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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) is a major cause of mortality due to cancer worldwide. In recent years, immunotherapy, especially regarding immunotherapy, immune checkpoint inhibitors have come out of unparalleled interest for the management of NSCLC and remarkably improved patient outcomes. This article aims to explore the mechanism of immunotherapy in NSCLC, as well as the research progress of PD-1/PD-L1, CTLA-4 pathways, and other emerging immunotherapy methods such as oncolytic viruses and CAR-T cells. First, mechanisms of immunotherapy in NSCLC were assessed, with particular emphasis on the roles of the PD-1/PD-L1 and CTLA-4 pathways. Secondly, the part of clinical application summarizes currently approved and investigational drugs, including Nivolumab, Pembrolizumab, and Atezolizumab, are summarized. Next, we overview the recent research progress concerning novel immunotherapeutic agents and biomarkers, discussing side effects of immunotherapy. Finally, we present our views with regard to future perspectives of NSCLC immunotherapy, investigating how the concept of precision medicine and personalized treatment strategies can lead to higher therapeutic efficacy. The innovation of this study lies in a comprehensive and systematic overview of various methods of immunotherapy for non-small cell lung cancer, including immune checkpoint inhibitors, oncolytic viruses, and CAR-T cells, and proposes the potential of promoting personalized treatment through precision medicine.

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

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Introduction

Non-small cell lung cancer (NSCLC) is a high-aggressive tumor that has high incidence and mortality rates throughout the world [1]. Generally, the prognosis is poor, with a high probability of recurrence even after therapy, because of the rapid progression of the disease. Traditional conventional treatments are surgery, radiotherapy, and chemotherapy which, although capable of controlling the diseases to some extent, have quite significant limitations and drawbacks [2]. Surgical treatment is suitable only for early-stage NSCLC patients, while most patients are usually diagnosed with late-stage or inoperable cancer; thus, the surgical scope is limited [3]. Radiotherapy and chemotherapy, being conventional treatments, reduce the size of tumors and prolong the survival of patients to a certain extent, but their effectiveness is often impeded by tumor resistance and serious side effects [4]. Under these circumstances, immunotherapy has emerged as the most promising alternative, offering new hope for patients with NSCLC [5]. In turn, it can activate the immune system of the patient to recognize tumor cells and attack them, which is very specific and induces long-lasting antitumor effects. Up to date, several advantages of immunotherapy over conventional treatments have been evidenced in the management of NSCLC. First of all, it is better tolerated; it has relatively few side effects and is able to ensure a better quality of life for the patients. Secondly, overcoming resistance issues associated with traditional therapies may help maintain the effectiveness of immunotherapy during long-term use. Moreover, immunotherapy can activate the memory effect of the immune system and afford preventive efficacy against the recurrence of a tumor, which is hardly achievable with the help of traditional treatments [6]. Although traditional therapies can to some extent control NSCLC, due to their limitations, the treatment efficacy and prognosis of patients are still not ideal. The emergence of immunotherapy has brought new hope to this field. This study focuses on immunotherapy, aiming to fill the gap in current treatment methods and evaluate the advantages of immunotherapy compared to traditional treatments, such as fewer side effects, higher tolerance, and preventive effects on tumor recurrence.

Mechanisms of immunotherapy in NSCLC

The mechanism of immunotherapy for non-small cell lung cancer (NSCLC) primarily consists of six key steps (**Figure 1**). First, cancer cells within the tumor tissue begin to release certain characteristic substances. These substances are captured and recognized by specialized cells within the immune system. These specialized cells then relay the information to the immune system's combat cells—T cells—activating them. Once activated, the T cells move toward the area where the cancer cells are located, preparing to launch an attack. However, cancer cells have a self-protection mechanism that allows them to bind with certain structures on the T cells, thereby inhibiting the T cells' ability to attack. It is at this critical juncture that PD-1/PD-L1 inhibitor drugs step in and start causing interference so that the self-protection mechanism of the cancer cells gets blocked [7]; the T cells regain their functionality and can keep on identifying and killing the cancer cells [8]. This, in essence, boosts one's immune system to effectively act against the menace of cancer.

PD-1/PD-L1 pathway

The PD-1/PD-L1 pathway is one of the crucial immune regulation pathways. The two key proteins involved in this axis include the receptor-that is, programmed cell death protein 1 (PD-1) and its ligand, which is a protein known as Programmed death-ligand 1 (PD-L1). PD-1 is a receptor expressed on the surface of activated T cells, B cells, and some other immune cells [9]. The ligand PD-L1 is expressed by a wide array of cell types, including tumor cells and antigen-presenting cells such as dendritic cells and macrophages [7]. The pathway plays a critical role in balancing the immune response, preventing autoimmune responses. However, within the tumor microenvironment, this mechanism is often exploited for immune surveillance evasion [10]. In fact, the pathway of PD-1/PD-L1 plays an important role in immune escape mechanisms in NSCLC. The tumor cells can upregulate the expression of PD-L1 to interact with the PD-1 receptor on T cells, which inhibits the activity of T cells and thus allows tumor cells to escape from immune surveillance [11]. This interaction provides a new approach for the treatment of non-small cell lung cancer (NSCLC). PD-1/PD-L1 inhibitors restore T cell activity by blocking the interaction between PD-1 and PD-L1, helping the immune system recognize and destroy tumor cells. PD-1 inhibitors such as nivolumab and pembrolizumab block their interaction with PD-L1 by binding to PD-1 [12]; PD-L1 inhibitors such as atezolizumab bind to PD-L1, preventing its binding to PD-1 and relieving its inhibition on T cells [13].

CTLA-4 pathway

Another important immune checkpoint pathway is the CTLA-4 pathway, which modulates the amplitude of the immune activity and impairs autoimmune reactions. The pathway includes CTLA-4 and B7 molecules [14]. In NSCLC, the tumor cells can facilitate CTLA-4 expression or enhance the activity of the B7 molecule to restrain further T cell function, promoting immune escape for tumor cells. Engagement of the CTLA-4 pathway inhibits T cells from fully exerting their antitumor function-promoting tumor growth and spread [15]. 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 [16]. CTLA-4 inhibitors can also 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 [17]. These viruses not only directly destroy tumor cells but also activate the host immune system to combat the tumor [18]. NSCLC cells express specific receptors that can be recognized and bound by oncolytic viruses. For example, some adenoviruses can selectively infect NSCLC cells by recognizing the Coxsackievirus and Adenovirus Receptor (CAR) on their surface [19]. Oncolytic viruses have the advantage of replicating and spreading more easily in NSCLC cells, whose cells typically have defective antiviral defences. Oncolytic viruses once inside NSCLC cells replicate, release new virus particles, break the cell membrane, and lyses and kill the cell. Oncolytic viruses exert their direct oncolytic effect, but can also stimulate the host immune response against NSCLC cells [20].

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

Immunotherapy in the form of Chimeric Antigen Receptor T-cell Therapy is a very sophisticated form in which the patient's T cells are genetically altered to express chimeric antigen receptors (CARs) to recognize and kill tumour cells. To date, this therapeutic modality has been quite successful in haematological malignancies

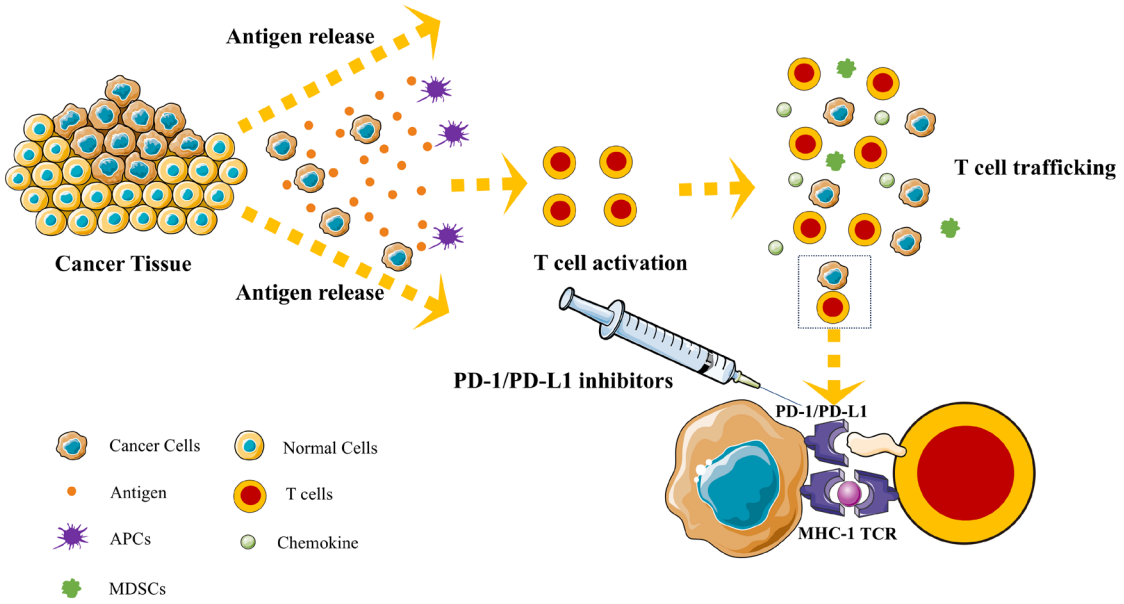

Figure 1. Plot of the mechanism of immunotherapy for non-small cell lung cancer (NSCLC).

and is being studied for its applicability in solid tumours, including NSCLC [21], [22]. The major process is peripheral blood collection and sorting of T cells; the addition of a gene encoding for a single chain antibody (scFv) that recognizes tumour-specific antigens, including a chimeric antigen receptor (CAR)-a chain that activates the T cell signalling domain. Viral vectors (mostly lentiviruses or retroviruses) are used to deliver this gene to the T cells [23]. The modified CAR-T cells are expanded in vitro and then intravenously injected back into the body. In vivo, through the specificity of the CAR structure, the modified CAR-T cells bind to antigens on the surface of tumor cells. After binding to the tumor cells, the CAR-T cells are activated to release cytotoxic particles (such as perforin and granzyme), which kill tumor cells [24].

Immunotherapy for non-small cell lung cancer (NSCLC) mainly involves several mechanisms: PD-1/PD-L1 pathway inhibitors restore T cell immune function by blocking the interaction between tumor cells and T cells; CTLA-4 inhibitors enhance immune responses by relieving inhibition of T cells; Oncolytic viruses selectively infect and kill tumor cells while activating the immune system; CAR-T cell therapy involves genetically modifying T cells to recognize and kill tumor cells. These methods collectively enhance the immune system's attack on tumors, providing new directions for NSCLC treatment.

Clinical applications and research progress

In recent years, immunotherapeutic approaches to non-small cell lung cancer (NSCLC) have impressively developed in the clinic, particularly with the use of immune checkpoint inhibitors, drastically improving survival and quality of life for patients [25], [26]. We summarized some immune checkpoint inhibitors commonly used in clinical practice and their characteristics (**Table 1**).

Nivolumab (Opdivo)

Nivolumab (Opdivo) is the first PD-1 inhibitor approved for the treatment of NSCLC. It is under investigation in two pivotal clinical trials; CheckMate-017 and CheckMate-057 were designed to test Nivolumab against docetaxel in patients with advanced squamous NSCLC [27], [28]. Both studies demonstrated that the median overall survival(OS) in the Nivolumab group was 9.2 months, while in the docetaxel group, it was 6.0 months. Whereas the overall survival rate at 1 year was 42% in the Nivolumab group, it was 24% in the docetaxel group. These clinical trials have underlined the great step forward that Nivolumab has achieved in treating NSCLC by highly increasing both overall survival (OS) and progression-free survival (PFS) of patients with advanced NSCLC.

New immune checkpoints

The enormous success of therapies with PD-1/PD-L1 and CTLA-4 inhibitors in cancer treatment has shifted the investigations to other novel immune checkpoints to overcome the inefficacy of the existing therapies. LAG-3 (lymphocyte activation gene 3) is a receptor expressed on activated T cells, natural killer (NK) cells, and some B cells, typically inhibiting T cell function by binding to MHC class II molecules. Preliminary studies have shown that the combination of LAG-3 inhibitors and PD-1 inhibitors can overcome resistance to PD-1 monotherapy and improve efficacy [29]. TIM-3 (T-cell immunoglobulin and mucin 3) is expressed in T cells, NK cells, and monocytes as a negative regulatory molecule that inhibits T cell function. When TIM-3 binds to its ligands (such as Galectin-9), it can induce immune suppression signals [30]. TIM-3 inhibitors may release T cell inhibition through this mechanism and enhance the immune system's anti-tumor ability, especially in PD-1-resistant patients [31]. 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

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	ORR: 20%-30%
Pembrolizumab (Keytruda)	PD-1 inhibitor	Advanced or metastatic NSCLC patients with high PD-L1 expression, as a first-line therapy	Combined with chemotherapy	ORR: 40%-50%(In patients with PD-L1 expression ≥50%)
Atezolizumab (Tecentriq)	PD-L1 inhibitor	Advanced or metastatic NSCLC patients with progression after chemotherapy	Combined with chemotherapy and bevacizumab	ORR: 15%-20%
Ipilimumab (Yervoy)	CTLA-4 inhibitor	Primarily for melanoma treatment, shows potential in NSCLC	Combined with Nivolumab	ORR: 15%-20%

[32]. Preliminary studies have shown that in some patients, the combination of TIGIT inhibitors and PD-L1 inhibitors (such as Atezolizumab) exhibits enhanced anti-tumor activity. B7-H3 (CD276) is a molecule expressed on multiple cell types, including tumor cells, that participates in immune suppression and plays a role in tumor immune escape [33]. VISTA (V-domain Ig suppressor of T cell activation) is a negative immune regulatory molecule expressed on myeloid cells and some T cells [34]. 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 [35], [36]. Research into new immune checkpoints is rapidly in development with a view to overcoming the limitations of current immunotherapies and offering patients more treatment options [37]. Further investigation of these novel immune checkpoints and their roles within the tumor microenvironment will continue to lead to the development of new inhibitors and combination therapies aimed at improving therapeutic efficacy in NSCLC and other cancers.

Oncolytic viruses

Four strains of oncolytic viruses have been primarily developed: Oncorine (H101) [38], Talimogene laherparepvec (T-VEC) [39], Reovirus [40], and measles virus [41]. H101 is a genetically modified adenovirus and has become the first approved in China for the treatment of head and neck squamous cell carcinoma. Its research in NSCLC has been promising, especially when combined with chemotherapy, enhancing the efficacy of the treatment. T-VEC is a genetically modified herpes simplex virus (HSV) used for the treatment of unresectable melanoma; its possible use in NSCLC is being explored [42]. Early-phase clinical trials showed that T-VEC induces an immune response in NSCLC patients; when combined with PD-1 inhibitors, it has synergistic effects. Reovirus is a naturally occurring virus that selectively infects and kills tumor cells. Clinical trials in NSCLC have demonstrated good safety of Reovirus with potential efficacy, especially in combination with immune checkpoint inhibitors. Genetic modification of the measles virus is used for the treatment of a variety of cancers including NSCLC. Preclinical studies using the measles virus demonstrate that it is selectively capable of infecting and destroying NSCLC cells, inducing a potent anti-tumor immune response.

Biomarkers

Identifying and applying biomarkers are important in identifying and applying the prediction of treatment response and optimization of treatment plans for improving efficacy in immunotherapies for non-small cell lung cancer (NSCLC). Tumor mutation burden (TMB) is defined as the total number of mutations present in the tumor genome per million base pairs. High TMB usually correlates with the generation of neo-antigens, which in general would more potently induce an immune response. Therefore, TMB is also considered an important biomarker for the prediction of responses to immune therapy [43]. CheckMate-227 was a clinical trial for testing the efficiency of Nivolumab (PD-1 inhibitor) in combination with Ipilimumab (CTLA-4 inhibitor) in high TMB NSCLC. Results of the study proved that in the case of high TMB (≥10 mutations/Mb) progression-free survival (PFS) and overall survival (OS) rates were significantly longer following combination treatment, demonstrating that high TMB is associated with better outcomes [44]. Thus, testing of TMB could be one of the important criteria for the selection of appropriate candidates for immunotherapy.

Circulating tumor DNA (ctDNA) is a tumor-derived free DNA fragment released into the bloodstream and has become an emerging biomarker in NSCLC immunotherapy. 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 [45]. Currently, the primary methods for detecting ctDNA include digital PCR (dPCR), next-generation sequencing (NGS), and BEAMing technology. Research has shown that patients with high levels of ctDNA before immunotherapy experience a significant decrease in ctDNA levels after treatment, indicating a more favorable treatment response and serving as a predictor of treatment outcomes. Efficacy monitoring can also be conducted, and by regularly monitoring ctDNA levels, the effectiveness of immunotherapy can be evaluated in real-time. An increase in ctDNA levels implies that an increase in levels may signify the progress or recurrence of a disease, with early intervention resulting in better outcomes for the patients [46]. Analyzing ctDNA may also be used to monitor new drug-resistant mutations so that adjustments in treatment can be made. Compared with traditional methods of tissue biopsy, testing of ctDNA can be done through simple blood extraction and hence reduces the pain and risk for patients. It provides an indication of the heterogeneity of tumors throughout the body and offers more complete genomic information compared with single tissue biopsy [47]. While detection technologies for ctDNA continue to improve, increased

sensitivity and specificity, especially with respect to the detection of low-frequency mutations, is still highly desirable. Detection processes and methods of analysis need to be standardized to ensure that the results from different laboratories are comparable. Large-scale clinical investigation of the effectiveness and reliability of the ctDNA prediction for responses to immune therapy and monitoring drug resistance will be further required in future studies.

Neoantigen refers to a kind of antigen that is produced by a special mutation of tumor cells and is not expressed in normal cells. These neoantigens can be recognized by the immune system, inducing a potent anti-tumor response. Neoantigen load means the amount of neoantigen produced in tumor cells, and the higher neoantigen load usually had better immune therapy response [48]. The main mechanism of action thereby involves neoantigen presentation to T cells through major histocompatibility complex (MHC) molecules, thus stimulating T cells to recognize and attack tumor cells. Neoantigen presentation increases the possibility of tumor recognition by the immune system and, as a result, enhances the 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, with patients with high antigen burden showing better treatment outcomes [49]. This indicates that neoantigen burden can be used as a biomarker for selecting suitable immunotherapy patients, and 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

While immunotherapy has shown significant efficacy in the treatment of NSCLC, it also carries some side effects, similar to other treatment modalities. These side effects are primarily immune-related adverse events (irAEs), which occur when the activated immune system attacks normal tissues [50]. 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 [51]. Common side effects of PD-1/PD-L1 and CTLA-4 inhibitors can include severe diarrhea and colitis, which may necessitate corticosteroid treatment. Another common concern is abnormalities in liver function, usually evidenced by rises in transaminases and jaundice. More serious is pneumonitis, representing a well-known side effect of immunotherapy, presenting with symptoms including cough, shortness of breath, and chest pain, requiring treatment with corticosteroids and other immunosuppressants. Thyroid dysfunctions, which include hypothyroidism or hyperthyroidism, are often treated with the replacement of thyroid hormone or with antithyroid medications [52]. Some patients may develop new-onset diabetes mellitus can occur; preexisting diabetes mellitus can deteriorate, sometimes requiring insulin therapy.

In summary, although immunotherapy has achieved significant efficacy in the treatment of non-small cell lung cancer (NSCLC), its side effects cannot be ignored, mainly including rash, itching, pneumonia, thyroid dysfunction, which may reduce the quality of life of patients. Early detection, timely intervention, and individualized management plans are crucial to reduce the occurrence of these side effects. These measures can effectively reduce side effects and ensure that patients receive maximum efficacy and benefits from immunotherapy.

Future prospects

The successes of PD-1/PD-L1 and CTLA-4 inhibitors represent the foundation in the NSCLC application of immune checkpoint blockade. Several other immune checkpoint targets are presently under investigation, including among others LAG-3, TIM-3, and TIGIT. For example, Relatlimab (a LAG-3 inhibitor) has shown enhanced efficacy in early clinical trials when used in combination with PD-1 inhibitor nivolumab. In a phase III clinical trial, the combination of Relatlimab and nivolumab was used to treat melanoma patients, and the results showed that the combination therapy had significant survival benefits compared to using nivolumab alone [53]. These newer checkpoint inhibitors will offer further therapeutic options for NSCLC patients, including those who become resistant to current therapies. Future dual immune checkpoint inhibition, such as combinations involving PD-1/PD-L1 inhibitors and CTLA-4 inhibitors, may further enhance the activity of T cells and be associated with increased efficacy and survival benefits [54]. Biomarkers predictive of responses to immunotherapy, such as tumor mutational burden (TMB), microsatellite instability (MSI), and specific gene mutations, are currently under deep research. These biomarkers enable the identification of patients who are most likely to benefit from immunotherapy and support the optimization of treatment plans. Moreover, analyzing circulating tumor DNA (ctDNA) and other biomarkers in the blood can also present real-time monitoring of tumor dynamics, evaluate treatment effectiveness, and monitor resistance early [55]. Other emerging therapies are oncolytic virus therapy and CAR-T cell therapy, both of which have promising application prospects. In the future, oncolytic virus therapy could be combined with immune checkpoint inhibitors for better efficacy. While CAR-T cell therapy is mainly used for hematological malignancies, it is also being explored for solid tumors, including NSCLC. Through genetic modification, T cells can be enhanced to better recognize and kill tumor cells, potentially becoming a significant treatment option in the future. In summary, immunotherapy for NSCLC has made remarkable progress in recent years, with even greater prospects ahead. 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 [56]. Through ongoing research and clinical trials, immunotherapy is expected to play an increasingly important role in the treatment of NSCLC, improving patient survival rates and quality of life.

Conclusion

In our review, we gave an overview of immune therapy pathways related to NSCLC: the mechanism of action of the PD-1/PD-L1, CTLA-4, oncolytic viruses, and CAR-T cells. Then, we summarized the action mechanism of both the traditional and novel immune checkpoint inhibitors, oncolytic virus, and clinical application and research progress of biomarkers. Furthermore, the review also referred to the possible immunotherapy-related side effects and provided an overview of future perspectives in this rapidly changing field. With the present extensive review, we would like to contribute to a better understanding of the current status and future promises 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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