

PD-1 Blockade in Treatment of NSCLC: A Comprehensive Review of Clinical Efficacy, Safety and Cost-effective

Zeyue Li*

Cancer Institute, University College London, London, the United Kingdom

* Corresponding author: zczlikx@ucl.ac.uk

Abstract. Non-small cell lung cancer, also called NSCLC, makes up 85% incidence in lung cancer, presents a considerable challenge for its high mortality rate and poor prognosis. In recent years, the invention of programmed cell death 1 (PD-1) inhibitor nivolumab, which is a type of immune checkpoint inhibitors, emerging as a groundbreaking drug, has offered a potential solution to tackle the inescapable drawbacks of traditional cancer treatments. Several clinical trials assessing nivolumab's efficacy and safety in the form of monotherapy or combination therapy, demonstrated that nivolumab has remarkably increased the progression-free survival and overall survival for NSCLC, in both first- and second-line. Notably, compared to chemotherapy drugs, nivolumab showed a favorable safety profile with fewer immune-related adverse events. Given the high cost and escalating use of nivolumab, finding more cost-effective treatment regimen is imperative. The purpose of this review is to delve into the clinical efficacy and safety of PD-1 inhibitor nivolumab as immunotherapy remedy against NSCLC, providing some therapeutic recommendations for cost-effective. While continued research and development are vital to further enhance nivolumab's potential as a more potent tool to combat cancer.

Keywords: Programmed cell death 1 (PD-1); Immune checkpoint inhibitors (ICIs); non-small cell lung cancer (NSCLC); Nivolumab.

1. Introduction

Lung cancer, ranking as the second most diagnosed malignancies around the globe, has been imposing threat to humankind with its significantly high mortality rate. Out of all incidences of lung cancer, non-small cell lung cancer (NSCLC) comprises 85% of the whole incidences. Treatment to NSCLC is often challenging, due to the fact that over 50% of the patients are already in an advanced stage after diagnosis. Conventional therapies physicians usually take include surgery, chemotherapy, and radiotherapy. Although showed efficacy in treating NSCLC over the past several decades, these approaches often come with limitations, such as adverse side effects, restriction on patients' condition, and development of resistance [1].

Recent years, the discovery of immune checkpoint inhibitors (ICIs) has gained tremendous attention, due to their revolutionized breakthrough in cancer immunotherapy [2]. ICIs utilizes immune system to fight against different types of malignancies by blocking checkpoint proteins. The PD-1 and CTLA-4 are frequently inhibited from binding with their partner proteins. In response to urgent need of novel cancer treatment regimens, several ICIs have gradually been approved by the US FDA from 2015. The PD-1 inhibitor, nivolumab was the first ICI officially approved in the fight against NSCLC, showing its potential benefit in overall survival (OS) and safety profile [2]. The purpose of this review paper is to delve into nivolumab's efficacy and safety profile for treatment in NSCLC, providing some therapeutic recommendations for cost-effective, shedding light on its substantial benefit to humankind and future directions of cancer immunotherapy.

2. Mechanisms

PD-1, also called CD279, belongs to the B7 family, performing as a regulatory inhibitory receptor primarily found on activated T/B lymphocytes and natural killer cells. As illustrated in Figure 1, PD-1 becomes activated when it binds to its ligands, primarily PD-L1 but sometimes PD-L2, which



located on the surfaces of antigen-presenting cells, including dendritic cells, as well as tumor cells [3]. Upon activation, a series of events simultaneously occur due to the negative feedback pathway of PD-1/PD-L1, suppression of T/B cell receptor, decreased generation of cytokines and anti-apoptotic proteins [3], eventually leading to T cell exhaustion (figure 1) [3].

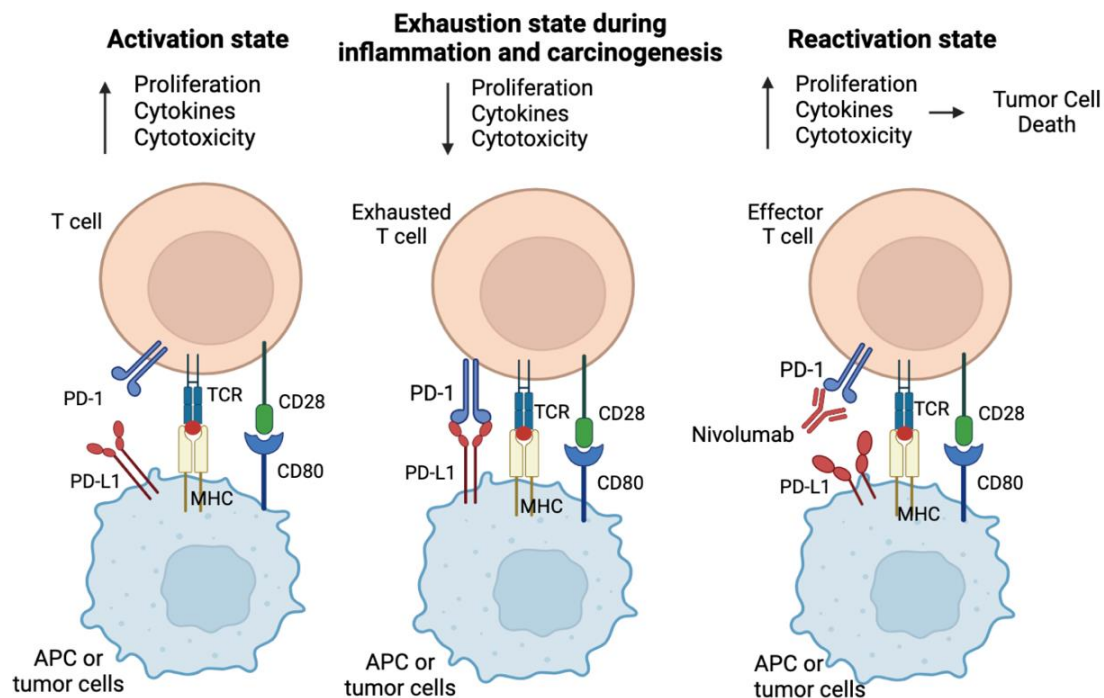


Figure 1. The function mechanisms of nivolumab

In NSCLC, elevated expression of PD-1 is also seen on tumor cells, which illustrates that cancer cells take advantage of this specific mechanism to prevent immune surveillance and create a suitable environment for continuous tumorigenesis. Nivolumab (trade name Opdivo), approved in 2015 by FDA to put into clinical treatment of NSCLC, is a monoclonal antibody inhibitor, fully humanized as immunoglobulin G4 (IgG4), which selectively targets PD-1 and its goal is to effectively inhibit interaction of PD-1 and its ligands [3]. This blockade can partially reverse the exhausted state of T cells and promote the infiltration of CD8⁺ T cells, thereby restarting the immune response to treat NSCLC patients.

3. Efficacy

NSCLC, being a significant global challenge with its poor prognosis and high mortality rate, is urgently in need of novel therapeutic approaches to improve the patient's outcome and increase the OS. In recent times, the clinical effectiveness of nivolumab has been assessed through numerous clinical trials as a standalone treatment, in combination with other ICIs or chemotherapy drugs and adjuvant therapy in multiple lines to treat NSCLC, receiving encouraging results which significantly improve the progression-free survival (PFS) and OS.

3.1. Nivolumab Monotherapy as First-Line Treatment

Although nivolumab has demonstrated prolonged PFS and OS in most clinical trials, it was first-line monotherapy failed to illustrate its outstanding efficiency in NSCLC treatment. In one phase III CheckMate 026 clinical trials (NCT02041533), where 423 patients were recruited to assess nivolumab's effectiveness as a primary standalone treatment option, comparing it to different types of chemotherapy drugs. Inclusion criteria required the participants to be 18 years older. Patients should also have newly confirmed stage IV or recurrent NSCLC, followed by the expression of PD-L1 equals to 1% or higher. These patients were divided randomly to nivolumab (intravenously at 3mg/kg every 2 weeks) treatment group or chemotherapy drugs (in 3-week cycles for up to 6 cycles)

controls [4]. In the nivolumab therapeutic patients (PD-L1 expression $\geq 5\%$), the PFS and 95% CI was 4.21 months and 0.91 in comparison with 5.88 months and 1.45 in chemotherapy group ($P = 0.25$), and an OS of 14.36 months was observed in patients receiving nivolumab treatment compared with 13.21 months treated with chemotherapy drugs (95% CI, 0.80 to 1.30). Contrary to initial hopes, the trial did not demonstrate a notable advantage in PFS for nivolumab therapy over platinum-based chemotherapy with untreated NSCLC. This outcome highlighted the complexity of NSCLC treatment decisions and emphasized the need for a more nuanced approach [4].

3.2. Combination Therapy with CTLA-4 Inhibitor Ipilimumab as First-Line Treatment

The challenges encountered by nivolumab monotherapy has switched researchers' eyes on combination therapy. In CheckMate 227 (NCT02477826), another phase III clinical trials assessing efficacy of a combination therapy for recurrent or untreated patients with stage IV (PD-L1 expression $\geq 1\%$), consisting of nivolumab and ipilimumab in comparison to chemotherapy, which performed the same disease stage as CheckMate 026 [5]. The results showed that the median PFS was significantly longer (7.2 months, 97.5% CI 0.41) in first line nivolumab plus ipilimumab compared with chemotherapy (5.5 months, 97.5% CI 0.81) regardless of PD-L1 expression ($P \leq 0.25$), with a specific focus on individuals with a high tumor mutation burden. This trial has successfully provided the brand-new concept for combined immunotherapy [5].

3.3. Nivolumab as a Second-Line Treatment Option

Besides its role in first-line treatment, nivolumab has also been proved to have remarkable prognosis when used as a second-line treatment option for advanced NSCLC patients and have received primary treatment. CheckMate 017 clinical trial (NCT01642004), aiming to compare the OS of nivolumab with a chemotherapy drug docetaxel. The 272 enrolled participants must have experienced recurrence or disease progression after primary treatment, no matter which forms of therapies received [6]. The median OS was longer in nivolumab (9.2 months) treatment patients than chemotherapy drug (6 months) group. When it comes to the PFS, a longer 0.7 months survival was recognized in patients receiving nivolumab than docetaxel. Nivolumab treatment not only showed higher OS and PFS but also remarkably decreased the risk of mortality by 41% compared to docetaxel group. Moreover, the effectiveness of nivolumab was validated to be unaffected by PD-L1 expression level [6].

3.4. Nivolumab as a Neoadjuvant Therapy in Combination with Chemotherapy

Recently, the efficacy of nivolumab has expanded beyond the former regimens of first-line and second-line therapy. It has emerged in early phase trials to service as a hopeful neoadjuvant strategy in the management of NSCLC but clinical data from phase III study is urgently needed for validation [7]. CheckMate 816 (NCT02998528), evaluating the neoadjuvant effectiveness of nivolumab with chemotherapy combination has played a vital role in shaping the novel treatment strategies for resectable NSCLC. The mainly focused outcomes were event-free survival (EFS) along with pathologic complete response (pCR) rate. Participants treated with this neoadjuvant combined therapy followed by resection showed groundbreaking results, where increasing EFS by 10.6 months (from 20.8 months to 31.6 months, hazard ratio, 0.63, p -value = 0.005). At the same time, the pCRs were observed in 43 of 179 (24.0%) participants in nivolumab plus chemotherapy arm, where only 4 out of 179 (2.2%) in the arm of chemotherapy drug alone (p -value < 0.001) [7]. CheckMate 816 trial emphasized efficacy of nivolumab in shrinking tumor size before the surgical resection, increasing the feasibility of conducting surgery for more patients not eligible before. Moreover, application of nivolumab and chemotherapy as neoadjuvant therapy may raise the possibility of improving long-term prognosis for NSCLC patients [7].

To conclude, although initial research on first-line nivolumab monotherapy had faced challenges in CheckMate 026 trial [4], the presence of combination therapy of nivolumab with other type of ICIs such as ipilimumab has been recognized to be of significant clinical benefit to naive NSCLC, as demonstrated in CheckMate 277 [5]. Besides being used in first-line treatment, nivolumab continues

to exhibit effectiveness in second-line treatment, outweighing chemotherapy in both OS and PFS in CheckMate 017 trial [6]. Furthermore, the CheckMate 816 emphasized the novel directions of nivolumab as a neoadjuvant therapy combined with chemotherapy drugs, with its potential to considerably improve EFS and pathological complete response. Such unprecedented findings and clinical trials could largely offer new hopes for NSCLC patients [7].

4. Safety

Although the clinical efficacy of nivolumab in different lines either as monotherapy or combination therapy has gained significant attention and several clinical trials [7-10] has successfully proved its importance in treating NSCLC. Besides utilizing nivolumab for its outstanding efficacy, understanding its safety profile is another concern taken patient's quality of life into account [8].

4.1. Common Adverse Events and Their Interplay with Nivolumab

Nivolumab treatment may lead to immune-related adverse events (irAEs) and general side effects. IrAEs for nivolumab therapy, although less frequent in contrast to anti-CTLA4 therapies, can also be serious and even cause death if no early detection and immediate mitigation are carried out [9]. In a retrospective study of nivolumab monotherapy conducted by Toi et al. [10], researchers examined the incidence and type of irAE in 70 participants, including those with squamous cell carcinoma and nonsquamous NSCLC. Of all the 28 (35%) patients who presented with irAEs, skin reaction was the most frequently observed irAE, with 22 patients reported, followed by hypothyroidism made up 21% of irAE group. The other irAEs include myositis/peripheral neuropathy (18%), pneumonitis (18%), hyperthyroidism (4%), and diarrhea (7%). And it is worth mentioning that the incidence of irAE was validated to be irrelevant with sex, age, performance status, pathological subtype as well as smoking history [10].

Although irAE can become serious and even fatal if not treated immediately, recent studies carried out by Baldini et al. [9] demonstrated that NSCLC patients who experienced irAEs after receiving nivolumab tend to have a noticeably better clinical outcome. Among all the participants with nivolumab-treated NSCLC in an Italian expanded access program, 17.8% (342 out of 1959) patients reported an irAE regardless of grade. To researchers' surprise, their response rate was notably higher with irAEs patients (27.2%) than those without controls (15.2%, p-value < 0.0001). Moreover, the disease control rate for irAEs group was also 20.3% (p-value < 0.0001) higher than in non-irAEs group. Favorable outcomes in irAEs group remained the same in median PFS as well as median OS [9]. This intriguing finding highlights the complex relationship among the immune system, treatment outcomes, and safety considerations in nivolumab therapy [9].

4.2. Safety Profile of Nivolumab and other ICIs in NSCLC

As a new drug that was approved in 2015, nivolumab still lacks real-world clinical data obtained from randomized clinical trials to validate its safety. Two notable trials, CheckMate 227 (NCT02477826) [5], and CheckMate 017 (NCT01642004) [6], have contributed greatly to our understanding of nivolumab's safety profile in both first-line and second-line therapy against NSCLC.

Previously mentioned as CheckMate 017, the study assessed nivolumab as a second-line therapy option for patients who have undergone prior treatment, comparing it with the chemotherapy drug docetaxel. Results indicated a lower occurrence of treatment-related adverse events (AEs) in the arm of nivolumab, when contrasted with the docetaxel arm, with only 58% of patients experienced AEs of any grade, compared to 86% in patients treated with docetaxel. The lower incidence of AEs in nivolumab group has proved its improved safety profile as a second-line monotherapy approach, offering a promising alternative for NSCLC patients [6].

As a first-line treatment option, nivolumab also exhibited tolerable safety profile when used with ipilimumab as combination immunotherapy [5]. CheckMate 227 demonstrated that AEs reported were similar in combination immunotherapy arm versus chemotherapy arm, 75.2% versus 80.7%

respectively, showing a relatively safe treatment outcomes for nivolumab combination immunotherapy [5]. Additionally, CheckMate 012 were conducted by assessing the safety of nivolumab plus ipilimumab at different dose. Nivolumab was given every 2 weeks equally in two cohorts while ipilimumab was given every 6 or 12 weeks to assess the safety profile of combination immunotherapy. Results showed that both groups have durable and similar occurrence of irAE [8]. Valuable insights were also provided to ensure the safety profile of nivolumab combination therapy [8].

Clinical trials such as CheckMate 017, CheckMate 227 and CheckMate 012 has underscored the distinct safety profile of novel immune checkpoint inhibitors in contrast to conventional chemotherapy, where systemic toxicity is more often seen [6].

4.3. Strategies to Mitigate IrAEs

While the irAEs related to nivolumab is generally tolerable and safe according to the trials mentioned above, strategies should be utilized to mitigate irAEs in order to enhance the quality of life. Corticosteroids administration is the mainstay to manage irAE. For grade 1 irAEs, it is necessary to enhance the monitoring process while continuing ICI therapy. ICI therapy can be resumed for grade 2 irAE when the symptoms returned to grade 1 after discontinuation of ICI therapy. When it comes to grade 3 and 4, immediate ICI therapy discontinuation and high-dose corticosteroids should be carried out. However, rechallenging could be given to patients with grade 3 irAEs if symptoms revert to grade 1 but ICI therapy should be perpetually discontinued for patients who experienced grade 4 irAEs [11].

It is known that early detection and prompt reporting are necessary and essential for the success of management. However, the importance of educating participants of potential irAEs in advance is often neglected. Informing patients of possible irAEs and the outcomes they may cause is also a critical part to maximize the opportunities of treatment effectiveness. Knowing the potential irAEs can equip patients the ability to best care of themselves via reporting immediately to clinicians and reducing anxiety [12]. Different teaching sources should be made to educate participants depending on their sociodemographic characteristics, psychosocial condition as well as any specific needs case by case. Furthermore, when irAEs are experienced, reinforcement of teaching to patients is critical for patient's understanding and cooperation. However, with the more and more exposure to ICIs in such a fast-developing world, the range and types of irAEs are increasing, requiring regular review and update via the patient-centered collaboration within clinical staffs [12].

5. Economics of ICIs: achieving cost-effective approach

Although nivolumab therapy has showed improved OS and PFS, as well as demonstrated its safety profile over chemotherapy, financial burden of ICI treatment is one of the big concerns patients with NSCLC usually worry about. High costs of ICI treatment will ultimately lead to financial toxicity to patients. Patients who cannot afford the price might forgo or delay the treatment, causing decreased quality of life. What's worse, the risk of bankruptcy can increase for the whole family of patients. Currently, the rising prevalence of NSCLC further compounds the financial burden of treatment, amplifying healthcare expenditures. The cost-effectiveness assessment of these novel ICI treatment and ways to balance or even reduce the cost of ICIs are critical to work out.

In a comprehensive analysis study in Switzerland with the objective of evaluating nivolumab's cost-effectiveness comparing to docetaxel, clinical data extracted from CheckMate 057 trial (NCT01673867) was utilized to construct a Markov model, evaluating cost-effectiveness. This assessment was predicated on factors such as drug prices and the actual costs incurred by NSCLC participants. Incremental cost-effectiveness ratios (ICERs) was measured as outcomes and standard for comparative analysis. Results demonstrated that, at its current pricing, nivolumab failed to achieve cost-effectiveness as a treatment modality over chemotherapy. The likelihood of nivolumab to be

cost-effective was relatively low, at a mere 14.1%. This outcomes mirrored analogous observations reported in other countries including the United Kingdom and Canada [13].

One strategy to obtain balance between cost and effectiveness is to reduce the dose of ICIs. In one study conducted by Yoo and his team [14] analyzing efficacy of nivolumab in low-dose approach to NSCLC patients in stage IIIB or IV, 20 or 100mg fixed dose every 3 weeks were given to patients, in contrast to 3mg/kg every 2 weeks in standard pattern. Outcomes were assessed and compared in the form of PFS and OS. Among 47 individuals, an exploration into the effectiveness of low-dose nivolumab was carried out, revealing an objective response rate of 16.7%, while standard-dose group demonstrated a 13.8% objective response rate (p-value = 0.788). These findings suggested that the application of low-dose nivolumab could warrant consideration in the future as a potential alternative, especially for patients with substantial financial burdens. However, it is noteworthy that further extensive investigations and more detailed clinical trials are still required to substantiate these primary observations [14].

6. Conclusion

Based on the clinical trials mentioned above, nivolumab is regarded as a promising breakthrough in the journey of fighting against NSCLC, representing a revolutionary PD-1 inhibitor in the field of targeted immunotherapy. Whether combined with other immune checkpoint inhibitors or chemotherapy drug, nivolumab has demonstrated remarkable improvements in prolonging OS and PFS compared to conventional cancer therapies.

The application of nivolumab has expanded beyond just first-line and second-line of treatments, but also showed promising efficacy when employed as a neoadjuvant therapy in conjunction with chemotherapy. In terms of drug safety, clinical trials such as CheckMate 227, and CheckMate 017, have consistently illustrated the tolerable drug safety of nivolumab, accompanied by a lower incidence of irAEs.

Noticeably, the development of irAEs was also observed to be associated with better treatment response, underscoring a complex interaction between the immune system and clinical outcomes. As the use of ICI drugs continues to grow, it is of vital importance to explore more cost-effective treatment regimens to alleviate the financial burden for both patients and healthcare systems. In conclusion, further research and development hold the promise of expanding nivolumab's utility as a useful tool to combat various types of cancer.

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