Proceedings of ICEGEE 2026 Symposium: AI-Based Medicine and Biological Data Analysis
DOI: 10.54254/2753-8818/2026.AU32051

Immunotherapy Role in Non-Small Cell Lung Cancer Treatment

Qixuan Nie

The Village School, Houston, USA
niemichael335@gmail.com

Abstract. Lung cancer has one of the highest death rates of all cancers. It is a serious health risk that must be addressed. Non-small cell lung cancer makes up 85% of lung cancer cases, which should be the main focus of treatments. But even with new approaches like immune checkpoint inhibition, the treatment works for only a small group of patients. This review discusses the biological foundations of lung cancer immunotherapy, the function of immune checkpoint inhibitors (ICIs), and the unpredictable nature of the lung tumor microenvironment. The paper then evaluates the use of ICIs, possible combination therapies, and major limitations currently faced in the field. These limitations include resistance mechanisms, immune-related side effects, and tumor heterogeneity. New strategies, such as biomarker-guided immunotherapy, novel immune treatments, and technologies that support the field, are also evaluated and discussed as possible solutions. In the end, evidence has shown the impact and influence of immunotherapy in cancer treatment. Future progress in lung cancer immunotherapy will depend on precision treatment strategies, combination approaches, and new immune therapies to lay a foundation for sustained, consistent clinical outcomes.

Keywords: Non-small Cell Lung Cancer, Cancer Immunotherapy, Immune Checkpoint Inhibitors, Therapeutic Resistance

1. Introduction

Lung cancer is one of the largest public health challenges in the world, with a global cancer death toll of 1.8 million per year. This form of illness ranks high among diagnosed cancers yet stands out due to its high mortality rate. Even with programs pushing earlier detection, diagnosis frequently happens late, leading to limited options. Screening advances exist; still, progression often goes unnoticed until severe symptoms appear. Most instances (close to 85 percent) fall under non-small cell lung cancer, or NSCLC. That subtype dominates the statistics, driving most fatalities linked to the disease. Because of its reach and resistance, long-term control remains a central goal in tackling this condition.

Traditional therapies for lung cancer are widely accepted and useful to some extent, but they are toxic and not durable. Late diagnosis greatly limits the range of treatments since surgery can be curative only in early stages, and patients are most commonly diagnosed in advanced-stage disease. A further common limitation of chemotherapy and radiology is the potential systemic toxicity.

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.AU32051

Furthermore, there has also been a major drawback regarding resistance, as has been evidenced in targeted therapy. Targeting treatments have also demonstrated efficacy in certain subpopulations of lung cancer patients based on distinct genetic changes; nevertheless, resistance to targeted treatments also develops. All of these limitations emphasize that existing treatments are unable to maintain cancer control long-term for lung cancer patients.

Cancer immunotherapy, specifically immune checkpoint inhibition, has created a new perspective in lung cancer treatment by directly stimulating the patient's immune system to combat tumor cells rather than relying on external forces. Clinical trials have shown that PD-1/PD-L1-targeted immune checkpoint inhibitors have not only provided certain clinical benefits but also demonstrated a potential long-term cure effect. These findings have generated high expectations for the durable responses achievable with immunotherapy. Nevertheless, in clinical practice, there is also a wide range of responses to the same drug among patients. A substantial proportion of patients don't respond to the treatment, and while most responders may enter remission, some are at a higher risk of developing resistant clones after initial response.

It is one of the key issues in treating lung cancer by immunotherapy because the results vary. Although immunotherapy is a new style, it is unpredictable and irregular in clinical practice. Additional work in the area should rely on better knowledge of the lung tumor microenvironment and the therapeutic resistance mechanisms. This review evaluates how immunotherapy works and how it can be used clinically in the treatment of lung cancer, especially NSCLC. It presents the biological foundation of immunotherapy, its recent clinical applications, major limitations, and new biomarker-oriented applications that are expected to enhance treatment specificity and patient outcome.

2. Lung cancer epidemiology and the foundation of NSCLC immunotherapy

2.1. Lung cancer epidemiology and immunological background

Lung cancer stands as the leading cause of cancer-related mortality worldwide, accounting for 1.8 million deaths each year [1]. With an incidence rate of 226,650 and a death toll of 124,730 as of 2025, lung cancer is a problem that must be further addressed. Current treatments of chemotherapy, radiation, and hormonal therapies are not effective in the long run, and there are often cases of relapse. This data reflects the scale of lung cancer's reach. But it also reveals deeper problems in treatment reliability. A stronger approach must last longer and work better, one that adapts under pressure. Current methods fail when tested over time. What remains clear is that improvement isn't optional. It's required [2].

The majority of lung cancers are divided into two categories, including non-small cell and small cell. Non-small type constitutes more than 85 per cent of the diagnosed cases. Since in most cases, smoking would cause genetic damage to such tumors, particularly to protective genes like TP53, the gene changes would be numerous. Such alterations leave distinct stamps on the surface of cancer cells using the MHC structure. These signals distinguish the diseased cells from the healthy tissue. This can be seen as the immune responses can now have a better target, thus detecting abnormal growths better [3].

2.2. The lung tumor microenvironment

The powerful immune surveillance in many cases cannot work due to the lung tumor microenvironment (TME). The TME is a rich population comprising cancer cells, structural tissues,

DOI: 10.54254/2753-8818/2026.AU32051

immune agents, chemical signals, and energy-related states. Even in cases where immunity functions normally, lung cancers tend to expand into a TME, which has a continuous defense blockage. The immune system fails to cooperate with tumor cells. They instead interrelate with support cells, inflammatory proteins, and abnormal blood vessels to interfere with normal immune functioning. Such mutations weaken T cells and trigger evasion of cancer cells by the immune system. VEGF is a significant part of such a process. Besides stimulating blood vessel growth, VEGF also inhibits the immune system by preventing the maturation of dendritic cells and T-cell suppression. Low oxygen conditions and chronic inflammation are also favorable for immune escape. Collectively, these processes produce a tumor micro-environment that encourages cancer development and suppresses healthy immune functions [4].

2.3. Key immune effectors

This adverse tumor microenvironment influences major immune cells. Cytotoxic T cells, which are CD8+, are the primary tumor-killing cells. They are commonly suppressed and tired in the microenvironment of lung tumor thereby lowering their cancer-killing capabilities. The CD4+ helper T cells are also important since they initiate immune responses, activate other T cells, and aid B cells to fulfill their functions. In cancer, however, these cells might fail to perform their normal role.

In addition, an immunosuppressive tumor environment can increase regulatory T cells (Tregs), which suppress anti-tumor immune responses. Natural killer (NK) cells are responsible for early immune surveillance, but in lung cancer, their ability to kill tumor cells is often reduced. This further weakens immune control [5].

2.4. The paradox of lung cancer

This is one of the main paradoxes of lung cancer. Even though lung cancer is very immunogenic, the cancer usually evades immunological destruction. The existence of immune cells may result in the classification of tumors as hot or cold. Active immunocytes are present in hot tumors, and immunotherapy is more effective in them. The cold tumors are characterized by minimal infiltration of the immune cells and a highly immunosuppressive milieu. Due to this variation, patients react differently to clinical responses. Knowledge of this paradox justifies the utilization of immune checkpoint inhibitors that are meant to reestablish anti-tumor immunity by deleting inhibitory signals on immune cells [6].

3. Immune checkpoints and the applications of immunology in NSCLC

3.1. Immune checkpoints

Immune checkpoints are regulatory pathways that regulate immune response, preventing excessive immune activation and autoimmunity. They act as a kind of inhibitory mechanism, preventing adverse immune effects. In cancer, tumor cells exploit these pathways to evade immune detection and freely spread [7].

Therefore, understanding these pathways is essential for progress in cancer treatment. The programmed cell death protein-1 (PD-1) pathway is the most clinically relevant immune checkpoint in lung cancer. PD-1 is expressed on active T cells, while its ligand PD-L1 is upregulated on tumor and immune cells in the TME. The binding of PD-L1 to PD-1 inhibits T-cell proliferation, cytokine production, and cytotoxic function, leading to T-cell exhaustion and allowing the cancer to effectively evade immune surveillance [8].

DOI: 10.54254/2753-8818/2026.AU32051

3.2. Immune checkpoint inhibitors in NSCLC

Immune checkpoint blockers targeting PD-1 or PD-L1 have changed how non-small cell lung cancer is treated. Now common at diagnosis or later stages, these drugs appear in many treatment plans. Given by themselves or paired with chemo, they outperform older methods in extending life. Their effects often last longer than those seen with standard approaches, with some individuals keeping cancer under check for years. Such lasting responses could signal a turning point, especially for cancers like NSCLC that typically carry a grim outlook [9].

Early in T-cell activation, CTLA-4 acts as a checkpoint molecule that interferes with stimulatory cues when antigens are presented. This protein, known as cytotoxic T-lymphocyte-associated antigen 4, serves as a parallel route in immune regulation. Although inhibiting CTLA-4 is able to enhance immune priming, it activates a broader immune response, which can bring about increased toxicity, making PD-1/PD-L1 inhibition the dominant approach in lung cancer immunotherapy [10]

The advantage of immune checkpoint inhibitors is that it alters a patient's own natural immune system rather than directly targeting tumor cells as is done in traditional therapies. Immunotherapy has a more favorable toxicity profile, and disease control is more durable in comparison to conventional chemotherapy, thus the possibility of developing sustained immune-mediated tumor control. These attributes have changed the patient goals in NSCLC from short-term tumor regression to cure.

Despite such advancements, responses to ICIs in NSCLC remain highly variable; in fact, most patients show little to no response to ICI therapy and may possess primary/secondary resistance to the treatment. Although biomarkers such as PD-L1 show promise in helping define future treatment approaches, it is not yet able to completely and accurately predict treatment response.

3.3. Combination strategies in NSCLC

ICIs have provided a new perspective on cancer treatment and significantly improved cancer outcomes in NSCLC. But single-treatment methods remain insufficient for many patients. The problem of the immunosuppressive TME is still a challenge to overcome. Thus, combination strategies have become a major focus in lung cancer immunotherapy. They aim to strengthen antitumor immune responses while targeting multiple barriers to immune activation [11].

A combination of immunotherapy and chemotherapy has proven to be one of the most popular approaches. Chemotherapy alone can promote tumor antigen release and immunogenic cell death as well as augment the process of antigen-presenting cells, leading to T-cell priming and providing tumors with a susceptibility to immune checkpoint blockade. It has been demonstrated in clinical trials that immunotherapy can enhance the response rate and survival of patients in combination with chemotherapy when compared to chemotherapy alone. Due to this advantage, such a combination is commonly used as an initial intervention in the treatment of advanced NSCLC [12].

Radiotherapy has also been researched as a complement to immunotherapy since it is capable of transforming the tumor microenvironment. Local radiation may enhance the platform release of tumor antigens, elevate the expression of PD-L1, and enable more immune cells to penetrate into the tumor. This has the capacity to create immune effects outside its treated region. Radiotherapy should be used together with immunotherapy to enhance the immune management of tumors, although the optimal time and the dose of the drug are still under investigation [13].

Overall, combination treatments are an important step in improving lung cancer immunotherapy. However, they also bring new challenges, especially related to safety and patient selection. These issues will be discussed in later sections.

DOI: 10.54254/2753-8818/2026.AU32051

4. Limitations of lung cancer immunotherapy

4.1. Resistance to immunotherapy

Even though cancer therapies using immunotherapy have been introduced, the therapy is only useful to a limited number of patients. This form of treatment is still responsive to only a few patients. These drawbacks raise three key issues in immunotherapy of lung cancer, which include resistance to treatment, adverse effects of immunotherapy, and biological heterogeneity. The values of such issues include a better comprehension of the existing treatments and creation of more effective therapies in the future [14].

Resistance is the most important barrier to effective immunotherapy in lung cancer. It can be divided into primary resistance, where tumors do not respond to treatment at all, and secondary resistance, where tumors initially respond but later escape immune control [15].

STK11 gene mutations are a common cause of primary resistance in NSCLC. Loss of STK11 function reduces immune activity and limits T-cell activation. This creates a "cold" tumor microenvironment, which makes tumors less responsive to immunotherapy.

The mutations of KEAP1 have also been associated with aggressive tumor progression and primary and secondary resistance to immune checkpoint inhibitors (ICI). The mutations aid the tumor cells to survive oxidative stress by turning on the NRF2 pathway. They also alter the metabolism of tumors with the result that more glutamine is utilized by the cancer cells and less by the T cells. This impairs the immune responses and decreases the ability to treat. These results demonstrate that tumor genetics are one of the major factors of immunotherapy [16].

4.2. Immune-related adverse events

The immune-oriented immune checkpoint inhibitors may also lead to immune-related adverse events (irAEs) as a result of the oversensitivity of immune suppression. These medications activate the entire immune system as a whole, and not just at the point of the tumor, which generates side effects such as those of autoimmune diseases. IrAEs can have numerous targets, such as the lungs, gut, skin, and endocrine glands. Though ICIs, in general, are better tolerated compared to chemotherapy, the cases of severe irAEs (Grade 3 or 4) are estimated at 7-13% of NSCLC patients [17].

Checkpoint inhibitor pneumonitis is one of these toxicities that ought to be given serious attention during immunotherapy. Apparently, the number one cause of PD-L1 monotherapy, identified to occur in approximately 12 percent of patients and the chief reason for treatment discontinuation, irAEs can happen at any time during treatment initiation or many months following the treatment procedures. Although many irAEs are manageable with immunosuppressive therapy, severe toxicity poses a great challenge and obstacle to creating a long-term treatment strategy for patients receiving immunotherapies.

4.3. Tumor heterogeneity and unpredictability

Tumor heterogeneity is another major challenge in immunotherapy. It contributes to the unpredictable treatment outcomes in lung cancer. The challenge of NSCLC is made worse by its having both inter-tumor and intra-tumor heterogeneity. Even a cancer diagnosed in the same manner by the same individual may have different patterns of its genes in another. Within a mass, a cell does not remain identical. Some cells evolve genetically. This distorts the immune system of the

DOI: 10.54254/2753-8818/2026.AU32051

surrounding. What was once a very useful medication might stop working merely because the tumor has changed its shape underneath the skin. Such variation creates some complexity in the course of formulating therapy strategies, as well as depleting the effectiveness of current biological markers.

The weakness of the existing treatment of lung cancer is shown in immune resistance, side effects, and unpredictable outcomes of treatment. Due to all these issues, there is a need to adopt new treatment methods. These strategies can extend beyond conventional immune checkpoint inhibitors and even prevention-based strategies. The success of these challenges will determine the future of care. Consequently, new plans are being formulated with regard to improved targeting and sustainability.

5. Emerging strategies and future directions in NSCLC immunotherapy

5.1. Precision and biomarker-guided immunotherapy

Precision and biomarker-guided treatment are important ways to improve outcomes in patients with non-small cell lung cancer (NSCLC). Current immune checkpoint inhibitors, such as PD-1 and PD-L1 inhibitors, are limited in predicting treatment response because tumors are complex and change over time in the tumor microenvironment. New multi-omic approaches combine genomic, transcriptomic, and immune data to better understand tumor–immune interactions. In addition, treatment resistance can be monitored using circulating tumor DNA through liquid biopsy, which may allow more personalized treatment in the future.

5.2. Emerging immunotherapeutic modalities

To overcome resistance to immune checkpoint inhibitors, new immunotherapy methods are being developed for NSCLC. One important example is personalized neoantigen cancer vaccines. These vaccines target tumor-specific mutations and stimulate strong T-cell responses. They can also be used with immune checkpoint inhibitors to improve and prolong treatment effects [11].

Other methods are CAR T-cell and T-cell receptor (TCR)-modified T cells. They are, however, not commonly used in NSCLC since solid tumors have immunosuppressive conditions. Another prospective one is bispecific antibodies. They attach two targets simultaneously and aid in stimulating the immune cells in tumors. And now, on top of PD-1 and PD-L1, there are other checkpoints of the immune system, like LAG-3 and TIGIT, that are under investigation in order to further optimize the work of T-cells [18].

5.3. Technological integration and future treatment pathways

Immunotherapy of lung cancer is becoming more and more reliant on the use of advances in technology. Drug delivery systems formed by nanotechnology have the potential to enhance the accuracy in treatment since the drugs will collect in the tumor tissue. This causes limited harm to the normal tissues due to increased permeability and retention (EPR) effect and targeting. Nanoparticles may also be engineered to transport drugs or cytokines to the tumor microenvironment [19]. Stimulus-responsive designs are also available in some systems with the drug release regulated by a set of signals, including low pH or enzymes.

Now showing clearer views inside tumors, new imaging methods work alongside smarter computer models. Because artificial intelligence digs deeper into patterns, scientists see fresh links between cancer behavior and body defenses. While data grows richer, treatment reactions come into sharper focus. Even early signs of immune activity guide decisions more precisely today. As results

DOI: 10.54254/2753-8818/2026.AU32051

improve, timing matters before surgery gains strength from prep doses. After cutting out growths, follow-up therapy steps in where immunity rises. When protection holds firm, cancer stays quieter for longer stretches. Driven by protein signals, each step fits a larger plan taking shape across clinics [20].

6. Conclusion

These immunotherapy effects have improved the treatment of cancer, mostly in non-small cell lung cancer, which will be the major topic in this paper. Other than eliminating tumor cells directly, Immune checkpoint inhibitors offer an alternative view, offering a renewed outlook by reorganizing the immune system and have proven to have numerous advantages and hopes of sustained reactions that were not very often possible with conventional treatments. Immunotherapy is a significant step forward in the treatment of cancer, and the needs of patients respond differently to the treatment. The problems that are associated with this difference are in terms of treatment resistance, immune-related side effects, and high tumor heterogeneity. This is the reason why not every patient responds to immunotherapy. Better-targeted treatment methods are required to achieve better results. They are improved choices of patients using biomarkers, multi-omic profiling, and combination therapies that can potentially aid in decreasing opposition and adverse effects. Moreover, novel immunotherapy practices are also proving to be effective in enhancing the accuracy and effectiveness of treatment. Immunotherapy is currently playing the role of a significant treatment for lung cancer, and the success of immunotherapy in the future will hinge on future research in the field of immunology, genomics, and bioengineering.

References

[1] Zhou, J., Xu, Y., Liu, J., Feng, L., Yu, J., & Chen, D. (2024). Global burden of lung cancer in 2022 and projections to 2050: Incidence and mortality estimates from GLOBOCAN. Cancer Epidemiology, 93(102693), 102693.

[2] American Cancer Society. (2023, January 12). Lung Cancer Statistics | How Common is Lung Cancer? Www.cancer.org; American Cancer Society. https: //www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html

[3] Li, W., Zhao, Y., Zhang, H., Zheng, W., Wang, R., & Gu, X. (2023). Predictive value of tumor mutational burden for PD-1/PD-L1 inhibitors in NSCLC: A meta-analysis. Medicine, 102(40), e34990.

[4] Zhao, Y., Guo, S., Deng, J., Shen, J., Du, F., Wu, X., Chen, Y., Li, M., Chen, M., Li, X., Li, W., Gu, L., Sun, Y., Wen, Q., Li, J., & Xiao, Z. (2022). VEGF/VEGFR-Targeted Therapy and Immunotherapy in Non-small Cell Lung Cancer: Targeting the Tumor Microenvironment. International Journal of Biological Sciences, 18(9), 3845–3858.

[5] Mariniello, A., Borgeaud, M., Weiner, M., Frisone, D., Kim, F., & Addeo, A. (2025). Primary and Acquired Resistance to Immunotherapy with Checkpoint Inhibitors in NSCLC: From Bedside to Bench and Back. BioDrugs, 39(2), 215–235.

[6] Madeddu, C., Donisi, C., Liscia, N., Lai, E., Scartozzi, M., & Macciò, A. (2022). EGFR-Mutated Non-Small Cell Lung Cancer and Resistance to Immunotherapy: Role of the Tumor Microenvironment. International Journal of Molecular Sciences, 23(12), 6489.

[7] National Cancer Institute. (2011, February 2). Immune checkpoint inhibitor. National Cancer Institute. https: //www.cancer.gov/publications/dictionaries/cancer-terms/def/immune-checkpoint-inhibitor

[8] J. Davies, DNP, MSN, RN, APRN, CNS-BC, ACNP-BC, AOCNP, M. (2019). PD-1/PD-L1 Inhibitors for Non–Small Cell Lung Cancer: Incorporating Care Step Pathways for Effective Side-Effect Management. Journal of the Advanced Practitioner in Oncology, 10(Suppl 1), 21.

[9] Isla, D., Sánchez, A., Casal, J., Cobo, M., Majem, M., Reguart, N., Zugazagoitia, J., & Bernabé, R. (2023). PD-1/PD-L1 Inhibitors as Monotherapy in the First-Line Treatment of Advanced Non-Small Cell Lung Cancer Patients with High PD-L1 Expression: An Expert Position Statement. Journal of Clinical Medicine, 12(15), 5063.

[10] Buchbinder, E., & Hodi, F. S. (2015). Cytotoxic T lymphocyte antigen-4 and immune checkpoint blockade. Journal of Clinical Investigation, 125(9), 3377–3383.

DOI: 10.54254/2753-8818/2026.AU32051

[11] Rother, C., John, T., & Wong, A. (2024). Biomarkers for immunotherapy resistance in non-small cell lung cancer. Frontiers in Oncology, 14: 1489977.
[12] Wang, T., Zhang, L., & Cheng, Y. (2024). Clinical status and perspective on the application of immunotherapy combined with chemotherapy in advanced non-small cell lung cancer: a review. Chinese Clinical Oncology, 13(2), 26–26.
[13] Yu, S., Wang, Y., He, P., Shao, B., Liu, F., Xiang, Z., Yang, T., Zeng, Y., He, T., Ma, J., Wang, X., & Liu, L. (2022). Effective Combinations of Immunotherapy and Radiotherapy for Cancer Treatment. Frontiers in Oncology, 12: 809304.
[14] Gupta, S., & Shukla, S. (2022). Limitations of Immunotherapy in Cancer. Cureus, 14(10).
[15] Zhou, S., & Yang, H. (2023). Immunotherapy resistance in non-small-cell lung cancer: From mechanism to clinical strategies. Frontiers in Immunology, 14, 1129465.
[16] Ricciuti, B., & Garassino, M. C. (2024). Precision Immunotherapy for STK11/KEAP1-Mutant NSCLC. Journal of Thoracic Oncology, 19(6), 877–882.
[17] O'Kane, G. M., Labbé, C., Doherty, M. K., Young, K., Albaba, H., & Leighl, N. B. (2017). Monitoring and Management of Immune-Related Adverse Events Associated With Programmed Cell Death Protein-1 Axis Inhibitors in Lung Cancer. The Oncologist, 22(1), 70–80.
[18] Wang, Y. (2025). Advances in cancer immunotherapy and future directions in personalized medicine. Open Life Sciences, 20(1), 20251179.
[19] Yi, M., Li, Y., Jie, H., & Deng, S. (2025). Nanotechnology-Driven Drug Delivery Systems for Lung Cancer: Computational Advances and Clinical Perspectives. Thoracic Cancer, 16(14).
[20] Qin, L., Li, Y., Liu, J., & An, X. (2025). Advancements in cellular immunotherapy: overcoming resistance in lung and colorectal cancer. Frontiers in Immunology, 16: 1554256.