Non-small Cell Lung Cancer Immunotherapies

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Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. In a healthy body, cells grow and die in a regulated manner (*Module 5: What Is Cancer?*). However, cancer occurs when this normal process of cell division is disrupted, leading to the formation of a tumor. Malignant tumors are cancerous and can invade nearby tissues and organs, as well as metastasize and spread to other parts of the body through the bloodstream or lymphatic system (*Module 5: What Is Cancer?*). The body has a natural system in place to defend the body from outside dangers such as bacteria, viruses, and fungi. This system is known as the immune system and its primary function is to recognize and eliminate foreign substances that could potentially harm the body. Likewise, the immune system recognizes cancer as a threat by analyzing specific markers on the surface of cancer cells that make them different from healthy cells (Gonzalez et al., 2018). Once the immune system recognizes a cancer cell it will activate defense mechanisms such as natural killer cells and cytotoxic T cells to destroy the threat (Gonzalez et al., 2018). Cancer cells can evade the immune system through numerous methods that include but are not limited to reducing antigens on their surface to make it difficult for T cells to recognize them as abnormal, releasing cytokines to inhibit the activity of immune cells, and resisting apoptosis (Gonzalez et al., 2018). Immunotherapy is a medical treatment that harnesses the body's immune system to destroy abnormal cells (*What Is Immunotherapy?*). Examples of immunotherapy include checkpoint inhibitors which are drugs that block certain proteins that inhibit the immune system's response, monoclonal antibodies which are designed to target specific proteins on the surface of cancer cells and mark them for destruction, and cytokines which are proteins that regulate the immune system and can be used to boost the immune response against cancer cells (*What Is Immunotherapy?*) .

Non-small-cell lung cancer (NSCLC) is a heterogeneous class of tumors and represents approximately 85 percent of all new lung cancer diagnoses (Gridelli et al, 2015). Smoking tobacco, radon exposure, and air pollution increase the risk of developing NSCLC. Most patients are diagnosed at advanced stages due to inadequate screening programs. Diagnostic approaches utilized for NSCLC are X-rays, CT and PET imaging, and histological examination of tumor biopsies. 53 percent of people diagnosed with the disease are 70 or older, with most men being diagnosed between the ages 80 and 84 and most women being diagnosed between the ages of 75 and 79 (*Lung Cancer - Non-Small Cell: Statistics*, n.d.). Strategies for managing NSCLC include surgery, radiotherapy, chemotherapy, immunotherapy, and targeted approaches with anti-angiogenic monoclonal antibodies or tyrosine kinase inhibitors if the tumor contains oncogene mutations (Gridelli et al, 2015). Common mutations in oncogenes associated with NSCLC tumors are in the epidermal growth factor receptor (*EGFR)* and anaplastic lymphoma kinase (*ALK).*

NSCLC cells can evade the immune system by exploiting immune checkpoint pathways, which are regulatory mechanisms that prevent excessive immune responses. Upregulation of checkpoints such as programmed death-ligand 1 (PD-L1) that interact with corresponding receptors on T cells leads to T cell exhaustion or inactivation. This interaction inhibits the immune system's ability to attack the NSCLC cells. Kristen Ras Sarcoma Activating mutations in the viral oncogene homolog (KRAS) are present in approximately one-third of lung adenocarcinomas. Mitogen-activated protein kinase (MAPK) is triggered by activated RAS and phosphorylates tristetraprolin in a p38-dependent manner. (Chen N. et al, 2017). Furthermore, activated RAS stabilizes PD-L1 mRNA (Coelho M.A. et al, 2017). In NSCLC cell lines, tristetraprolin inhibition plus mRNA stabilization boost PD-L1 expression. Epidermal growth factor receptor (EGFR) activation causes PD-L1 expression in non-small cell lung cancer (NSCLC) cells upstream of KRAS. Approximately 10–25% of lung adenocarcinomas have EGFR mutations, which results in overexpression of the checkpoint (Lamberti G et al, 2020). Blocking PD-L1 can help the body's immune system fight NSCLC since it would prevent T cell inactivation. FDA-approved drugs such as

atezolizumab target PD-L1 and boost the immune response against cancer cells. This leads to tumor shrinkage and slower growth (*Lung Cancer Immunotherapy | Immune Checkpoint Inhibitors*, 2023). Atezolizumab is a monoclonal antibody against PD-L1 and is known to significantly increase the survival of patients than those treated with platinum-based chemotherapy. Out of 572 patients enrolled in a clinical study, the median overall survival was longer by 7.1 months in the atezolizumab treated group than in the group treated with chemotherapy (Herbst et al., 2021). Although the treatment works to elongate the patient's lifespan, it has its limitations. The dysregulation of PD-L1 can slow tumor growth by preventing the inactivation or exhaustion of T cells, however, this treatment is not useful in the situation in which cancer cells reduce the expression of MHC. This reduction would prevent T cells from recognizing the abnormal cells thus making the monoclonal antibody treatment against PD-L1 ineffective.

There are several ongoing clinical trials occurring to study the use of different immunotherapies in treating NSCLC. For example, a phase 3 clinical trial of domvanalimab and zimberelimab plus chemotherapy is being compared to pembrolizumab plus chemotherapy for individuals with NSCLC that has metastasized (NCT05502237). Domvanalimab and zimberelimab are new monoclonal antibodies. Domvanalimab has been shown to reduce the immune suppressive effects of the T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) receptor. TIGIT is a checkpoint receptor expressed on immune cells such as T cells and NK cells that inhibit the immune system's natural ability to detect and kill cancer cells. Zimberelimab is a new potential treatment that can be used to inhibit PD-1. Combining both antibodies may target different pathways by which tumors evade the immune system, thus potentially helping the immune system to attack the tumor cells. Roughly 720 participants will be randomly assigned to receive 1 of 3 treatment combinations: domvanalimab and zimberelimab plus chemotherapy, pembrolizumab plus chemotherapy, and zimberelimab plus chemotherapy. Participants in the study must be at least 18, have newly diagnosed untreated Stage 4 NSCLC that has spread to both lungs, the area around the lungs, or other organs, and must have an available tumor tissue sample. Participants will be excluded from the study if they have a tumor that tests positive for genetic alterations including *EGFR* or *ALK*, have a mix of small cell lung cancer as well as NSCLC, have any other form of cancer within the past three years, have received previous treatment, have had an organ or tissue transplant, have an auto-immune disease that requires systemic steroids, have brain metastasis with symptoms that require management, have received ICI, have certain medical or psychiatric conditions, and are currently or planning to get pregnant. The main goal of this trial is to learn whether new treatments plus chemotherapy will increase the lifespan of individuals with Stage 4 NSCLC.

Another clinical trial that is also in phase 3 is testing the effectiveness of domvanalimab when it is paired with durvalumab after chemotherapy and radiation (NCT05211895). Durvalumab is a standalone medicine which blocks the PD-L1 signal that prevents the immune system from detecting cancer cells. It is FDA-approved, however, the combination of durvalumab and domvanalimab is a potential new treatment that can help individuals with stage 3 NSCLC. Roughly 860 participants will randomly be assigned to 2 treatment options. The first half of the participants will receive durvalumab plus domvantalimab and the other half will receive durvalumab plus a placebo. Participants must be at least 18, have stage 3 NSCLC that can't be surgically removed, has been treated with chemotherapy and radiation, has not gotten worse after treatment, and has recieved chemotherapy that contains either a treatment called cislatin or carboplatin plus another drug such as etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel, or pemetrexed. Individuals will be excluded from the study if they currently have another type of cancer apart from NSCLC, have certain genetic mutations such as *EGFR* or ALK, have received gemcitabine, have received bone marrow, stem cell, or organ transplantation, have participated in another clinical trial with durvalumab or domvanalimab, have certain medical or psychiatric conditions, be pregnant or plan on becoming pregnant.

Future Directions:

Immunotherapy is becoming the standard of care for patients with metastatic, locally progressed, and resectable nonsmall cell lung cancer (Mamadani H. et al, 2022). For future directions, the

combination of different treatments must be explored to discover the most effective treatment plan that may involve the use of immunotherapy and other therapies such as chemotherapy for treating NSCLC.

Conclusion:

Non-small cell lung cancer is a deadly disease that has no current cure. The use of immunotherapies that target PD-1 and PD-L1 immune checkpoints has shown benefits to many patients. Current treatments such as the use of monoclonal antibodies like atezolizumab have increased patient life span by a median of 7.1 months. Using a combination of different monoclonal antibodies and other forms of treatment such as chemotherapy are currently being tested in clinical trials. Information gathered from future research can lead to a more effective treatment plan for patients with NSCLC.

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