# Exploring Immunotherapy in Non-Small Cell Lung Cancer: A Review

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Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells in the body. The immune system is the body's natural defence mechanism against harmful pathogens and abnormal cells. The immune system should recognize and eliminate cancer cells. However, the cancer cells often evade these mechanisms by various means, such as suppressing immune responses or hiding from immune surveillance. Nonetheless, immunotherapy has emerged over the past couple of decades and is a treatment approach which uses the body's own immune system to target and destroy cancer cells. Immunotherapy is an attractive option because it offers a more targeted and potentially less toxic treatment option compared to traditional therapies, with the potential for long term benefit. In this review, we will dive into the minutiae of non-small cell lung cancer (NSCLC) and explore the intricate connections between the immune system and cancer, focusing on the potential of immunotherapy for better treatment outcomes. Immunotherapy, like pembrolizumab and nivolumab, shows promising results in treating NSCLC by boosting the immune system to fight cancer cells.

Lung cancer is by far the most fatal cause of cancer-related deaths worldwide and is responsible for more fatalities than breast, prostate, and pancreas cancers combined (John, 2023). NSCLC is the most prevalent subtype of lung cancer and accounts for roughly 85% of all lung cancers. NSCLC comprises a large range of lung malignancies, namely adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, constituting a greater number of lung cancer cases. Unlike Small Cell Lung Cancer (SCLC), NSCLC tumours tend to grow more slowly and are generally diagnosed at later stages (Macro, 2021).

Non- Small Cell Lung Cancer (NSCLC) stems from a myriad of risk factors, notably cigarette smoking and passive smoking. The exponential growth in cigarette consumption since 1880 has undoubtedly contributed to the tenaciously high lung cancer rates (Gregory, 2013). Dietary factors, such as consumption of cured meats and deep-fried cooking, also raise the risk of developing NSCLC. Furthermore, lack of physical activity increases the chances of contracting NSCLC. Finally, inherited factors, such as genetic differences in susceptibility genes like *TP53* and *EGFR*, play a role in the tendency of certain families to develop the disease (Julian, 2008).

Researchers globally are motivated to investigate the epidemiological factors and demographic impact of NSCLC, driving interest in understanding its growth. The study of Surveillance, Epidemiology, and End Result (SEER) data on Non-Small Cell Lung Cancer (NSCLC) shows a divergence in the presentation and progression of the disease between younger (≤40 years) and older (>40 years) patients. The younger cohort comprising 2775 patients showed a higher percentage of African Americans, Asian or Pacific islanders, women, and stage IV disease when compared to the older cohort comprising 236,313 patients. These factors explain how socio-economic factors, cultural influence, etiology, healthcare disparities, and disease-specific factors can change different individual experiences who undergo this branch of cancer. Adenocarcinoma is more prevalent in younger patients while squamous cell carcinoma is more common in older patients. Socio-economic, cultural, and healthcare factors significantly shape the experience of people with NSCLC. For instance, these factors can influence access to

healthcare services, treatment options, and overall health outcomes for patients. Age, gender, cancer subtype, race, disease stage, and the quality of care received also play pivotal roles in determining the prognosis. Therefore, understanding and addressing these multifaceted influences are essential for improving patient experiences and outcomes in NSCLC. Further research is required to find better ways to diagnose and treat NSCLC (Janakiraman, 2010).

In NSCLC one of the most common underlying mutations is in the *KRAS* oncogene. *KRAS* mutations are found in approximately 20 to 25% of NSCLC cases, with the *KRAS G12C* variant being particularly prevalent (Alfred, 2021). *EGFR*, or Epidermal Growth Factor Receptor, is another common mutation. In NSCLC, *EGFR*, a protein found on the surface of cells, plays a very important role in cell growth and division. Abnormal cell growth leads to rapid NSCLC progression, often delaying symptoms onset and complicating the treatment for the patient. Changes in genes make cells grow out of control, causing cancer to spread. These genetic alterations disrupt the normal cell growth and division processes, supplying cancer growth. The survival outcomes for patients diagnosed with NSCLC vary notably based on factors like age, metastasis patterns and the level of treatment received. Historically, the overall medium survival rate for NSCLC patients with distant metastases (cancer which has proliferated throughout the body) is relatively low, typically ranging from a few months to a few years, with a median overall survival of 5.9 months for patients over 80 years old. Age at diagnosis, metastasis patterns and available treatment all play significant roles in determining the prognosis for individuals with NSCLC (Yu, 2020).

NSCLC is typically treated through surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy. Early stage NSCLC is often treated with surgery to remove the tumour, while advanced stages may require chemotherapy, radiation, or targeted therapy to shrink the tumour and slow its development. Immunotherapy has also emerged to be a promising treatment option, using the body’s immune system to fight cancer cells.

NSCLC uses a myriad of mechanisms to evade the immune system, which compromises its ability to fight off the cancer cells efficaciously. Dysregulation of dendritic cells and T cells in NSCLC compromises their normal functions. Dendritic cells, responsible for presenting cancer cell antigens to activate immune responses, may exhibit impaired functions. Similarly, T cells, crucial for directly attacking cancerous cells, may also be compromised. This dysregulation allows NSCLC to evade immune detection, promoting cancer growth and spread. To treat NSCLC, immunotherapy targets specific proteins such as PD-1/PD-L1 to boost the immune system’s ability to fight off the cancer cells effectively. By blocking these proteins, immunotherapy helps the immune system identify and destroy the cancer cells better, countering the evasion tactics of NSCLC against the immune system.

Next, immunotherapy shows promising results as a treatment for NSCLC, extending a significant improvement over our conventional chemotherapy. Immunotherapy treatment for NSCLC, including vaccines and immune checkpoint inhibitors like nivolumab and ipilimumab, led to remarkable improvements in the overall survival rates for NSCLC patients. These treatments, such as vaccines and immune checkpoint inhibitors like nivolumab and ipilimumab, work by stimulating the immune system to recognize and attack cancer cells. For example, immune checkpoint inhibitors target proteins like PD-1/PD-L1, which cancer cells exploit to

evade detection by the immune system. By blocking these proteins, immunotherapy helps the immune system identify and destroy cancer cells more effectively, leading to better overall survival rates for NSCLC patients. With the ability to enhance the body's natural defences against cancer, immunotherapy proves a momentous advancement in managing those suffering NSCLC (Zhou, 2016).

Despite the promising aspects and potential of immunotherapy for NSCLC, it still encounters several challenges, including variable efficacy among different agents, potential unfavourable effects, and complexities in patient selection. While certain clinical trials have shown encouraging outcomes regarding the efficacy of immunotherapy in extending survival among NSCLC patients, others have yielded inconclusive or negative results in terms of significant improvements in overall survival. The variability in trial outcomes highlights the complexity inherent in evaluating the effectiveness of immunotherapeutic agents across different patient cohorts and treatment regimens. Factors such as patient characteristics, disease stage, and treatment protocols may contribute to the heterogeneous response observed in clinical trials. Additionally, challenges in accurately assessing treatment response and defining meaningful clinical endpoints further complicate the interpretation of the trial data. Therefore, a comprehensive understanding of the contextual factors influencing the trial outcomes is crucial for optimizing the application of immunotherapy in NSCLC management. However, understanding the relationship between factors like PD-L1 levels and treatment outcomes remains ambiguous today. Further research is vital to address these challenges and to better immunotherapy for NSCLC.

In NSCLC, the effectiveness of immune checkpoint inhibitors (ICIs) has been profoundly studied. Especially, pembrolizumab has shown outstanding results as a first-line treatment for patients with high PD-L1 expression which remarkably extends the progression free survival (PFS) and overall survival (OS) compared to the traditional chemotherapy. In addition, clinical trials investigating atezolizumab and durvalumab have shown promising outcomes, ultimately leading to them being FDA-approved for treating advanced NSCLC. Despite their effectiveness, the use of ICIs can cause immune-related adverse events (irAEs), conclusively requiring meticulous monitoring and management. Overall, ICIs represent a significant advancement in NSCLC treatment, offering better results and a hopeful alternative to standard therapies (Malhotra, 2017).

The clinical trial titled "Correlation Between Specific Gene Mutation and Local Immune Microenvironment and Immunotherapy Efficacy in NSCLC" was conducted at the Guangzhou Institute of Respiratory Disease, and the goal of this study is to understand why some non-small cell lung cancer (NSCLC) patients do not respond well to immunotherapy (NCT04405661). The study focused on genetic mutations in tumours and how they affect the immune system. The Guangzhou Institute of Respiratory Disease examines 100 Chinese NSCLC patients aged 18–70 who are candidates for PD-1/PD-L1 inhibitor therapy. In this trial, they adopt a different approach from traditional clinical trials that introduce novel treatments. Instead, the clinical trial aims to elucidate the factors influencing treatment response and resistance in real-world clinical settings. Through an extensive analysis of the patient data and biospecimens, including formalin-fixed paraffin-embedded (FFPE) tissue and whole blood samples, researchers aim to uncover important insights into the relationship between gene mutations, the immune

microenvironment, and treatment outcomes. The study's main outcome measures include assessing the connection between specific gene mutations and the immune microenvironment as well as their association with objective response rate (ORR) and progression free survival (PFS) in immunotherapy treated NSCLC patients. This involves examining the presence and activity of immune cells such as T cells, B cells, dendritic cells, and macrophages, as well as analyzing the levels of cytokines, chemokines, and other signalling molecules within the tumour microenvironment. Furthermore, secondary outcome measures include evaluating the overall survival (OS) of gene mutations and the immune microenvironment. The importance of this research lies in its potential to help doctors create treatments that fit each patient's genes and biomarkers that show how well someone will respond to treatment; the study hopes to make better and more focused therapies for NSCLC. This progression holds the potential for improving outcomes among lung cancer patients and may also expedite advancements in the treatment paradigm for this malignancy.

Next, the ongoing clinical trial, DEDICATION-1, is a Phase 3 study in which Radboud University Medical Centre is recruiting 750 patients with NSCLC (NCT04909684). Its main goal is to explore the efficacy and safety of different doses of pembrolizumab, a drug designed to treat patients with advanced NSCLC. Pembrolizumab functions by blocking the PD-1 receptors on T cells, thereby improving the immune system's ability to recognize and attack cancer cells. Patients enrolled in this clinical trial must have advanced-stage NSCLC and be in a strong enough condition to undergo these treatments. However, people with disabilities or those who have had special therapies or drug regimens in the past may not be eligible for clinical trials. The goal of this trial is to find solutions to some limitations which have already been observed such as variable efficacy among different doses of pembrolizumab, potential adverse effects and complexities in patient selection. Treatment with pembrolizumab is specific to particular doses, which are narrowed down to determine an optimal dose that is both effective and safe. In addition, the prediction of the treatment can not only better serve the needs of each patient, but also reduce costs and improve the quality of care. Retrospectively, the current data and previous research may suggest different lines of investigation in the future. One attention has been given to explaining new biomarkers that could better indicate response to treatment, using pembrolizumab in combination with other therapeutic agents for improved efficacy and checking for the long-term toxicity and safety of the drug. Thus, by adhering to specific clinical protocols and treatment algorithms, akin to purification processes create a more refined and effective personalized treatment for every patient.

In this review, we discussed the use and impact of immunotherapy treatment for patients with NSCLC. Immunotherapy emerges as a very promising avenue in NSCLC treatment due to its capacity to augment the body's immune system to fight against cancer cells, which as a result, enhances the treatment's efficacy. Specifically, agents like pembrolizumab and atezolizumab have shown significant impact, prolonging the survival rates and improving the overall outcome for NSCLC patients. Current research endeavours are focused on ameliorating existing treatments and uncovering novel predictive biomarkers to tailor therapies to individual patients, while also addressing hurdles such as treatment resistance. Looking forward, the potential of immunotherapy in NSCLC appears to be transformational, poised to revolutionize the treatment paradigm by offering personalized and efficacious therapy options, therefore, potentially extending both quality of life and survival rates for those affected by NSCLC.

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NCT04405661

NCT04909684