Immunotherapy Usage in NSCLC

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Cancer is a disease characterized by uncontrolled cell growth and division, often leading to tumors and the spread of abnormal cells throughout the body. To combat cancer, the body possesses the immune system, a complex network of cells, tissues, and organs, that serve as the body's defense mechanism, identifying and eliminating harmful invaders, including infections and abnormal cells. Though ideally, the immune system should detect and destroy cancer cells through immune surveillance and cytotoxic T cells, cancer is occasionally able to evade these mechanisms by suppressing immune responses or disguising itself as normal tissue. Immunotherapy is a form of cancer treatment that enhances or restores the immune system's ability to recognize and attack cancer cells. This approach is particularly attractive because it can specifically target cancer cells, potentially offering long-term immune protection and fewer side effects compared to traditional treatments like chemotherapy and radiation.

Lung cancer, specifically (Non small-cell-lung cancer) NSCLC, is one of the most frequent and lethal types of cancer worldwide, responsible for 1.8 million diagnoses and 1.6 million deaths each year worldwide. This is more than any other type of cancer, and with 85% of all lung tumors being NSCLC, it is very important to fully understand the causes of lung cancer and be able to properly treat it. The primary cause of the cancer is the widespread habit of smoking or eating tobacco, as well as the increased amount of air pollution in developed countries. (Gridelli, 2015). The primary cases of NSCLC are people who live in more developing regions of the world where there are less smoking regulations, such as South America, Eastern Europe, China, etc, though the number of NSCLC cases is decreasing in developed countries. Mutations play a prominent role, in carcinogen exposure, with the tumors of smokers containing 10 mutations in the DNA, compared to those that never smoked and important driver mutations like epidermal-growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*), which are oncogenes, can help cells develop independent mutations, leading to diversity of the original tumor (Gridelli 2015). Typically, people afflicted with NSCLC live for about less than a year (Chang 2024). Usually, people with this disease are treated based on what stage and characteristics of their tumor they display. Surgical resections, chemotherapy, and drugs that target specific driver mutations are typically used for most treatments. Tyrosine inhibitors that block mutations like *EGFR* and *ALK* are also used, and other inhibitors are also being developed due to the likelihood of the tumor developing resistance to these inhibitors. In addition to these, immunotherapy has also become an increasingly viable option. An example of this is targeting the cell checkpoints for cancer cells, such as the receptor for programmed cell death protein *(PD-1*). *PD-1* has been reported to have fewer side effects and also greater efficacy than normal toxic chemotherapy. As a result, ICI (Immune Checkpoint Inhibitors) have been used more frequently than other forms of chemotherapy in treating cancers, including NSCLC. However, about 50% of all patients who have been treated via ICI have progressed to

the next stage of NSCLC, demonstrating that the tumors are starting to become resistant to treatments that use *PD-1*. (Lurienne 2020). As a result, there is still much needed research and development before ICI can become a reliable treatment.

Non-small cell lung cancer (NSCLC) has multiple mechanisms to evade the immune system, though immunotherapy does have some favorable outcomes for NSCLC. Unlike other NSCLC variants, *EGFR*-mutant tumors are characterized by an immunosuppressive tumor microenvironment (TME) with low tumor mutational burden (TMB), weak antigen presentation, and poor infiltration of cytotoxic T cells (*CD8+ T* cells). These tumors often exhibit upregulated *CD47*, a “don’t eat me” signal that inhibits macrophage-mediated phagocytosis, allowing cancer cells to evade innate immune destruction (Li Yang 2024). Additionally, *EGFR* signaling activates the ERK and AKT pathways, which enhance the transcription of *c-Myc* and *NF-κB*, leading to immunosuppressive gene expression and further reinforcing immune escape (Li Yang 2024). The tumor microenvironment of *EGFR*-mutant NSCLC is filled with regulatory T cells (Tregs), tumor-associated macrophages (*TAMs*), and myeloid-derived suppressor cells (*MDSCs*), which suppress anti-tumor immunity and promote tumor progression (Hirva 2022). Given these immune-evasive features, immune checkpoint inhibitors (ICIs) targeting *PD-1/PD-L1*, such as pembrolizumab, nivolumab, and atezolizumab, have demonstrated poor efficacy in *EGFR*-mutant NSCLC compared to their success in other lung cancer subtypes (Hirva 2022). Studies have indicated that patients with *EGFR* mutations have lower *PD-L1* expression, reducing their likelihood of responding to ICIs (Hirva 2022). As a result of these challenges, the exploration of novel immunotherapeutic strategies is underway. One promising avenue is *CD47* blockade, which enhances macrophage-mediated phagocytosis and promotes innate immune activation (Li Yang 2024). Preclinical studies have shown that combining *CD47* inhibitors with *EGFR* tyrosine kinase inhibitors (TKIs) like osimertinib significantly improves tumor control compared to monotherapy by overcoming immune suppression and enhancing tumor cell clearance (Li Yang 2024). Other investigational approaches include dual checkpoint blockade (e.g., anti-*PD-1* plus anti-*TIGIT* or anti-*LAG-3*), chimeric antigen receptor (*CAR*) T cell therapy, and natural killer (NK) cell-based therapies aimed at bypassing T cell exhaustion (Hirva 2022). Despite these promising strategies, the overall efficacy of immunotherapy in *EGFR*-mutant NSCLC remains limited due to rapid resistance, lack of durable responses, and potential toxicity from combination treatments. (Hirva 2022). Furthermore, while several ICIs are FDA-approved for NSCLC, their use in *EGFR*-mutant cases is restricted to patients who have progressed on TKIs and chemotherapy, as first-line immunotherapy remains ineffective (Hirva 2022). No *CD47*-targeting therapies have yet received FDA approval, but investigations are being conducted for their potential role in enhancing innate immunity and overcoming immune evasion in *EGFR*-mutant NSCLC. The future of immunotherapy in this disease setting lies in combination approaches that integrate targeted therapies, immune modulators, and novel checkpoint inhibitors to enhance the immune response and improve clinical outcomes (Hirva 2022).

Currently, ongoing clinical trials in non-small-cell lung cancer (NSCLC) focus on improving outcomes, like OS (overall survival) and PFS (Progression-Free survival), for patients who have limited treatment options for advanced NSCLC. One phase III trial evaluated the efficacy of durvalumab, an anti-programmed death ligand 1 (*PD-L1*) antibody, as therapy in patients with stage III NSCLC who had not progressed after at least two cycles of platinum-based chemoradiotherapy (NCT02125461). The study (NCT02125461) included patients with stage III NSCLC who had stable disease following chemoradiotherapy. Those excluded from the trial were people with prior immunotherapy exposure, autoimmune diseases, or severe organ dysfunction in the PACIFIC (Platinum-based, concurrent chemoradiation therapy). Another clinical study of NSCLC patients in the UK shows how exclusion criteria in random clinical trials (RCTs) often exclude a significant proportion of real-world patients due to factors like prior malignancies, renal impairment, or concurrent medication use. The (NCT02125461) trial tested durvalumab, a *PD-L1* checkpoint inhibitor, which works by blocking *PD-L1* interactions with *PD-1* receptors on T cells, allowing the immune system to better recognize and attack cancer cells. This strategy helps overcome tumor immune evasion, a common challenge in NSCLC. Patients in the study received durvalumab at 10 mg/kg intravenously every two weeks for up to 12 months, starting 1 to 42 days after completing chemoradiotherapy. Earlier studies showed that most NSCLC patients who undergo chemoradiotherapy eventually experience disease progression due to residual tumor cells evading immune detection. The (NCT02125461) trial addressed this limitation by introducing durvalumab as a consolidation therapy, aiming to sustain an anti-tumor immune response and delay progression. Further directions include broadening inclusion criteria to ensure clinical trials better reflect real-world patient populations, combining durvalumab with other agents, such as targeted therapies or immune-modulating drugs to further improve long-term outcomes, identifying biomarkers (e.g., *PD-L1* expression levels, tumor mutational burden) to predict which patients would derive the most benefit from durvalumab, and developing strategies to mitigate immune-related adverse events, particularly pneumonia and other inflammatory responses.

The disease discussed, NSCLC, is a common type of lung cancer that grows and spreads more slowly than small cell lung cancer but still presents significant treatment challenges. Fortunately, immunotherapy has emerged as a potentially effective treatment for NSCLC, but one that still requires further exploration, particularly in patients with high *PD-L1* expression, as it helps the immune system recognize and attack cancer cells that would otherwise evade detection. Among the most widely used immunotherapies are checkpoint inhibitors, such as *PD-1/PD-L1* and *CTLA-4* inhibitors, which have significantly improved survival rates and offered durable responses, especially in advanced-stage cases. However, researchers are now focusing on overcoming key obstacles, such as resistance to immunotherapy, identifying better biomarkers for patient selection, and enhancing treatment effectiveness through combination therapies. Looking ahead, if these challenges can be

addressed, immunotherapy has the potential to revolutionize NSCLC treatment by making it more personalized and effective, potentially leading to long-term remission and even cures in some cases.

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