



Review of immunotherapy in non-small cell lung cancer: mechanisms, clinical applications, and future prospects

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Abstract

Non-small cell lung cancer (NSCLC) ranks among the top contributors to cancer-related mortality globally. Recently, immunotherapy, particularly immune checkpoint inhibitors, has achieved groundbreaking progress in the treatment of NSCLC, significantly improving patient outcomes. This review explored the mechanisms of immunotherapy in NSCLC, with a focus on the roles of the PD-1/PD-L1 and CTLA-4 pathways. The discussion then shifted toward the currently approved and investigational immunotherapy drugs, including Nivolumab, Pembrolizumab, and Atezolizumab. Subsection sections review the recent progress of research on novel immunotherapeutic agents and biomarkers and discuss the side effects of immunotherapy. Finally, we provide an outlook on the prospects of NSCLC immunotherapy, exploring how precision medicine and personalized treatment strategies can further enhance therapeutic efficacy. In conclusion, immunotherapy for NSCLC has made significant advancements in both mechanistic research and clinical application.

Key words non-small cell lung cancer (NSCLC), PD-1/PD-L1 pathway, CTLA-4, oncolytic virus, immunotherapy

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Introduction

Non-small cell lung cancer (NSCLC) is a highly aggressive tumor with significant global incidence and mortality rates [1]. The disease progresses rapidly, often leading to poor prognosis, with a high risk of recurrence post-treatment. Traditional treatments, including surgery, radiotherapy, and chemotherapy, have merits in controlling the disease to an extent, yet coupled with significant limitations [2]. Surgical treatment is primarily suitable for early-stage NSCLC patients; however, the majority of the patients are diagnosed at an advanced or inoperable stage, limiting the scope of surgery [3]. Radiotherapy and chemotherapy can reduce tumor size and prolong patient survival, but their efficacy is often hampered by tumor resistance and severe side effects [4]. Chemotherapy drugs typically lack the ability to selectively target tumor cells, causing damage to healthy cells, leading to nausea, vomiting, hair loss, and immune system suppression. Radiotherapy often harms surrounding healthy tissue, leading to various complications. In this context, immunotherapy has emerged as a promising alternative, offering new hope to NSCLC patients [5]. Immunotherapy activates and enhances the patient's immune system to recognize and attack tumor cells, offering high specificity and long-lasting antitumor effects. Immunotherapy has demonstrated several advantages over traditional treatments in managing NSCLC. Immunotherapy has better tolerability, relatively fewer side effects, and helps maintain a better quality of life for patients. It can overcome the resistance issues associated with traditional therapies, maintaining efficacy over long-term use. Additionally, immunotherapy can stimulate the immune system's memory effect, providing preventive benefits against tumor recurrence, which is difficult to achieve with traditional treatments [6]. In summary, despite the challenges in treating NSCLC, the advent of immunotherapy provides a new avenue for improving patient outcomes. Advancements in immunotherapy development and research are expected to make it a leading treatment for NSCLC, enhancing patient survival and quality of life.

Mechanisms of immunotherapy in NSCLC

The mechanism of immunotherapy for NSCLC primarily consists of six key steps (**Figure 1**). First, cancer cells within the tumor tissue release specific substances. Specialized immune system cells capture and recognize these substances and convey the information to the immune system's T cells, triggering its activation. Subsequently, the activated T cells advance towards the cancer cells, preparing to launch an attack. However, cancer cells have a self-protection mechanism that allows them to bind with specific structures on the T cells, thereby inhibiting the T cells' ability to attack. At this pivotal juncture, PD-1/PD-L1 inhibitors disrupt the cancer cells' self-protection mechanism, allowing the T cells to regain their function and continue recognizing and killing the cancer cells. This process effectively enhances the immune system's ability to fight against cancer.

PD-1/PD-L1 pathway

The PD-1/PD-L1 pathway is a crucial regulatory mechanism in the immune system, primarily involving the programmed cell death protein 1 (PD-1) receptor and its ligand, programmed death-ligand 1 (PD-L1). These components play crucial roles in immune regulation. PD-1 is a receptor found on the surface of activated T cells, B cells, and other immune cells [7]. It interacts with PD-L1, a ligand expressed in various cell types, including tumor cells and antigen-presenting cells such as dendritic cells and macrophages [8]. This pathway is essential for maintaining immune system balance and preventing autoimmune responses. However, in

tumor microenvironment, this mechanism is often exploited to evade immune surveillance [9]. In NSCLC, the PD-1/PD-L1 pathway plays a crucial role in the mechanism of immune evasion. Tumor cells can upregulate PD-L1 expression, which binds to PD-1 on T cells, inhibiting their activity and facilitating immune surveillance [10]. Targeting this pathway provides a promising strategy for NSCLC treatment. PD-1/PD-L1 inhibitors disrupt the interaction between PD-1 and PD-L1, reactivating T-cell function and enhancing the immune system's ability to recognize and eliminate tumor cells. Specifically, PD-1 inhibitors like Nivolumab and Pembrolizumab bind to the PD-1 receptor, blocking its interaction with PD-L1, which in turn lifts the suppression of T-cells. Similarly, PD-L1 inhibitors like Atezolizumab bind to PD-L1, preventing its interaction with PD-1 and also releasing T-cell inhibition.

CTLA-4 pathway

The CTLA-4 pathway is another crucial immune checkpoint that regulates immune system activity and prevents autoimmune reactions involving CTLA-4 and B7 molecules [11]. In NSCLC, tumor cells promote CTLA-4 expression or enhance B7 activity, thereby inhibiting T cell function and facilitating immune evasion. The activation of the CTLA-4 pathway prevents T cells from exerting their antitumor effects, promoting tumor growth and spread [12]. CTLA-4 inhibitors block the interaction between CTLA-4 and B7 molecules, releasing the inhibition on T cells, thereby restoring and enhancing their antitumor activity. Specifically, CTLA-4 inhibitors like Ipilimumab bind to CTLA-4, preventing its interaction with B7 molecules and enhancing T cell activation and proliferation [13]. CTLA-4 inhibitors increase the activity of antigen-presenting cells, leading to the presentation of more tumor antigens to T-cells and enhancing the immune response.

Oncolytic viruses

Oncolytic viruses, as a novel immunotherapy mechanism, use naturally occurring or genetically engineered viruses to selectively infect and kill tumor cells [14]. These viruses directly destroy tumor cells and activate the host immune system to combat the tumor [15]. NSCLC cells express specific receptors targeted by oncolytic viruses. For instance, certain adenoviruses selectively infect NSCLC cells by binding to the Coxsackievirus and Adenovirus Receptor (CAR) present on their surfaces [16]. NSCLC cells typically have defective antiviral defence mechanisms, which facilitate the replication and dissemination of oncolytic viruses. Oncolytic viruses, upon entering NSCLC cells, proliferate and release new viral particles, and disrupting the cell membrane, leading to cell lysis and death. Besides directly killing NSCLC cells, oncolytic viruses can also stimulate the host immune system's antitumor response [17], [18].

Chimeric antigen receptor T-cells (CAR-T cells)

Chimeric Antigen Receptor T-cell Therapy is an advanced immunotherapy that genetically modifies a patient's T-cells to express chimeric antigen receptors (CARs), which can specifically recognize and kill tumor cells. This therapy has achieved significant success in hematological malignancies and is being explored for its application in solid tumors, including NSCLC [19], [20]. The procedure begins with the extraction and isolation of T-cells from the patient's peripheral blood. Subsequently, it introduces a gene that encodes a single-chain antibody (scFv) capable of recognizing tumor-specific antigens, along with a chimeric antigen receptor (CAR) that activates the T-cell signaling

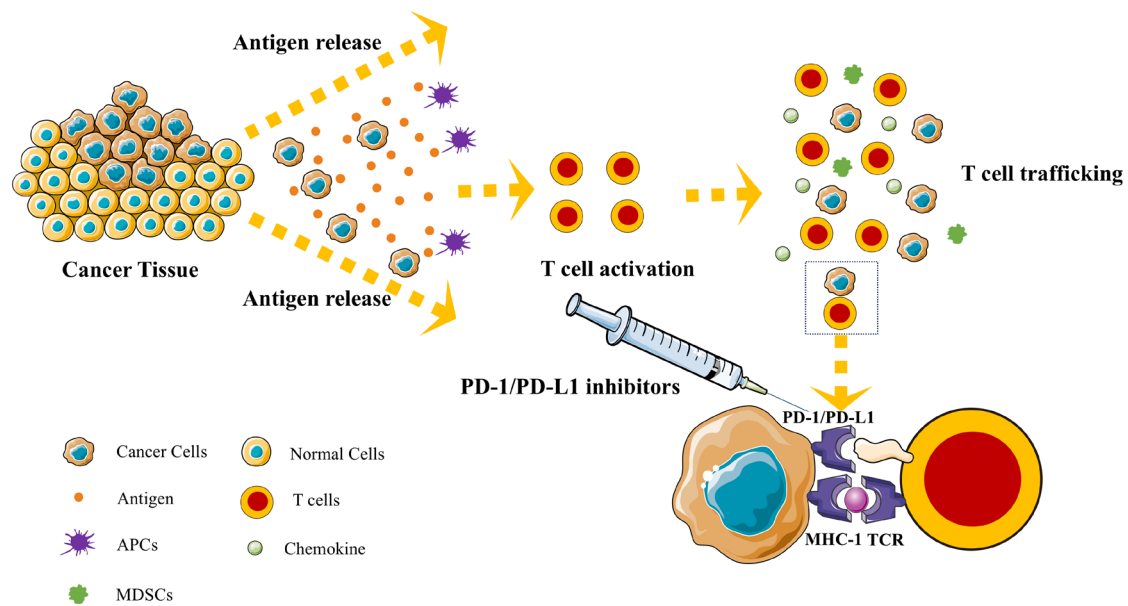


Figure 1. Plot of the mechanism of immunotherapy for non-small cell lung cancer (NSCLC).

domain. This gene is delivered into the T cells using viral vectors, typically lentiviruses or retroviruses [21]. The genetically modified CAR-T cells undergo *in vitro* expansion before being reintroduced into the patient via intravenous injection. Once administered, the cells recognize and bind to antigens on the surface of tumor cells through their CAR structure specificity *in vivo*. Following binding to tumor cells, the CAR-T cells are activated and release cytotoxic particles (such as perforin and granzyme), killing tumor cells [22].

Overall, traditional immunotherapy (PD-1/PD-L1 inhibitors) has broad applicability and durability. However, it also has limited response rates, drug resistance, and side effects. Such therapies have established themselves as critical components of cancer treatment, offering a valuable foundation for developing novel immunotherapeutic approaches. New immunotherapy is characterized by high specificity and efficiency, but may face challenges such as immune system interference, safety, and limited efficacy. These therapies may show greater potential in personalized treatment and specific cancer types.

Clinical applications and research progress

Recent advances in the clinical application of immunotherapy in NSCLC have been particularly notable with the use of immune checkpoint inhibitors, significantly improving patient survival and quality of life. The commonly used immune checkpoint inhibitors and their characteristics are summarized in clinical practice (**Table 1**).

Nivolumab (Opdivo)

Nivolumab (Opdivo) is the first PD-1 inhibitor approved for the treatment of NSCLC. It is involved in two key clinical trials, CheckMate-017 and CheckMate-057, which compared the efficacy of Nivolumab with docetaxel in patients with advanced squamous NSCLC [23], [24]. The findings revealed a median overall survival (OS) of 9.2 months for the Nivolumab group, surpassing the 6.0

months recorded for the docetaxel group. The 1-year survival rate in the Nivolumab group was 42%, significantly higher than the 24% observed in the docetaxel group. These clinical trials highlight the substantial progress Nivolumab has achieved in the treatment of NSCLC, notably extending both the overall survival (OS) and progression-free survival (PFS) of patients with advanced NSCLC.

New immune checkpoints

The remarkable success of PD-1/PD-L1 and CTLA-4 inhibitors in cancer therapy enables researchers to explore novel immune checkpoints to enhance the efficacy and overcome the limitations of current treatments. LAG-3 (lymphocyte activation gene 3), a receptor found on activated T cells, natural killer (NK) cells, and some B cells, typically inhibits T cell function through its interaction with MHC class II molecules. Studies indicate that the combination of LAG-3 inhibitors and PD-1 inhibitors can overcome resistance to PD-1 monotherapy and improve efficacy [25]. TIM-3 (T-cell immunoglobulin and mucin 3) is expressed on T-cells, NK cells, and monocytes as a negative regulatory molecule that inhibits T-cell function when it binds to its ligands (such as Galectin-9). This interaction can induce immune suppression signals [26]. TIM-3 inhibitors may release T-cell inhibition through this mechanism and enhance the immune system's antitumor ability, especially in PD-1-resistant patients [27]. TIGIT (T-cell immunoglobulin and ITIM domain) is expressed on T cells and NK cells, binds to CD155, transmits inhibitory signals, reduces the activity of T cells and NK cells, and can also compete with CD226 to bind to CD155, thereby inhibiting immune activation [28]. Preliminary studies have shown that in some patients, the combination of TIGIT inhibitors and PD-L1 inhibitors (such as Atezolizumab) exhibits enhanced antitumor activity. B7-H3 (CD276), expressed on multiple cell types, including tumor cells, participates in immune suppression and plays a role in tumor immune escape [29]. VISTA (V-domain Ig suppressor of T cell

Table 1. Characteristics of immune checkpoint inhibitors in the treatment of NSCLC.

Drug/Therapy	Target	Primary indication	Combination therapy strategy	Major efficacy
Nivolumab (Opdivo)	PD-1 inhibitor	Advanced or metastatic NSCLC patients with progression after chemotherapy	Combined with Ipilimumab	Significantly prolongs OS in advanced NSCLC patients, good tolerability
Pembrolizumab (Keytruda)	PD-1 inhibitor	Advanced or metastatic NSCLC patients with high PD-L1 expression, as a first-line therapy	Combined with chemotherapy	Significantly prolongs OS and PFS, especially in patients with PD-L1 expression $\geq 50\%$
Atezolizumab (Tecentriq)	PD-L1 inhibitor	Advanced or metastatic NSCLC patients with progression after chemotherapy	Combined with chemotherapy and bevacizumab	Significantly prolongs OS, especially in non-squamous cell carcinoma patients
Ipilimumab (Yervoy)	CTLA-4 inhibitor	Primarily for melanoma treatment, shows potential in NSCLC	Combined with Nivolumab	Combined therapy shows enhanced antitumor activity, especially in patients with high tumor mutation burden

activation) is a negative immune regulatory molecule expressed on myeloid cells and some T cells [30]. It suppresses T cell activation and proliferation by binding to its ligands. As a new immune checkpoint, VISTA inhibitors are undergoing early clinical trials to explore their potential in cancer treatment [31], [32]. Research on new immune checkpoints is rapidly developing, with the aim of overcoming the limitations of existing immunotherapy and providing patients with more treatment options [33]. An in-depth understanding of these checkpoints underlying mechanisms and their roles in the tumor microenvironment might enable researchers to develop new inhibitors and combination therapies to enhance the therapeutic efficacy of NSCLC and other cancers.

Oncolytic viruses

Oncolytic viruses have primarily developed four strains: Oncorine (H101) [34], Talimogene laherparepvec (T-VEC) [35], Reovirus [36], and measles virus [37]. H101 is a genetically modified adenovirus that was first approved in China for the treatment of head and neck squamous cell carcinoma. Its research in NSCLC has shown potential, especially when used in conjunction with chemotherapy, to enhance treatment efficacy. T-VEC is a modified herpes simplex virus (HSV) approved for unresectable melanoma and is under investigation for its efficacy in NSCLC [38]. Early clinical trials indicate that T-VEC induces an immune response in NSCLC patients and exhibits a synergistic effect when combined with PD-1 inhibitors. Reovirus, a naturally occurring virus, selectively infect and kill tumor cells. Clinical trials in NSCLC indicate that Reovirus has good safety and potential efficacy, particularly when combined with immune checkpoint inhibitors. The genetically engineered measles virus is used to treat various cancers, including NSCLC. Preclinical studies show that the measles virus can selectively infect and kill NSCLC cells, causing a strong antitumor immune response.

Biomarkers

Identifying and applying biomarkers significantly enhances treatment response prediction, optimizes treatment plans, and improves efficacy in immunotherapy in NSCLC. Tumor mutation burden (TMB) is the number of mutations present in the tumor genome per million base pairs (Mb). High TMB is often associated with the generation of new antigens, which can more effectively stimulate immune responses. Therefore, TMB is considered an important biomarker for predicting immune therapy responses [39]. In the CheckMate-227 clinical trial, the efficacy of Nivolumab (PD-1 inhibitor) in combination with Ipilimumab (CTLA-4 inhibitor) was evaluated in patients with high TMB NSCLC. The results indicated that patients with high TMB (≥ 10 mutations/Mb) experienced significantly longer progression-free survival (PFS) and overall survival (OS), underscoring the association of high TMB with improved therapeutic outcomes [40]. Therefore, TMB testing can be an important criterion for screening suitable immunotherapy patients.

Circulating tumor DNA (ctDNA) emerges as a pivotal biomarker in NSCLC immunotherapy, consisting of free DNA fragments released from tumor cells into the bloodstream. ctDNA has demonstrated significant potential in cancer detection and monitoring, particularly in NSCLC immunotherapy, where it offers dynamic, non-invasive insights into tumor characteristics and treatment response [41]. Currently, the primary methods for detecting ctDNA include digital PCR (dPCR), next-generation sequencing (NGS), and BEAMing technology. The ctDNA has been shown to decrease after immunotherapy treatment, indicating a more favorable treatment response and serving as a predictor of treatment outcomes. Furthermore, regular monitoring of ctDNA

levels allows for real-time assessment of immunotherapy efficacy. An increase in ctDNA levels may indicate disease progression or recurrence, and early intervention can improve patient prognosis [42]. Analysis of ctDNA also facilitates the identification of new drug-resistant mutations, enabling timely adjustments to treatment plans. Compared with traditional tissue biopsies, ctDNA testing can be performed through simple blood extraction, reducing the pain and risk for patients. ctDNA can reflect the heterogeneity of tumors throughout the body and provide more comprehensive genomic information than single-tissue biopsies [43]. Despite the continuous advancement of ctDNA detection technology, there is still a need to improve its sensitivity and specificity further, especially in low-frequency mutation detection. Standardized detection processes and analytical methods need to be established to ensure comparability of results between different laboratories. Consequently, extensive clinical studies are imperative to confirm the utility of ctDNA in predicting immunotherapy responses and monitoring for drug resistance.

Neoantigen, an antigen produced by unique mutations in tumor cells that are not expressed in normal cells, can be detected by the immune system, leading to a robust antitumor response. Neoantigen load refers to the number of neoantigens produced in tumor cells, and a higher neoantigen load is usually associated with better immune therapy response [44]. Its mechanism of action involves the presentation on T-cells through major histocompatibility complex (MHC) molecules, triggering T-cells to recognize and attack tumor cells. Neoantigen increases the probability of the immune system recognizing tumors, thereby enhancing immune surveillance function. The KEYNOTE-010 clinical trial evaluated the efficacy of Pembrolizumab (PD-1 inhibitor) in PD-L1 positive NSCLC patients, indicating a positive correlation between neoantigen burden and Pembrolizumab treatment response. Specifically, patients with high antigen burdens are showing better treatment outcomes [45], highlighting the potential of neoantigen burden to be used as a biomarker for selecting suitable immunotherapy patients. Patients with a high antigen burden are more likely to benefit from immune checkpoint inhibitor therapy. In the future, it can be combined with other biomarkers such as TMB, PD-L1 expression, and TILs to improve prediction accuracy.

Adverse reactions

Despite significant efficacy in the treatment of NSCLC, immunotherapy has also carried some side effects, such as immune-related adverse events (irAEs), which occur when the activated immune system attacks normal tissues [46]. Common adverse reactions include mild to moderate rashes, varying degrees of itching, and rare but severe conditions like Stevens-Johnson syndrome and toxic epidermal necrolysis, which require urgent care [47]. Additionally, PD-1/PD-L1 and CTLA-4 inhibitors often cause severe diarrhea and colitis, potentially requiring corticosteroid intervention. Abnormal liver function, indicated by elevated transaminases and jaundice, represents another serious concern. Pneumonitis is a serious adverse effect of immunotherapy, presenting symptoms such as cough, shortness of breath, and chest pain, and it may require treatment with corticosteroids and other immunosuppressants. Thyroid dysfunctions, including hypothyroidism or hyperthyroidism, often need thyroid hormone replacement or antithyroid medications [48]. Some patients may develop new-onset diabetes or exacerbation of existing diabetes, which might require insulin therapy.

Despite its efficacy in NSCLC treatment, the side effects associated with immunotherapy require vigilant monitoring by clinicians and patients. Early detection, timely intervention, and individualized management are crucial to minimizing the adverse

impact on patients' quality of life and optimizing the benefits of immunotherapy.

Future prospects

Building on the success of PD-1/PD-L1 and CTLA-4 inhibitors in treating NSCLC, researchers are investigating additional immune checkpoint targets, including LAG-3, TIM-3, and TIGIT. These novel inhibitors could expand treatment options for NSCLC patients, particularly those resistant to current therapies. Future strategies might include dual immune checkpoint inhibition, such as combining PD-1/PD-L1 inhibitors with CTLA-4 inhibitors, to potentially enhance T-cell activity, leading to higher efficacy and longer survival [49], [50]. Current research is exploring biomarkers that predict responses to immunotherapy, such as tumor mutational burden (TMB), microsatellite instability (MSI), and specific gene mutations. These biomarkers help identify patients most likely to respond to immunotherapy, enabling the optimization of treatment plans. Additionally, analyzing circulating tumor DNA (ctDNA) and other biomarkers in the blood can provide real-time monitoring of tumor dynamics, assess treatment effectiveness, and detect resistance early [51]. Emerging therapies like oncolytic virus therapy and CAR-T cell therapy show promising application prospects. Future combinations of oncolytic virus therapy with immune checkpoint inhibitors may enhance efficacy. Although CAR-T cell therapy is mainly used for hematological malignancies, its application in solid tumors, including NSCLC, is under exploration. Through genetic modification, T-cells can be enhanced to recognize better and kill tumor cells, potentially becoming a significant treatment option in the future. In summary, immunotherapy for NSCLC has made remarkable progress recently. The development of new immune checkpoint inhibitors, application of combination therapies, advancement of personalized and precision medicine, exploration of emerging therapies, and strategies to overcome resistance provide additional treatment options and improved prognoses for NSCLC patients [49]. Ongoing research and clinical trials are expected to increasingly vitalize immunotherapy's role in NSCLC treatment, improving patient survival rates and quality of life.

Conclusion

The review provides an overview of immune therapy pathways pertinent to NSCLC, elucidating the mechanisms of action of PD-1/PD-L1, CTLA-4, oncolytic viruses, and CAR-T cells. It also summarized the mechanisms of action of traditional and novel immune checkpoint inhibitors, oncolytic viruses, and the clinical applications and research progress of biomarkers. Furthermore, the review highlighted the potential side effects associated with immunotherapy and offered insights into future directions in this rapidly evolving field. This comprehensive examination aims to deepen understanding of the current landscape and future potential of immunotherapy in NSCLC.

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Availability of data and materials

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Ethical policy

Not applicable.

Author contributions

PH conceptualized, designed, conducted research, wrote the draft and approve the final manuscript.

Competing interests

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