ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 12, 2022

Online - 2455-3891
Print - 0974-2441

Review Article

# IMMUNOTHERAPY AS NOVEL TREATMENT OF LUNG CANCER: A SYSTEMATIC REVIEW

**CHOWDHURY MOBASWAR HOSSAIN[1]*, SUBARNAREKHA MAITRA[2], NAZMUN LYLE[3], MEETA GERA[4], SOUVIK PAUL[2], DISHARI DUTTA[5]**

**[1]Department of Pharmaceutical Technology, Maulana Abul Kalam Azad University of Technology, Kalyani, West Bengal, India. [2]Department of Pharmacology, Guru Nanak Institute of Pharmaceutical Science and Technology, Panihati, West Bengal, India. [3]International Institute of Innovation and Technology, Kolkata, West Bengal, India. [4]Department of Biochemical Engineering and Biotechnology, Indian Institute of Technology, New Delhi, India. [5]Bengal School of Technology-A Colleges of Pharmacy, Hooghly, West Bengal, India. Email: drcmhossain@gmail.com**

*Received: 14 August 2022, Revised and Accepted: 23 September 2022*

**ABSTRACT**

Lung cancer is the top cause of cancer-related fatalities in both men and women around the world, and the second most commonly diagnosed cancer in both men and women. For many patients, traditional chemotherapy (CT) fails to give long-term benefit. Moreover, newer medicines targeting activating mutations in EGFR or ALK have shown increased response rates over CT in the minority of patients with these mutations; however, the majority of patients do not have actionable mutations and will not benefit from targeted therapies. In addition, several combinations of chemotherapeutic medicines with the angiogenesis inhibitor bevacizumab have provided only minor additional benefits. However, immunotherapy using checkpoint inhibitors has shown to have a lot of potential in the treatment of advanced non-SCLC (NSCLC) in recent trials. These new medications encourage the host immune system to recognize tumor cells as foreign invaders and halting their growth. They help alleviate immune system suppression, which allows tumor development to be tolerated. In checkpoint immunotherapy, humanized monoclonal antibodies targeting checkpoint signals such as programmed cell death receptor (PD-1) and programmed cell death ligand are employed (PD-L1). The immune system can be triggered to fight the tumor by inhibiting these receptors and signals. Immunotherapy for advanced lung cancer has created a new paradigm of therapeutic options, with increased survival and response rates and a less severe but distinct side profile when compared to CT. The PD-1 inhibitors nivolumab and pembrolizumab, as well as the PD-L1 inhibitor atezolizumab, have been approved by regulatory authorities for the treatment of advanced NSCLC. Hence, the current review article focuses on the role of immunotherapy, newer agents used for checkpoint inhibitors in lung cancer, their epidemiology, risk factors, side-effect profiles, therapeutic indications, and their mechanism of action for the successful treatment of lung cancer.

**Keywords:** Lung cancer, Immunotherapy, Immune checkpoint inhibitors, Non-SCLC, Antigen-specific cancer vaccines, c-MET oncogene.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i12.46133. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

## INTRODUCTION

Lung cancer is a malignant lung tumor that grows uncontrollably in the tissues of the lungs [1]. In spite of significant progress in the overall management of lung cancer, it ranks as a leading cause of death worldwide. It is reported to spread outside the lungs to adjacent tissues and other parts of the body along with brain [2,3]. According to GLOBACON report, lung cancer accounts for more than 1.8 million deaths (18%) per year and 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 [4,5]. Many factors are responsible for lung cancer, but the major causes are smoking including second-hand smoke, exposure to toxins, and hereditary factors. Clinical onset mostly associated with heavy symptomatic burden include cough, severe chest pain, wheezing, noticeable weight loss, and rapid decline of overall health [6] On the basis of histology, lung cancer is categorized into two types: Small cell lung cancer (SCLC) and non-SCLC (NSCLC). About 85% of lung cancer cases are NSCLC, while SCLC accounts for 13–15% [7]. Adenocarcinoma (including BAC) accounts for 32–40%, squamous (SQ) for 25–30%, and large cells for 8–16% [8]. SCLC has few treatment options and a dismal prognosis. There are two forms of SCLC disease: Limited stage and extensive stage. It is the most lethal neuroendocrine tumor because of its high mutational burden, which is characterized by rapid growth and early metastasis; over 70% of new diagnoses proceed to Stage IV.

Treatment of lung cancer has no real progress till date and still becomes a challenge [9]. A greater understanding of the molecular process and progression of cancer may help in the treatment and prevention of lung cancer [10]. Surgery, chemotherapy (CT), radiation therapy, targeted medication therapy, immunotherapy, and a combination of CT and immune therapy are all options for treatment (6). CT is the only palliative, systemic treatment for metastatic tumors [11]. Invention of oncogenic drivers has developed advanced targeted therapies, leading to a breakthrough in cancer treatment [12]. At present, immunotherapy is recognized as a revolution in lung cancer treatment [4]. Because of the long-term efficacy with little adverse effects, immunotherapy becomes well accepted and is likely to develop an effective possible therapy for cancer treatment. Therefore, in the last few decades, it has become an important part of treating different types of cancer [4,9,13]. The basic principle of this treatment is to use the patient's immune system to identify and kill tumors efficiently [14]. Immunotherapy works by stimulating or improving the natural defenses of the immune system which can be able to detect and attack cancer cells efficiently. The in-depth knowledge of the molecular mechanism and the progress of innovative treatments and technologies promote immunotherapy as a promising treatment method for NSCLC as well as SLC [15]. NSCLC and SLC are treated with immunotherapy, especially immune checkpoint inhibitors (ICI), such as inhibitors of programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) [16]. The immune system does not attack normal cells in the body; it does through "checkpoint" proteins which act like keys that regulate in the switch on or off manner to control the immune response. T-cell immunological function is regulated by immune checkpoints, which are inhibitory pathways in the immune system [17]. Checkpoints protect cancer cells from immune system attack. Checkpoint mechanisms, which are designed to protect normal tissues from inflammation-mediated injury and prevent autoimmunity, can be used by cancer cells to elude immune detection. Drugs that inhibit these checkpoints (called checkpoint inhibitors) are effective in lung cancer treatment. T lymphocyte antigen-4 and PD-1 receptors are expressed on the surface of cytotoxic T lymphocytes. NSCLC tumor cells produce PD-L1, which binds to the PD-1 receptor on T cells and protects tumor cells from being killed by the immune system. In immunotherapy, monoclonal antibodies are used for NSCLC that target on T cells or ligands

on the surface of the tumor cells, which, in turn, kill the tumor cells. Monoclonal antibodies such as Pembrolizumab and Nivolumab target PD-1 on T cells, preventing it from activating and adhering to tumors that express PD-L1. This boosts immune activity [18]. Atezolizumab and durvalumab are monoclonal antibodies that target PD-L1-expressing tumor cells and protect them from triggering PD-1 on T cells, preventing T cell suppression. Anti-PD-(L)1 therapy plays an important role in lung cancer immunotherapy, emphasizing the importance of immune evasion mechanisms such as the PD-1/PD-L1 axis, as well as the importance of the tumor immunological microenvironment in lung cancer treatment. Nivolumab, atezolizumab, and pembrolizumab are first-line treatments for advanced NSCLC. They can be used in patients with any histology (pembrolizumab) or non-SQ histology (atezolizumab), as well as in PDL-1 positive individuals in combination with ipilimumab or ipilimumab plus nivolumab. Durvalumab, in combination with platinum-based CT and radiation treatment, has been approved for patients with Stage III NSCLC. These ICI engage the antitumor immune system, resulting in anticancer outcomes in terms of overall response rate, progression-free survival, and overall survival (OS). That is why immunotherapy for lung cancer has become the first-line treatment method [15]. The mesenchymal-epithelial transition (MET) (c-MET) gene is crucial because it is detected in 5–22% of lung cancer patients who are resistant to first-generation epidermal growth factor receptor tyrosine kinase inhibitors (TKI) [19]. The c-MET proto-oncogene, as well as its protein MET (MET; also known as hepatocyte growth factor [HGF] receptor) and a cognate ligand, has been discovered in NSCLC [20].

This review focuses on immunotherapy as a new potential therapy for the treatment of lung cancer. It explores the classification and epidemiology of lung cancer, associated risk factors, pathogenesis, and targeted MET gene is described. Furthermore, the role of immunotherapy as a possible futuristic approach to lung cancer treatment has been discussed thoroughly. It summarizes the key outcomes reported with the use of new checkpoint inhibitors in lung cancer. The role of different CTLA-4 inhibitors such as ipilimumab and tremelimumab, as well as different ICI such as: The use of PD-1 and PD-L1 inhibitors is also mentioned. It also stated the application of vaccines, prospects of immunotherapy, etc. Immunotherapy has significantly enhanced the treatment of lung cancer and will continue to play a promising role for the benefit of patients. Although it is critical to examine predictive indications in response to immunotherapy, understanding the role of immunotherapy in patients with restricted stage SCLC who are also receiving radiation and CT deserves additional attention [21,22]. Furthermore, cross-talk between multi ICI, their full mechanisms of action, and the combination strategy of immunotherapy and CT are all important topics of cancer research [23] (Fig. 1).

## EPIDEMIOLOGY

Lung cancer patients are diagnosed at an alarmingly higher level and account for around 12% of the total cancer patients [24]. Cigarette smoking was reported as the major cause earlier, but several other factors have also been discovered that make these cases a little difficult to interpret in terms of cause of incidence. Lung cancer incidence rates are reported to be similar among white women and African-American. African-American men have reported to be more prone to lung cancer incidence than white men. According to reports, in China, the rate of lung cancer is higher in men than in women. Prostrate cancer male patients are the most common, followed by lung cancer and breast cancer female patients are the most common, followed by lung cancer. In Europe, lung cancer deaths are declining in men whereas rising in women, with cigarette smoking being the major risk factor. It has been observed that African-Americans and non-Hispanic whites have greater lung cancer death rates than Hispanics, Native Americans, and Asians/Pacific Islanders [25].

There are major geographic, racial, and gender differences in suspecting the major cause [26]. The incidence of adenocarcinoma in men and women has climbed rapidly in recent decades and it is now comparable to the incidence of SQ cell carcinoma. Age is reported to be one of the causes of incidence and mortality as reported by authors, which states that most patients were above the age of 44 and rarely diagnosed at a younger age. It has been also reported that old age is one of the factors of lung cancer incidence, but it is more evident in women than in men. Younger age group patients are decreasing and this decrease is again more evident in men than in women, which may be due to the reduced risk factor most probably in men [24].

According to statistics, in 87 countries for men and 26 countries for women, lung cancer is the leading cause of cancer death. Regional variation is also evident in the occurrence of lung cancer as substantial geographic variation is reported within countries. Trends in its regional distribution are recorded, providing insight into the factors that influence lung cancer risk [24]. According to a study conducted by researchers, Central, Eastern Asia, and Eastern Europe have the greatest death rates, whereas Northern Africa, South Central Asia, and Central America sub-Saharan Africa and Western Africa have the lowest rate. North Korea, Denmark, Hungary, Canada, and Northern America had the highest female lung cancer mortality rates (per 100,000). The continents of Northern Europe, Eastern Asia, Western Europe, Oceania, and the Caribbean, respectively, are Northern Europe, Eastern Asia, Western Europe, Oceania, and the Caribbean [27].

Socioeconomic status is also considered as a factor related to the incidence of lung cancer. Lower socioeconomic class people who have less income education are often victims of lung cancer due to more physical, psychosocial stress, and other occupational risk factors [28].

The queer/questioning (LGBTQ) community, lesbian, gay, bisexual, and transgender have reported to have more lung cancer incidence due to their smoking habits, which is 68% higher than other sexually aligned people [29].

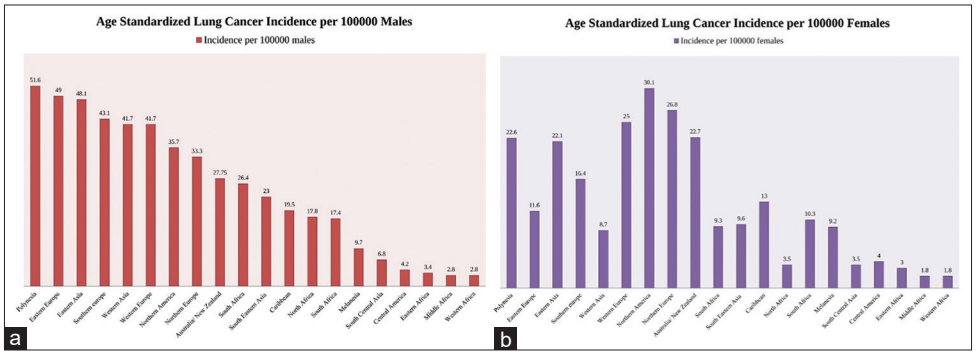


**Fig. 1: (a) Incidence in Different Regions Lung Cancer Rates by Sex, Age-Standardized, in Men in 2020. The greatest national rates in Men are displayed in descending order of the world (W) age-standardized rate of males. Source: Globocan 2020 [23]. (b) Incidence in Different Regions Lung Cancer Rates by Sex, Age-Standardized, in Women in 2020. The greatest national rates in Women are displayed in descending order of the world (W) age-standardized rate of females. Source: Globocan 2020 [23].**

**RISK FACTORS**

The impacts of tobacco, obesity, and infection are the risk factors that contribute to cancer development and that, together, influence the notable geographical heterogeneity in incidence rates. SCLC is unique because it usually does not occur in never-smokers [24].

**CIGARETTE SMOKING**

Cigarette smoking has been blamed for the onset of the lung cancer epidemic in the 20th century [30]. Tobacco smoke contains 4000 chemicals, including at least 69 known carcinogens and other toxicants linked to major diseases, as evidenced by the report, which claims that 20 carcinogens derived from tobacco smoke cause lung tumors in laboratory animals or humans and are a likely the cause of lung cancer induction [31]. Polycyclic aromatic hydrocarbons (PAH) and the tobacco specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone among the various carcinogenic components contained in tobacco smoke, 1-butanone is thought to have a crucial role. Among the various carcinogenic components contained in tobacco smoke, -1-butanone is thought to have a crucial role. Bidi and hookah in India, khii-yoo in Thailand, and water pipes in China have all been related to an increased risk of lung cancer. Electronic nicotine administration systems allow nicotine to be delivered to the lung epithelium through an electronic device, and long-term proof of lung cancer can be collected from such a source.

**GENETIC RISK FACTORS**

Family history and high penetrance genes – Lung cancer induction inheritance has been linked to early lung cancer incidence in smokers and non-smokers; however, it is unclear how much of this risk is due to shared genes among family members and how much is due to household environmental conditions. The effect of genetics on lung cancer induction in nonsmokers has been investigated. Oncogenic driver mutations are genes that have been linked to lung cancer and can increase the risk of lung cancer in non-smokers [32].

**GENETIC POLYMORPHISMS**

All carcinogens activated by Phase I enzymes, such as cytochrome P450s, can bind to deoxyribonucleic acid (DNA), forming DNA adducts capable of causing mutations and finally commencing carcinogenesis, according to reports. The inability to repair DNA damage caused by activated carcinogens is a host factor that influences lung cancer incidence [33].

**DIET AND ALCOHOL**

Diets have reported to be controlling of lung cancer incidence. Healthy diets consisting of fruits and vegetables have reported to be protective against lung cancer incidence, whereas the formation of nitrosamine while preparing fried red meat or high intake of red meat influences the incidence of lung cancer. The intake of vitamin a supplements has been also been studied as reported which states that beta-carotene intake can increase the risk whereas other vitamins help in prevention [34].

**EXPOSURE TO SECOND HAND SMOKE**

The side-stream smoke or indirect carcinogenic exposure that results from the combustion of tobacco is referred to as second hand smoke. This has been accused for the numerous deaths occurring each year [30].

**CHRONIC INFLAMMATION FROM INFECTIONS AND OTHER MEDICAL CONDITIONS**

Asthma inflammation has a critical part in lung cancer development. Patients with chronic obstructive pulmonary disease have a higher risk of lung cancer, regardless of whether or not they smoke. Asthma, alpha-1 antitrypsin deficiency, and pulmonary fibrosis have also been linked to an increased risk of lung cancer. Lung cancer is also caused by pulmonary TB, which produces scarring in the lungs [35].

Air pollution places with the high level of air pollutants have more lung cancer patients then places with good air quality. It also accounts to 5% of all deaths due to lung cancer which has been induced due to outdoor pollution [36].

**IONISING RADIATION**

Radiation is used to treat lung and chest cancers, but it also raises the risk of lung cancer in healthy people. Humans are all exposed to radon gas, yet there are significant regional differences. When vast portions of the lungs are exposed to high doses of radiation over time during radiation therapy, the risk of radiation pneumonitis increases. In war-torn places, exposure to radiation from atomic bomb explosions is also a major cause of lung cancer [37,38].

**OCCUPATIONAL EXPOSURE**

Lung cancer is caused by occupational exposure to asbestos, silica, radon, heavy metals, and polycyclic aromatic hydrocarbons. Other carcinogens include nickel compounds, chromium compounds, coal products, mustard gas, uranium, arsenic, beryllium, silica, vinyl chloride, cadmium, and chloromethyl ethers [39].

**OTHER RISK FACTORS**

As estrogen and progesterone receptors are found in both normal lung and lung cancer cell lines; estradiol has a proliferative effect on cancer cell lines [40].

**PATHOGENESIS**

The lungs are part of the lower respiratory tract, which begins at the trace of the bronchi and branch into the bronchi and into the bronchia. At the terminal bronchioles, the driving area ends. The bronchioles divide in the respiratory zone into alveolar ducts which lead to an alveolar bag containing alveoli, which are used for gas exchange [41]. The pleura is a thin membrane that lines the inside wall of the chest cavity outside each lung. The cavity pleural is formed as a result of this. A little quantity of fluid is normally present in the pleural cavity, which aids in the smooth movement of the lungs in the chest while breathing [42].

Lung cancer can emerge from differentiated or undifferentiated cells in the central (SCLC and SQ cell carcinoma) or peripheral (adenocarcinoma) airway compartments [43].

People with a low DNA repair capacity of multiple DNA repair pathways are predisposed to lung cancer, according to studies. For distinct types of damaged DNA, four DNA repair mechanisms are active. Small lesions are repaired using the base excision repair pathway, while big lesions are repaired using the nucleotide excision repair pathway. To fix replication errors, mismatch repair is utilized. The two mechanisms for repairing double-strand DNA breaks are homologous recombination and non-homologous end-joining [44].

The etiology of lung cancer is also influenced by a genetic component, which pertains to the host's vulnerability to lung cancer, whether or not they have been exposed to carcinogens. [45]. Carriers who smoked cigarettes were more than 3 times as likely than non-smokers to get lung cancer [45]. There are specific gene mutations linked to the etiology of each kind of lung cancer. The K-ras proto-oncogene is responsible for 10–30% of lung adenocarcinomas, while the EML4-ALK tyrosine kinase is responsible for 4% of non-small-cell lung carcinomas [46]. The tyrosine kinase of the neuregulin receptors ERBB2 and ERBB1, which belong to the transmembrane receptor family, is frequently aberrant in NSCLCs but not in SCLCs [47].

The basal bronchial cell, a potential stem cell in the middle compartment of conducting bronchial airways, gives rise to ADC. In terminal bronchioles, this potential stem cell can differentiate into ciliated or mucous cells, which can afterward give birth to central ADC and possibly neuroendocrine cells [48]. Pneumocytic markers are frequently seen in

lung cancer cells. Because TTF-1 and Napsin A are expressed in around 85% of lung adenocarcinoma cases, they can be used as adenocarcinoma or adenocarcinoma differentiation markers in poorly differentiated tumors with limited biopsy material [49]. When SCC becomes large enough, it can develop voids in the center region of the lung and along the main airways [49]. The fibroblast growth factor receptor 1 (FGFR1) gene, which is encoded by the FGFR1 gene and is located on chromosome 8p11, has emerged as a major oncogene in SCC. FGFR1 is activated in a number of malignancies through a variety of methods, including gene fusion and mutations, which activate downstream signaling pathways, resulting in enhanced cell proliferation and survival [50].

Tobacco-related malignancies are metabolized by two types of enzymes: Phase I and Phase II enzymes, which detoxify tobacco. While Phase I enzymes (cytochrome P450, monooxygenases) activate carcinoma in intermediate processes, Phase II enzymes balance their effects by converting the same reactive intermediates (oxygen reactives) into inactive, more water-soluble, and hence readily excreted conjugates [51].

## MET GENE

In a number of malignancies, including NSCLC, the HGF receptor (MET) is a possible therapeutic target [52]. The MET oncogene is a critical component of the invasive growth genetic program, a biological process that causes cells to separate from one another, scatter, migrate, and invade distant places [53]. In a variety of human malignancies, MET has also been connected to a high tumor grade and a poor prognosis. The discovery and confirmation of activating germ line MET mutations in hereditary papillary renal carcinoma provided the first direct evidence linking MET to human oncogenesis [54]. The activation of the MET pathway in NSCLC is hypothesized to happen through a variety of pathways that regulate features that affect cancer cell survival, proliferation, and invasiveness [52]. In NSCLC, MET gene amplification was analyzed with several assays, including *in situ*, in-loc fluorescence, and real-time polymerase chain reaction fluorescence *in situ* hybridization [7]. MET gene mutations may occur in the extracellular domain of semaphorins, in the region of the juxta membrane, and in the kinase domain in NSCLC. Mis-sense mutations in the exon 2 Sema domain, necessary for MET dimerisation, were reported as germline mutations. Missense changes were identified [55].

The MET proto-oncogene was found as a fusion partner with the TPR gene's translocated promoter region in a chemically altered osteosarcoma-derived cell line [56]. The MET proto-oncogene is found on the long arm of human chromosome 7 band q31 and encodes the membrane tyrosine kinase receptor MET (c-MET) [53]. Tyrosine MET receptor kinase is enabled by its cognate ligand HGF, and phosphorylation of the receptors activates downstream pathways of mitogenous-activated protein kinase (MAPK), 3-kinase phosphatidylinositol, and Cμ phospholipase [57]. The protein is first encoded, then processed proteolytically to yield and subunits, which are subsequently disulfide-bonded together to form the mature receptor [19]. Mammalian HGF and scatter factor, as well as their splicing isoforms and a bacterial leucine-rich surface protein known as Internalin B, all include MET ligands [20]. MET dimerizes and activates the receptor when it interacts with its ligand, HGF, which is released by stromal cells [19].

The binding of HGF to MET causes the receptor to catalyze. When the receptor is activated by dimerization, the activation loop is unlocked by transphosphorylation of Tyr 1234 and Tyr 1235, which are required for enzymatic activity [53]. As a result, the signaling pathways RAS/ERK/MAPK, PI3K/AKT, Wnt/b-catenin, and STAT are all activated. Depending on the biological context, these pathways can enhance cell proliferation, survival, migration, motility, invasion, angiogenesis, and epithelial-to-mesenchymal transition [52].

## MET GENE COPY NUMBER IN NSCLC

Since it was shown that MET amplification (20%) can cause acquired resistance to EGFR TKIs in subsets of EGFR-mutant individuals with lung adenocarcinoma that were previously sensitive to these treatments, the impact of MET gene copy number on lung cancer has sparked interest [58]. In fact, *in vitro* research suggests that both small TKI compounds and MET direct monoclonal antibodies are active in cell lines with MET exon 14 mutations, allowing tumor cells to employ MET in the PI3K pathway to sustain viability [20,58].

In the presence of activating EGFR mutations, lung tumors can show novo resistance (primary resistance) to the treatment of TKI. By activating the PI3K-AKT Pathway by MET, HGF binding enhances the EGFR TKI's ability to effectively block the signaling cascade [53]. The JAK/STAT cascade is important for enhancing cell motility, migration, and metastasis because of the many downstream pathways induced by MET [57].

## IMMUNOTHERAPY

Traditional cancer immunotherapy treatment methods include bacterial/viral infection to boost the immune response and tumor vaccination [4]. The idea of treating neoplastic disease with the immune system stretches back to the 18$^{th}$ century. The first to describe the relationship between immunological state and cancer were Wilhelm Busch and Friedrich Fehleisen. After developing erysipelas, a superficial skin infection caused most usually by Streptococcus pyogenes, they observed tumors spontaneously regressing [59].

## INNATE IMMUNITY

Innate immunity, which involves macrophages and neutrophils, is a non-specific initial line of protection [60].

M1 macrophages can be reeducated into M2 macrophages by lung cancer cells. Sentinel cells of the innate immune system may recognize nonspecific structurally preserved compounds that can be distinguished from the host's molecules using Toll-like receptors on their surfaces [61].

## IMMUNOSURVEILLANCE

Innate immune cells respond to "danger" signals produced by growing tumors as a result of genotoxic stress caused by cell transformation and disruption of the microenvironment [62]. Before a particular effector CD8+ cytotoxic T lymphocytes can be activated, antigen-presenting cells (APCs) must first make contact with the relevant CD4+ T-helper cell. T-cell activation necessitates two signals [63] (Fig. 2).

These signals, in the right circumstances, cause inflammation and activate antitumor effector cells such macrophages, dendritic cells (DCs), natural killer cells (NK cells), mastocytes, and neutrophils.

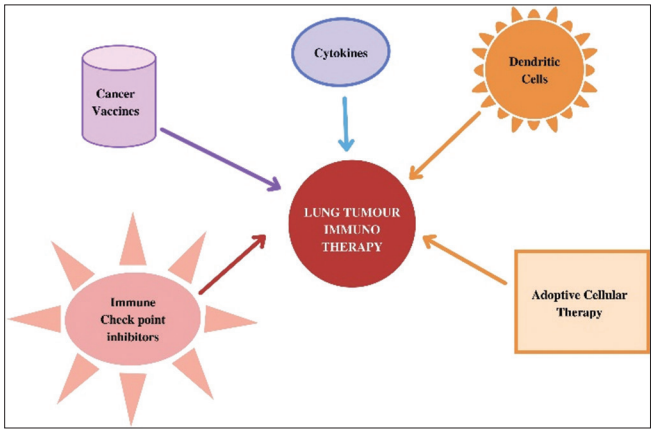


**Fig. 2: Immunotherapy for lung tumours includes the use of immune checkpoint inhibitors, cancer vaccine treatment, adoptive injection of in vitro immune cells, immunotherapy using dendritic cells (DCs), & synthesized cytokines [61].**

Under ideal conditions, these signals induce inflammation and activate antitumor innate effector cells, which include innate immune cells and professional APCs, such as macrophages, DCs, NK cells, mastocytes, and neutrophils, which play a role in the first line of defense against pathogens and rely on the production and release of cytokines [62]. When APCs are activated, DCs engage with CD4+ and CD8 + T cells to confirm that the tumor antigen is foreign, signaling the proliferation of various T cell subtypes that recognize the tumor antigen [64]. The MHC-peptide APC molecule must engage with the t-cell specific receptor, and the costimulatory molecules B7.1 and B7.2 must be activated. If the second signal is not activated, immune tolerance occurs and tumors can evade the immune system using a single mechanism [63]. Cytotoxic T lymphocyte antigen 4 and programmed cell death 1 are two of the most potent T-cell immune control points (PD1). In different places and times during the life span of the T cell, they exert their biological effects [65]. As a result, they work in tandem to ensure that T cell responses retain self-tolerance while also efficiently protecting the body from infections and cancer [59].

Cytotoxic medicine can cause immunogenic cell death, resulting in the production of molecular signals that encourage APC to take up dying cancer cells' detritus and cross-present tumor antigens to T cells [6].

There have been several adoptional immunotherapies with different killer cells including lymphokin-activated killer cells (LAK, until) and monoclonal anti-CD3-induced killer cells. A number of adoptive immunotherapies have been reported. Today, cytokine-induced killer, which can quickly proliferate *in vitro*, with strong anti-torrenal activity and a broader range of targeted tumors than other reported anti-torrenal cells, has been found to be a newly developed type of cells with an anti-torrenal effector [66].

## TARGETING LUNG TUMORS WITH PASSIVE IMMUNOTHERAPY

In the treatment of lymphoma (e.g., rituximab) and breast cancer, humanized antibodies that target specific tumor-associated antigens are now frequently employed (e.g., trastuzumab). Passive immunotherapy, on the other hand, has had no effect on lung cancer so far [9].

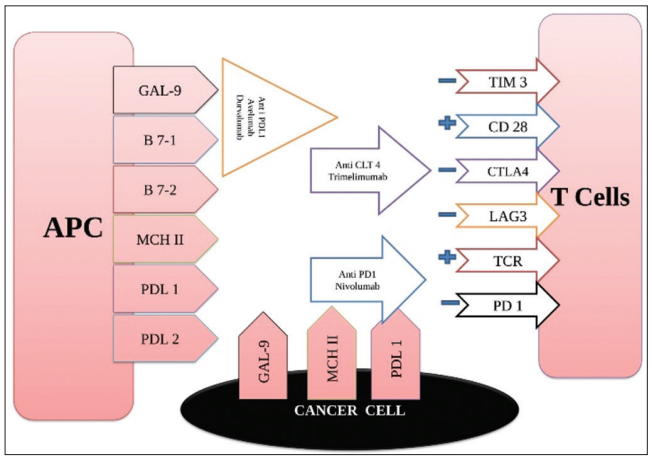


**Fig. 3: T cell response is determined by a number of receptor-ligand interactions. Antigen-specific T cell proliferation and activation occur when the TCR binds to the APC MHC II receptor presenting antigen. Binding of LAG-3 to the APC MHC, on the other hand, might obstruct the process. PD-1 on T cells can also inhibit this response by attaching to PD-L1 on APCs, tumour cells, or Tregs. Atezolizumab, durvalumab, and avelumab inhibit PD-1, whereas atezolizumab, durvalumab, and avelumab inhibit PD-L1, causing T cell activation. T cells can also be activated by B7-1 or B7-2 binding to CD28.This reaction is blocked when CTLA-4 binds to B7-1 or B7-2 instead. CTLA-4 is inhibited by ipilimumab and tremelimumab, allowing T cells to be activated. [64].**

## ICI

One intriguing method in lung cancer immunotherapy is to disable immunological regulators to ensure that the immune response to tumors is effective. T-cell monoclonal antimicrocardiac antibodies, such as ligand, programmed mortality ligand 1 or cytotoxic T-lymphocyte antigen (mAbs) 4, are used to do this (PD-L1). The blockage of these proteins removes T-cell activation inhibitory signals and produces t-cell antitumor response mediation. However, with other tumor types, such as prostate cancer, the same method has not always worked [65]. The monoclonal antibody apilimumab binds to CTLA-4 and prevents it from interacting with its ligand [6]. Antitumor activity is increased when the suppression of CD28/B7 T-cell activation is reduced [67] (Fig. 3).

## PD-1/PD-L1 INHIBITORS

When T cells are activated due to inflammatory or peripheral tissue infection, the programmed cell Death-1 receptor (PD-1) is located on cytotoxic T cells and T-regulatory cells. By attaching the ligand PD-1 to the receptor, it is inactivated, reducing the immune response to stimuli and causing immune suppression [68]. In clinical practice, PD-L1 expression is currently assessed on tumor cells since it predicts the likelihood of an antibody PD-(L)1 response [69]. Patients who have taken CT but whose cancer has progressed despite treatment may benefit from antibodies that attach to PD-1 or PD-L1. When the fraction of tumor cells that express PD-L1 is high, the anti-PD-1 antibody pembrolizumab can be utilized as a first-line treatment for metastatic NSCLC; these patients respond better to immunotherapy than CT [70].

## ANTI-PD-1 AGENTS

Phase 2/3 development was spurred by nivolumab's promising safety and responsiveness in advanced NSCLC earlier-phase research. In patients with advanced pretreated NSCLC SQ, the Phase 3 Check Mate 017 trial compared the anti-PD-1 drug nivolumab with docetaxel, and this study resulted in the FDA's first NSCLC approval [64,68,70].

## ANTI-PD-L1 AGENTS

Atezolizumab, unlike the PD-1 inhibitors listed above, is a newer checkpoint inhibitor that targets PD-L1. It blocks the interactions between PD-L1 and PD-1, as well as PD-L1 and B7-1, but not PD-L2 and PD-1, which could have biological and therapeutic consequences [64].

New medicines, on the other hand, are being explored in conjunction with anti-PD1/PD-L1 antibodies with the goal of actively stimulating the immune response. For example, Utomilumab is a completely human IgG2 agonist monoclonal antibody that targets CD137, a costimulatory receptor expressed on activated immune cells (effector and regulatory T cells, NK cells, and DCs), increasing cytotoxic T-cell and NK-cell activity and triggering an anticancer response [6].

## ANTIANGIOGENIC AGENTS

When compared with docetaxel monotherapy as a second-line treatment after platinum-based combination CT failure, ramucirumab in combination with docetaxel has been found to significantly improve OS in all NSCLC histologies. The combination of nintedanib and docetaxel is beneficial only in the treatment of adenocarcinoma [71].

## ANTIGEN-SPECIFIC IMMUNOTHERAPY

Cancer vaccinations that are therapeutic-immunogenic tumor-associated antigens in the form of peptides, recombinant proteins, gangliosides, or whole tumor cells are mixed with an adjuvant to increase the immune response to a vaccination. Immunoadjuvants might be in the form of phospholipids, aluminum formulations, viral vectors, DCs, or liposomes. Vaccination approaches for lung cancer have been tested. We examine those in the last stages of development [72].

**ANTIGEN-SPECIFIC VACCINES**

An antigen should be expressed consistently, different from normal cells and better be tumor-borne and immunogenic in the tumor type of interest [63]. Vaccines are pharmaceutical preparations of pathogens' antigen macromolecules, which generate an immediate immune response in the body and establish a long-lasting antigen memory, generally forming antibodies to the antigen [73]. Despite the fact that lung cancer is regarded to be a cancer with a low immunogenicity, certain investigations have shown cytotoxic T cells. However, this indication of an immune response in lung cancer patients has not been linked to a significant improvement in outcome, and it is thought that more aggressive and/or targeted immune system stimulation is necessary. As a result, a number of vaccinations to treat this malignancy have been produced. An adjuvant is frequently included as part of the vaccine to optimize the immune response to vaccination [63].

**MAGE-A3 VACCINE**

MAGE-A3 is a protein produced nearly solely by cancer cells and it has been discovered in 35–50% of NSCLCs. Because prior pilot trials demonstrated that clinical responses were more common in patients with minimal tumor burden, MAGE-A3 is one of the few immunotherapies being studied in the adjuvant setting [60].

**TG4010 VACCINE**

Mucin 1 (MUC1), a full-length cancer antigen, and human IL-2, both encoded by a modified vaccinia Ankara strain, are used to make TG4010 (MVA). In numerous clinical trials, the administration of TG4010 in combination with CT resulted in better clinical outcomes than the usual CT regimen [58].

**BLP-25 ANTI-MUC1 VACCINE**

MUC1 is a glycoprotein expressed by a variety of epithelial tissues that aids cellular attachment through ICAM-1 [21,22]. When produced by malignant cells, MUC1 differs structurally from its non-malignant counterpart. The exposed peptide core of MUC1, which is expressed by cancer cells, is targeted by BLP-25, a liposomal vaccine [74].

**GANGLIOSIDE VACCINE**

The vaccines PAMAM-GD2 and PAMAM-GD3 (tetramericpolyamidoamine scaffold) are highly immunogeneous and elicit the selectively interreactive, GD2, and GD3 humor response on the surface of the tumor cell. While humoral immunity against gangliosides is a helpful biomarker and may be therapy relevant, this is not necessary. Instead, vaccine-induced cellular immunity is more important to cancer treatment [75].

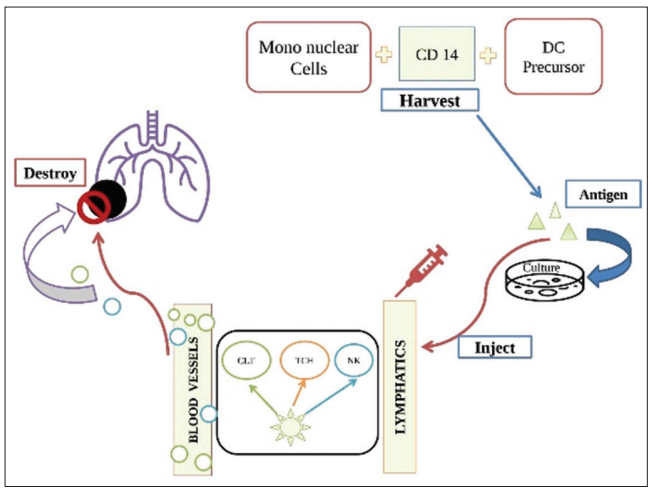


**Fig. 4: DC vaccines can be given to patients as immature antigen-loaded DCs that develop in vivo when they come into contact with T cells or mature DCs matured in culture with CD40 ligand or other compounds like lipopolysaccharide (LPS). Under the skin or intravenously infused DCs move to regional lymph nodes and interact with tumor-specific T-cell precursors. CTLs are released into the bloodstream and subsequently travel into tissues, where they encounter and kill antigen-expressing cells (such as tumour cells) [78].**

**CIMAVAX-EGF VACCINE**

The anticancer effect of CIMAvax-EGF vaccination is achieved by targeting the immune system and creating anti-EGF antibodies, resulting in a decrease in circulating EGF in serum. As a result, the remaining EGF is less likely to bind to the EGFR receptor on cancer cells' surfaces. When EGF is removed, neoplastic cells lose a crucial pro-proliferation and pro-survival signal [76].

**MONOCYTE-DERIVED DCS VACCINE**

Ex *vivo*, MoDCs have been studied extensively in vaccination trials, indicating their potential to cross-prime T cells 8–10 and generate antitumor cytokines including IL-12. In a subgroup of treated patients, this resulted in antitumor activity, suggesting MoDCs' potential as a beneficial vaccine component [77] (Fig. 4).

**CARBOHYDRATE VACCINE**

Among the many antigens studied, carbohydrate antigens have been found to be the most suitable and therapeutically relevant [78]. Antibodies against these antigens have been associated with the future bacterial invasion resistance. Two to 4 antigens for use in infectious disease vaccines have been relatively straightforward to come by: To detect them, post-infection ("immune") sera are employed [79].

**P53 CANCER VACCINE**

In 90% of SCLC patients, the p53 gene is mutated. Wild-type p53 has a short half-life and is only detected in trace amounts in normal cells, but mutant p53 has a much longer half-life and is found in much higher concentrations in tumor cells. This difference in protein expression between normal and malignant cells could be used as a foundation for immunotherapy, with the p53 protein being recommended as a possible antigenic target for immunotherapeutic methods [80].

**NANOPARTICLES FOR VACCINE**

Many immunomodulatory drugs, such as recombinant cytokines, can be altered by nanoparticle forms of antigens and immunomodulatory compounds, which promote multivalent receptor cross-linking, alter intracellular processing, promote cytosolic delivery, and physically localize synergistic cues within the same intracellular compartment [81].

**GENETIC VACCINE**

For significant Bermuda grass pollen allergen CYND 1, immunization was utilized in combination with various adjuvants such as bupivacain, bestatin, liposom, or CpG and elicited Th1 responses linked with IgG2a responses in mice. It was reported that the vaccine seem to prevent IgE induction and suppressed the continued production of IgE in a murine model [75].

**GENE THERAPY AND GENE TRANSFER VECTORS**

Gene therapy is not a unique independent category but rather a strategy which uses a direct transmission vector for the expression of gene-derivative proteins which modify alternative functional cells. Cytokines and costimulatory molecules directly transfer genetically into tumor cells from and to ex-vides is an attractive way to increase the immune stimulation of non-immunogenic cells. The transference of the gene *in vivo* cytokines may also target normal cells in the tumor environment, thus achieving high local cytokine concentrations that will prevent systemically administered toxicity [82].

## FUTURE DIRECTIONS OF LUNG CANCER IMMUNOTHERAPY

The treatment modality for advanced/metastatic lung cancer has changed drastically in the past 10 years. Lung cancer patients can get first-line therapies that include immunotherapy as a single modality or in combination with CT. Cancer immunotherapy has sparked a lot of attention due to its promising outcomes in obtaining significant and long-lasting treatment responses with minimally tolerable effects. Compared with CT or radiotherapy, cancer immunotherapy has a number of advantages. Immunotherapy is gaining popularity in this area because of its favorable benefits, low risk ratio, and long-term effectiveness [83]. It also showed a considerable benefit by limiting tumor growth after patients' responses to traditional therapies had ceased. ICIs have ushered in a new era in the treatment of advanced NSCLC, despite the fact that they have only been utilized for a short time. Clinicians now have a wide range of treatment options, including PD-1 inhibitor monotherapy or PD-1/PD-L1 inhibitor plus CT, and an increasing proportion of patients are seeing long-term improvements [84]. To maximize the benefit of immunotherapy, better predictive biomarkers are needed, and more research is needed to discover the mechanism of ICI resistance and how to overcome it. Identifying predictive indicators that can predict the antitumor effect and survival benefit of immunotherapies before they are treated is one of the most important future endeavors in cancer immunotherapy [85]. Another key strategy in tumor treatment is combination therapy. More research is needed to determine the role of immunotherapeutic medicines in combination with one another, as well as CT, targeted therapy, and other cancer treatment alternatives. In conclusion, ICIs have changed the treatment landscape for advanced NSCLC, and the future translational and clinical research is expected to improve patient outcomes even more.

## CONCLUSION

Immunotherapy is a crucial treatment option for NSCLC patients. The key to getting the best results is to tailor the treatment to each patient. While the goal should be to use "CT-free" protocols in the first line, its crucial to recognize which patients are not helped by these treatments. In the first line, protocols combining immunotherapy and CT are critical, especially for non-smokers. A deeper knowledge of the mechanisms that contribute to an effective antitumor response is required to extend clinical benefit to the majority of patients and to prevent medication resistance. The discovery of new combination tactics will shed light on cancer immunotherapy's next level advances.

## ACKNOWLEDGMENTS

Declared None.

## AUTHORS CONTRIBUTION

The review paper was written with the combined effort and contribution of all the authors. Prof. C.M. Hossain has decided on the title of the review article and designed the structure of the paper. Moreover, he has prepared, reviewed, and edited the original draft of the review article with detailed conceptualization. Subarnarekha Maitra has written part of this paper. Dr. Nazmun Lyle has written part of the manuscript and formatted the draft. Souvil Paul helped to draw the images. Dr. Meeta Gera has written the part of the manuscript. DiashariDutta also helped to write a part of this manuscript.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## FUNDING

None.

## REFERENCES

1. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, *et al*. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014;311:1998-2006. doi: 10.1001/jama.2014.3741, PMID 24846037
2. Nakano T, Shimizu K, Kawashima O, Kamiyoshihara M, Kakegawa S, Sugano M, *et al*. Establishment of a human lung cancer cell line with high metastatic potential to multiple organs: Gene expression associated with metastatic potential in human lung cancer. Oncol Rep 2012;28:1727-35. doi: 10.3892/or.2012.1972, PMID 22922681
3. Sharma P, Mehta M, Dhanjal DS, Kaur S, Gupta G, Singh H, *et al*. Emerging trends in the novel drug delivery approaches for the treatment of lung cancer. Chem Biol Interact 2019;309:108720. doi: 10.1016/j.cbi.2019.06.033, PMID 31226287
4. Yu S, Wang R, Tang H, Wang L, Zhang Z, Yang S, *et al*. Evolution of lung cancer in the context of immunotherapy. Clin Med Insights Oncol 2020;14:1179554920979697. doi: 10.1177/1179554920979697, PMID 33447125
5. Khaltaev N, Axelrod S. Global lung cancer mortality trends and lifestyle modifications: Preliminary analysis. Chin Med J (Engl) 2020;133:1526-32. doi: 10.1097/CM9.0000000000000918, PMID 32568874
6. Pavan A, Attili I, Pasello G, Guarneri V, Conte PF, Bonanno L. Immunotherapy in small-cell lung cancer: From molecular promises to clinical challenges. J Immunother Cancer 2019;7:205. doi: 10.1186/s40425-019-0690-1, PMID 31383005
7. Go H, Jeon YK, Park HJ, Sung SW, Seo JW, Chung DH. High MET gene copy number leads to shorter survival in patients with non-small cell lung cancer. J Thorac Oncol 2010;5:305-13. doi: 10.1097/JTO.0b013e3181ce3d1d, PMID 20107422
8. Zarogoulidis K, Zarogoulidis P, Darwiche K, Boutsikou E, Machairiotis N, Tsakiridis K, *et al*. Treatment of non-small cell lung cancer (NSCLC). J Thorac Dis 2013;5 Suppl 4:S389-96. doi: 10.3978/j.issn.2072-1439.2013.07.10, PMID 24102012
9. Steven A, Fisher SA, Robinson BW. Immunotherapy for lung cancer. Respirology 2016;21:821-33. doi: 10.1111/resp.12789, PMID 27101251
10. Jaggi P. A review article on lung cancer diagnosis and treatment. Res Rev J Med Health Sci 2017;6:1-9.
11. Visconti R, Morra F, Guggino G, Celetti A. The between now and then of lung cancer chemotherapy and immunotherapy. Int J Mol Sci 2017;18:1374. doi: 10.3390/ijms18071374, PMID 28653990
12. Sun J, Zhang Z, Bao S, Yan C, Hou P, Wu N, *et al*. Identification of tumor immune infiltration-associated lncRNAs for improving prognosis and immunotherapy response of patients with non-small cell lung cancer. J Immunother Cancer 2020;8:e000110. doi: 10.1136/jitc-2019-000110, PMID 32041817
13. Hopkins AM, Wagner J, Kichenadasse G, Modi N, Rowland A, Sorich MJ. Patient-reported outcomes as a prognostic marker of survival in patients with advanced nonsmall cell lung cancer treated with immunotherapy. Int J Cancer 2020;147:3085-9. doi: 10.1002/ijc.33133, PMID 32492185
14. Sanmamed MF, Nie X, Desai SS, Villaroel-Espindola F, Badri T, Zhao D, *et al*. A burned-out CD8+ T-cell subset expands in the tumor microenvironment and curbs cancer Immunotherapy. Cancer Discov 2021;11:1700-15. doi: 10.1158/2159-8290.CD-20-0962, PMID 33658301
15. Esposito G, Palumbo G, Carillio G, Manzo A, Montanino A, Sforza V, *et al*. Immunotherapy in small cell lung cancer. Cancers (Basel) 2020;12:2522. doi: 10.3390/cancers12092522, PMID 32899891
16. Horvath L, Thienpont B, Zhao L, Wolf D, Pircher A. Overcoming immunotherapy resistance in non-small cell lung cancer (NSCLC)-Novel approaches and future outlook. Mol Cancer 2020;19:141. doi: 10.1186/s12943-020-01260-z, PMID 32917214
17. Nasser NJ, Gorenberg M, Agbarya A. First line immunotherapy for non-small cell lung cancer. Pharmaceuticals (Basel) 2020;13:373. doi: 10.3390/ph13110373, PMID 33171686
18. Welsh J, Menon H, Chen D, Verma V, Tang C, Altan M, *et al*. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: A randomized phase I/II trial. J Immunother Cancer 2020;8:e001001. doi: 10.1136/jitc-2020-001001, PMID 33051340
19. Wang Q, Yang S, Wang K, Sun SY. MET inhibitors for targeted therapy of EGFR TKI-resistant lung cancer. J Hematol Oncol 2019;12:63. doi: 10.1186/s13045-019-0759-9, PMID 31227004
20. Rehman S, Dy GK. MET inhibition in non-small cell lung cancer. E M J Respir 2018; 6:100-11.
21. He B, Dong D, She Y, Zhou C, Fang M, Zhu Y, *et al*. Predicting response to immunotherapy in advanced non-small-cell lung cancer using tumor mutational burden radiomic biomarker. J Immunother Cancer 2020;8:e000550. doi: 10.1136/jitc-2020-000550, PMID 32636239

22. Wang F, Wang S, Zhou Q. The resistance mechanisms of lung cancer immunotherapy. Front Oncol 2020;10:568059. doi: 10.3389/fonc.2020.568059, PMID 33194652
23. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49. doi: 10.3322/caac.21660, PMID 33538338
24. Cruz CS, Tanoue LT, Matthay RA. Lung cancer: Epidemiology, etiology, and prevention. Clin Chest Med 2011;32:605-44. doi: 10.1016/j.ccm.2011.09.001, PMID 22054876
25. Schabath MB, Cress D, Muñoz-Antonia T. Racial and ethnic differences in the epidemiology and genomics of lung cancer. Cancer Control 2016;23:338-46. doi: 10.1177/107327481602300405, PMID 27842323
26. Saha SP, Bhalla DK, Whayne TF Jr., Gairola CG. Cigarette smoke and adverse health effects: An overview of research trends and future needs. Int J Angiol 2007;16:77-83. doi: 10.1055/s-0031-1278254, PMID 22477297
27. Islami F, Torre LA, Jemal A. Global trends of lung cancer mortality and smoking prevalence. Transl Lung Cancer Res 2015;4:327-38. doi: 10.3978/j.issn.2218-6751.2015.08.04, PMID 26380174
28. Schneiderman N, Ironson G, Siegel SD. Stress and health: Psychological, behavioral, and biological determinants. Annu Rev Clin Psychol 2005;1:607-28. doi: 10.1146/annurev.clinpsy.1.102803.144141, PMID 17716101
29. Quinn GP, Sanchez JA, Sutton SK, Vadaparampil ST, Nguyen GT, Green BL, *et al*. Cancer and lesbian, gay, bisexual, transgender/transsexual, and queer/questioning (LGBTQ) populations. CA Cancer J Clin 2015;65:384-400. doi: 10.3322/caac.21288, PMID 26186412
30. Benjamin R. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the surgeon general. Centers for Disease Control and Prevention (CDCP). 2010;978. ISBN-13: 978-0-16-084078-4.
31. Hecht SS. Tobacco smoke carcinogens and lung cancer. Curr Cancer Res 2011;6:53-74.
32. Furrukh M. Tobacco smoking and lung cancer: Perception-changing facts. Sultan Qaboos Univ Med J 2013;13:345-58. doi: 10.12816/0003255, PMID 23984018
33. Stiborova M. Formation of covalent dna adducts by enzymatically activated carcinogens and drugs *in vitro* and their determination by 32P-postlabeling. J Vis Exp 2018;133:57177. doi: 10.3791/57177, PMID 29630053
34. Donaldson MS. Nutrition and cancer: A review of the evidence for an anti-cancer diet. Nutr J 2004;3:19. doi: 10.1186/1475-2891-3-19, PMID 15496224
35. Adcock IM, Caramori G, Barnes PJ. Chronic obstructive pulmonary disease and lung cancer: New molecular insights. Respiration 2011;81:265-84. doi: 10.1159/000324601, PMID 21430413
36. Turner MC, Andersen ZJ, Baccarelli A, Diver WR, Gapstur SM, Pope CA, *et al*. Outdoor air pollution and cancer: An overview of the current evidence and public health recommendations. CA Cancer J Clin 2020;70:460-79. doi: 10.3322/caac.21632, PMID 32964460
37. Jain V, Berman AT. Radiation pneumonitis: Old problem, new tricks. Cancers (Basel) 2018;10:222. doi: 10.3390/cancers10070222, PMID 29970850
38. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e1S-29. doi: 10.1378/chest.12-2345, PMID 23649439
39. Field RW, Withers BL. Occupational and environmental causes of lung cancer. Clin Chest Med 2012;33:681-703. doi: 10.1016/j.ccm.2012.07.001, PMID 23153609
40. Chakraborty S, Ganti AK, Marr A, Batra SK. Lung cancer in women: Role of estrogens. Expert Rev Respir Med 2010;4:509-18. doi: 10.1586/ers.10.50, PMID 20658912
41. Hsia CC, Hyde DM, Weibel ER. Lung structure and the intrinsic challenges of gas exchange. Compr Physiol 2016;6:827-95. doi: 10.1002/cphy.c150028, PMID 27065169
42. Charalampidis C, Youroukou A, Lazaridis G, Baka S, Mpoukovinas I, Karavasilis V, et al. Pleura space anatomy. J Thorac Dis 2015;7:S27-S-32. doi: 10.3978/j.issn.2072-1439.2015.01.48.
43. Mankekar G. Epidemiology, pathogenesis, and risk factors. In: Invasive Fungal Rhinosinusitis. Berlin: Springer; 2014. p. 7-14.
44. Kiyohara C, Takayama K, Nakanishi Y. Lung cancer risk and genetic polymorphisms in DNA repair pathways: A meta-analysis. J Nucleic Acids 2010;2010:701760. doi: 10.4061/2010/701760, PMID 20981350
45. Goldstraw P, Ball D, Jett JR, Le Chevalier T, Lim E, Nicholson AG, *et al*. Non-small-cell lung cancer. Lancet 2011;378:1727-40. doi: 10.1016/S0140-6736(10)62101-0, PMID 21565398
46. Henschke CI, Yip R, Smith JP, Wolf AS, Flores RM, Liang M, *et al*. CT screening for lung cancer: Part-solid nodules in baseline and annual repeat rounds. AJR Am J Roentgenol 2016;207:1176-84. doi: 10.2214/AJR.16.16043, PMID 27726410
47. Fong KM, Sekido Y, Minna JD. Molecular pathogenesis of lung cancer. J Thorac Cardiovasc Surg 1999;118:1136-52. doi: 10.1016/S0022-5223(99)70121-2, PMID 10595998
48. Brambilla E, Gazdar A. Pathogenesis of lung cancer signalling pathways: Roadmap for therapies. Eur Respir J 2009;33:1485-97. doi: 10.1183/09031936.00014009, PMID 19483050
49. Zheng M. Classification and pathology of lung cancer. Surg Oncol Clin N Am 2016;25:447-68. doi: 10.1016/j.soc.2016.02.003, PMID 27261908
50. Monaco SE, Rodriguez EF, Mahaffey AL, Dacic S. FGFR1 amplification in squamous cell carcinoma of the lung with correlation of primary and metastatic tumor status. Am J Clin Pathol 2016;145:55-61. doi: 10.1093/ajcp/aqv013, PMID 26712871
51. Thomas L, Doyle LA, Edelman MJ. Lung cancer in women: Emerging differences in epidemiology, biology, and therapy. Chest 2005;128:370-81. doi: 10.1378/chest.128.1.370, PMID 16002959
52. Drilon A, Cappuzzo F, Ou SI, Camidge DR. Targeting MET in lung cancer: Will expectations finally be MET? J Thorac Oncol 2017;12:15-26. doi: 10.1016/j.jtho.2016.10.014, PMID 27794501
53. Zorzetto M, Ferrari S, Saracino L, Inghilleri S, Stella GM. MET genetic lesions in non-small-cell lung cancer: Pharmacological and clinical implications. Transl Lung Cancer Res 2012;1:194-207. doi: 10.3978/j.issn.2218-6751.2012.09.03, PMID 25806181
54. Krishnaswamy S, Kanteti R, Duke-Cohan JS, Loganathan S, Liu W, Ma PC, *et al*. Ethnic differences and functional analysis of MET mutations in lung cancer. Clin Cancer Res 2009;15:5714-23. doi: 10.1158/1078-0432.CCR-09-0070, PMID 19723643
55. Gelsomino F, Facchinetti F, Haspinger ER, Garassino MC, Trusolino L, De Braud F, *et al*. Targeting the MET gene for the treatment of non-small-cell lung cancer. Crit Rev Oncol Hematol 2014;89:284-99. doi: 10.1016/j.critrevonc.2013.11.006, PMID 24355409
56. Salgia R. MET in lung cancer: Biomarker selection based on scientific rationale. Mol Cancer Ther 2017;16:555-65. doi: 10.1158/1535-7163.MCT-16-0472, PMID 28373408
57. Okuda K, Sasaki H, Yukiue H, Yano M, Fujii Y. Met gene copy number predicts the prognosis for completely resected non-small cell lung cancer. Cancer Sci 2008;99:2280-5. doi: 10.1111/j.1349-7006.2008.00916.x, PMID 19037978
58. Toschi L, Cappuzzo F. Clinical implications of MET gene copy number in lung cancer. Future Oncol 2010;6:239-47. doi: 10.2217/fon.09.164, PMID 20146583
59. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: From T cell basic science to clinical practice. Nat Rev Immunol 2020;20:651-68. doi: 10.1038/s41577-020-0306-5, PMID 32433532
60. Domingues D, Turner A, Silva MD, Marques DS, Mellidez JC, Wannesson L, *et al*. Immunotherapy and lung cancer: Current developments and novel targeted therapies. Immunotherapy 2014;6:1221-35. doi: 10.2217/imt.14.82, PMID 25496336
61. Yang L, Wang L, Zhang Y. Immunotherapy for lung cancer: Advances and prospects. Am J Clin Exp Immunol 2016;5:1-20. PMID 27168951
62. Murphy JF. Trends in cancer immunotherapy. Clin Med Insights Oncol 2010;4:67-80. doi: 10.4137/CMO.S4795
63. Bradbury PA, Shepherd FA. Immunotherapy for lung cancer. J Thorac Oncol 2008;3(6 Suppl 2):S164-70. doi: 10.1097/JTO.0b013e318174e9a7, PMID 18520304
64. Somasundaram A, Burns TF. The next generation of immunotherapy: Keeping lung cancer in check. J Hematol Oncol 2017;10:87. doi: 10.1186/s13045-017-0456-5, PMID 28434399
65. Zhang S, Pease DF, Kulkarni AA, Kumar M, Shanley RM, Xu B, *et al*. Real-world outcomes and clinical predictors of immune checkpoint inhibitor monotherapy in advanced lung cancer. Clin Med Insights Oncol 2021;15:11795549211004489. doi: 10.1177/11795549211004489, PMID 34248362
66. Li R, Wang C, Liu L, Du C, Cao S, Yu J, *et al*. Autologous cytokine-induced killer cell immunotherapy in lung cancer: A phase II clinical study. Cancer Immunol Immunother 2012;61:2125-33. doi: 10.1007/s00262-012-1260-2, PMID 22581306
67. Khanna P, Blais N, Gaudreau PO, Corrales-Rodriguez L. Immunotherapy comes of age in lung cancer. Clin Lung Cancer 2017;18:13-22. doi: 10.1016/j.cllc.2016.06.006, PMID 27461776
68. Naylor EC, Desani JK, Chung PK. Targeted therapy and immunotherapy

for lung cancer. Surg Oncol Clin N Am 2016;25:601-9. doi: 10.1016/j.soc.2016.02.011, PMID 27261918

69. Früh M, Peters S. Genomic features of response to combination immunotherapy in lung cancer. Cancer Cell 2018;33:791-3. doi: 10.1016/j.ccell.2018.04.005, PMID 29763618
70. Hendriks L, Besse B. New windows open for immunotherapy in lung cancer. Nature 2018;558:376-7.
71. Brueckl WM, Reck M, Rittmeyer A, Kollmeier J, Wesseler C, Wiest GH, *et al*. Efficacy of docetaxel plus ramucirumab as palliative third-line therapy following second-line immune-checkpoint-inhibitor treatment in patients with non-small-cell lung cancer stage IV. Clin Med Insights Oncol 2020;14:1179554920951358. doi: 10.1177/1179554920951358, PMID 32884390
72. Declerck S, Vansteenkiste J. Immunotherapy for lung cancer: Ongoing clinical trials. Future Oncol 2014;10:91-105. doi: 10.2217/fon.13.166, PMID 24143916
73. Irvine DJ, Hanson MC, Rakhra K, Tokatlian T. Synthetic nanoparticles for vaccines and immunotherapy. Chem Rev 2015;115:11109-46. doi: 10.1021/acs.chemrev.5b00109, PMID 26154342
74. Hall RD, Gray JE, Chiappori AA. Beyond the standard of care: A review of novel immunotherapy trials for the treatment of lung cancer. Cancer Control 2013;20:22-31. doi: 10.1177/107327481302000105, PMID 23302904
75. Tong W, Maira M, Roychoudhury R, Galan A, Brahimi F, Gilbert M, *et al*. Vaccination with tumor-ganglioside glycomimetics activates a selective immunity that affords cancer therapy. Cell Chem Biol 2019;26:1013-26.e4. doi: 10.1016/j.chembiol.2019.03.018, PMID 31105061
76. Saavedra D, Crombet T. CIMAvax-EGF: A new therapeutic vaccine for advanced non-small cell lung cancer patients. Front Immunol 2017;8:269. doi: 10.3389/fimmu.2017.00269, PMID 28348561
77. Perez CR, De Palma M. Engineering dendritic cell vaccines to improve cancer immunotherapy. Nat Commun 2019;10:5408. doi: 10.1038/s41467-019-13368-y, PMID 31776331
78. Hirschowitz EA, Hiestand DM, Yannelli JR. Vaccines for lung cancer. J Thorac Oncol 2006;1:93-104. PMID 17409835
79. Slovin SF, Keding SJ, Ragupathi G. Carbohydrate vaccines as immunotherapy for cancer. Immunol Cell Biol 2005;83:418-28. doi: 10.1111/j.1440-1711.2005.01350.x, PMID 16033538
80. Antonia SJ, Mirza N, Fricke I, Chiappori A, Thompson P, Williams N, *et al*. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Clin Cancer Res 2006;12:878-87. doi: 10.1158/1078-0432.CCR-05-2013, PMID 16467102
81. Focke-Tejkl M, Valenta R. Safety of engineered allergen-specific immunotherapy vaccines. Curr Opin Allergy Clin Immunol 2012;12:555-63. doi: 10.1097/ACI.0b013e328357ca53, PMID 22885888
82. Hirschowitz EA, Yannelli JR. Immunotherapy for lung cancer. Proc Am Thorac Soc 2009;6:224-32. doi: 10.1513/pats.200806-048LC, PMID 19349492
83. Aldarouish M, Wang C. Trends and advances in tumor immunology and lung cancer immunotherapy. J Exp Clin Cancer Res 2016;35:157. doi: 10.1186/s13046-016-0439-3, PMID 27686848
84. Doroshow DB, Sanmamed MF, Hastings K, Politi K, Rimm DL, Chen L, *et al*. Immunotherapy in non-small cell lung cancer: Facts and hopes. Clin Cancer Res 2019;25:4592-602. doi: 10.1158/1078-0432.CCR-18-1538, PMID 30824587
85. Lim SM, Hong MH, Kim HR. Immunotherapy for non-small cell lung cancer: Current landscape and future perspectives. Immune Netw 2020;20:e10. doi: 10.4110/in.2020.20.e10, PMID 32158598