Immunotherapy in Non-small Cell Lung Cancer Treatment

Aniece Wong, Ashley Pearson

Cancer is a class of diseases where abnormal cells develop and divide uncontrollably, forming tumors. Metastatic cancer occurs when cancerous tumors spread to other parts of the body. Meanwhile, the immune system is a large and complex network of organs, white blood cells, and proteins that act as a first-line defense to fight and protect us from illnesses, infections, and other diseases (National Cancer Institute). In this context, certain immune cells: T cells, B cells, and NK cells can recognize cancer cells as abnormal and kill them, especially in the elimination stage when cancer cells are being successfully removed. Cancer can weaken the immune system by stopping the bone marrow from producing many blood cells that help to fight infection (Cancer Research UK). A solution to the problem is immunotherapy; immunotherapy is a cancer treatment that helps the immune system eliminate or control cancer. Immunotherapy is an effective treatment option to overcome cancer immune evasion. When the immune system can no longer control cancer, immunotherapy, particularly immune checkpoint inhibitors, can turn the activated T cells off, slowing down or preventing cancer growth. In this review, we provide an overview of Non-small Cell Lung Cancer, the type of immunotherapy used, and its innovation and future direction.

Lung cancer is known to be the deadliest cancer of all. Non-small Cell Lung Cancer (NSCLC) accounts for 85% of lung cancer; it is a disease where cancer cells form in the lung tissues. Symptoms of non-small cell lung cancer include shortness of breath and a cough that does not go away, weight loss, and chest pain (Ettinger, 2010). Nevertheless, sometimes lung cancer may only be found during a chest x-ray as it might not develop symptoms. There are three subtypes of NSCLC: squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma. Adenocarcinoma is the predominant and most common subtype. Around 40% of lung cancer cases are Adenocarcinoma (Denisenko, 2018). It is a cancer that begins from the small airway epithelial, type II alveolar cells that line the alveoli and secrete substances such as mucus (Zappa,2016). The primary risk factor for NSCLC is smoking; smoking cigarettes, pipes, or cigars can cause damage and mutation in lung cells, sometimes transforming them into cancerous cells (Ettinger, 2010). Other risk factors include radon exposure, use of asbestos, air pollution, other chemical exposures in the workplace, and secondhand smoke. Older people have a heightened risk of getting this type of cancer; the median age of diagnosis of NSCLC is 70 years old. However, younger people can still get diagnosed. This disease can affect both men and women but their survival and risk vary. Men are heavier smokers than women, therefore increasing their chances of getting the disease. Even though women have a significant risk for the development of lung cancer, studies have shown they have higher survival and disease-free survival compared to men. (Baiu, 2021) Individuals living in places with severe air pollution have a higher risk of lung cancer. In addition, having a personal or family history of lung cancer and carriers of *TP53* also serve as risk factors (Zappa, 2016). The marker on chromosome 15 that contains genes for subunits of nicotine acetylcholine receptors is associated with lung cancer. Cell changes such as cell proliferation, cell depolarization, apoptosis, and DNA mutations can occur when nicotine holds onto the protein on the cell surface. As a result, people with one copy of the marker have a 30% increased risk of developing lung cancer, while people with two copies have an increased risk of 70–80%(Zappa, 2016). Gene mutations are essential for the initial development of a tumor and its growth. The

epidermal growth factor receptor (EGFR) gene activates pathways that drive cell growth. *EGFR* gene mutations near the ATP cleft of the tyrosine kinase domain produce uncontrolled cell division through continuous, non-stop activation. Another type of mutation, *KRAS*, is the most commonly mutated oncogene in Adenocarcinoma; it affects the activation of RAS signaling. *EGFR* and *KRAS* mutations can induce growth arrest and cell death. Due to the poorer survival rate and symptom burden of cancer, most lung cancer patients are diagnosed when the cancer is at stage IV. Over half of lung cancer patients die within one year; less than 18% of patients survive for 5 years (Zappa, 2016). Stage I of lung cancer has a five-year survival of 68.4% while stage IV has a five-year survival of 5.8%. There are different types of treatment for NSCLC. The most consistent and successful option for cure is surgical resection. If the tumor is resectable and the patient can tolerate surgery, surgery to remove the tumor is most sufficient. Another option is radiotherapy which uses high-energy beams, x-rays, and other radiation to damage the DNA of cancer cells and kill or keep them from growing. In addition, chemotherapy is a drug treatment that stops the growth of cancer cells (Zappa, 2016). NSCLC can also be treated by immunotherapy; it uses the patient's immune system to fight cancer. There are immune checkpoint proteins on the surface of T cells that can help maintain the immune system in a controlled state (Denisenko, 2018).

In recent years, immunotherapy has emerged as a therapeutic approach against NSCLC and has significantly improved overall and progression-free survival, as well as the patient's quality of life in comparison to traditional chemotherapy (Putzu, 2023). Lung cancer cells have developed mechanisms to evade immune activation by blocking crucial steps in cytotoxic T cell response. (Qin,2016) There was significantly reduced MHCII expression by APCs in 78% of NSCLC tumor samples. The tumor cells cannot recognize immune cells because they downregulate or alter their MHCI expression. Immune checkpoint inhibitors (ICI) have been introduced as a treatment for non-small cell lung cancer. Instead of traditionally targeting the cancer cell, ICI targets tumor-mediated immune tolerance. Anti-PD-1 and PD-L1 antibodies act in the effector phase of the cancer-immunity cycle. In this phase, effector T cells attack cancer cells. However, binding of PD-L1 expressed on the cancer cell surface to PD-1 expressed on the surface of effector T cells suppresses the attack by effector T cells on cancer cells. They prevent the PD-1/PD-L1 interaction, thus facilitating T cell attacks (Onoi, 2020). Clinical responses appear to correlate with the expression of PD-L1 on both T cells and tumor-infiltrating immune cells. Immune checkpoint inhibitors (ICI) advance therapeutic approaches and provide more effective treatment for NSCLC patients. PD-1 inhibitors and PD-L1 inhibitors show improvement in overall survival. Particularly, more than 15% of patients treated with immunotherapy can achieve long-term survival (Putzu, 2023). Nivolumab is a monoclonal antibody that binds to the protein PD-1 on the surface of immune cells, T cells. This type of ICI prevents cancer cells from suppressing the immune system. Pembrolizumab is a humanized IgG4 antibody that binds with the PD-1 on T cells' surface, allowing the immune system to attack and kill the cancerous cells (National Cancer Institute). The FDA approved Nivolumab and Pembrolizumab since they showed responses and improved survival rates for patients. However, there are immune-related toxicities that can range from hypothyroidism or skin rash to more serious and uncommon manifestations such as colitis, pneumonitis autoimmune hepatitis, and encephalitis. Despite the majority of patients being successfully treated, up to 2% of patients treated with ICI have died from immune-related adverse events (IRAEs), demonstrating limitations in this therapy. Another potential treatment is combining ICIs with chemotherapy; it

has been discovered that it improves antigen presentation on T cells and eliminates immunosuppressive elements of the tumor immune microenvironment. (Doroshow, 2019) The outcome of the objective response rate achieved by patients treated with the immune combination is higher than chemotherapy alone. In addition, both Pembrolizumab and Atezolizumab in combination with chemotherapy improve overall survival in the treatment of NSCLC. Immunotherapy still consists of many uncertainties, it is still at the exploring stage; more studies should be done to reliably treat patients with immunotherapy.

A phase III clinical trial compares the effectiveness of Nivolumab and Ipilimumab combined with chemotherapy to chemotherapy alone (NCT03215706). Participants must be 18 years and older with historically confirmed Stage IV or recurrent NSCLC squamous or non-squamous histology with no prior systemic anticancer therapy. Their Eastern Cooperative Oncology Group (ECOG) Performance Status, which is a way for physicians to track changes in a patient's level of functioning as a result of treatment during the trial, has to be ≤ 1. Patients' CT or MRI results should show measurable disease and meet the solid tumors version 1.1 criteria which is a treatment efficacy evaluation. Eligible participants must have PD-L1 immunohistochemistry (IHC) testing with results performed by a central laboratory. In addition, patients with known epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (ALK) translocations that are sensitive to available targeted inhibitor therapy are excluded. Moreover, participants with Central Nervous System (CNS) tumors who are not adequately treated are not accepted. Module A of the trial combines Ipilimumab and Nivolumab with chemotherapy and module B is just chemotherapy. Ipilimumab and Nivolumab are immune checkpoint inhibitors that target T cells whereas chemotherapy kills both cancer cells and fast-growing healthy cells. The study's primary outcome measure is overall survival (OS), which is measured from the start of randomization to the date of death. The group with combined immunotherapy and chemotherapy showed significantly improved overall survival versus chemotherapy alone. These data support combination therapy as a new potential first-line treatment option for NSCLC patients. Secondly, a randomized phase II trial is conducted to assess the long-term benefit of PD-1 inhibition in NSCLC patients who experienced a response between 6 and 12 months after initiation of ICI (NCT04880382). Adults of all sexes that have a medical history of advanced non-small cell lung cancer or metastatic disease in which the tumor has no oncogenic addiction: no activating EGFR mutation, and no ALK or ROS1 rearrangement are eligible except for females that are pregnant or breastfeeding. Patients must have received ICI treatment and perform objective response according to RECIST v1.1 criteria at 6 months or more and less than 12 months after ICI treatment onset. They should be willing to commit to the schedule and have at least one lesion that can be biopsied for research purposes. Lastly, volunteers should not be hypersensitive to active substances or excipients and have concomitant diseases or conditions that might pose a risk to the study. The study tests ICI treatment continuation and discontinuation. For one group, after achieving an objective response, first or second-line treatment by immune checkpoint inhibitor will continue to be carried out until disease progression or unacceptable toxicity. After achieving a response, ICI treatment will be discontinued for the other group. The study mainly measures the progression-free rate (PFR) which demonstrates the long-term benefit. The study is still in progress and has not presented any results. With many recent breakthroughs in immunotherapy, it is essential to continue to improve and enhance it to benefit more people with NSCLC. The next step is to identify patients who are at risk of primary or acquired resistance

and develop more combination therapies to be available to all NSCLC patients. Treatment should be more individualized on a case-by-case basis to address individual needs and risks. In the future, one of the challenges will involve targeting the correct immunotherapy to the correct immune microenvironment at an appropriate time. The clinical trials show ongoing studies of immunotherapy and how they are being conducted. Immunotherapy is still at the exploring stage and more trials should be conducted to advance the therapy as a treatment.

Non-small Cell Lung Cancer is the most common type of lung cancer, abnormal cells in the lungs proliferate out of control. Immunotherapy, alone or in combination with other cancer treatments has substantially improved overall and progression-free survival of NSCLC patients. As a result, immunotherapy has been approved by the FDA to treat patients as a first-line therapy. For NSCLC, Immune Checkpoint Inhibitors (ICI) act as an “off switch” to help keep the activated T cells from attacking other cells. First-line nivolumab plus ipilimumab continued to demonstrate durable long-term efficacy in patients with advanced NSCLC (Paz-Ares, 2022). However, it is important to acknowledge some of the toxicities and side effects. People in the field are working on individualizing the treatment and enhancing the immune environment. Moreover, they are trying to discover more combinations with immunotherapy. In the future, as improvement is being undertaken, with fewer toxicities, more NSCLC patients can benefit from and be treated with immunotherapy.

References

Baiu, I., Titan, A. L., Martin, L. W., Wolf, A., & Backhus, L. (2021). The role of gender in non-small cell lung cancer: a narrative review. Journal of thoracic disease, 13(6), 3816

Denisenko, T. V., Budkevich, I. N., & Zhivotovsky, B. (2018). Cell death-based treatment of lung adenocarcinoma. Cell death & disease, 9(2), 117. https://doi.org/10.1038/s41419-017-0063-y

Doroshow, D. B., Sanmamed, M. F., Hastings, K., Politi, K., Rimm, D. L., Chen, L., Melero, I., Schalper, K. A., & Herbst, R. S. (2019). Immunotherapy in Non-Small Cell Lung Cancer: Facts and Hopes. Clinical cancer research : an official journal of the American Association for Cancer Research, 25(15), 4592–4602. https://doi.org/10.1158/1078-0432.CCR-18-1538

Ettinger, D. S., Akerley, W., Bepler, G., Blum, M. G., Chang, A., Cheney, R. T., ... & Yang, S. C. (2010). Non–small cell lung cancer. Journal of the national comprehensive cancer network, 8(7), 740-801.

Koury, J., Lucero, M., Cato, C., Chang, L., Geiger, J., Henry, D., Hernandez, J., Hung, F., Kaur, P., Teskey, G., & Tran, A. (2018). Immunotherapies: Exploiting the Immune System for Cancer Treatment. *Journal of immunology research*, *2018*, 9585614. https://doi.org/10.1155/2018/9585614

Mithoowani, H., & Febbraro, M. (2022). Non-Small-Cell Lung Cancer in 2022: A Review for General Practitioners in Oncology. Current oncology (Toronto, Ont.), 29(3), 1828–1839. https://doi.org/10.3390/curroncol29030150

Onoi, K., Chihara, Y., Uchino, J., Shimamoto, T., Morimoto, Y., Iwasaku, M., Kaneko, Y., Yamada, T., & Takayama, K. (2020). Immune Checkpoint Inhibitors for Lung Cancer Treatment: A Review. Journal of Clinical Medicine, 9(5), 1362. https://doi.org/10.3390/jcm9051362

Paz-Ares, L. G., Ramalingam, S. S., Ciuleanu, T. E., Lee, J. S., Urban, L., Caro, R. B., Park, K., Sakai, H., Ohe, Y., Nishio, M., Audigier-Valette, C., Burgers, J. A., Pluzanski, A., Sangha, R., Gallardo, C., Takeda, M., Linardou, H., Lupinacci, L., Lee, K. H., Caserta, C., … Reck, M. (2022). First-Line Nivolumab Plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes From the Randomized, Open-Label, Phase 3 CheckMate 227 Part 1 Trial. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*, *17*(2), 289–308. https://doi.org/10.1016/j.jtho.2021.09.010

Putzu, C., Canova, S., Paliogiannis, P., Lobrano, R., Sala, L., Cortinovis, D. L., & Colonese, F. (2023). Duration of Immunotherapy in Non-Small Cell Lung Cancer Survivors: A Lifelong Commitment? Cancers, 15(3), 689. https://doi.org/10.3390/cancers15030689

Qin, A., Coffey, D. G., Warren, E. H. (2016). Mechanisms of immune evasion and current status

of checkpoint inhibitors in non-small cell lung cancer. Cancer Medicine, 5(9), 2567-2578. https://doi.org/10.1002/cam4.819

“The Immune System and Cancer.” *Cancer Research UK*, 6 Nov. 2023, www.cancerresearchuk.org/about-cancer/what-is-cancer/body-systems-and-cancer/the-immune-system-and-cancer#:~:text=Cancer%20can%20weaken%20the%20immune%20system%20by%20spreading%20into%20the,making%20so%20many%20blood%20cells.

“What Is Cancer?” *National Cancer Institute*, 2021, www.cancer.gov/about-cancer/understanding/what-is-cancer.

Zappa, C., & Mousa, S. A. (2016). Non-small cell lung cancer: current treatment and future advances. Translational lung cancer research, 5(3), 288–300. https://doi.org/10.21037/tlcr.2016.06.07