



# EMERGING ADVANCED TECHNIQUES IN TREATMENT REGIMEN OF NON-SMALL CELL LUNG CANCER

**Lahari Samudrala<sup>1\*</sup>, Akkenapelli Sri Tejaswini<sup>2</sup>, Allakonda Teena<sup>2</sup>, Bandela Sai Ram<sup>2</sup>,  
T. Ramarao<sup>3</sup>**

1. Assistant Professor, Department of Pharm.D, CMR college of pharmacy, Kandlakoya, Hyderabad, Telangana-501401.

2. B. Pharmacy students, Department of Pharm. D, CMR college of pharmacy, Kandlakoya, Hyderabad, Telangana-501401.

3. Principal, Professor, CMR college of pharmacy, Kandlakoya, Hyderabad, Telangana 501401.

Corresponding author: Samudrala. Lahari

Designation: Assistant Professor, Department of PharmD, CMR college of Pharmacy  
Kandlakoya, Medchal 501401.

## Abstract

Cancer is a disease characterized by altered signalling and metabolism, leading to uncontrolled cell division and survival, influenced by various molecules, factors, and conditions. Lung cancer has a poor prognosis, with over half of patients dying within one year and less than 18% having a 5-year survival rate. Non-small cell lung cancer (NSCLC) is the most common, with risk factors including smoking. Lung cancer is a life-threatening tumour, and surgical treatment is becoming more mature due to advancements in equipment and awareness. The concept of minimally invasive, precise, and intelligent surgical methods has revolutionized the treatment strategy. This review discusses the evolution of lung cancer surgery, including TV-assisted thoracic surgery, and the use of nanotechnology in lung cancer imaging and surgery-nanomedicine combinations. The review highlights the Current treatments include surgery, chemotherapy, radiotherapy, and immunotherapy, with biomarker testing improving survival in NSCLC patients. Natural nutraceuticals like Pear, Green tea, Salmon fish, Ginger and have been found to be effective in treating lung cancer. However, there has been a lack of clinical use due to factors like low solubility, limited absorption, and severe side effects. This review summarizes the advanced treatments in Non-small cell lung cancer.

**Keywords:** carcinoma, libtayo, pneumectomy, segmentectomy, sternotomy.

## INTRODUCTION

Lung cancer is a life-threatening tumour, and surgical treatment is becoming more mature due to advancements in equipment and awareness<sup>(1)</sup>. This review discusses the evolution of lung cancer surgery, including TV-assisted thoracic surgery, and the use of nanotechnology in lung cancer imaging and surgery-nanomedicine combinations. The review highlights the Current treatments include surgery, chemotherapy, radiotherapy, and immunotherapy, with biomarker testing improving survival in NSCLC patients<sup>(2)</sup>. Natural nutraceuticals like Pear, Green tea, Salmon fish, Ginger and have been found to be effective in treating lung cancer. However, there has been a lack of clinical use due to factors like low solubility, limited absorption, and severe side effects. This review summarizes the advanced treatments in Non-small cell lung cancer<sup>(3)</sup>. Cancer is a disease characterized by altered signalling and metabolism, leading to uncontrolled cell division and survival, influenced by various molecules, factors, and conditions<sup>(4)</sup>. Histologically and clinically, Lung cancer is a diverse group of malignancies primarily arising from lung airway cells, primarily affecting the respiratory tract<sup>(5)</sup>. Cancer that starts in the lung is called primary lung cancer. Cancer that spreads to your lungs from some where else in your body is called secondary lung cancer.

There are different types of primary lung cancer and they are divided into 2 main groups:

- Small cell lung cancer(SCLC) 15-20%
- Non-small cell lung cancer(NSCLC) 80-85%<sup>(8)</sup>.

Non-SCLC refers to a nondescriptive term that encompasses most malignant lung tumours in the US, including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma<sup>(6)</sup>. Adenocarcinoma of the lung, a type of lung cancer, develops in mucus-secreting cells in the outer lung and is more common in smokers, non-smokers, and younger individuals compared to other types<sup>(7,9)</sup>. Squamous cell carcinoma usually forms in the central part of your lungs. Squamous cell pathology, characterized by keratin and/or intercellular desmosomes, can be subtyped into nonkeratinizing, keratinizing, and basaloid carcinomas. These can present as Pancoast tumours and hypercalcemia, with brain repetition being a common site of repetition. Large cell carcinoma (LCC) is a malignant epithelial neoplasm lacking cytologic features like glandular, squamous, or neuroendocrine cancers. It consists of round to polygonal cells with prominent nucleoli<sup>(8)</sup>.

Lung cancer, accounting for 13% of all cancers, is the leading cause of cancer-related deaths worldwide. In 2022, the American Cancer Society reported 236,740 new cases and 130,180 deaths. Advanced disease prognosis is poor, with only 15% diagnosed early, and 17.4% 5-year overall survival<sup>(10)</sup>. Tobacco use is responsible for 90% of lung cancers, with patients with a 40 pack/year smoking history having a 20% higher risk. Adenocarcinoma is believed to have originated from filter-cigarette invention in the 1960s. Lung cancer is the leading cause of cancer death in men and the second most common in women worldwide<sup>(11,12)</sup>.

## Symptoms

Coughing up blood (hemoptysis), Shortness of breath, Chest pain (in advanced lung cancer), Pleural effusion (fluid in the chest)<sup>(13)</sup>.

## Risk factors:

Smoking (80-90% of all lung cancer cases), Family history(genetics),Exposure to carcinogenic chemicals and heavy metals (radon gas, asbestos, arsenic, chromium, nickel),Pulmonary fibrosis, HIV infection and alcohol consumption, Exposure to secondhand smoke, Previous radiation therapy<sup>(14)</sup>.

## Diagnosis:

Radiologic staging, CT scan (computed tomography)<sup>(15)</sup>, PET scan (positron emission tomography)

Invasive staging Bronchoscopic TBNA (transbronchial needle aspiration) , CP-EBUS Bronchoscopy

RP-EBUS Bronchoscopy, Navigation Bronchoscopy, Endoscopic-TBNA, Mediastinoscopy, Thoracoscopy

Biopsy<sup>(16)</sup>.

## Treatments:

### Nano Technology

Nanotechnology offers new cancer diagnostic approaches, including nanoparticle surfaces modified to target tumour receptors. Microfluidic arrays and array-based sensing methods offer low detection thresholds, short assay times, and high throughput. Precision nanomedicines could improve drug pharmacokinetics and therapeutic indexes<sup>(17)</sup>.

### Photothermal therapy(PTT)

Photothermal therapy (PTT) is a highly studied procedure involving nano systems as active curing instruments. PTT involves cancer cell lysis at high temperatures caused by exposure to near-infrared (NIR) light. Nano agents enhance heat production at the lesional site, using nano-sized particles as NIR absorbents. Gold nano shells were the first NIR absorbents used in PTT, with evidence-based effectiveness. However, nano shells are currently only available for FDA-sanctioned clinical studies. Other materials like semiconductors, graphene nanoparticles, poly pyrrole nanoparticles, and copper sulphide nanocrystals are being considered as alternatives.

### Photodynamic therapy

Photodynamic therapy (PDT) is an emerging therapeutic solution using nanomaterials to activate specific wavelengths, producing reactive singlet oxygen. Nano-sized materials can be used as photosensitive agents in cancer therapy to enhance the specificity of PDT. Combining nanoparticles with PDT methods, such as poly(vinyl alcohol)-porphyrin nanoparticles (PPNs), can create a synergy between diagnostics and therapy. These nanoplatforms release active agents at specific tumour sites, achieve a 100% survival rate in mice, and achieve a precision of approximately 95%. Porphyrin-silica nanoparticles are another promising approach due to their fluorescence and ability to inhibit tumour growth<sup>(18)</sup>.

## Drawbacks

Nanoparticles (NPs) have the potential to penetrate body membranes, making them useful for cancer treatment but also posing potential harm to healthy cells and DNA. They can cross the Blood Brain Barrier (BBB) and deliver drugs directly to the brain, but may also reach the brain, potentially causing life-threatening consequences. Special disposal methodologies are needed to prevent NPs from entering water supply or the environment. Biodegradable components are essential for lung cancer treatment. However, manufacturing is difficult and expensive, and further understanding of biological interactions and particle engineering is needed to optimize anticancer nanodrug delivery systems. Persistent use of NPs with drug delivery may lead to an engineered human race<sup>(19)</sup>.

## Target Therapy

Conventional chemotherapy and radiation treatments often fail to eliminate neoplastic cells due to high doses, causing irreversible damage to normal tissues. Biotherapy, or targeted therapies, is a potential option. New clinical trials are testing proteins, inhibitors, antibodies, cells, vaccines, and genetic treatments. Biological molecules approved for treating NSCLC include cetuximab, onartuzumab, nivolumab, necitumumab.

### Cetuximab

Cetuximab is a monoclonal antibody targeting the EGFR in 80%-85% of NSCLC patients. It can be combined with chemotherapy for advanced lung cancer treatment, increasing survival rates. Presently, there are promising studies using cetuximab in combination with other drugs, such as cisplatin. And docetaxel also being used as a neoadjuvant treatment for early-stage NSCLC. However, severe allergic reactions can occur. Respiratory reactions, elevated blood pressure, rashes, acne, fever and diarrhoea are some other side effects<sup>(20)</sup>.

### Onartuzumab

Onartuzumab, a 5D5 antibody, targets hepatocyte growth factor  $\alpha$ -chain binding to the receptor tyrosine kinase MET, potentially offering a therapeutic strategy. A phase II trial in advanced NSCLC patients randomized between erlotinib plus placebo and onartuzumab. Results showed overexpression of Met improved progression-free survival and overall survival.

### Nivolumab

Nivolumab is a human IgG4 programmed death 1 (PD-1) antibody approved for non-small cell lung cancer (NSCLC) in 2015. It disrupts the negative signal that mediates T-cell activation and proliferation by binding to PD-1 on activated immune cells. Nivolumab is active in advanced NSCLC and superior to docetaxel in terms of overall response rate, progression-free survival, and overall survival. It has been shown to produce durable responses and encouraging survival rates in cases with heavily pretreated NSCLC. The combination of nivolumab and platinum-based doublet chemotherapy has shown potential benefits beyond single-modality chemotherapy, making it a treatment option for cases with rapidly progressing disease or patients who do not express PD-L1.

## **Necitumumab**

The US FDA has approved the EGFR antagonist, necitumumab, for intravenous use in combination with gemcitabine and cisplatin for first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC). Necitumumab, an IgG1 monoclonal antibody, acts by binding to EGFR and blocking its ligand binding, potentially inhibiting EGFR-dependent pathways and tumour-cell proliferation and metastasis. The FDA's approval provides a new option for certain patients with squamous cell lung cancer<sup>(21)</sup>

## **Immunotherapy**

Immunotherapy with checkpoint inhibitors is the standard treatment for advanced nondriver-mutated non-squamous NSCLC, mainly using anti-programmed cell death protein 1 and anti-PD-L1 and anti-cytotoxic T-lymphocyte antigen. The therapy selection is guided by immunohistochemistry, allowing patient stratification into three groups of PD-L1 expression. Challenges in anatomopathological examination include less invasive procedures, increased handling of biopsy specimens, and increasing molecular target identification<sup>(22)</sup>.

## **Mechanisms Underlying Anti-cancer Immune Responses And Immune Checkpoint Inhibitor Function**

The cancer-immunity cycle is a crucial process in antitumor immune responses, involving the release of cancer antigens, presentation, trafficking of T cells, infiltration, recognition, and killing of cancer cells. To maintain balance between immune activity and autoimmunity, immune checkpoint molecules regulate T lymphocyte activation and proliferation. Cancer cells can express ligands that stimulate these pathways and inhibit T-cell activation, potentially restoring the T-cell response to certain tumours, such as advanced non-small cell lung cancer<sup>(23)</sup>.

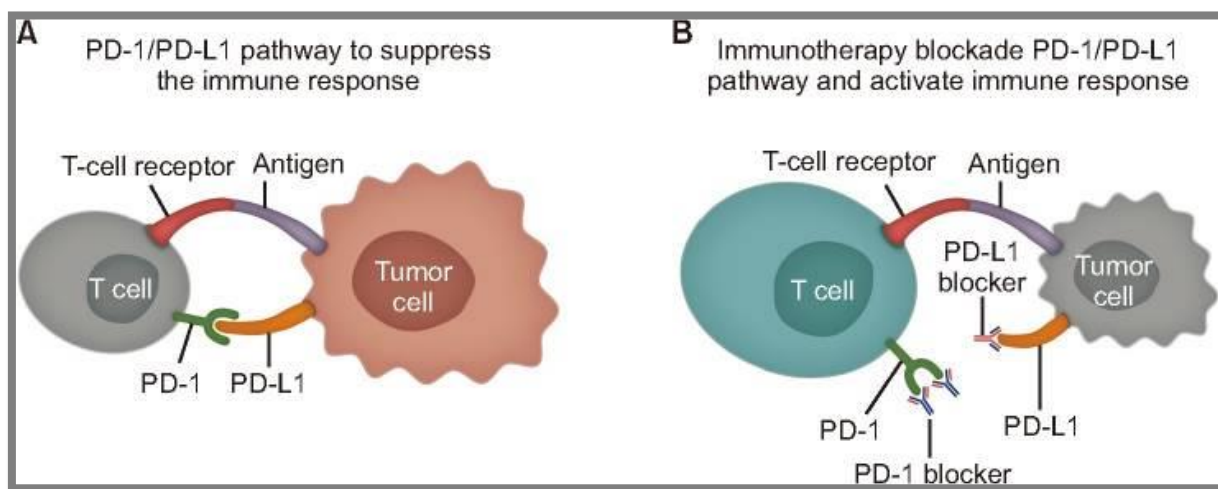


**Table:1**

**Indications for the use of current U.S. FDA-approved immune checkpoint inhibitors in lung cancer patient**

**Diagrammatic View Of Mechanism**

Agent	Indication	Line	Usage	Biomarker
Nivolumab	Metastatic NSCLC*	2 <sup>nd</sup> line	Monotherapy	Any
	Metastatic SCLC	3 <sup>rd</sup> line	Monotherapy	Any
Pembrolizumab	Metastatic nonsquamous NSCLC <sup>†</sup>	1 <sup>st</sup> line	Combination with pemetrexed and platinum	
	Metastatic squamous NSCLC	1 <sup>st</sup> line	Combination with carboplatin and paclitaxel	Any
Atezolizumab	Metastatic non-squamous NSCLC <sup>†</sup>	1 <sup>st</sup> line	Combination with bevacizumab, paclitaxel, and carboplatin	Any
	Metastatic NSCLC*	2 <sup>nd</sup> line	Monotherapy	Any
	Extensive-stage SCLC	1 <sup>st</sup> line	Combination with carboplatin and etoposide	Any
Durvalumab	Unresectable, stage III NSCLC <sup>§</sup>	2 <sup>nd</sup> line	Monotherapy	Any



## **The present applications of immunotherapy**

Since 2015, the FDA has approved four different ICIs for treating non-small cell lung cancer (NSCLC), including anti-PD-1 nivolumab, pembrolizumab, anti-PD-L1 atezolizumab, and durvalumab. Progress in this field will guide clinical practice in China, where two-thirds of NSCLC patients have negative driver gene mutations. Immunotherapy has become a first-line scheme for advanced NSCLC, with a combination regimen recommended for patients without pembrolizumab contraindication<sup>(24)</sup>. Advantages of immunotherapy include more effectiveness, longer curative effects, mild side effects, and longer effectiveness for patients with two consecutive years of treatment<sup>(25)</sup>.

## **ICIs-based combination therapy as the first-line treatment for advanced NSCLC**

Phase III trials have evaluated the efficacy and safety of ICIs-based combination therapy for advanced NSCLC. Results showed significant improvements in OS, PFS, and ORR compared to controls. The FDA approved another ICI, tiragolumab, in 2021, demonstrating that combining TIGIT and PD-L1 inhibitors may enhance antitumor activity by potentially amplifying the immune response.

## **Adoptive cell therapy(ACT) and cancer vaccine for advanced NSCLC**

TCR-T therapy has been tested in four iterations, primarily targeting solid tumours, including NSCLC (26). TCR is a molecule on the surface that particularly recognises and mediates immune responses (27). ADP-A2M4CD8, a novel therapy, is being investigated. In the SURPASS trial, 13/15 patients showed disease control and RECIST responses. Cancer vaccines like CIMAvax-EGF have shown efficiency in clinical trials, with CIMAvax-EGF increasing median survival time and well-tolerated. OSE2101, a vaccine modifying epitopes, has shown better prognosis and fewer severe adverse events. Multiple clinical trials are ongoing for ACT and cancer vaccine in NSCLC<sup>(26)</sup>.

## **CHEMO RADIOTHERAPY**

Radiotherapy alone has shown promising response rates for locally advanced non-small cell lung cancer (NSCLC), but the outcomes have been poor. Sequential chemo radiotherapy has increased overall survival from 5% to 10% with chemotherapy, while concurrent chemo radiotherapy has improved it to 15% with an absolute survival benefit of 4.5%. Concurrent chemo radiotherapy is associated with lower toxicity, making it the preferred strategy for fit patients. Several regimens have been established in combination with radiotherapy, such as doublet chemotherapy and platinum-based chemotherapy regimens. However, no clear advantages are reported in locally advanced disease. Novel chemotherapy agents or targeted therapies have shown disappointing results in combination with radiotherapy, with no sufficient evidence to support their routine use in chemo radiotherapy protocols<sup>(28)</sup>.

## Chemo Radiotherapy In Non-Small Cell Lung Cancer

Sequential chemotherapy (CRT) has shown an increase in overall survival (OS) from 5% to 10% at 5 years, while concurrent CRT offers a 4.5% absolute survival benefit. However, sequential therapy carries less toxicity risk for oesophagitis and pneumonitis. Currently, the custom treatment for localized inoperable NSCLC is concurrent CRT with a platinum-based doublet and 60Gy radiotherapy delivery daily over 6 weeks followed by two cycles of consolidation chemotherapy<sup>(29)</sup>. However, survival rates are low, with median survival of 20-28 months and 5-year OS of 15-20%. Combining CRT with immunotherapy is being evaluated, as radiotherapy can modulate the immune system and initiate innate and adaptive immunity<sup>(30)</sup>.

## Systemic Therapy

Concurrent chemotherapy therapy (CHRT) improves long-term survival in stage III non-squamous non-small cell lung cancer (NSCLC) patients by about 5%, but at the expense of increased toxicity, mainly acute esophagitis<sup>(31)</sup>. Multiple CHT schedules are routinely used in concomitant CHRT, including two cycles of cisplatin-etoposide or platinum-vinorelbine given every three weeks. The PROCLAIM phase III trial randomized patients to RT combined with two cycles of concomitant cisplatin-etoposide followed by consolidation with platinum-based doublet or concomitant cisplatin-pemetrexed followed by consolidation with pemetrexed. The pemetrexed-based regimen was associated with lower incidence of drug-related adverse events, particularly grade 3-4 neutropenia<sup>(32)</sup>. Weekly carboplatin-paclitaxel combined with concomitant RT remains a viable option, particularly in patients with other comorbidities and adequate pulmonary reserve. Consolidation docetaxel is still used in some centres, particularly after concurrent CHRT with weekly carboplatin-paclitaxel, due to inadequate systemic exposure<sup>(33)</sup>.

## Surgery

The following types of surgery may be used for NSCLC:

- **Lobectomy.** The lungs have 5 lobes, 3 in the right lung and 2 in the left lung. A lobectomy is the removal of an entire lobe of the lung. It is currently thought to be the most effective type of surgery, even when the lung tumour is very small. Clinical trials are underway to study if less extensive surgeries have similar outcomes for tumours that are 2 centimetres or smaller<sup>(34,35)</sup>.
- **A wedge resection.** If the surgeon cannot remove an entire lobe of the lung, the surgeon can remove the tumour, surrounded by a margin of healthy lung.
- **Segmentectomy.** This is another way to remove the cancer when an entire lobe of the lung cannot be removed. In a segmentectomy, the surgeon removes the portion of the lung where the cancer developed. Typically, more lung tissue and lymph nodes are removed during a segmentectomy compared to a wedge resection.
- **Pneumonectomy.** If the tumour is close to the centre of the chest, the surgeon may have to remove the entire lung. A pneumonectomy has more risks than a lobectomy and your doctor will need to consider the health of your heart and lungs before performing this surgery<sup>(36)</sup>.



- **Thoracotomy.** Surgeon makes a cut that runs around the side of the chest. This is called thoracotomy. Sometimes the cut may only be a few centimetres long. But it can also be longer and run from under the nipple around to your back under the shoulder blade<sup>(37)</sup>.
- **Sternotomy.** During a sternotomy, your surgeon makes a cut through the length of the breastbone. It gives them access to both the left and right sides of the chest<sup>(38)</sup>.
- **Keyhole surgery.** Keyhole surgery can remove small,early,non small cell lung cancers. The medical name for this operation is video assisted thoracoscopic surgery (VATS).The surgeon makes 1, 2 or 3 small cuts on the side of your chest. They use a long, bendy tube called a thoracoscope<sup>(39)</sup>.
- The recovery time from lung surgery depends on the removal of lung tissue and the patient's health. Exercise is crucial for recovery, preventing side effects and reducing hospital stay. Patients may need guidance from the healthcare team or cancer rehabilitation programs<sup>(35)</sup>.

## OTHER DRUGS

### 1.LIBTAYO (Cemiplimab)

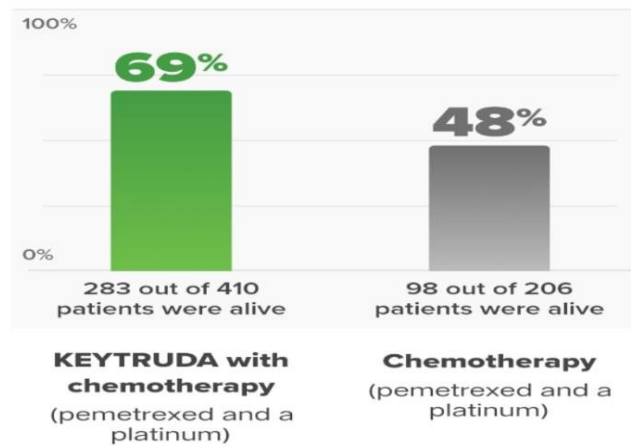
Libtayo is a prescription medication for adults with non-small cell lung cancer (NSCLC) and can be used in combination with platinum chemotherapy for locally advanced lung cancer, metastatic lung cancer, and tumours without abnormal genes. As a single agent it is used as first line treatment of adult patient with NSCLC who have high PD-L1 expression (tumour proportion score is less than or equal to 50%) as determined of an FDA approved test, with no EGFR,ALK, or ROS1 aberrations and locally used for patients who are not candidates for surgical resections or chemoradiation<sup>(40,41)</sup>.

Libtayo leads to severe and fatal immune-mediated adverse reactions such as:

Immune mediated pneumonitis, Immune mediated colitis, Immune mediated hepatitis, Immune mediated endocrinopathies, Immune mediated nephritis along with renal dysfunction, Immune mediated dermatology adverse reactions .It also cause other adverse effects like adrenal insufficiency, hypophysitis ,thyroid disorders, diabetes mellitus<sup>(42)</sup>.

### 2.KEYTRUDA (Pembrolizumab)

Keytruda is a prescription medication used to treat non-small cell lung cancer (NSCLC). It can be used alongside chemotherapy medicines like pemetrexed and platinum for advanced NSCLC, or alone for advanced NSCLC without surgery or radiation. It can also be used alone for advanced NSCLC if platinum-based chemotherapy fails or if the tumour has abnormal EGFR or ALK genes. KEYTRUDA can be used alone in adults to prevent lung cancer from recurring after surgery, platinum-based chemotherapy, and stage IB or II or IIIA NSCLC<sup>(43,44)</sup>.

**More patients lived longer**

A clinical trial compared KEYTRUDA combination with chemotherapy in advanced non-squamous, non-small cell lung cancer patients with no prior drug treatment, EGFR or ALK gene abnormalities, and chemotherapy alone<sup>(44)</sup>.

Signs and symptoms of immune system problems caused by Keytruda:

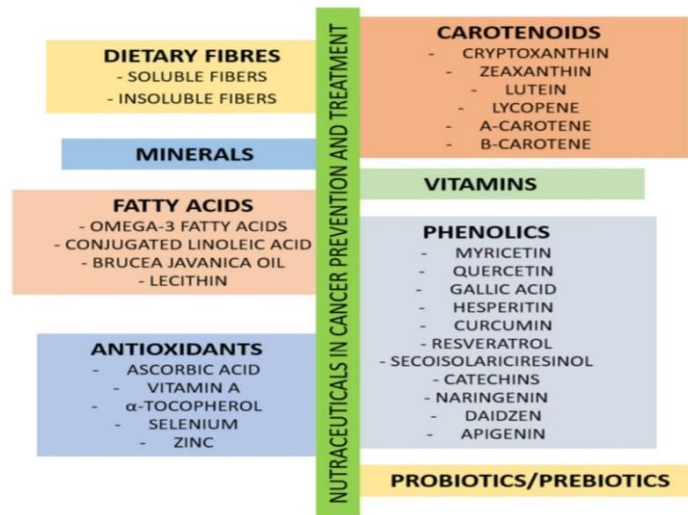
- Lung problems
- Intestinal problems
- Liver problems
- Hormone gland problems
- Kidney failure<sup>(43)</sup>.

**TAGRISSE (Osimertinib)**

AstraZeneca is exploring Tagrisso, a third-generation, irreversible EGFR-TKI, for treating multiple stages of NSCLC. Approved in over 100 countries, it is used for 1st-line treatment and adjuvant treatment of early-stage NSCLC. AstraZeneca is also conducting Phase III trials on earlier lung cancer stages, including neoadjuvant resectable, adjuvant resectable and local advanced unresectable settings. The company is also researching ways to address tumour resistance mechanisms. Tagrisso, a targeted therapy for EGFR-positive NSCLC, contains osimertinib, an active drug in an oral tablet available in 40 and 80 mg strengths<sup>(46)</sup>

**Side effects:**

- Cardiomyopathy
- Long QT syndrome (abnormal heart rhythm)
- Stevens-Johnson syndrome (serious skin rash) and Pneumonitis<sup>(47)</sup>.



## NUTRACEUTICALS<sup>(48)</sup>

### GREEN TEA

Green tea consumption reduces lung cancer risk, with active components like Theabrownin and EGCG mediating its antitumor activity. Theabrownin promotes apoptosis, cell cycle arrest, and inhibits lung cancer cell proliferation. EGCG also sensitizes cells to cisplatin and TKIs<sup>(49)</sup>.



### OMEGA-3 FATTY ACID

Research indicates that omega-3 fatty acid supplementation can improve nutritional status in cancer patients through various mechanisms. These polyunsaturated fatty acids, found in seeds and marine products, suppress inflammatory and oxidative responses, improve appetite, and enhance weight gain. They have been evaluated in various types of cancer, including colorectal, oral, breast, and hematologic. However, more randomized, controlled clinical studies are needed to confirm their effectiveness<sup>(50)</sup>.



## 6-SHOGAOL

The study investigates the anticancer effect of 6-shogaol on human non-small cell lung cancer A549 cells. It found that 6-shogaol inhibited cell proliferation by inducing autophagic cell death, but not apoptosis. It also inhibited survival signalling through the AKT/mTOR signalling pathway, blocking the activation of AKT and downstream targets. The findings suggest 6-shogaol may be a promising chemo preventive agent against lung cancer<sup>(51)</sup>.



## NATURAL METHODS

Healthy living involves adopting healthy habits and maintaining a healthy lifestyle, which can significantly improve quality of life, especially during and after lung cancer treatment.

- MEDITATION
- YOGA
- MASSAGE
- HYPNOSIS
- STOP SMOKING
- PHYSICAL ACTIVITY

## CONCLUSION

Cancer is a disease characterized by altered signalling and metabolism, leading to uncontrolled cell division and survival. Lung cancer is a diverse group of malignancies primarily arising from lung airway cells, affecting the respiratory tract. Primary lung cancer is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Non-SCLC includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for 13% of all cancers. In 2022, the American Cancer Society reported 236,740 new cases and 130,180 deaths. Tobacco use is responsible for 90% of lung cancers, with patients with a 40 pack/year smoking history having a 20% higher risk. Symptoms include coughing up blood, shortness of breath, chest pain, and peripheral effusion. Risk factors include smoking, family history, exposure to carcinogenic chemicals and heavy metals, pulmonary fibrosis, HIV infection, alcohol consumption, secondary smoke, and previous radiation therapy. Treatments

include nanotechnology, target therapy, immunotherapy, chemotherapy, surgery, other drugs, nutraceuticals, and natural methods. Nanotechnology offers new cancer diagnostic approaches, such as nanoparticle surfaces modified to target tumour receptors. Photothermal therapy (PTT) involves cancer cell lysis at high temperatures caused by exposure to near-infrared (NIR) light.

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