# Lung Cancer Immunosuppression and Therapeutic Targeting Of Myeloid- Derived Suppressor Cells

By

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## Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University .
2. The thesis does not contain material previously published or written by a third party ,except where this is appropriately cited through full and accurate referencing .
3. The thesis does not contain material which has been accepted ,or submitted ,for any other degree or diploma at a university or other institution.
4. I have acknowledge all main sources of help.

**Student's Full Name & Signature**

.....

Aditi Nandy (17146017)

# Approval

*The thesis titled "Lung Cancer Immunosuppression And Therapeutic Targeting Of Myeloid-Derived Suppressor Cells " submitted by Aditi Nandy (17146017), has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor Of Pharmacy (Hons.) on*

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## *Ethics Statement :*

*The study does not involve any kind of animal and human trial .*

## Abstract

*Myeloid derived suppressor cells or MDSC are immune cells derived from the common myeloid progenitor which is able to develop erythrocytes , platelets or other granulocytes .They are separated into two different subsets ; PMN-MDSC and M-MDSC . MDSCs inhibit the immune system and are involved in tumor maintenance and development. It also impede therapies that use immunotherapy or other non-immune methods to cure cancer. MDSCs were first identified as suppressors of T cells, namely CD8+ T-cell responses. The fact that MDSCs have a high number of immunosuppressive mechanisms does not imply that all of them are active at the same time. The type of MDSCs that multiplied in response to sickness, as well as the stage of the disease and the site of suppression, all influence the frequency of a particular immunosuppressive mechanism. MDSCs will most likely adopt a dominant suppressive mechanism at any one time, which will change as the disease advances. As a result, evaluating the significance of MDSCs in cancer should entail an examination of their functional activity as well as one or two chemicals produced by these cells. It also implies that targeting a single mechanism for therapeutic reasons may be ineffective unless that mechanism has been determined to be prevalent in the type of cancer being treated.*

## Keywords

*Myeloid derived suppressor cells, immunosuppressive mechanisms , CD8+ T-cell responses, myeloid progenitor .*

# Dedication

*Dedicated to my parents .*

# Acknowledgement

First and foremost , I would like to express my deepest gratitude towards Almighty ,for giving me blessing ,the strength ,the patience and chance to complete my project work properly. I'm really fortunate that I had the kind and supportive supervision of Ms. Marzia Alam (Lecturer of Pharmacy Department of BRAC University). Her constant encouragement and careful monitoring motivated to do my work properly. She was very helpful to me whenever I faced any problem in my work and helped me to resolve any kind of inaccuracy in my work. Moreover, I would like to express my special thanks to Dr. Eva Rahman Kabir, Chairperson of the Department of Pharmacy BRAC University who gave me the opportunity to conduct my project work.

In the end, I acknowledge my sincere gratitude to my parents, friends and seniors for their devotion, support and faith in my ability throughout the whole journey.

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## List of Acronyms

PGE2 - Prostaglandin E2

OV - Oncolytic virus

NCI - National Cancer Institute

NIH - National Institutes of Health

PCI - Prophylactic Cranial Irradiation

SCC - Squamous cell carcinoma

EGFR - Epidermal growth factor receptor

ALK - Anaplastic lymphoma kinase

ROS -Reactive oxygen species

NHL- Non-Hodgkin lymphoma

EBV- Epstein-Barr virus

NK -Natural killer cells

NKT -Natural killer T cells

TEXs - Tumor-derived exosomes

Tregs - Regulatory T cells

TAMs - Tumor-associated M2 macrophages

ICIs - Immune checkpoint inhibitors

CTLA-4- Cytotoxic T-lymphocyte antigen 4

PD 1- Programmed death 1

LAG-3- Lymphocyte antigen gene 3

GM-CSF- Granulocyte-macrophage colony-stimulating factor

G-CSF - Granulocyte colony-stimulating factor

M-CSF- Macrophage colony-stimulating factor

IFN- Interferon

IL - Interleukin

STAT3- Signal transducer and activator of transcription 3

GM-CSF - Granulocyte-macrophage CSF

M-CSF- Macrophage CSF

G-CSF- Granulocyte CSF

ILT3 - Immunoglobulin-like transcript 3

CCL -CC chemokine ligand

CXCL - CXC chemokine ligand

NO -Nitric oxide

COX2 - Cyclooxygenase-2

ARG - Arginase enzyme

LC - Lung cancer

WHO - The World Health Organization

## Glossary

Oncolytic virus - Oncolytic viruses are a type of immunotherapy that involves infecting and killing cancer cells using viruses.

Sputum cytology - Sputum cytology involves looking through a microscope at a sample of sputum (mucus) to see if there are any abnormal cells.

Thoracentesis - Thoracentesis is a technique that removes fluid or air from the lungs' surrounding area.

External beam radiotherapy - External beam therapy (EBT) is a technique for targeting a patient's tumor with high-energy x-ray or electron beams. A linear accelerator produces beams that are targeted to eliminate cancer cells while sparing normal tissues in the surrounding area. EBT can also help people with advanced cancer or cancer that has spread to other parts of their body.

Angiogenesis inhibitors : Angiogenesis inhibitors are different from other cancer-fighting drugs in that they stop the formation of blood vessels that promote tumor growth rather than stopping tumor cells from growing.

LAG 3 - Lymphocyte Activation Gene-3 (LAG-3) is a CD4-related MHC-class II binding protein produced on activated T and NK cells that regulates lymphocyte homeostasis through a variety of inhibitory mechanisms.

Non-Hodgkin lymphoma - The type of cancer that starts in the lymphatic system, which is part of the body's immune system. White blood cells called lymphocytes proliferate improperly in non-lymphoma Hodgkin's and can form tumors throughout the body.

Anaplastic lymphoma kinase - ALK is a receptor tyrosine kinase that belongs to the insulin receptor superfamily and shares a lot of similarities with leukocyte tyrosine kinase.

Epstein-Barr virus - Epstein-Barr virus (EBV) is a type of herpes virus that is also known as human herpes virus 4. It's one of the most frequent viruses in humans. EBV is a virus that can be found all over the world. EBV infects the majority of people at some point in their lives. The most typical way for EBV to spread is through body fluids, particularly saliva. Infectious mononucleosis, usually known as mono, and other ailments can be caused by EBV.

Immune checkpoint inhibitors - When proteins on the surface of immune cells known as T cells recognize and bind to partner proteins on other cells, such as tumor cells, immune checkpoints are activated. Immune checkpoint proteins are what they're called. T cells receive a "off" signal when the checkpoint and partner proteins bind together. The immune system may be unable to destroy the cancer as a result of this.

11. CTLA-4 - CTLA -4 is a protein that is expressed on T cells after they have been activated and binds tightly to co-stimulatory molecules on antigen-presenting cells, preventing them from binding to T cells. CTLA-4 inhibits T cell activity by acting as a stopping mechanism.

# Chapter 1

## 1.1 Introduction

Cancer is one of the most feared diseases of the twentieth century, and its prevalence and incidence are increasing in the twenty-first .The situation is so dire that one out of every four people may develop cancer during their lifetime. Every year, more than 11 lakh new instances of cancer are registered , compared to more than 14 million worldwide.(PS & BJ, 2016a) What causes cancer to spread? This fundamental topic remains unanswered, for the apparent reason that longitudinal tumor growth observation is nearly always unfeasible, both in humans and in model systems .As a result, we rely on historical inferences based on the makeup of excised tumors to understand tumor genesis .In other words, our knowledge of the temporal process of tumor evolution is largely based on data acquired at a single time point: when the tumor reaches the specimen table at the end of the process .However, this situation is not as bad as it may appear, because the tumor genome (or, more precisely, the genomes of all the cells in the tumor) provides a hidden but detailed record of a tumor's progression..(Graham TA & A, 2017). It is probably more important in the development of cancer that the body's immune cells cannot identify and destroy newly formed cancer cells in the development of cancer, rather than the transformation from normal cells to malignant cells. Cancer risk is increased in people whose immune systems are reduced owing to a variety of factors such as chronic stress, aging, chronic debilitating disease, past chemotherapy, and drug usage such as analgesics, antibiotics, and corticosteroids. (PS & BJ, 2016b) Only 5-10% of all cancer cases are caused by genetic abnormalities, with the remainder 90-95% owing to environmental and lifestyle factors . Among the lifestyle variables are cigarette smoking, diet (fried foods, red meat), alcohol, sun exposure, environmental contaminants, infections, stress, obesity, and inactivity. Tobacco is responsible for about 25%-30% of all cancer-related deaths, according to the research, followed by food (30-35%), infections (15-20%), and other factors like radiation, stress, physical activity, and environmental pollutants .As a result, stopping smoking, increasing fruit and vegetable consumption, moderate alcohol consumption, calorie restriction, exercise, avoidance of direct sunlight, minimal meat consumption, whole grain consumption, immunizations, and regular check-ups are all recommended for cancer prevention.. .(P et al., 2008). Several lines of evidence imply that human carcinogenesis is a multistep process involving genetic changes that cause normal human cells to convert into highly malignant variations. In the human population, several distinct types of cancer have been found, with an age-dependent incidence involving four to seven stochastic rate-limiting events (MJ, 1993). The transition from normal cells to cancer cells, as well as the maintenance of malignancy and phenotypes, is linked to genetic and post-genomic dysregulation, altered cell signaling responses, and abnormal interactions with the milieu .

As tumor cells encounter changing selective pressures generated by the cells themselves, the microenvironment, and pharmacological therapies, these modifications are constantly developing. Tumors are also complex ecosystems in which a range of non-tumor cells coexist in a constantly developing way with diverse, sometimes heterogeneous, sub clonal tumor populations. Even more complicated are the connections between molecules and cells that emerge as a result of these changes in ecosystems .To comprehend and forecast the activity of cancer cells, the cancer research community is increasingly embracing complexity and employing a combination of systems biology methodologies and integrated studies. Understanding the causes of tumor growth and developing more effective cancer medicines are being aided by systems biology techniques. These methods work in tandem with significant technical improvements that allow for data capture on a larger scale, with finer accuracy, higher dimensionality, and greater consistency than ever before .(Du & Elemento, 2014) The systemic symptoms of the tumor are produced by sources other than direct or metastatic spread. The most common indications and symptoms include unexpected weight loss, fever, tiredness, and changes in skin condition. The metastatic form of cancer spreads from its primary site of growth to other sites through spreading to neighboring cells or tissues, lymphatic spread to regional lymph nodes, or hematogenous spread through the blood to various parts of the body. In 2018, it is expected that there will be 18.1 million new cancer cases (17.0 million excluding non-melanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding non-melanoma skin cancer). Lung cancer is the most commonly diagnosed cancer (11.6 % of all cases) and the leading cause of cancer death (18.4 % of all cancer deaths) in both sexes, closely followed by female breast cancer

(11.6%), prostate cancer (7.1 %), and colorectal cancer (6.1 %) in terms of incidence and colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) in terms of mortality.

Lung cancer is the most prevalent type of cancer in men and the main cause of death, followed by prostate and colon cancer (in terms of incidence), liver and stomach cancer (in terms of mortality) (in terms of mortality). Breast cancer is the most commonly diagnosed cancer in women and the main cause of cancer-related death, followed by colorectal and lung cancer (occurrence) and cervical cancer (incidence) (mortality). The most commonly diagnosed cancer and the leading cause of cancer death, on the other hand, differ significantly between nations and within each country, depending on economic development and other social and lifestyle factors. It's worth noting that most low- and middle-income nations lack access to high -quality cancer registry data, which is necessary for planning and executing evidence-based cancer control initiatives. The Global Initiative for Cancer Registry Development is an international collaboration that promotes better estimation, as well as the collecting and utilization of local data, to help countries prioritize and assess their cancer-prevention activities CA: A Clinician's Guide to Cancer 2018;0:1-31. The American Cancer Society

(ACS) is a non-profit organization dedicated to fighting cancer. (F et al., 2018). Several tumor -derived soluble factors (TDSF), such as interleukin 10 (IL10), transforming growth factor (TGF), and vascular endothelial growth factor, are involved in cancer immunosuppression. They produce an immunosuppressive network that stretches from the main tumor to the lymphatic organs subsequent to it. Blood vessels in the periphery (VEGF).In response to tumor development, TDSF activates immature bone marrow cells and regulatory T cells in a tumor-specific immune response, limiting dendritic cell maturation and T cell activation. Cancer immunosuppression is mediated by a number of tumor-derived soluble factors (TDSF), including interleukin 10 (IL10), transforming growth factor (TGF), and vascular endothelial growth factor. They form an immunosuppressive network that stretches from the primary tumor to the lymphatic organs below it. TDSF stimulates immature bone marrow cells and regulatory T cells in a tumor-specific immune response in response to tumor progression, limiting dendritic cell maturation and T cell activation.
. (R. Kim, Emi, & Tanabe, 2006).

## 1.2 Rationale of the study

Immune suppression is linked to tumor growth and chronic inflammation, and myeloid-derived suppressor cells (MDSC) have been involved in both. (Ortiz, Lu, Ramachandran, & Gabrilovich, 2014a). The growth of myeloid-derived suppressor cells (MDSCs) has been linked to disease progression in cancer patients. The features of MDSCs in lung cancer, on the other hand, are poorly characterized. (Yamauchi et al., 2018). Given the importance of myeloid cells in lung cancer immunotherapy response, investigating the chemokine and cytokine pathways involved in the recruitment and maintenance of these immunosuppressive cells could lead to new therapeutic combinations with ICI. (Sangaletti, Ferrara, Tripodo, Garassino, & Colombo, 2021). MDSCs are found in a variety of diseases, but they are particularly problematic in cancer, where they thwart both natural antitumor immunity and immunotherapy. A variety of pro-inflammatory mediators are produced by tumor and host cells in the tumor microenvironment (TME), which stimulate MDSCs and cause their accumulation and suppressive action .MDSCs block T cell activation, induce other immunosuppressive cell populations, regulate inflammation in the TME, and support the immune system flipping to one that tolerates and enhances tumor growth through a variety of ways.
MDSCs have been the subject of intensive research in recent years because they are found in most cancer patients and are potent immune-suppressive cells. ("Myeloid-Derived Suppressor Cells: Critical Cells Driving Immune Suppression in the Tumor Microenvironment - ScienceDirect," n.d.).This review describes the therapeutic targeting activities of myeloid derived suppressor cells in lung cancer. Clinical experience indicates that the medicine has an effect on MDSC levels in lung cancer patients.

Wang et al. found that 9 partial remission cases had significantly reduced MDSC percentages, 3 stable disease cases had invariable MDSC percentages, and 8 advancing disease cases had significantly higher MDSC percentages in 20 patients with advanced NSCLC who received systemic chemotherapy .(S. Wang et al., 2014a). MDSCs have been found to be on the rise in lung cancer patients , and this has been linked to tumor development, increased disease severity, and poor prognosis and survival. ("Immunosuppressive Role of Myeloid-Derived Suppressor Cells and Therapeutic Targeting in Lung Cancer," n.d.)

## 1.3 Aim of the Review

The target of this review is to compile all the possible therapeutic targeting activities of myeloid derived suppressor cell in lung cancer immunosuppression and how they are related with lung cancer treatments.

## 1.4 Objective of the study

The objectives of this review are,

To compile information of myeloid derived cell suppressor

To collect information of therapeutic targeting activities of MDSC in lung cancer immunosuppression .

To identify the relevant knowledge regarding lung cancer immunosuppression .

# Chapter 2

## Methodology

The information compiled for this review was collected through a three-staged process :

Collection of possibly relevant articles using several sources
Selection of definitely relevant articles
Analysis of selected studies

A systematic review of articles was performed to summarize these recent advances. The information was collected from relevant articles PubMed along with other reliable sources. Basically , those articles were chosen on the basis of updated information about therapeutic

targeting of MDSC in lung cancer. Then the references were searched via Mendeley library and inserted them into the review paper .Also , a bibliography of all the references that have already been cited were created.

# Chapter 3

## 3.1 Mechanism of carcinogenesis

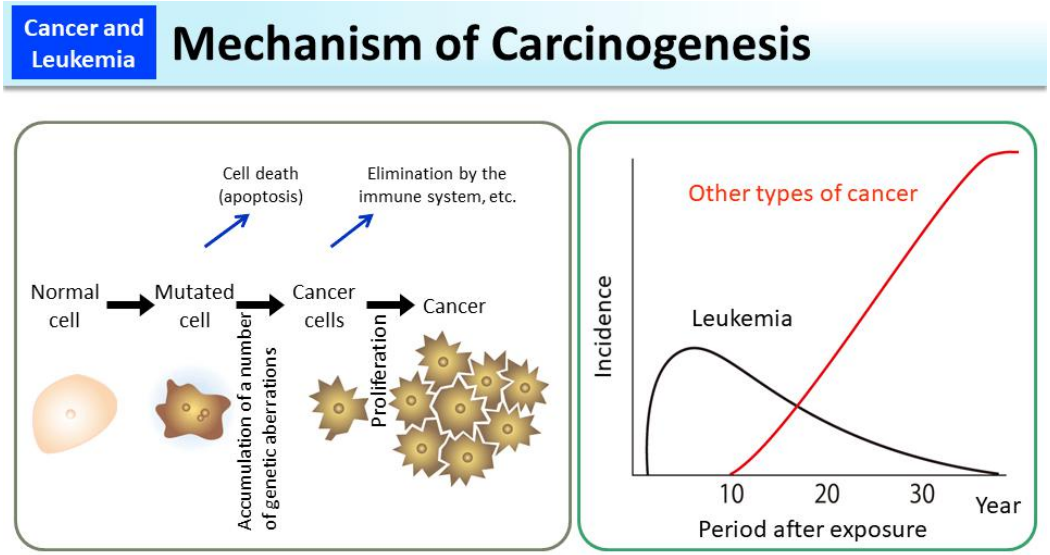


*Figure 1: Mechanism of carcinogenesis.* ("Mechanism of Carcinogenesis [MOE]," n.d.)

*One of the outcomes of this specific DNA damage is cancer. There are a number of common mechanisms that can cause sickness and tumor growth in the body, the majority of which can be fatal if not recognized and treated early. Translocations on DNA, for example, can activate proto-oncogenes. Burkitt's lymphomas, for example, are caused by the translocation of the c-Myc proto-oncogene across chromosomes. Point mutations, which have been seen in malignant neoplasms, can also activate proto-oncogenes. This can be caused by point mutations in genes that code for guanosine triphosphate-binding proteins (second messengers in signal transduction pathways). A tumor-suppressor gene that is normally responsible for regulating cellular proliferation could be inactivated by a mutation, resulting in tumor growth. This occurs in many colon and lung cancers. By understanding these abnormalities at the molecular level, researchers in the field of cancer research can gain invaluable insights that will aid in more effective*

*treatment of this disease. ("Investigating the Molecular Mechanisms of Cancer," n.d.)*

## 3.2 Cancer treatment

*In the past, neoplastic cells were commonly used to cure cancer. Surgery, radiation, chemotherapy, and immunotherapy have all been investigated as options for concentrating on the fast dividing mutant tumor cells. (JJ, KF, & F, 2018). Cancer can be treated in a variety of ways. The sort of treatment you receive will be determined by the type of cancer you have and its stage of progression..*

### 3.2.1 Biomarker Testing for Cancer Treatment

*Biomarker testing is a method of identifying genes, proteins, and other substances (referred to as biomarkers or tumor markers) that can provide information about cancer. Biomarker testing can assist you and your doctor in deciding on a cancer treatment plan.. (NCI, 2015)*

### Chemotherapy :

*Chemotherapy is a successful treatment choice for the vast majority of human cancers, and in rare situations, it can even be curative. Chemotherapy's significance in improving cancer patients' survival and quality of life will become increasingly more essential. Several scientific efforts, including drug development, pharmacology, preclinical experiments, quantitative response criteria, and a series of clinical trials in which the importance of dose schedule, chemotherapeutic agent sequencing, and, in particular, combination chemotherapy, were investigated, have all contributed to this progress.. (H, 2003).*

### Hormone therapy:

*Hormone therapy is a type of treatment that slows or stops the progression of cancers that rely on hormones to grow, such as breast and prostate tumors. Hormone therapy is commonly used in conjunction with other cancer treatments. The type of cancer, whether it has spread and how far it has spread, whether it requires hormones to develop, and whether you have other health problems all influence your treatment options.. (NCI, 2015).*

## Immunotherapy to Treat Cancer :

Immunotherapy is a method of treating cancer by inducing or enhancing an immune response against it. Immunotherapy's popularity has ebbed and flowed during the last century. Immunotherapy has gained popularity in recent years, owing to evidence that treatment routinely increases overall survival in advanced-stage cancer patients. Because of the lasting and powerful response it generates across a diverse spectrum of malignancies, antitumor immunotherapy has broad potential and could be utilized to treat a variety of advanced-stage tumors. (McCune, 2016)

## Radiation Therapy:

Every year, more than 14 million new instances of cancer are identified around the world; radiation treatment (RT) has the potential to increase cure rates for 3.5 million patients and give palliative relief for another 3.5 million .These cautious figures are predicated on the notion that RT can help about half of all cancer patients. (MB, M, & J, 2006). RT is now widely regarded as an important component of any good cancer treatment program, regardless of a country's economic situation. RT can cure localized tumors; it can also provide local control (complete response with no recurrence in the treated region) or symptom reduction in locally advanced or disseminated malignancies. It's frequently utilized in conjunction with surgery, either pre- or post-operatively, as well as systemic chemotherapy before, during, or after RT .(MB et al., 2014)

## Stem Cell Transplant

Stem cell transplants help cancer patients whose blood-forming stem cells have been damaged by high-dose chemotherapy or radiation therapy. (NCI, 2015)

## Surgery :

Treatment for cancer will only be effective if it is founded on a valid understanding of what cancer is and thus capable of influencing the disease's path. To find proof that the most common cancer treatment, surgery, has an effect on the disease's progression. Because surgery has never been proved to impact the course of cancer in a randomized controlled experiment, seven other indirect ways to assess its usefulness were used. Cancer screening no longer just excludes breast cancer, but also colon, lung, prostate, and ovarian cancer. This proves that cancer surgery is based on a faulty understanding of the disease. Survival rates after treatments based on an alternative paradigm that assumes cancer is a systemic disease were found to be superior to those after surgery, reinforcing the conclusion that cancer is a systemic disease and that cancer surgery

is unlikely to be beneficial in the vast majority of cases. With the exception of a few life-threatening instances, there are no benefits to be gained by cancer surgery. (D.J, 2014)

## Targeted therapy

A type of cancer treatment known as targeted therapy seeks to stop cancer cells from growing, dividing, or spreading. This is the foundation of precision medicine. As scientists learn more about the DNA changes and proteins that cause cancer, they will be better equipped to develop medicines that target these proteins. Targeted therapy inhibits the growth and spread of tumors by interfering with specific proteins. To treat cancer, they employ a variety of techniques. They can-

Assist the immune system in the destruction of cancer cells. One of the reasons cancer cells thrive is their ability to conceal from your defense system. Certain targeted medicines can label cancer cells, making it easier for the immune system to identify and eliminate them. Other targeted medicines can help your immune system fight cancer more effectively. Stop the growth of cancer cells. Healthy cells in your body normally only divide to generate new cells when they receive strong signals. These signals bind to proteins on the cell surface, instructing it to divide. This method aids in the formation of new cells only when they are required by your body. However, whether or not signals are present, certain cancer cells have alterations in their surface proteins that tell them to divide. Some targeted medicines block these proteins from instructing cells to divide by interfering with them. This method aids in the slowing of cancer's uncontrollable progression.

Stop signals that aid in the formation of blood vessels . To develop beyond a particular size, tumors must produce new blood vessels. These new blood vessels grow in response to tumor signals, a process known as angiogenesis. Angiogenesis inhibitors, a type of targeted therapy, work by interfering with these signals and preventing the formation of a blood supply. Tumors remain tiny in the absence of a blood supply. If a tumor already has a blood supply, these therapies can cause the tumor to shrink by causing blood vessels to die .

To cancer cells, deliver cell-killing chemicals. Toxins, chemotherapeutic medicines, and radiation are sometimes coupled with monoclonal antibodies. When these monoclonal antibodies bind to cancer cell targets on the surface, the cells absorb the cell-killing chemicals and die. Cells that do not contain the target will be unaffected .

Induce the demise of cancer cells . When healthy cells become damaged or are no longer needed, they die in a timely manner. Cancer cells, on the other hand, find strategies to prevent dying. Cancer cells may die as a result of some targeted therapy.

Deprive cancer of the hormones it need to thrive. Certain hormones are required for the growth of certain breast and prostate cancers. Hormone therapy is a sort of targeted therapy that can be used in two ways. Some hormone therapies stop the body from producing certain hormones. Others, such as cancer cells, prohibit hormones from working on your cells..

Systemic chemotherapy, which is used to treat cancer, can have serious side effects. Oncologists have been treating tumors for decades, but this has the potential to harm the tumor-bearing host and its immune system. Patients' immune systems and their activation by biological therapies have received a lot of interest recently. Biological therapies, including as immunotherapy and oncolytic virus (OV) therapy, are often more physiological and better tolerated than conventional treatments. The current study clarified how these treatments operate and why they might be tolerated better :

Immunotherapies, unlike chemotherapy, cause the adaptive immune system's memory function to be activated.

Immunotherapies aim to boost the immune system specifically against cancer with little side effects, thanks to immunological tolerance mechanisms that maintain the body intact in the presence of B and T cells with antigen-receptor specificities. and;

The type I interferon response produced by OVs is an inherent immune defense system that has been around for ages. As a result, immune-supportive biological and physiological therapies may be effective in the treatment of cancer.. (Schirrmacher, 2019)

In the year 2000, the World Health Organization estimated that 6 million people had cancer around the world. Lung cancer was the most frequent cancer worldwide, accounting for one million people, or one-sixth of the total. (Parkin, 2001) . Lung cancer was first recognized as a reportable disease a century ago, and it currently accounts for more cancer-related fatalities worldwide than any other malignancy. Adler published Primary Malignant Growths of the Lungs and Bronchi in 1912, in which he listed all cases of lung cancer found in the published literature around the world. Only 374 cases were confirmed by him. (ADLER, 1913). Small cell carcinoma and non-small cell carcinoma are the two types of lung cancer (e.g., adenocarcinoma,

squamous cell carcinoma, large cell carcinoma). Treatment decisions and prognosis are based on these categorization. The signs and symptoms vary depending on the type of tumor and the number of metastases. The diagnostic examination of patients with suspected lung cancer includes tissue diagnosis, a full staging work-up, including evaluation of metastases, and a functional patient evaluation. To get a histologic diagnosis, sputum cytology, thoracentesis, accessible lymph node biopsy, bronchoscopy, transthoracic needle aspiration, video-assisted

thoracoscopy, or thoracotomy can all be employed. Metastatic sickness is detected through a patient's medical history and physical examination, blood tests, chest computed tomography, positron emission tomography, and tissue confirmation of mediastinal involvement. Whether or not additional testing for metastases is required is determined by the clinical presentation. Treatment and prognosis are heavily influenced by the tumor's kind and stage. (IG, C, R, & RE, 2007). The World Health Organization divides lung cancer into numerous subtypes, but for doctors, it can be separated into two broad groups: small cell and non-small cell lung cancers, with the latter containing adenocarcinoma, squamous cell, large cell, and bronchoalveolar carcinomas . (Maghfoor & Perry, 2005).

## 3.3 What is lung cancer

Lung cancer is a type of cancer that develops in the lungs. Lung cancer causes aberrant cells to cluster together and form a tumor. Cancer cells, unlike normal cells, grow out of control, killing the healthy lung tissue around them. Malignant tumors are the term for these types of tumors. Cancer cells spread throughout the body, preventing organs from working normally. ("Lung Cancer Basics | American Lung Association," n.d.-a). Lung tumors now have a new classification, according to the World Health Organization. This classification takes into account the fact that lung cancers have a lot of histological heterogeneity. It differentiates between epidermoid carcinomas, adenocarcinomas, small cell lung carcinomas, big cell lung carcinomas, large cell neuroendocrine carcinomas, adenosquamous carcinomas, sarcomatoid and pleomorphic carcinomas, and a number of other lung malignancies. (de Sousa & Carvalho, 2018). Lung cancer is a prevalent condition that leads to significant morbidity and mortality. Physicians have become pessimistic and nihilist as a result of patients' often bad prognoses. Lung cancer is more common than breast cancer and cervical cancer, yet when it comes to resources dedicated to patient care and research, as well as the number of specialist clinics and healthcare professionals with a declared interest, lung cancer always seems to fall in second place. (Sethi, 2002). The phenotype of lung cancer has likewise been simplified and treated as a single entity, with little attention paid to phenotype heterogeneity. Historically, epidemiologists have viewed lung cancer as a single phenotype, with some studies looking at the risk of certain histological kinds, but without any mechanistically focused hypothesis. In general, adenocarcinoma has been the most common histological type among never smokers, but small cell carcinoma is uncommon. Adenocarcinoma has surpassed squamous cell carcinoma as the most common histological form among smokers over the previous four decades .Changes in cigarette design have been blamed for this shift. (Alberg, Shopland, & Cummings, 2014). These histological abnormalities are now known to correspond to discrete genetic fingerprints that have clinical implications. (FR et al., 2017). The discovery of smoking as a cause of lung cancer is largely considered as a pioneering achievement in epidemiological research.

The methodologies developed in this lung cancer study, such as evidence integration for causal inference, were immediately applied to other malignancies and chronic diseases, and are still in

use today. (Glass TA, SN, MA, & JM, 2013). The majority of lung cancer tumors in persons who have never smoked are produced by the accumulation of mutations caused by natural processes in the body, according to a genomic examination of people who have never smoked. This study, coordinated by researchers at the National Cancer Institute (NCI), part of the National Institutes of Health (NIH), describes three molecular subtypes of lung cancer in persons who have never smoked for the first time in people who have never smoked. Over 2 million people are diagnosed with the disease every year all over the world. The majority of people who get lung cancer have smoked before, although 10% to 20% of lung cancer patients have never smoked. Never smokers develop lung cancer at a younger age and in greater numbers than smokers. Some lung cancers among never smokers may be explained by environmental risk factors such as secondhand cigarette smoke, radon, air pollution, and asbestos, as well as previous lung disease, but experts are still unsure what causes the bulk of these malignancies. ("NIH Study Illuminates Origins of Lung Cancer in Never Smokers | National Institutes of Health (NIH)," n.d.). Lung cancer is the leading cause of mortality from cancer worldwide. Lung cancer is the most common cause of death, and stopping smoking is the most effective approach to reduce lung cancer mortality. Former smokers have a lower risk of lung cancer in the short term, but they have a higher risk for the remainder of their lives than never-smokers. For these patients, novel chemoprevention approaches such as prostacyclin analogs either orally or inhaled show promise. In high-risk heavy smokers over 50, low-dose spiral computed tomography screening decreased lung cancer mortality by 20%. Patients that were screened, however, had to be followed up with in experienced centers due to the high false -positive rate (96 percent). An increasing percentage of individuals with advanced lung cancer have genetic drivers in genes that can be treated with oral tyrosine kinase inhibitors. (PA, 2012). Lung cancer has long-term effects on a person's physical, emotional, social, and spiritual well-being. Changes in functional status caused by biological symptoms of lung cancer, as well as therapeutic side effects, have repeatedly shown to have an influence on patients in the literature. It also stresses the fact that lung cancer patients experience a wide range of symptoms at once. The distress associated with lung cancer symptoms has been determined to be the most significant when compared to other cancer types. Rather of focusing on individual symptoms, researchers have recently focused on symptom cluster as understanding these clusters may help with the management of continuous and unrelieved symptoms. Although recent efforts have been made to address these issues, the relationship between aspects of patients' symptom experiences can be complex, and the mechanisms underlying this association are not fully understood at this time. Disparities in methodology are also significant barriers to producing comparable results, despite recent efforts to address these issues. (Ellis, 2012). According to accumulating evidence, women's lung cancer risks differ from men's lung cancer risks. Higher amounts of DNA adducts, lower DNA repair capability, increased frequency of mutations in tumor suppressor genes, and hormonal variations may all contribute to women's heightened vulnerability to tobacco's harmful effects. There are numerous sex and gender disparities in lung cancer presentation, including a higher proportion of adenocarcinoma in women, a higher representation of women in lung cancer cohorts of younger patients, and

women who do not smoke are more likely to be diagnosed with lung cancer than males. These distinctions should be taken into account when developing lung cancer screening, prevention, and treatment guidelines. (MP & DE, 2004). According to current research, at least 10-20 genetic alterations are necessary to generate a lung cancer cell from a normal one. Oncogenes (dominant biological factors that promote or predisposition a cell to divide) are activated by these alterations, and tumor suppressor genes are deleted. (Sethi, 1997). Patients with a history of cigarette smoking and/or symptoms such as hemoptysis or a persistent cough should be evaluated for lung cancer. Although radiological studies can help with staging, a tissue diagnosis is required to confirm the presence of a tumor. Although early discovery and referral are critical for the best chance of a cure, primary prevention by smoking cessation is the most critical measure. (RE & PV, 1997). Lung cancer is one of the rare malignancies with a known cause. Tobacco usage and lung cancer have been linked for more than 60 years. (R & AB, 1950). Lung cancer affects about 90% of smokers and people who have smoked in the past.

The global incidence of lung cancer roughly reflects the prevalence of smoking. (J et al., 2010). Global tobacco use has steadily increased since the introduction of manufactured cigarettes nearly 125 years ago. More than one billion smokers, or roughly a quarter of the adult population of the world, are estimated to exist today . ("WHO Report on the Global Tobacco Epidemic, 2009: Implementing Smoke-Free Environments," n.d.). In the major developed countries, tobacco control programs are being established. However, cigarette smoking is quickly increasing in both sexes in many developing nations, owing to population growth and greater tobacco marketing targeting in these areas, particularly among the youth. . (Adjei, 2013).

Lung cancer risk is dose-dependent, although stopping smoking can dramatically reduce it, particularly if done early in life. Lung cancer has become more common in numerous countries as cigarette usage has increased. Switching to filters or low-tar/low-nicotine cigarettes does not lessen the risk of lung cancer. Continued tobacco use following a cancer diagnosis is linked to poor therapeutic results, such as higher treatment-related toxicity, an increased risk of a second

primary cancer, a lower quality of life, and a lower chance of survival. Tobacco quitting in cancer patients may enhance treatment outcomes, yet physicians frequently do not provide cessation support. Tobacco's negative health effects can be decreased through coordinating efforts to prevent tobacco exposure, appropriately assessing nicotine usage in healthcare settings, and providing tobacco cessation support . (GW & KM, 2013).

## 3.4 Signs and symptoms of lung cancer:

Lung cancer can vary from person to person, when it causes symptoms in its early stages however the following are frequent lung cancer symptoms:

A cough that persists or worsens, or a change in an existing chronic cough. -A

cough that causes blood to flow

Coughing, laughing, or deep breathing causes chest, back, or shoulder pain.

Shortness of breath that comes unexpectedly during everyday activity

Weight loss that isn't explained

A feeling of exhaustion or weakness

Infections in the lungs, such as bronchitis or pneumonia, occur often.

-Wheezing or hoarseness

Swelling of the face or neck , Difficulty swallowing or pain when swallowing are some of the less prevalent signs of lung cancer.

Even if the majority of these symptoms are caused by something other than lung cancer, it's still important to see a doctor. Lung cancer that is detected early may have more treatment choices.. ("What Are the Symptoms and Signs of Lung Cancer? | CTCA," n.d.).

## 3.5 Causes of lung cancer:

Lung cancer, also known as bronchogenic carcinoma, is a type of cancer that begins in the lung parenchyma or inside the bronchi. (Siddiqui & Siddiqui, 2021).

### 3.5.1 Smoking

The most important risk factor for lung cancer is smoking cigarettes. More than 70% of the cases are caused by it. Tobacco smoke contains over 60 different harmful chemicals (cancer-producing). f you smoke more than 25 cigarettes a day, you are 25 times more likely to develop lung cancer than a nonsmoker. While smoking cigarettes is by far the most major risk factor, other tobacco products can also increase your chance of lung cancer as well as other cancers such as esophageal cancer and mouth cancer.

These products include:

cigars

pipe tobacco

snuff (a powdered form of tobacco)

chewing tobacco

Lung cancer has also been connected to cannabis use. The majority of cannabis smokers combine the two. They inhale more deeply and hold the smoke in their lungs for longer than people who smoke regular cigarettes, although consuming less tobacco. Four joints (homemade cigarettes with a tobacco and cannabis mixture) are estimated to be as damaging to the lungs as twenty cigarettes. It can be fatal even if you don't mix cannabis with tobacco. This is due to the presence of carcinogens in cannabis.("Lung Cancer - Causes - NHS," n.d.)

## 3.5.2 Secondhand smoking or passive smoking:

Adults who have never smoked develop lung cancer through secondhand smoke.

Nonsmokers exposed to secondhand smoke at home or at work had a 20-30% higher risk of lung cancer

-Each year, secondhand smoking kills more than 7,300 nonsmokers in the United States.

-Nonsmokers inhale many of the same cancer-causing chemicals and toxins as smokers.

-Even short exposure to secondhand smoke can harm cells in ways that set the cancer process in motion

Passive smoking, commonly known as secondhand smoke, raises lung cancer risk in the same manner that active smoking does. The greater the duration and intensity of secondhand smoke exposure, the greater the risk of lung cancer. (Alberg et al., 2014)

## 3.5.3 Exposure to radon gas:

When the elements uranium, thorium, and radium spontaneously decay in rocks and soil, radon is created. It's a colorless, odorless, and tasteless gas that rises from the earth and disperses into the air. Radon decays quickly, releasing a little amount of radioactivity. If inhaled, these radioactive particles can cause damage to the cells lining the lungs. The only malignancy associated to long-term exposure to radon is lung cancer. Exposure to both radon gas and cigarette smoke increases the risk of lung cancer more than either cause alone.. ("Radon and Cancer - National Cancer Institute," n.d.).

### 3.5.4 Hazardous chemicals and particle pollution :

Lung cancer can be caused by exposure to certain hazardous substances.Working with asbestos, uranium, arsenic, cadmium, chromium, nickel, and other petroleum products is exceedingly

hazardous. If you think you're inhaling dangerous drugs at work, talk to your doctor about how to stay safe. Particle pollution, on the other hand, is a word that depicts a mixture of very minute solid and liquid particles found in the air we breathe. Particle pollution, such as that caused by automobile exhaust, has been linked to an increased risk of lung cancer.("Lung Cancer Causes & Risk Factors | American Lung Association," n.d.)

### 3.5.5 Genes

Lung cancer risk may also be influenced by genetic factors. If you have a family history of lung cancer, you may be at a higher risk of developing the disease. It's crucial to tell your doctor if anyone else in your family has or has had lung cancer. ("Lung Cancer Causes & Risk Factors | American Lung Association," n.d.) Contact with specific chemicals and compounds can cause lung cancer in rare cases, mainly as a result of job. According to recent study, air pollution can trigger lung cancer. However, determining the risk for individual people is challenging since it relies on several factors, including the air quality where they reside and the amount of pollution they are exposed to. For the most part, the risk is negligible.

Lung cancer is caused primarily by smoking. Lung cancer is not contagious and cannot be spread to others. ("Causes and Risk Factors of Lung Cancer - Macmillan Cancer Support," n.d.)

## 3.6 Types of lung cancer:

The ability to accurately determine the tumor type in patients with primary lung cancer has a substantial impact on treatment options. However, lung cancer typing methodologies and processes are not standardized. Due to low tumor sample volumes and poor quality of some samples, the categorization of primary lung cancers using microscopic preoperative biopsy specimens poses a diagnostic challenge using current technology. (Gilad et al., 2012).

### i. Small cell lung cancer:

Small cell lung cancer (SCLC) is a deadly neuroendocrine cancer associated to cigarette smoking. Patients usually have a short history of symptoms and are frequently identified with metastatic disease (60-65 percent). SCLC is a heterogeneous disease with clones that are chemo-sensitive as well as chemo-resistant. As a result, a large proportion of individuals react to first-line treatment but succumb to the cancer quickly. Limited and widespread SCLC are the two stages of the disease. Standard treatment for patients with limited stage disease includes four cycles of cisplatin and etoposide-based combination chemotherapy, early thoracic radiation during the first cycle of chemotherapy, and consideration of prophylactic cranial irradiation (PCI) in the subset of patients who respond well . (Bernhardt & Jalal, 2016). SCLC accounts for

around 15% of lung cancer cases, while NSCLC accounts for about 85%. Lung cancer incidence has decreased since the late 1980s, coinciding with a decrease in smoking, the primary cause of lung cancer. Surgery, chemotherapy, radiation, and immunotherapy are some of the current treatments. Lung cancer's high incidence and prevalence provide fertile ground for fresh research into the role of public health measures, genetics, and novel treatment methods. (Schiller, 2001).

## ii. Non-Small Cell Lung Cancer (NSCLC):

Non-small-cell lung cancer (NSCLC), a diverse group of cancers, accounts for almost 85% of all new lung cancer diagnoses. Tobacco use is the most significant risk factor for developing this disease, but radon exposure and air pollution also play a role. Due to inadequate screening programs and late development of clinical indications, the majority of patients are diagnosed with advanced-stage disease with a bad prognosis. NSCLC can be diagnosed by X-ray, CT, and PET imaging, as well as histological examination of tumor specimens.

If tumors contain oncogene mutations, precise cancer staging is required to determine the appropriate treatment plan, which may include surgery, radiochemotherapy, immunotherapy, and targeted medicines such as anti-angiogenic monoclonal antibodies or tyrosine kinase inhibitors.. (C et al., 2015).

There are three different types of NSCLC lung cancer-

Adenocarcinoma: Non-small cell lung cancer that is usually found on the periphery of the lung. It starts in epithelial cells, which line the cavities and surfaces of the body and form glands.
. ("Lung Cancer Basics | American Lung Association," n.d.-a)

Squamous cell carcinoma: Squamous cell carcinoma of the lung (SCC), commonly known as squamous cell lung cancer, is a kind of non-small cell lung cancer (NSCLC). The center of the lung and the main airway, such as the left or right bronchus, are the most common sites for squamous cell lung cancers. Tobacco smoke is the most common source of cellular damage. This exercise examines the diagnosis and treatment of lung squamous cell carcinoma, emphasizing the importance of taking a multidisciplinary approach to patient care.. (Sabbula & Anjum, 2021)

iii.Large cell carcinoma: A large cell carcinoma is an undifferentiated cancer that lacks the characteristics of squamous cell, small cell, or adenocarcinomas. Light microscopy is used to rule out the presence of different forms of lung cancer cells. Large cell carcinoma grows quickly, and by the time it is diagnosed, it is usually fairly large. Large cell carcinomas account for the majority of colony stimulating factor-producing lung malignancies previously documented. These colony promoting substances are thought to play a role in large cell carcinoma progression. Large cell carcinoma has a radiographic appearance that is often greater than 4 cm

in diameter. The mass's borders are lobulated and weakly defined, and cavitation is uncommon. . ("[Large Cell Carcinoma] - PubMed," n.d.)

### iv. Carcinoid:

Carcinoid tumors are a kind of lung cancer that is quite uncommon. Carcinoid tumors make up just 1% to 2% of lung malignancies. They normally take their time to mature. They're a form of neuroendocrine tumor, which means they start in specific cells found in the lungs and throughout the body called neuroendocrine cells. The causes of carcinoid tumors in the lungs are unknown. They discovered that while conventional carcinoid tumors do not appear to be associated to smoking, atypical carcinoid tumors are found more frequently in smokers. ("Lung Carcinoid Tumors: Causes, Symptoms, Diagnosis, and Treatment," n.d.)

## 3.7 Lung cancer stages

Lung cancer staging often uses the letters T, N, and M:

T stands for the size of the tumor and its location in the lungs or body.

Node involvement is represented by the letter N. This indicates whether the cancer has migrated to the lymph nodes around the lungs.

The letter M stands for metastases. This refers to whether the cancer has spread.

Lung cancer has the potential to spread to other parts of the body, including the liver, bones, brain, kidneys, adrenal glands, and other lungs. ("Stages of Lung Cancer: Stages 1-4, Limited vs. Extensive," n.d.)

The TNM components of the anatomic staging system are discussed, as well as a framework for describing lung cancer that involves several pulmonary locations. TNM combinations are categorized based on their prognosis, with patient-level, tumor-level, and environment-level aspects all influencing survival. Anatomic staging remains the standard language for reporting illness extent despite the absence of molecular and immunologic information.. (IT, 2020).

### 3.7.1 Stages of NSCLC:

The location of the cancer, whether it has spread, and if it has progressed to other parts of the body are all factors in staging. Because doctors use diagnostic tests to identify the cancer's stage, it's conceivable that the staging won't be complete until all of the tests have been done. Knowing the stage can help the doctor determine the best course of treatment and assess the prognosis, or chance of recovery, for a patient. Distinct forms of cancer have different stages. In general, a lower NSCLC stage is associated with a better prognosis. However, based solely on the stage of

disease, no clinician can predict how long a patient will live with lung cancer. This is because each person's lung cancer is unique, and treatment for each tumor differs.

The stage of NSCLC is determined by a number of factors, including:

The tumor's size and location

Whether it has spread to the lymph nodes and/or other body areas.

NSCLC is divided into five stages: stage 0 (zero), stage I, stage II, and stage III (1 through 4).

Finding out if the cancer can be totally removed by a surgeon is one technique to assess NSCLC staging. The surgeon must remove the cancer, as well as the surrounding, healthy lung tissue

and, in certain cases, neighboring lymph nodes, to entirely eliminate the lung cancer. ("Lung Cancer - Non-Small Cell: Stages | Cancer.Net," n.d.-a) .

Occult stage-

At this stage, neither imaging nor bronchoscopy are capable of detecting malignancy. Doctors are unable to pinpoint its precise position as a result. Sputum (lung mucus) and bronchial washings, on the other hand, can include cancer cells (a sample of cells from inside the airways). Because the cancer hasn't moved to other places of the body, there's a strong chance it won't. ("Understand How Lung Cancer Is Staged and Graded | CTCA," n.d.)

Stage 0 :

Doctors may uncover abnormal cells in the lining of your airways. These could turn cancerous and harm normal tissue nearby, but they haven't spread to other regions of the body yet. The subtypes of stage 0 NSCLC are:

Adenocarcinoma in situ– When abnormal cells are discovered in the glandular tissue that lines the lungs, this is referred to as pulmonary fibrosis.

Squamous cell carcinoma in situ– when abnormal cells are found in the tissues surrounding the lungs These cells have the potential to becoming cancerous, causing damage to surrounding tissues. ("Understand How Lung Cancer Is Staged and Graded | CTCA," n.d.)

*Stage 1*

*A stage 1 lung cancer is a tiny tumor that hasn't progressed to any lymph nodes and can be removed entirely by a surgeon .Based on the tumor's size, Stage 1 is divided into two sub stages.:*

*-Tumors in Stage 1A are 3 centimeters (cm) or less in diameter. Tumors in stage 1A can be classified as 1A1, 1A2, or 1A3 depending on their size.*

*-Tumors that are larger than 3 cm in diameter but less than 4 cm in diameter are classified as stage 1B. ("Lung Cancer - Non-Small Cell: Stages | Cancer.Net," n.d.-b)*

*Stage 2:*

*When your doctor discovers one or more tumors in one lung, it is called stage 11 lung cancer. It's*

*possible that the malignancy has spread to nearby lymph nodes. It hasn't, however, reached far-flung locations such as your bones or other organs. Depending on the size of the tumor and the location of any affected lymph nodes, your cancer may be localized or regional. Surgical removal of stage 11 cancer is common. Stage 11 lung cancer is divided into two subgroups, according to doctors . TNM stands for three primary criteria on which the evaluation is based.*

*Tumor (how big and where it is)*

*Nodes (Is the cancer in nearby lymph nodes?)*

*Metastasis (how far the cancer has spread to other parts of the body) ("Stage 2 Lung Cancer: Types, Symptoms, Diagnosis, Treatment, & Prognosis," n.d.)*

*Stage 3 :*

*Stage 3 NSCLC cases are divided into three subtypes.*

*Stage 3A: In certain cases, the lung cancer tumor has progressed to lymph nodes in the same area of the chest as the original tumor—usually lymph nodes in the trachea, aorta, or where the trachea splits into bronchi. At least one of the following requirements must be met by the cancer. Although the infection has extended to the main bronchus, it has not yet reached the carina. The cancer has spread across the lungs' innermost regions.*

*Pneumonitis has caused the collapse of a section or the complete lung.*

*In some situations, the cancer has spread to lymph nodes near the bronchus or in the lung, in the same location of the chest where the original tumor was discovered.*

*Furthermore, the cancer must meet at least one of the following criteria. The tumor is more than 5 cm in diameter but less than 7 cm in diameter.*

The cancer has reached at least one of the following:

In the same area of the lung where the first tumor was discovered, at least one more tumor has emerged.

-The chest's lining

-The chest wall's inner lining

-The tissue that surrounds the heart and lines the outside of the sac

-The diaphragm's regulating nerve

The cancer may have spread to lymph nodes near the bronchus or within the lung, in the same chest location as the original tumor in certain cases.

Furthermore, at least one of the following conditions must be met by the cancer. -

The lung cancer tumor has expanded to a diameter of more than 7 centimeters . A new tumor has grown in the same lobe, or lung region, as the previous one. The lung cancer tumor might be any size, and it has spread to other parts of the body, including the trachea, carina, and esophagus.

Stage 3B:

The lung cancer tumor is 5 cm or smaller in some cases, and the cancer has spread to lymph nodes above the collarbone in the same chest location as the original tumor, or lymph nodes on the opposite side of the chest.

At least one of the following conditions is also met by the cancer:

Although the cancer has spread to the main bronchus, it has not yet spread to the carina.

The malignancy has spread to the deepest tissue around the lung.

Pneumonitis or a section of or the entire lung has collapsed. In some situations, the lung tumor has spread to lymph nodes on the same side of the chest as the original tumor, usually near the aorta or heart, the trachea, or where the trachea splits into the bronchi.

Furthermore, the cancer must meet at least one of the following criteria:

At least one further tumor has appeared in the same or a different lobe of the lung as the first.The lung cancer tumor has progressed to the chest wall, the inner lining of the chest wall, the diaphragm, and the diaphragm's nerve, among other places.

Stage 3C: The lung cancer tumor could be of any size, and it has spread to lymph nodes on both sides of the chest .The cancer must also meet at least one of the following requirements :In the same or a different lung lobe, at least one additional tumor has appeared. The lung cancer tumor has progressed to the chest wall, the inner lining of the chest wall, the diaphragm, and the diaphragm's nerve, among other places. ("Understand How Lung Cancer Is Staged and Graded | CTCA," n.d.)

Stage 4:

Stage 4 lung cancer is the most advanced kind, and it is metastatic, meaning it has gone beyond the lung to other parts of the body. Metastasis occurs when cancer cells separate from the main tumor and spread throughout the body via the blood or lymph system. The brain, the bones, the liver, and the adrenal glands are all popular targets. Because they are formed up of lung cancer cells, any metastatic tumors that arise in another part of the body are still called lung cancer at that time. NSCLC has gone beyond the lung where it began in stage 4, making it metastatic.

Stage 4 NSCLC is separated into two sub stages: 4A and 4B, depending on how far it has spread. The tumor size in stage 4A might vary, and it may or may not have migrated to the lymph nodes.

One (or more) of the following may also be true:

Disease has only moved to one additional organ, such as the brain, liver, adrenal gland, or kidney (where the cancer did not begin).

It has spread to the lining of the lungs or the fluid around the heart.

In addition to the primary tumor, there are several tumors in the lungs.

The cancer has progressed to many locations or organs outside of the lung at stage 4B.

Although malignancies in either of these sub stages are classified as stage 4, they may require different treatments. Stage 4B is the most prevalent, but it's also the most hardest to cure and has a lower survival rate. ("Stage 4 Lung Cancer: Symptoms & Treatments | CTCA," n.d.)

### 3.7.2 Stages of SCLC:

SCLC is categorized into two stages: limited stage or extensive stage.

Limited stage:

The cancer has only spread to one area of the chest in the limited stage of SCLC .It could have started in one lung and spread to lymph nodes in the same location of the chest as the cancer .In limited-stage SCLC, radiation is usually only needed in one region of the body.

Extensive stage: The cancer has spread throughout the lung and may have metastasized to the other lung, lymph nodes in the opposite chest area, fluid around the lung, or other sites such as the bones. ("Understand How Lung Cancer Is Staged and Graded | CTCA," n.d.)

## 3.8 Treatment of lung cancer

Different treatment processes of lung cancer are given below

### 3.8.1 Chemotherapy

Chemotherapy is a form of lung cancer treatment in which chemicals are used to kill cancer cells. Chemotherapy is another name for it. Chemotherapy is the most common treatment for small-cell lung cancer (SCLC), although it can also be used before, after, or instead of surgery to treat non-small-cell lung cancer (NSCLC) (NSCLC).

Adjuvant therapy is chemo given after lung cancer surgery to treat any cancer that has not yet been removed.

Chemotherapy given before surgery to shrink the tumor is known as neoadjuvant therapy.

This treatment is available to elderly people with lung cancer. If surgery isn't an option, chemotherapy and radiation therapy may be used to shrink the tumor.. ("Chemo for Lung Cancer: Treatments and Side Effects," n.d.). Chemotherapy is frequently coupled with radiation therapy in the treatment of lung cancer. Chemotherapy and radiation may be more effective in killing cancer cells when used jointly. Chemotherapy can help some people with lung cancer keep their tumors small so that radiation can remove them more efficiently.

It may also prevent cancer cells from returning following radiation treatment. While chemo and radiation therapy together can be a potent weapon in the fight against lung cancer, they can also have significant adverse effects. Chemotherapy for lung cancer comprises the administration of a

variety of drugs. The drugs are usually given through a vein (intravenously) or through a tube connected to one of your chest's blood veins. Some patients may be given capsules or tablets to use instead of pills.

Before you start chemotherapy, your doctor may prescribe vitamins or give you a vitamin injection. These can help to mitigate some of the undesirable effects.

Chemotherapy might cause the following side effects:

exhaustion
nausea
vomiting
mouth ulcers
hair loss

These side effects should fade as treatment progresses, or you may be able to take alternative medications to help you feel better while undergoing chemotherapy. ("Lung Cancer - Treatment NHS," n.d.)

## 3.8.2 Radiation therapy:

Lung cancer radiation therapy is the use of high-energy X-rays to destroy or stop cancer cells from developing. Radiation can come from the outside (external) or from radioactive materials implanted into the lung cancer tumor (internal/implant). The most common method is to employ external radiation. Radiation is directed towards the lung cancer tumor and exclusively destroys cancer cells in that location of the lungs.. ("Radiation Therapy for Lung Cancer | American Lung Association," n.d.). High-energy x-ray beams are used to kill cancer cells by damaging their DNA in radiation therapy for lung cancer.

It's extremely successful at reducing or eliminating tumors at precise locations throughout the body. Patients with lung cancer that is confined to the chest but cannot be surgically removed can benefit from the treatment. We can now send high doses of radiation straight to your tumor with perfect precision using the most current tools. In compared to more traditional ways, the methods we deploy can reduce the number of sessions required for radiation treatment while simultaneously lowering the risk of adverse effects..

Patients whose condition does not respond to surgery or chemotherapy can benefit from radiation therapy as a palliative measure to improve their quality of life.. ("Radiation Therapy for Lung Cancer | Memorial Sloan Kettering Cancer Center," n.d.). Radiotherapy is a common therapeutic

option for lung cancer. Technological advancements have made it possible to better focus radiotherapy to tumors while reducing unintentional irradiation of surrounding normal tissues. This has broadened the indications for radiotherapy in lung cancer, improving outcomes in terms of survival and toxicity reduction. This review looks at the current use of radiotherapy in lung cancer, reviews the data, and suggests future prospects for lung cancer radiotherapy. (Vinod & Hau, 2020).

The 3 main ways that radiotherapy can be given are:

conventional external beam radiotherapy - Radiation beams are directed towards the portions of your body that are affected.

stereotactic radiotherapy – a more precise form of external beam radiotherapy in which a number of high-energy beams provide a larger dose of radiation to the tumor

while avoiding as much healthy tissue as feasible.

- internal radiotherapy - A narrow tube, known as a catheter, is introduced into your lung.

A little amount of radioactive material is injected into the catheter and applied to the tumor for a few minutes before being removed. For lung cancer, external beam radiotherapy is utilized more frequently than internal radiotherapy, especially when a cure is expected. Stereotactic radiotherapy is more successful than conventional radiotherapy in treating very small cancers.. ("Lung Cancer - Treatment - NHS," n.d.)

## 3.8.3 Surgery:

Surgery is the preferred treatment choice for people with early-stage non-small-cell lung cancer, or NSCLC. Unfortunately, most patients with advanced or metastatic disease are not surgical candidates. If their lungs are in good enough shape, people with NSCLC that hasn't spread can usually withstand surgery. Surgery is rarely utilized in the treatment of small-cell lung cancer (SCLC).

Because SCLC develops so quickly and widely throughout the body, surgical removal is usually impossible . ("Surgery for Lung Cancer (Thoracotomy): Benefits and Risks," n.d.).

There are different types of lung surgery.

Removing one lobe (lobectomy) The lobes of the lungs are divided into groups. There are two lobes in the left lung and three in the right lung. A lobectomy occurs when one of the lungs' lobes is surgically removed. Your surgeon will recommend this operation if the cancer is limited to one part of the lung.:.

Lung cancer surgery of this type is the most common. ("Types of Surgery for Lung Cancer | Cancer Research UK," n.d.)

Segmentectomy or wedge resection:

These are two types of lobectomy operations that remove a portion of the lobe. If your surgeon believes that removing a complete lobe will prevent your lung from functioning properly, he or she may pick either of these options.. ("Surgery for Lung Cancer (Thoracotomy): Benefits and Risks," n.d.)

Sleeve resection: A lung tumor in a lobe of the lung and a section of the main bronchus were removed during surgery (airway). The bronchus is reunited at its ends, and any residual lobes are reattached. The purpose of this surgery is to save a section of the lung. Sleeve lobectomy is another term for this procedure.. ("Definition of Sleeve Resection - NCI Dictionary of Cancer Terms - National Cancer Institute," n.d.).

Pneumonectomy :

The cancerous lung is removed by your surgeon. If your tumor is close to the middle of your chest or if a lobectomy isn't enough to remove it, you may need this procedure. ("Surgery for Lung Cancer (Thoracotomy): Benefits and Risks," n.d.).

Open surgery:

A cut is made around the side of your chest by your surgeon. This is referred to as a thoracotomy. It's not uncommon for the cut to be only a few centimeters long. It can also be longer, extending from behind the nipple to your back, just below the shoulder blade. ("Types of Surgery for Lung Cancer | Cancer Research UK," n.d.).

*Laser therapy:*

*This treatment can burn away little tumors in your airway linings or larger tumors that are restricting your airways. Before the operation, your doctor will usually administer general anesthetic. They insert a bronchoscope down your neck and place it adjacent to your lung tumor after you're asleep. The tumor is then destroyed using a laser on the device's end. It's possible that you'll need laser therapy more than once to achieve the optimum outcomes.*

*Targeted Therapy:*

*Targeted therapy is a term used to describe a treatment for individuals who have anomalies in their tumors that can be detected via biomarker testing.*

*Biomarker testing examines the tumor's DNA for alterations. Mutations, additions, deletions, and rearrangements in the DNA are examples of these changes. Some lung cancer medications can specifically target these alterations. Because they focus on what is wrong with the cancer cell rather than harming normal, healthy cells, these lung cancer treatments frequently have fewer side effects . These treatments are directed at specific targets on or within tumor cells. Targeted therapy for lung cancer are not available to everyone. A unique test of your tumor called molecular testing or biomarker testing may be ordered by your doctor. Discuss your testing options and treatment alternatives with your doctor. Chemotherapy and targeted therapy medications function in distinct ways... ("Targeted Therapies for Lung Cancer | American Lung Association," n.d.)*

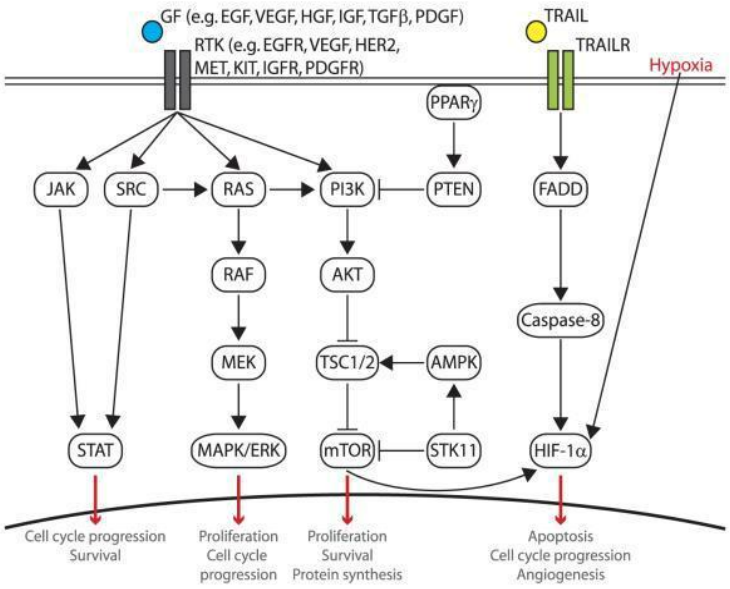


*FIGURE 2 Signaling pathways and their targeted therapies in NSCLC.*

Lung cancer development has been linked to abnormal signaling that results in the activation of growth stimulatory pathways or the blockage of growth inhibitory pathways.

Multiple signaling pathways are up-regulated when RTKs are activated by ligand binding, including the RAS/RAF/MEK pathway, the PI3K/AKT/mTOR system, and the STAT pathway. GF stands for growth factor. (Larsen et al., 2011)

## 3.8.4 Immunotherapy:

Many kinds of cancer, including lung cancer, are treated using immunotherapy. Its purpose is straightforward: to train your immune system to recognize cancer cells and fight them. Chemotherapy and radiation therapy, for example, assault lung cancer cells in methods that can harm both diseased and healthy cells. Immunotherapy, on the other hand, aids your body's natural defenses in fighting cancer, making it a potentially more effective treatment choice, with the potential to control the disease for years. Patients who have been diagnosed with lung cancer commonly ask us if this new medication is the "magic pill" they've read about or heard about, and if it will work for them. We tell them that immunotherapy has been proved to change some patients' aggressive cancers into manageable diseases, but it does not work for everyone.

This is due to the fact that lung tumors differ from person to person. The best treatment for a patient is determined by the kind, stage, molecular characteristics, and aggressiveness of their lung cancer, as well as whether or not the disease has spread to other parts of the body. ("Immunotherapy for Lung Cancer: Unleashing the Power of the Immune System | CTCA," n.d.). The term "immunotherapeutic" refers to a wide range of treatments aimed at causing tumor cells to be destroyed by the immune system. To boost the immune response against cancer, researchers have used therapeutic vaccines, immunomodulators, autologous cellular therapies, and monoclonal antibodies that target checkpoint inhibitor signals on activated T cells and/or cancer cells. Because immunotherapy has historically had minimal efficacy in lung cancer, it is sometimes considered that lung cancer is nonimmunogenic. (Holt, Podack, & Raez, 2011). Immunotherapy helps some people with lung cancer, but it doesn't help everyone.

This is due to the immune system's inability to recognize cancer cells that have certain genetic abnormalities. People with mutations in the epidermal growth factor receptor

(EGFR) or anaplastic lymphoma kinase (ALK), for example, do not respond well to immunotherapies . ("Immunotherapy for Lung Cancer - Roy Castle Lung Cancer Foundation," n.d.). Immunotherapies for lung cancer, such as checkpoint inhibitors, therapeutic vaccinations, and adoptive cell treatment, are still being studied by scientists. They're also experimenting with other combinations of these medications to see whether they can help. In advanced non-small-cell lung cancer, four immunotherapy medicines have been licensed for usage. All of these drugs are checkpoint inhibitors:

Atezolizumab (Tecentriq)
Durvalumab (Imfinzi)
Nivolumab (Opdivo)
Pembrolizumab (Keytruda)

Immune checkpoints are designed to keep your body's natural defenses from harming vital tissues. The medications prevent your body from fighting the tumor by blocking proteins (PD-1, PD-L1). However, immunotherapy does not function for all forms of metastatic NSCLC, and it is not appropriate for all patients.

### 3.8.4 Immunotherapy as First Treatment

Pembrolizumab is more likely than other approved treatments to respond to lung cancers with high levels of the protein PD-L1. PD-L1 levels are extremely high in about a third of late-stage NSCLC patients. ("Will Immunotherapy Help Metastatic Lung Cancer?," n.d.).

## 3.8.5 How is immunotherapy given?

Immunotherapies are injected into a vein in your arm via a drip. A long plastic tube placed into a vein in your chest could also be used to distribute it. A port-a-catheter or a power-port is what this is called. The frequency of treatments will vary depending on the sort of immunotherapy you're receiving. Nivolumab, for example, is given every two weeks, while Pembrolizumab is given every three weeks. Each treatment session lasts around 90 minutes.. ("Immunotherapy for Lung Cancer - Roy Castle Lung Cancer Foundation," n.d.).

Drugs that inhibit the EGFR gene have been shown to reduce or stop the progression of lung cancer. If the EGFR has particular mutations, this may be more likely. Drugs for lung cancer patients with mutations in the ALK and ROS genes are also available. Angiogenesis inhibitors can also be used to treat some lung tumors. ("Understanding Targeted Therapy | Cancer.Net," n.d.).

## 3.9 Immunosuppression:

Immunosuppression is defined as the suppression of the immune system and its ability to fight infection. Immunosuppression can be caused by diseases like AIDS or lymphoma, as well as medications like those used to treat cancer. Immunosuppression can also be purposefully caused by medicines, such as in the case of bone marrow or other organ transplantation, to prevent rejection. ("Medical Definition of Immunosuppression," n.d.). Many people who get organ transplants are given drugs to suppress their immune systems so that the organ is not rejected by the body. These "immunosuppressive" medications impair the immune system's ability to detect and destroy cancer cells, as well as combat cancer-causing infections. HIV infection impairs the immune system and raises the risk of cancer.

Transplant recipients have an elevated risk of a variety of malignancies, according to research. Infectious pathogens can cause some of these tumors, but not all of them. Non-Hodgkin lymphoma (NHL) and malignancies of the lung, kidney, and liver are the four most common cancers among transplant patients, and they occur more frequently in these people than in the overall population. NHL is caused by the Epstein-Barr virus (EBV), whereas liver cancer is caused by chronic hepatitis B (HBV) and hepatitis C (HCV) virus infection. Cancers of the lungs and kidneys are not known to be linked to infection. ("Risk Factors: Immunosuppression - National Cancer Institute," n.d.).

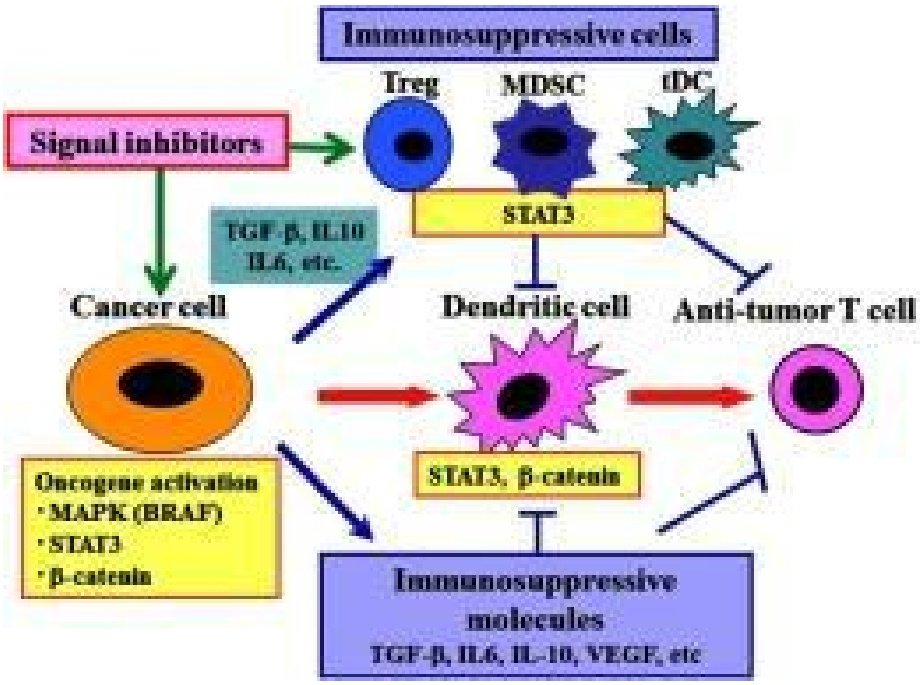


*Figure 3: Reversal of cancer-induced immunosuppression by targeting both cancer cells and immune cells using molecular targeted drugs.*
*("Reversal of Cancer-Induced Immunosuppression by Targeting Both Cancer... | Download Scientific Diagram," n.d.)*

*Immunosuppression can be caused by the direct impact of virus replication on lymphocyte functioning. As in measles, all lymphocyte classes can be affected, or the effect can be restricted to a single subtype, as in human T cell-lymphotropic virus type III. Second, immunosuppression can be influenced by viral or host-derived soluble compounds produced by infected cells. A third pathway is triggered by viral infection of macrophages, which alters their function in both natural and acquired immunity. Finally, immunosuppression can occur when a virus causes an imbalance in immune control, resulting in suppressor cell over activity. Understanding the processes by which viruses produce immunosuppression could aid in the development of treatments to reverse the effect. (Rouse & Horohov, 1986)*

In most circumstances, the immune system recognizes and removes aberrant cells, such as tumor cells. Natural killer (NK) cells, natural killer T (NKT) cells, and gamma delta T cells are immune cells that serve as the first line of defense against tumor cells, causing direct cytotoxicity and secreting large amounts of IFN-gamma to promote tumor cell death. The tumoricidal M1 phenotype, which is associated with phagocytosis and the release of pro-inflammatory cytokines that promote tumor cell elimination, is tilted toward macrophage polarization under these conditions.

The adaptive immune response is also activated, which helps to control tumor cell development. Dendritic cells acquire antigens from tumor cells and transfer them to naive CD8+ and CD4+ T cells, priming T cell activation with co-stimulatory signaling molecules and released cytokines. Activated CD8+ T cells, like NK cells, have a direct lethal effect on tumor cells and, like Th1 cells, release high amounts of IFN-gamma to promote tumor rejection. Despite the activity of these cell types, certain tumor cells can avoid this process over time, resulting in tumor growth. The tumor microenvironment (TME) is critical in this process. The tumor microenvironment (TME) is made up of fibroblasts, endothelial cells, and infiltrating leukocytes, all of which functions can be exploited or modified to promote tumor progression. Tumor growth can be fueled by a number of factors, including tumor cell-mediated immune cell evasion or immunosuppression, CD8+ T cell or NK cell exhaustion, the recruitment and expansion of immunosuppressive immune cell types, the presence of high levels of immunosuppressive cytokines and other immunosuppressive factors that impair immune cell functions, and/or a shift in polarization toward a tympanic state.

Type II polarization is associated with the release of Th2-like cytokines, M2 macrophage polarization, and the presence of type II NKT cells and N2 type neutrophils in the TME, all of which block the CD8+ T cell/NKT type I/Th1/M1 anti-tumor immune response. The properties of exhausted CD8+ T cells and NK cells, as well as the key mechanisms by which tumor cells, tumor-derived exosomes (TEXs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated M2 macrophages (TAMs) mediate immunosuppression in the TME, are depicted in various sections of this poster.

Many of the chemicals implicated in the immunosuppressive pathways discussed here are being investigated as potential cancer immunotherapy targets. ("Mechanisms of Immunosuppression in the Tumor Microenvironment," n.d.)

NSCLC, like other tumors, can create an immunosuppressive tumor microenvironment that promotes tumor growth. (Cho, 2017). Treg cells, which have high amounts of CTLA-4 on their surface and impede T-cell proliferation directly, have been detected in large numbers in NSCLC tumors. However, higher percentages of CD4(+)CD25(+) T cells were observed in non-small cell lung cancer tumor-infiltrating lymphocytes and ovarian cancer tumor-associated lymphocytes.. These CD4(+)CD25(+) T cells also secreted transforming growth factor-beta, which is consistent with the regulatory T cell phenotype. CD8(+) T cells exhibit low CD25 levels, despite the extensive expression of lymphocyte activation markers in tumor-associated T-cell populations. In order to see if CD25 expression on CD8 cells might be restored, researchers utilized anti-CD3 and anti-CD28 monoclonal antibodies to boost tumor-associated T cells.. (Santin et al., 2001). PD-1 expression was also found to be higher in tumor-infiltrating CD8+ T cells in NSCLC, which has been associated to immunological dysfunction. (Y. Zhang, Huang, Gong, Qin, & Shen, 2010). PD-L1 expression has also been found to be upregulated in NSCLC tumor cells. (Chen, Mu, & Huang, 2012). Furthermore, antigen-presentation system dysfunction appears to impede immunologic activity in the tumor microenvironment, since lung tumor cells can down-regulate MHC class I/tumor antigen expression on the surface, allowing them to escape the immune system. (Korkolopouloul, Kaklamanis2, Pezzella', Harris3, & Gatter', 1996)
. Lung tumor cells may emit immunosuppressive cytokines like IL-10 and TGF-. . (Domagala-Kulawik, Osinska, & Hoser, 2014).

Targeted antibodies associated with immunosuppression of lung cancer :

1.Amivantamab (Rybrevant™): Authorized for select categories of individuals with non-small cell lung cancer, this bispecific antibody targets tumor cells' EGFR and MET receptors (NSCLC). ("Immunotherapy for Lung Cancer - Cancer Research Institute (CRI)," n.d.)

2,Bevacizumab (Avastin®): Bevacizumab is an antibody that targets vascular endothelial growth factor. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody with human framework and complementarity-determining regions from mice .Bevacizumab has a molecular weight of about

149kDa. Bevacizumab is made in a mammalian cell expression system

(Chinese Hamster Ovary). ("Avastin (Bevacizumab): Uses, Dosage, Side Effects, Interactions, Warning," n.d.)

3.Necitumumab (Portrazza®): EGFR-targeting monoclonal antibody approved for subgroups of patients with advanced non-small cell lung cancer (NSCLC), including as a first-line therapy. ("Immunotherapy for Lung Cancer - Cancer Research Institute (CRI)," n.d.)

Ramucirumab (Cyramza®): Non-small cell lung cancer (NSCLC) that has spread to other regions of the body is treated with this drug and has gotten worse during or after another type of chemotherapy, docetaxel is used. CYRAMZA should not be given to people who have cancers with particular faulty genes unless they have already been treated with a drug that targets those abnormalities and their cancer worsened during therapy. ("CYRAMZA® (Ramucirumab) | VEGFR2 Inhibitor," n.d.).

## 3.9.1 Checkpoint inhibitors to treat lung cancer :

Immune checkpoints are activated when the immune system's T cells attach to a protein on a healthy cell or a malignant cell, according to the National Cancer Institute (NCI) Trusted Source. The immune system ignores the cell in this situation. As a result, cancer cells that connect to T cells with a protein are able to thrive and spread unabated.Cancer cells can't bind to T cells because of checkpoint inhibitors. As a result, the immune system will be able to locate and attack cancer cells. According to several studies, persons with NSCLC who use checkpoint inhibitors have statistically significant benefits. ("Checkpoint Inhibitors for Lung Cancer: What Are They?," n.d.).

Immune checkpoint inhibitors (ICIs), notably those targeting the PD-1/PD-L1 axis, have improved lung cancer patient outcomes significantly. Nivolumab and Pembrolizumab were approved by the US Food and Drug Administration as PD-1 blocking antibodies, whereas Atezolizumab, Avelumab, and Durvalumab were approved as PD-L1 blocking antibodies.. (Y. Yang, Yu, & Lu, 2020).

Another protein that a cancer cell may exploit to avoid detection by the immune system is CTLA-4. There is just one CTLA-4 inhibitor for NSCLC, according to the ACSTrusted Source. It's known as ipilimumab (Yervoy). This drug will be administered intravenously every six weeks. A doctor may prescribe Yervoy with or without chemotherapy, as well as Opdivo (for PD-1). They will not, however, give this drug on its own. ("Checkpoint Inhibitors for Lung Cancer: What Are They?," n.d.). Inhibition of immune checkpoints has recently emerged as the

most interesting and promising anticancer therapy option. These drugs have already cemented their place in the treatment of lung cancer. Immune checkpoint inhibition, on the other hand, is still in its infancy, and a slew of clinical trials are presently underway to figure out how to improve outcomes, anticipate responses, and overcome resistance. The findings of these studies will aid in determining how best to include these active medicines into our NSCLC therapy paradigms. (Seetharamu, Budman, & Sullivan, 2016).

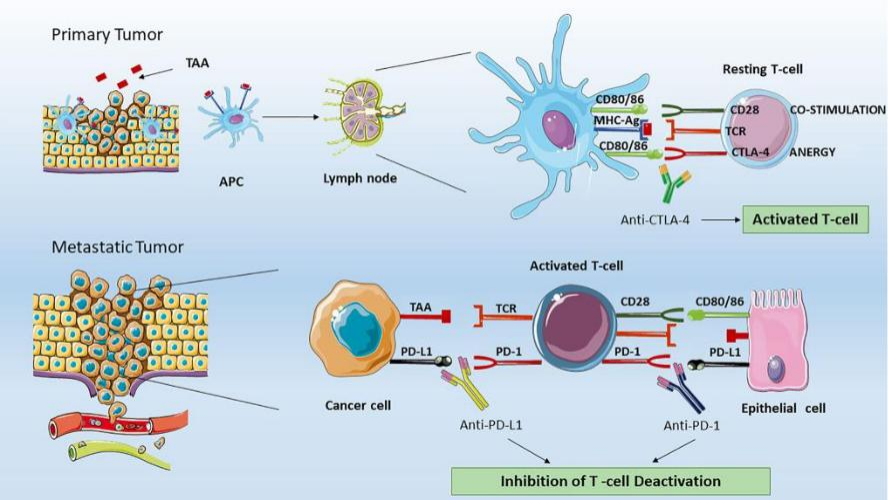


Figure 4: Mechanism of checkpoint inhibitors in oncology. (Franzin et al., 2020)

Immune checkpoint inhibitors, specifically PD-1-directed medicines, have revolutionized the treatment of non-small cell lung cancer (NSCLC) and are currently being tested in small cell lung cancer patients. After showing a survival benefit in patients with recurrent NSCLC in early studies, these medicines have now shown a survival advantage in some early-stage NSCLC patients. These drugs are still being studied in conjunction with chemotherapy and other checkpoint inhibitors. According to new research, combining these drugs with chemotherapy may improve survival when compared to chemotherapy alone. In individuals with recurrent small cell lung cancer, promising effects have also been found. The role of these medicines in the treatment of patients with small cell lung cancer is still being researched. Since the use of frontline Pembrolizumab in patients with advanced NSCLC is predicated on tumor PD-L1 expression, tumor PD-L1 testing has become standard of care. Other biomarkers are being studied to determine which patients are most likely to benefit from these treatments. Immune checkpoint inhibitors include a variety of negative side effects. Understanding the side effects and how to manage them is crucial when using immune checkpoint inhibitors to treat patients with lung cancer. (Zimmermann, Peters, Owinokoko, & Gadgeel, 2018). ICIs have proven to be

a game-changer in the treatment of cancers of many types, including lung cancer. We'd want to go through the mechanism of checkpoint inhibitors in further detail right now. Cancer cells are recognized and destroyed by the immune system in most cases. When immunity is insufficient, tumor cells adapt to the immune system and resist removal, resulting in uncontrolled tumor cell growth. Innate and adaptive components exist in the human immune system. The innate immune system relies on natural killer cells to function. T lymphocytes (CD4 and CD8) are crucial components of the adaptive immune system. Tumor cells employ many of sophisticated strategies for avoiding immune system detection and destruction. To avoid detection by the immune system, tumor cells predominantly use T-cell inhibitory pathways such as cytotoxic T-lymphocyte antigen 4 (CTLA -4), programmed death 1 (PD1), lymphocyte antigen gene 3 (LAG-3), and suppression of NK cell activity. ICIs work to reverse tumor cells' immune-suppressive processes by targeting PD1, PDL1, and CTLA-4. There are now two PD-1 inhibitors (Pembrolizumab and Nivolumab), one PDL1 inhibitor (Atezolizumab), and one CTLA-4 inhibitor (ipilimumab). (Pennock & Chow, 2015).



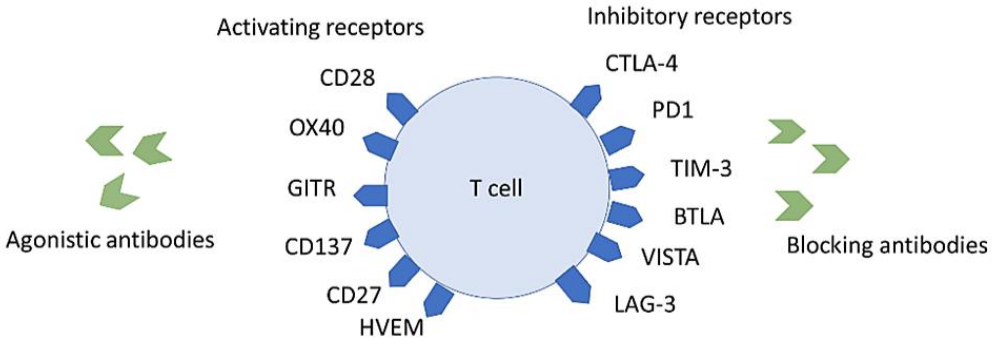


*Figure 5* : *Mechanism of immune suppression and immune checkpoint inhibitors.* (Maung, Ergin, Javed, Inga, & Khan, 2020).

*Immune checkpoint inhibitors (ICIs) are changing how advanced cancer patients are treated.. By stimulating T cells, the widespread use of these antibodies for diverse cancers results in an exciting anti-tumor immune response. Despite the fact that these immunostimulatory medications have a hopeful clinical benefit, a large percentage of patients still have a limited or no response for unknown reasons, sometimes at the expense of unpleasant side effects. MDSCs (myeloid-derived suppressor cells) are an immature myeloid cell that helps immunotherapy work. These cells not only suppress T cells directly, but also form an immunosuppressive network inside the tumor microenvironment, lowering anti-tumor responses. The interaction of MDSCs with immune/non-immune cells results in a number of positive feedback loops that have a deleterious influence on the tumor microenvironment. As a result, immunosuppressive cells are recruited, immunological checkpoints are up regulated, angiogenesis and hypoxia are stimulated, all of which contribute to ICI resistance. Targeting MDSCs might be a way to get around the problem. (Hou, Hou, Huang, Lei, & Chen, 2020).*

# Chapter 4

## 4.1 Myeloid-derived suppressor cell

MDSCs (myeloid-derived suppressor cells) are a diverse population of cells that are produced in a wide range of pathologic situations, from cancer to obesity. These cells show a pathogenic state of monocyte activity and immaturity in neutrophils. MDSCs have a unique set of genetic and metabolic characteristics, and may be recognized by specific surface molecules, according to new research. The capacity of these cells to block T cell function is one of their most notable characteristics, and this ability contributes to the pathogenesis of different disorders. (Veglia, Perego, & Gabrilovich, 2018). Immune suppression distinguishes MDSCs from other myeloid cell types since they are physically and phenotypically similar to neutrophils and monocytes. In recent years, the endoplasmic reticulum stress response has emerged as a key regulator of MDSC pathology activation. (Cubillos-Ruiz, Mohamed, & Rodriguez, 2017). Controlling the formation and harmful activity of immunosuppressive myeloid cells in cancer patients appears to be a key condition for cancer immunotherapies to be successful . (Cubillos-Ruiz et al., 2017).

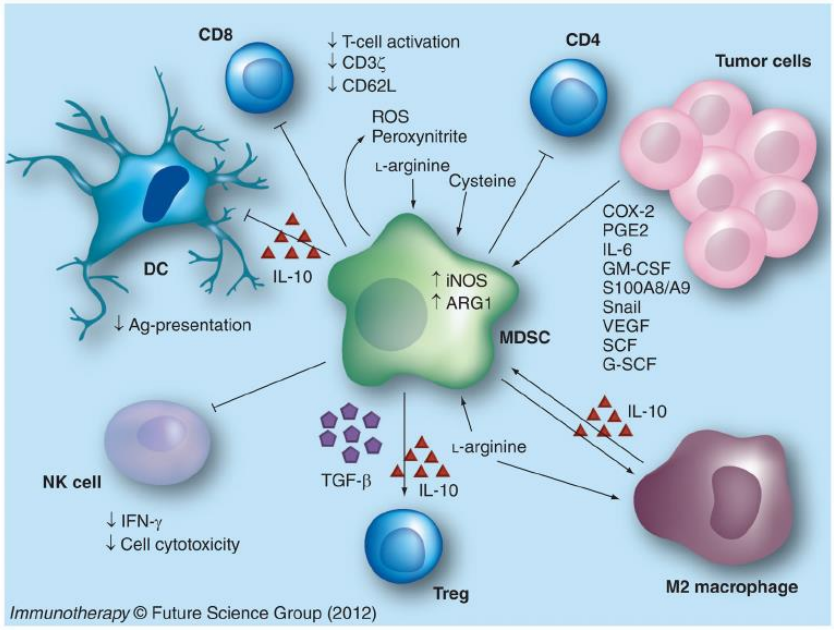


Figure 6 : Myeloid-derived suppressor cell accumulation in tumors suppresses antitumor activity. (K. Wang et al., 2019).

MDSCs are a type of immature myeloid cell that has a variety of functions in the antitumor immune response. MDSCs are hypothesized to be important in tumor-escape processes. MDSCs can cause tolerance to a variety of immune responses mediated by effector T cells and natural killer cells (NK cells).. M-MDSCs and G-MDSCs each have different ways of inhibiting effector

T cells. (Gabrilovich & Nagaraj, 2009a).

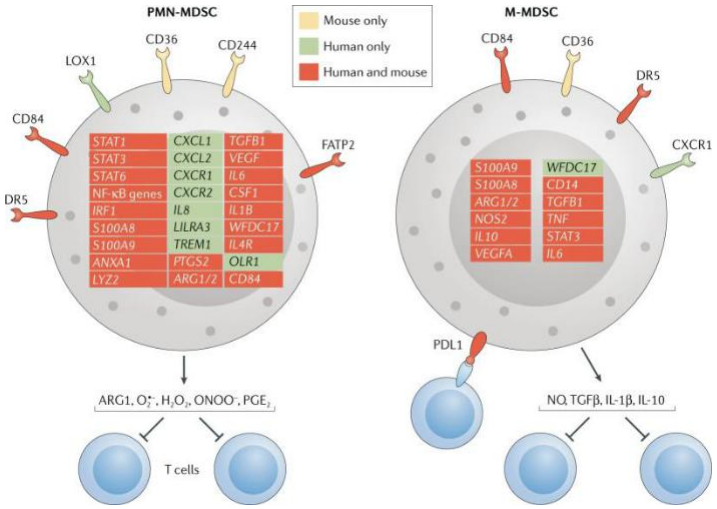


Figure 7: Distinguishing MDSCs from classical neutrophils and monocytes. ("Fig. 1: Distinguishing MDSCs from Classical Neutrophils and Monocytes. | Nature Reviews Immunology," n.d.)

MDSCs are known for suppressing immune responses mediated by T cells, B cells, and natural killer (NK) cells. M-MDSCs and PMN-MDSCs decrease immune responses by up-regulating signal transducer and activator of transcription 3 (STAT3) expression, producing ER stress, activating arginase 1, and expressing S100A8/A9. They also have distinct features that could affect their potential to control immunological responses in some ways.

PMN-MDSCs, for example, prefer to suppress the immune system by producing reactive oxygen species (ROS), peroxynitrite, arginase 1, and prostaglandin E2 (PGE2), whereas M-MDSCs prefer to suppress the immune system by producing nitric oxide (NO), immunosuppressive cytokines like IL-10 and TGF, and the expression of immune regulatory molecules like PD1. .(Gabrilovich, 2017)

MDSCs (myeloid-derived suppressor cells) are a prominent component of the immunosuppressive tumor microenvironment, according to recent research.. (Gabrilovich, Ostrand-Rosenberg, & Bronte, 2012a)(Umansky, Blattner, Gebhardt, & Utikal, 2016). They are a diverse population of immature myeloid cells that migrate from the bone marrow to the peripheral circulation and cancer patients' tumor lesions. Based on phenotypically and morphological characteristics, two MDSC subsets have been defined: CD11b+HLA-DR (human leukocyte antigen-D-related)/lowCD14+CD15 monocytic (M) and CD11b+HLA-DR/lowCD14+CD15 polymorphonuclear (PMN) MDSCs .(Bronte et al., 2016). Although M-MDSCs have a well-established phenotype, CD11b+HLA-DR/lowCD14CD15+ cells have been classified as granulocytes/neutrophils as well. (Brandau, Moses, & Lang, 2013)

## 4.2 Mechanisms of accumulation and activation of MDSCs in cancer:

In addition to the overlapping pathways that regulate both immature myeloid cell proliferation and suppressive function acquisition, separate mechanisms are expected to mediate these two effects. We previously proposed that two sets of signals are required for the accumulation of genuine MDSCs. (Groth et al., 2019). The first of these signals, granulocyte-macrophage CSF (GM-CSF), macrophage CSF (M-CSF), granulocyte CSF (G-CSF), and other yet-to-be-identified signals, promote the proliferation of immature myeloid cells. (Ortiz, Lu, Ramachandran, & Gabrilovich, 2014b) (Ortiz et al., 2015).

Another major regulator of MDSC function and differentiation has been identified as HIF-1. HIF-1 enhances MDSC suppressive function by up regulating iNOS and arginase and down regulating NADPH oxidase complex components at the tumor site, allowing MDSCs to differentiate into tumor-associated macrophages (TAMs). (Corzo et al., 2010). HIF-1 linked to the promoter of programmed cell death ligand-1 (PD-L1) in myeloid cells, according to a recent study. (Noman et al., 2014). More research is needed to determine whether this mechanism is a function of MDSCs or a marker of their transition to TAMs. MDSC differentiation has been demonstrated to be hampered by the canonical Wnt pathway. ,

while mature DC differentiation has been shown to be encouraged.. (H. Liu et al., 2013) (Capietto et al., 2013). In a unique pathway analysis, MDSCs in the periphery and at the tumor site were compared to normal immature myeloid cells, revealing the number of components enriched in MDSCs under diverse physiological conditions.. It's the first step toward fully comprehending how MDSC function is controlled. (Aliper, Frieden-Korovkina, Buzdin, Roumiantsev, & Zhavoronkov, 2014).

MDSCs are capable of suppressing both adaptive and innate immunological responses. Its immunosuppressive mechanisms have been identified, particularly in malignant progression, as it plays a significant role in tumor immune surveillance evasion.

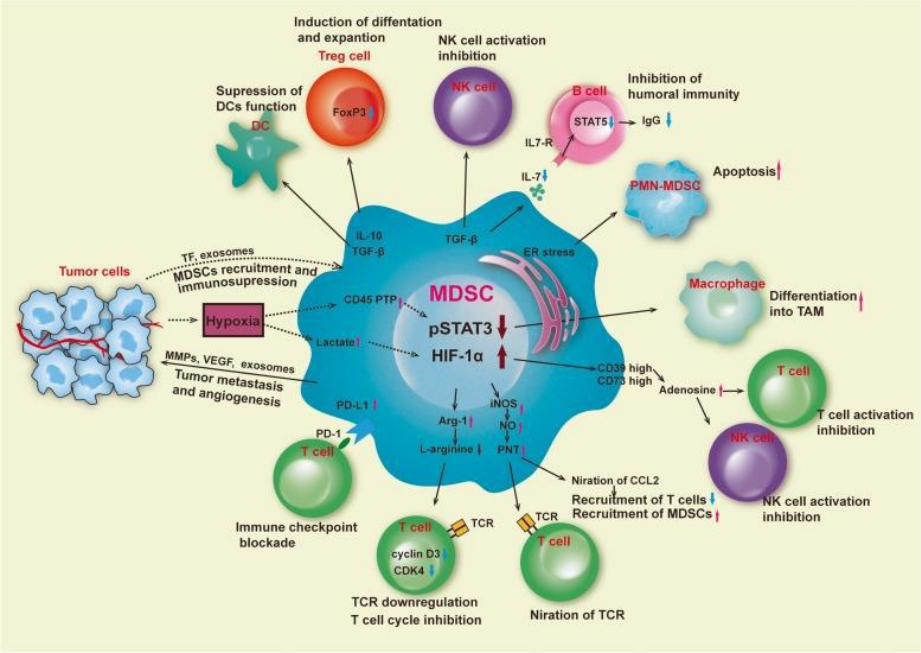


Figure 8 : Immunosuppressive activities of MDSCs in the tumor microenvironment.

## 4.3 MDSCs and Lung Cancer: What Role Do They Play?

In patients with lung cancer, MDSCs may provide prognostic and predictive information.

The evaluation of multiple cell subsets in patients' peripheral blood is required when using MDSCs as lung cancer biomarkers. The amount and frequency of CD14+HLA-DR/low MDSCs in the peripheral blood were significantly greater in SCLC patients than in controls, according to

Tian et al., and the frequency of MDSCs was linked to tumor stage. (Tian et al., 2015). According to the frequency and number of MDSCs, it was hypothesized that immunoglobulin-like transcript 3 (ILT3), which is expressed by MDSCs, might identify lung cancer patients from

*healthy controls. (de Goeje et al., 2015). MDSCs, together with Tregs and TAMs, are the most important immunosuppressive cells in the TME of lung cancer patients. . (Milette, Fiset, Walsh, Spicer, & Quail, 2019). The ratio of CD11b+CD14+ cells in NSCLC patients was significantly higher than in healthy participants, which was connected to poor performance and treatment response. (Feng et al., 2012). According to a study by Zhang et al, a higher frequency of B7H3+ MDSCs was linked to a shorter recurrence-free survival in NSCLC patients. (G. Zhang et al., 2015). The medication appears to affect MDSC levels in lung cancer patients, based on clinical experience. Wang et al. discovered that 9 partial remission instances had MDSC percentages that greatly declined, 3 stable disease cases were invariable, and 8 progressive disease cases had MDSC percentages that significantly increased in 20 patients with advanced NSCLC who received systemic chemotherapy. (S. Wang et al., 2014b). MDSCs (CD11b(+)CD14(-)CD33(+) cells) and lymphocyte subsets were examined in the PBMCs of 94 patients with non-small cell lung cancer (NSCLC) who were treated naively and 30 healthy people.*

*In patients with advanced NSCLC who were undergoing systemic chemotherapy, changes in the proportion of MDSCs were also discovered. Finally, MDSCs were co-cultured with CD8(+) cells to see how they influenced T lymphocyte IFN secretion. (S. Wang et al., 2014b). When compared to nonbevacizumab-based regimens, The percentage of granulocytic MDSCs was drastically reduced after three cycles of Bevacizumab-containing regimens . (Koinis et al., 2016). TNF-, CCL-2, and CCL -4 levels in the blood, along with increased NO generation in circulating MDSCs, may be an early signal of incomplete radiofrequency ablation and, as a result, a probable tumor return in NSCLC. (Schneider et al., 2015). The connection between MDSCs and lung cancer is frequently studied using animal models. B7H3+ MDSCs were only observed in the tumor microenvironment in mouse models of lung cancer, and their frequency increased as tumors progressed . (G. Zhang et al., 2015). Acute exposure to single-walled carbon nanotubes (SWCNT) increased the recruitment and accumulation of lung-associated MDSCs as well as MDSC-derived TGF-, resulting in an increase in lung tumor burden. (Shvedova et al., 2015). We all know that smoking is the leading cause of lung cancer. Smoking's impact on MDSC function has gotten little consideration. Ortiz et al. discovered that when mice were exposed to cigarette smoke (CS) alone, cells with the usual MDSC phenotype grew in many organs, but that these cells lacked immunosuppressive activity.*

*Gr-1+CD11b+ cells accumulated in the spleen and lung after CS was coupled with a single dose of urethane, and they exhibited a powerful immunosuppressive impact. (Marvel & Gabrilovich, 2015).*

*The presence of MDSCs was found to be inversely associated to treatment response and positively connected to shorter survival in lung cancer patients. (Feng et al., 2012) (C. Y. Liu et al., 2010). MDSCs suppress T-cells in lung cancer by direct interaction and methods involving a variety of mediators and pathways, including iNOS, ARG1, TGF-, IL-10, and Treg induction, according to several studies. (R. Yang et al., 2006)*

MDSCs attracts CC chemokine ligand (CCL) 2, CXC chemokine ligand (CXCL) 12, and CXCL5 to the tumor sites (Sawanobori et al., 2008). The tumor microenvironment induces MDSCs to develop immunosuppressive features, which are mediated by the transcription factors STAT1, STAT3, STAT6, and nuclear factor KB.. (Gabrilovich & Nagaraj, 2009b). .

COX-2 is thought to play a role in MDSC regulation by producing PGE2 and ARG1, according to data from animal lung cancer models . (Rodriguez et al., 2005). ARG1, an epithelial-mesenchymal transition activating transcription factor, boosts MDSCs in the mouse lung tumor microenvironment, increasing tumor formation and metastasis by increasing ARG1 intracellular expression. Targeting MDSCs with antibodies increased anticancer activity in various mouse lung cancer models by increasing effector and memory T-cell responses, as well as NK cell and antigen-presenting cell activity. (Sawant et al., 2013) (Srivastava et al., 2012).

Overall, the development of new therapeutic medicines to limit MDSC activity in human lung cancer may aid our experiences of their biological significance in the tumor microenvironment.

## 4.4 MDSCs Are a Potential Target for Therapeutic Development in Lung Cancer

MDSCs have been found to be regulated by a number of elements in recent years, along with their development. MDSC regulation is influenced by a variety of signaling pathways and cytokines. The JAK-STAT and NF-B signaling pathways regulate most of the variables, which then influence MDSC formation and activation. All of these parameters interact to form a complicated network control mechanism that controls MDSC formation and function. Tumor suppressor factors must be eradicated before tumor immunotherapy may be implemented successfully. Because MDSCs are the most important tumor suppressor factors, a therapy strategy that targets MDSCs is progressively gaining traction (Figure 9 ). By focusing on the number and function of MDSCs, tumor immunotherapy can be improved significantly. (Ma et al., 2018).

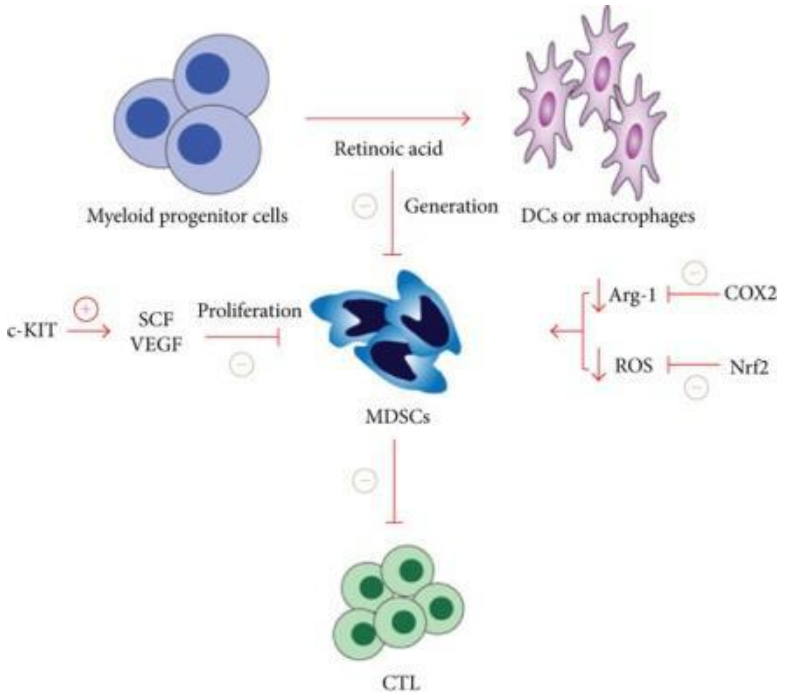


*Figure 9 : Targeting MDSCs in the treatment of lung cancer.*

*Retinoic acid inhibits MDSC differentiation by stimulating myeloid progenitor cell development to dendritic cells or macrophages. The signaling pathway regulated by SCF can be inhibited by c-KIT, which prevents MDSCs from amplification. COX2 inhibition in MDSCs reduces arginine-1 release, Nrf2 helps MDSCs remove ROS, and both COX2 and Nrf2 can restrict MDSC function. MDSCs' immunosuppressive action on effector T cells will be inhibited by the following approaches, which will improve antitumor immunity. Arg-1: arginine-1; Nrf2: nuclear factor erythroid 2 p45-related factor 2; ROS: reactive oxygen species; CTL: cytotoxic lymphocyte. (Ma et al., 2018)*

# Chapter 5

## Discussion

MDSCs, or myeloid-derived suppressor cells, have an impact in malignant transformation and tumor growth via immuno and non-immunosuppressive pathways. (Zahran et al., 2021). MDSCs are thought to be the immune system's main suppressor, preventing both innate and adaptive immunological responses. In comparison to resected tissues and lymph nodes from NSCLC patients . (Pogoda, Pyszniak, Rybojad, & Tabarkiewicz, 2016) . The immunosuppressive activity of MDSCs is mediated by arginases (ARG-1 and ARG-2), nitric oxide (NO), reactive oxygen species (ROS), peroxynitrite, the PD-1/PD-L1 axis, and other cytokines. By promoting their development into mature myeloid cells, eliminating them, reducing their activity, and inhibiting their accumulation, it can be used as a target for lung cancer immunotherapy. (Sheida, Razi, Keshavarz-Fathi, & Rezaei, 2021). Because MDSC enrichment and activation appear to be a common feature of cancer, targeting these cells could be used to treat a variety of cancers. To improve the efficacy of lung cancer medicines, it is crucial to combine the neutralization of various MDSC functions with existing therapeutic techniques. Despite promising preclinical evidence, further clinical research is needed to show the synergistic effects of blocking MDSC mobilization and functions in combination with existing immunotherapies. (Groth et al., 2018). Indeed, a number of studies have recently established that stimulation of MDSC suppresses natural killer (NK) and T cells in a number of diseases defined by persistent inflammation. Initially, this behavior was seen in tumor-bearing hosts as one of the tumor's methods for evading antitumor immunity. (Rabinovich, Gabrilovich, & Sotomayor, 2007). These findings, however, were eventually confirmed in a variety of chronic inflammatory non-malignant diseases. (Serafini, 2013) (Gabrilovich & Nagaraj, 2009c).

# Chapter 6

## Conclusion:

To elude the immune system and progress, tumor cells employ a variety of strategies. One of the primary processes is the creation of immunosuppressive time, in which MDSC plays an important role. Although there is growing evidence that MDSC can have a role in the development of IC and can be used to predict the efficacy of immune checkpoint inhibitors, there are still unknown mechanisms and interactions that need to be investigated further in this area. There's a lot of it. Changing the function and biology of MDSC has been demonstrated to have positive effects in preclinical and clinical trials. These findings imply that targeting MDSC could be a promising immunotherapeutic strategy that can be used in conjunction with other immunotherapeutic techniques like vaccination and immune checkpoint suppression. Using these strategies to treat IC could lead to more breakthroughs and overcome the limits of present treatments. However, more research is needed to back up these findings before they may be used in therapeutic settings. To begin with, in contrast to other immunosuppressive cells (e.g., Treg cells and TAMs), The molecular phenotype of MDSCs is not homogeneous. Second, the findings concerning the correlations between various MDSC subtypes and IC prognosis are inconsistent. For example, some studies claim that high PMN-MDSC counts indicate a bad prognosis (P1 et al., 2015) (H. R. Kim et al., 2019), whereas others claim that M-MDSCs have a stronger predictive value than PMN-MDSCs. (Sharma, Dubinett, & Salgia, 2012) (Vetsika et al., 2014) . Third, MDSC is found in both peripheral blood and tumor tissue, but extrapolating MDSC distribution in peripheral blood to tumor tissue distribution is difficult, and the functional level is uncertain. As a result, for IC patients, more research into the MDSC mechanism in tumor tissue is required. Finally, the pharmacological results of targeted MDSC treatment remain uncertain. The goal is to employ a comprehensive epidemiological model to completely comprehend the relationship between MDSC indicators and patient outcomes, as well as to reduce the number of potentially alterable factors that contribute to MDSC accumulation in IC patients. A stronger foundation for targeting MDSC alone or in combination with chemotherapeutic and/or immunotherapy regimens is provided by larger institutional trials.

## Future Direction

Conduct extensive research on studies focusing on : Differentiation of MDSCS from precursor and relationship with another myeloid cells in the tumor microenvironment .Fate mapping studies and genome-wide analysis related to MDSCS .

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