based on relevance, publication within the last 10 years, and adherence to predefined inclusion criteria.

Data Collection Techniques

Relevant studies were identified using a combination of keywords such as "PD-1," "PD-L1," "NSCLC," "lung cancer," and "immunotherapy." Abstracts and full texts were reviewed to ensure alignment with the research objectives. Inclusion criteria emphasized peer-reviewed articles written in English that reported on clinical trials or observational studies of PD-1 and PD-L1 inhibitors.

Data Analysis Techniques

The data were systematically analyzed using qualitative synthesis and descriptive statistics. Key outcomes, including overall survival (OS), progression-free survival (PFS), and objective response rates (ORR), were extracted and compared across different studies. Visual representations, such as tables and graphs, were

employed to facilitate understanding and interpretation of the findings.

Ethical Consideration

This study utilized literature with careful attention to research ethics and respect for the copyright of referenced sources. All references were cited accurately in accordance with academic standards to maintain scientific integrity. In addition, the study ensured compliance with copyright and licensing requirements of the literature used. These efforts were undertaken to guarantee that the research was carried out ethically, responsibly, and professionally.

Result

Literature search from PubMed, Google Scholar, and Science Direct resulted in 174 journal articles. The journal articles were sorted by title, abstract, keywords and 69 journal articles were obtained with details of 46 journal articles not processed further and 23 journal articles processed further. The journal articles were sorted by looking at the entire text and 19 journal articles were obtained which were processed and packaged in the form of a literature review.

Discussion

There are 4 examples of immune checkpoint inhibitor that are mainly used for immunotherapy, which is Atezolizumab, Pembrolizumab, Durvalumab, and Nivolumab.

Atezolizumab is an IgG1 monoclonal antibody that has been humanized and designed to target PD-L1, it acts differently from anti-PD-1 antibodies. Atezolizumab inhibits PD-L1 and B7- 1 binding, which may potentially boost immune responses, in addition to the PD-L1 and PD-1 interaction, which can reactivate weakened immune cells to eradicate cancer cells. Moreover, direct targeting of PD-L1 preserves the connection between PD-L2 and PD-1 and may reduce autoimmunity[9]. A preliminary stage shows that patients with recurrent SCLC showed good durability of response and manageable side effects while using atezolizumab monotherapy[10].

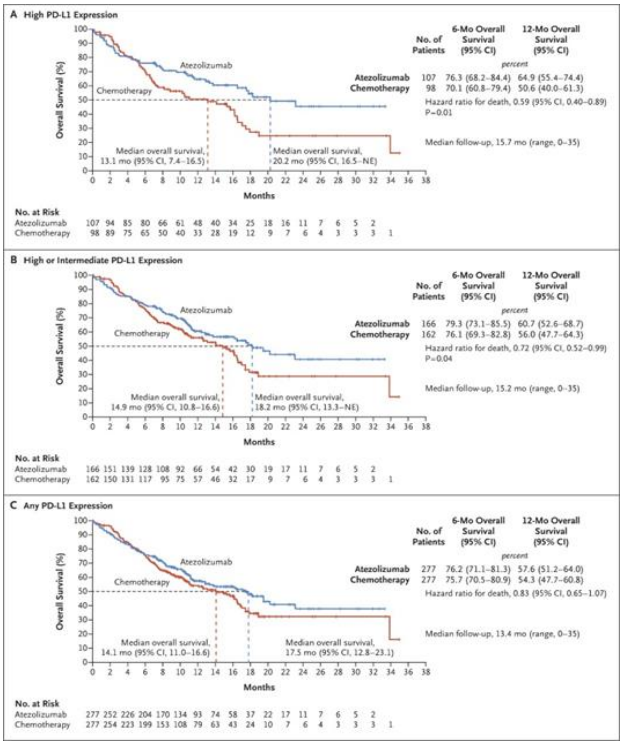


Figure 2. Overall survival in the Atezolizumab group and the Chemotherapy group

According to this chart, Patients with EGFR and ALK wild-type cancers who had high, high or intermediate, and any PD-L1 expression had median follow-up durations for survival of 15.7 months (range, 0 to 35), 15.2 months (range, 0 to 35), and 13.4 months (range, 0 to 35), respectively. Within the targeted patient group, 154 of 328 patients (47.0%) with high or intermediate PD-L1 expression, 101 of 205 patients (49.3%) with high PD-L1 expression, and 253 of 554 patients (45.7%) with any PD-L1 expression had passed away.

The median overall survival for patients with high PD-L1-expressing EGFR and ALK wild-type tumors was 7.1 months longer in the atezolizumab group compared to the treatment group (20.2 months vs. 13.1 months) (Figure 2A). The stratified hazard ratio for death was 0.72; 95% CI, 0.52 to 0.99; P = 0.04; the

median survival time for patients with EGFR and ALK wild-type tumors with high or intermediate PD-L1 expression was 18.2 months in the atezolizumab group and 14.9 months in the chemotherapy group (Figure 2B).

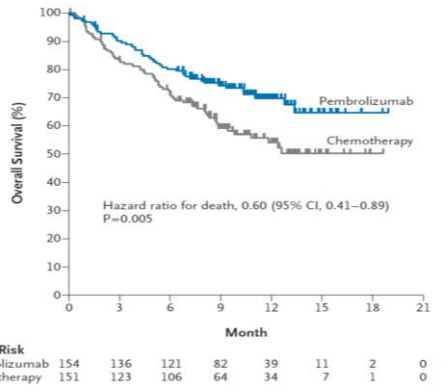
With atezolizumab, the patients' median overall survival was 17.5 months, but with chemotherapy, it was 14.1 months (Figure 2C shows the stratified hazard ratio for death, which was 0.83, 95% confidence interval, 0.65 to 1.07).

In patients with nonsquamous or squamous metastatic NSCLC who had not previously received chemotherapy, a phase 3 trial was performed using atezolizumab monotherapy as first-line treatment. When patients with EGFR and ALK wild-type tumors with strong PD-L1 expression received atezolizumab instead of chemotherapy, the median overall survival increased by 7.1 months. The reported safety profile, regardless of indication, histologic type, or therapeutic line, was in accord with that shown in other studies of atezolizumab monotherapy. In conclusion, it is discovered that among patients with previously untreated metastatic NSCLC with high expression of PD-L1, atezolizumab monotherapy led to a longer overall survival than platinum-based combination chemotherapy treatment[11].

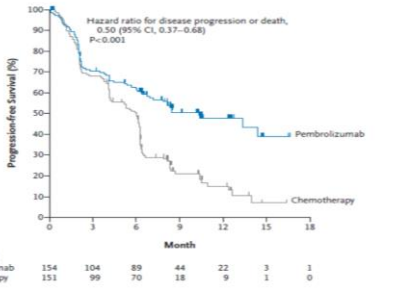
Pembrolizumab is an IgG4 kappa monoclonal antibody that is anti-PD1. Pembrolizumab has no cytotoxic action since it does not activate complement or engage Fc receptors when it binds to PD1. In assays for T-cell activation, the 50% effective inhibitory concentration falls between 0.1 and 0.3 nM. It is a lyophilized powder that is reconstituted for intravenous usage in a 0.9% sodium chloride solution to a final concentration of 1-3 mg/mL. After 4 hours at ambient temperature and 24 hours in the refrigerator, it remains stable. An intravenous infusion lasting 30 minutes is how it is given[12].

(Figure 3A) At the 6th months, the number of people still alive in the pembrolizumab group was 80.2% (95% CI, 72.9 to 85.7) and 72.4% (95% CI, 64.5 to 78.9) in the chemotherapy group. Although the median overall survival was not reached in either group, survival in the pembrolizumab group was significantly longer than in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P = .005).

A.



B.



C.

Variable	Pembrolizumab Group (N=154)	Chemotherapy Group (N=151)
Objective response†		
No. of patients	69	42
% (95% CI)	44.8 (36.8 to 53.0)	27.8 (20.8 to 35.7)
Time to response — mo‡		
Median	2.2	2.2
Range	1.4 to 8.2	1.8 to 12.2
Duration of response — mo‡§		
Median	NR	6.3
Range	1.9+ to 14.5+	2.1+ to 12.6+

Figure 3. (A). Overall survival in the pembrolizumab group and the Chemotherapy group. (B) Progression-free Survival in pembrolizumab group and chemotherapy group. (C). Objective Response Rate (ORR) time response in pembrolizumab group and chemotherapy group.

(Figure 3B) The median progression-free survival for the pembrolizumab group was 10.3 months (95% confidence interval [CI], 6.7 to not achieved) and for the chemotherapy group it was 6.0 months (95% CI, 4.2 to 6.2). At the 6th months, the estimated proportion of patients

who were still alive and had not experienced any disease progression was 50.3% (95% CI, 41.9 to 58.2) in the chemotherapy group and 62.1% (95% CI, 53.8 to 69.4) in the pembrolizumab group. The group receiving pembrolizumab had a significantly longer progression-free survival than the group receiving chemotherapy (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001).

(Figure 3C) As determined by RECIST, the pembrolizumab group's objective response rate was 44.8% (95% CI, 36.8 to 53.0) while the chemotherapy group's objective response rate was 27.8% (95% CI, 20.8 to 35.7).

In both groups, the median response time was 2.2 months. In the pembrolizumab group, the median length of response was not reached (range, 1.9+ to 14.5+ months), while in the chemotherapy group, it was 6.3 months (range, 2.1+ to 12.6+)[13].

The Objective Response Rate (ORR) for the pembrolizumab group is 44.8%, while for the chemotherapy group, it is 27.8%. This indicates that 44.8% of patients receiving pembrolizumab showed an objective response (tumor size reduction or disappearance) according to RECIST criteria, with the true value likely between 36.8% and 53.0%. In contrast, only 27.8% of patients in the chemotherapy group showed an objective response, with the true value likely between 20.8% and 35.7%. This demonstrates that pembrolizumab has a higher response rate compared to chemotherapy.

The median response in the pembrolizumab and chemotherapy groups shows that the response to pembrolizumab is more durable than to chemotherapy. This is because the median duration of response has not yet been reached, meaning some patients were still responding when data collection was stopped[13].

Durvalumab is a human Ig G1 monoclonal antibody that is selective and has a high affinity for blocking PD-L1 binding to both PD-1 and CD80. Human Ig G2 monoclonal antibody tremelimumab enhances the binding of CD80 and CD86 to CD28 by specifically targeting Cytotoxic T Lymphocyte Associated Antigen 4 (CTLA-4). While continued durvalumab treatment may improve T-cell activity and provide a durable anti tumor response, a limited early course of tremelimumab may diversify T-cell responses and increase tumor penetration. Tremelimumab is likely to enhance clinical activity when added to a durvalumab-based regimen because of their similar modes of action. This 6 addition may help overcome primary resistance to PD-(L)1 inhibition by facilitating new T-cell responses. According to clinical experience, concomitant chemotherapy can be beneficial for early disease control because it induces tumor cell (TC) death and the production of neoantigens, which may enhance immune priming[14].

Based on Figure 4, when compared to chemotherapy, first-line durvalumab treatment improve overall survival in patients with NSCLC and PD-L1 tumor cell ≥25%. In comparison to chemotherapy, durvalumab was linked to a numerically lower risk of death (HR, 0.76; 97.54% CI, 0.56-1.02; P =.04), with a 24-month OS rate of 38.3%, suggesting a longer-term treatment benefit. PD-L1 tumor cell ≥25% is an appropriate cutoff point for durvalumab monotherapy in patients with NSCLC, as evidenced by their improved outcomes when compared to patients with PD-L1 tumor cell <25%, even though patients with PD-L1 tumor cell between 25% - 49% had a reduction in risk of death equivalent to patients with PD-L1 tumor cell ≥50%[15].

Nivolumab, the first-in-human immunoglobulin G4 (IgG4) PD-1 immune checkpoint inhibitor (ICI), was created to limit the PD-1/PDL-1 interaction. It was originally licensed by the US Food and Drug Administration (FDA) for melanoma patients in 2014. Following that, the FDA approved nivolumab in 2015 for squamous lung cancer

(SLC) and metastatic non-small cell lung cancer (NSCLC). In clinical trials, nivolumab increases median overall survival (OS), progression-free survival (PFS), and objective response rates (ORR) with an acceptable safety profile in many patients[16].

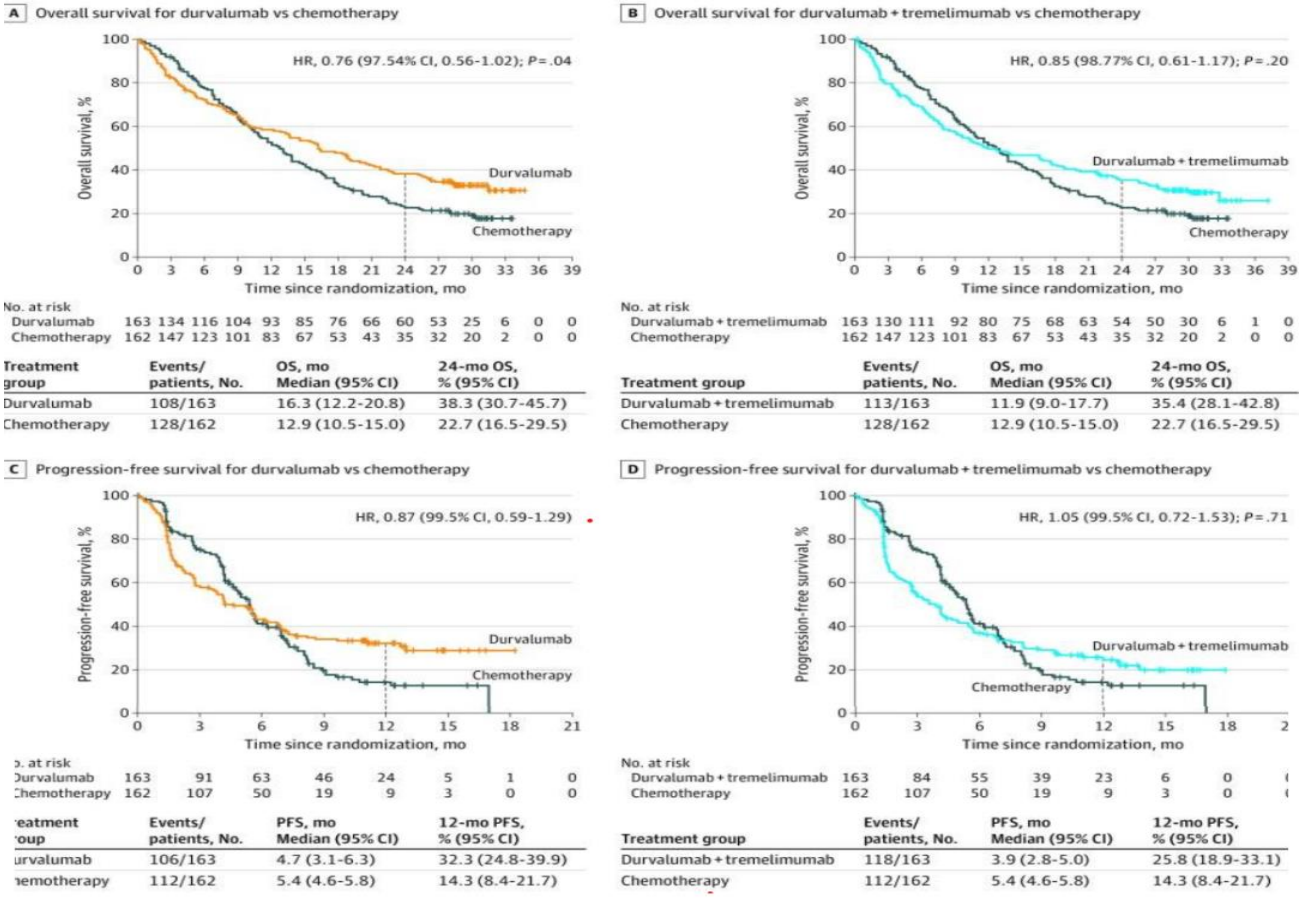


Figure 4. Overall Survival (OS) and Progression Free Survival (PFS) Among Patients With Programmed Cell Death Ligand 1

Table 1. Comparison table between Nivolumab and other drugs.

Trial	n	Arms	ORR (95%CI), %	Median OS (95%CI), months	Median PFS (95%CI), months	Grade 3-5 TRAEs, %
III(Checkmate017)	272 (Squamous)	Nivolumab 3mg/kg every 2 week	20(14-28)	9.2(7.3-13.3)	3.5(2.1-4.9)	7
		Docetaxel 75mg/m^2 every 3 week	9(5-15)	6(5.1-7.3)	2.8(2.1-3.5)	55
III(Checkmate057)	582 (Non-quamous)	Nivolumab 3mg/kg every 2 week	19(15-24)	12.2(9.7-15)	2.3(2.2-3.3)	10
		Docetaxel 75mg/m^2 every 3 week	12(9-17)	9.4(8.1-10.7)	4.2(3.5-4.9)	54
III(Checkmate078)	504	Nivolumab 3mg/kg every 2 week	16.6(12.8-21)	12(10.4-14)	2.8(2.4-3.4)	10
		Docetaxel 75mg/m^2 every 3 week	4.2(1.7-8.5)	9.6(7.6-11.2)	2.8(1.6-2.9)	48
III(Checkmate026)	541	Nivolumab 3mg/kg every 2 week	26(20-33)	14.4(11.7-17.4)	4.2(3-5.6)	18
		Platinum doublet	33(27-40)	13.2(10.7-17.1)	5.9(5.4-6.9)	51
III(Checkmate227)	269	Nivolumab + ipilimumab	45.3(36.9-54)		7.2(5.5-13.2)	31.2
		chemotherapy	26.9(20.2-34.4)		5.5(4.4-5.8)	36.1

From Table 1, A phase Ⅲ study of Checkmate026 shown that nivolumab was safer than PT-DC as the first-line therapy in NSCLC patients. A phase III investigation of the Checkmate017 trial compared the efficacy of nivolumab to docetaxel in 272 individuals with advanced squamous NSCLC. The median OS for the nivolumab group was 9.2 months, while the docetaxel group was 6.0 months. Nivolumab reduced the risk of death by 41% compared to docetaxel. After one year, nivolumab had a 42% overall survival rate, while docetaxel had a 24% rate. The ORR and median PFS for nivolumab were 20% and 3.5 months, respectively, while docetaxel were 9% and 2.8 months, respectively.

Non-squamous NSCLC trials were also undertaken concurrently. A phase Ⅲ international study of Checkmate 057 compared the effectiveness and safety of nivolumab to docetaxel in patients with non-squamous NSCLC. The median OS for the nivolumab group was 12.2 months, while the docetaxel group was 9.4 months. At one year, nivolumab had a 51% overall survival rate compared to 39% for docetaxel. The ORR for nivolumab was 19%, while docetaxel was 12%. Nivolumab had a greater 1-year PFS rate than docetaxel. After combining the data of CheckMate-017 and -057, the 4- year OS was 14% in patients receiving nivolumab compared to 5% with docetaxel. The three-year follow-up of the Checkmate 017 and Checkmate 057 trials indicated that nivolumab total survival rate was 17.0% superior to 8.0% of docetaxel, and patients were well tolerated, safe, and effective with nivolumab.

Nivolumab dose in treating patients with advanced NSCLC divided into 3 groups; 1 mg/kg, 3 mg/kg and 10 mg/kg. Following a 3-year follow-up, both squamous cell and nonsquamous NSCLC patients treated with nivolumab had an OS rate of 18.0%. A five-year follow-up study found that the 5-year OS rate for all treated patients was 16%, with similar rates for squamous (16%) and nonsquamous (15%) NSCLC. A study concluded by checkmate012 trial showed that Nivolumab demonstrated better tolerance than normal first-line chemotherapy. Patients treated with Nivolumab had a median OS of 19.4 months and a 1-year and 18-month OS rate of 73% and 57%, respectively, exceeding the expectations of chemotherapy alone (median OS of 8.1-10.3 months; 1- year OS rate of 30%-44%). Based on prior research, it can be stated that nivolumab had a greater favorable curative impact than chemotherapy, PT-DC or docetaxel in NSCLC, whether squamous or non-squamous cell carcinoma[17].

Anti PD-1/PD-L1 therapy has revolutionized the treatment of advanced NSCLC, particularly in improving the prognosis of the illness. It gave rise to a whole new community of patients, long-term survivors, who did not exist in that setting prior to the immunotherapy period[18].

The few examples of ICI taken have shown the improvement of survival rate from patients diagnosed with lung cancer rather than the conventional therapy. Seeing the success of the ICI research, First-line treatment for advanced non-small cell lung cancer (NSCLC) now includes immune checkpoint inhibitors (ICIs) that target the PD-1/PD-L1 axis. For instance, Pembrolizumab, a PD-1 inhibitor, is presently the standard of care for patients with PD-L1 expression over 50%. It can be used either alone or in combination with chemotherapy when PD-L1 expression is less than 50%[19].

Despite these promising results, several challenges remain. One key issue is the variability in patient responses, with some individuals showing primary or acquired resistance to immune checkpoint inhibitors. This highlights the importance of ongoing research into predictive biomarkers that can better identify which patients are most likely to benefit from these therapies. The results regarding research of immunotherapy showed

that in order to further improve the condition of the patients, this ICI treatment could also be combined with conventional therapy.

Conclusion

PD-1 and PD-L1 immune checkpoint inhibitors, such as atezolizumab, pembrolizumab, durvalumab, and nivolumab, have revolutionized the treatment of non-small cell lung cancer (NSCLC). These therapies have demonstrated significant improvements in both overall survival and progression-free survival compared to traditional chemotherapy. Atezolizumab and pembrolizumab, which target PD-L1 and PD-1, respectively, are particularly effective, offering substantial benefits in survival and response rates, especially for patients with high PD-L1 expression.

Durvalumab, often combined with tremelimumab or chemotherapy, has shown the ability to enhance T-cell responses and overcome resistance mechanisms, providing additional therapeutic value. Nivolumab, the first PD-1 inhibitor approved, continues to demonstrate broad efficacy across various NSCLC subtypes, making it a reliable option for diverse patient populations. These inhibitors not only improve survival outcomes but also reduce the need for aggressive and invasive treatments, thereby enhancing the overall quality of life for patients.

Future research is essential to further optimize the use of these therapies. Key areas of focus include improving combination strategies with other treatments, such as targeted therapies, radiation, and chemotherapy, and determining the optimal sequencing and duration of immune checkpoint inhibitor use. Investigating their role in earlier stages of disease, including adjuvant and neoadjuvant settings, could expand their benefits to a broader patient population.

Despite certain challenges, the integration of PD-1 and PD-L1 inhibitors into first-line treatment protocols offers renewed hope for NSCLC patients. With ongoing advancements, these therapies hold great promise for transforming the prognosis and treatment experience for lung cancer patients.

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