Chapter 12
Advancements in the Diagnosis and Therapeutics for Non-Small Cell Lung Carcinoma (NSCLC): From Genetic Mutations to Public Health Perspectives

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ABSTRACT

Lung cancer, particularly non-small cell lung carcinoma (NSCLC), poses significant challenges in oncology. Accounting for approximately 85% of lung cancer-related deaths, NSCLC's aggressive nature demands comprehensive management strategies. Environmental factors like smoking and air pollution, alongside genetic mutations in genes such as EGFR, KRAS, and ALK, contribute to its development. Recent advancements in diagnostic modalities, including low-dose CT scans and molecular profiling, facilitate early detection. Treatment paradigms have evolved to incorporate multimodal approaches, encompassing surgery, radiotherapy, chemotherapy, targeted therapies, and immunotherapy. Collaboration among healthcare professionals is crucial for effective patient care. As research continues to unfold, novel therapeutic strategies and personalized medicine approaches hold promise for improving outcomes in NSCLC patients.

1. INTRODUCTION

Approximately 85% of lung cancer cases globally are attributed to non-small cell lung cancer, or NSCLC for short. And even with new treatments and advances in early detection, it is still a leading cause of cancer death. Hence, it is a very harmful factor for health. Adenocarcinoma, large cell melanoma, and small cell melanoma are the three main types of NSCLC. Their varied reactions lead to the development of different varieties and require an array of treatments. Globally, about 1.8 million NSCLC cases are diagnosed annually. Table 1: Respiratory rates per 1,000 persons by region. Men have the highest rates (33 per 100,000 people) in Asia, while women have the lowest rates. Smoking habits, genetics, environmental toxins, access to healthcare, and other factors influence these differences. In addition, even though the number of smokers has decreased since 2000, the number of cases of NSCLC has increased, indicating how challenging this complaint is to combat (Graph 1). This chapter combines recent research with current medical practices to provide a comprehensive understanding of NSCLC. It investigates the underlying causes of inheritable changes, discovers novel diagnostic techniques, and develops superior treatments to improve patient care and outcomes. The tables and maps' data emphasize the necessity of subtype- and area-specific actions to address this global

health issue (Alduais et al., 2023; Ganti et al., 2021; Rodak et al., 2021; Laguna et al., 2024; Lin et al., 2024; Qin et al., 2025; Rakaee et al., 2025).

Figure 1. Types of NSCLC

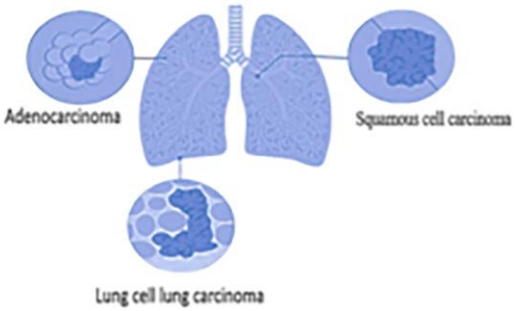
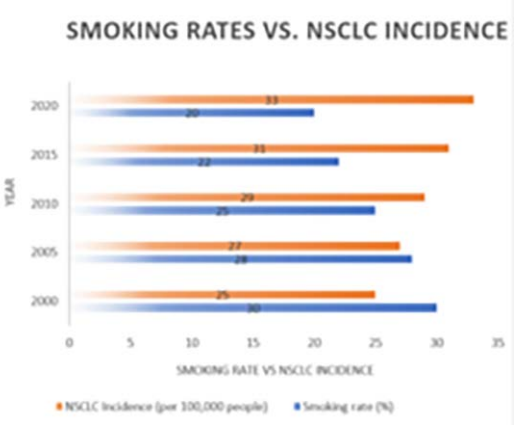


Table 1. NSCLC prevalence rates by region

Region	Prevalence Rate (per 100,000 people)
Asia	33 (Males), 14 (Females)
North America	31.9 (Males), 16.2 (Females)
Europe	28.1 (Males), 22.0 (Females)
South America	14.6 (Males), 11.7 (Females)
Africa	5.8 (Males), 3.2 (Females)
Australia	30.1 (Males), 28.5 (Females)

Figure 2. Smoking rates vs. NSCLC incidence



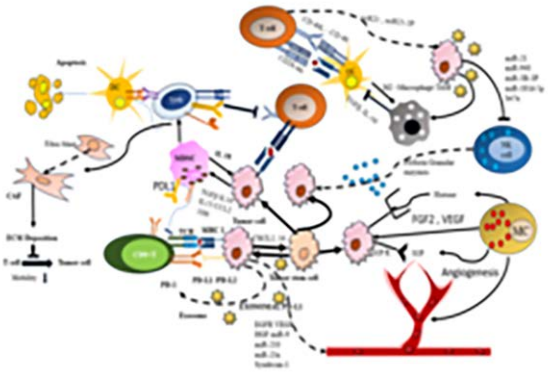
2. TUMOR MICROENVIRONMENT AND IMMUNE EVASION IN NSCLC

2.1 Role of the Tumor Microenvironment (TME)

i. Tumor Microenvironment (TME)

The tumor microenvironment, or TME, consists of numerous elements that support and suppress tumor growth and metastasis. Examples include ECM, signaling molecules (chemokines, growth factors, and cytokines), stroma (fibroblasts and endothelial cells), susceptible cells (T cells, macrophages, dendritic cells, and natural killer (NK) cells), and tumor cells. But behind the unsightly growth, cancer cells that can infiltrate neighbouring tissues and metastasize to distant sites form the ugly core of the excrescence, while stromal cells offer structural and functional support. Cancer can try to kill immune cells or demoralize them to bolster its own growth. Tissues are supported by the extracellular matrix (ECM), and interactions between these factors are facilitated by signaling molecules (Bożyk et al., 2022). The TME is necessary for excrescence growth, irruption, and metastasis because it alters vulnerable responses, alters the gravidity of cancer cells, and creates a protective environment for excrescence cells to thrive in. The stromal cells' influence, the modulation of vulnerable cells, and signaling pathways like those of CD8 T cells, dendritic cells, cancer-associated fibroblasts (CAFs), PD-L1, VEGF, and exosomes are highlighted in Figure 3.

Figure 3. Diagram of the tumor microenvironment



ii. Cellular and Non-Cellular Components of the Tumor Microenvironment

The assemblage of cellular and non-cellular elements that shapes fundamental processes during tumor progression and metastasis is known as the tumor microenvironment (TME). Cellular factors: Cancer-Associated Fibroblasts (CAFs) secrete growth-promoting factors, restructure the extracellular matrix (ECM) and activate angiogenesis, which stimulates cancer cell development, invasion, and spread (Bożyk et al., 2022; Farc et al., 2021; Escobedo-Calvario, A., et al., 2022). CAFs communicate with cancer cells to inject dynamic components to the TME through direct cell-cell contact and through a process called signaling patch stashing. Have either attack cancer — immune T cells, macrophages, dendritic cells, and NK cells — cells can either be reprogrammed to support tumor growth and suppress immune responses that target tumors (Tiwari et al., 2022; Li et al., 2024). The excrescence's growth and metastasis are aided by the formation of new blood vessels by endothelial cells, which grease angiogenesis. MSCs proliferate into different types of cells and modify the extracellular matrix (ECM), as well as sequester factors that promote tumor development and metastasis (Naser et al., 2022; Desai et al., 2025; El-Tanani et al., 2024). In the TME, Extracellular Matrix (ECM), a kind of proteins and glycoproteins, facilitates cell signaling and regulates cell gestation while serving as a structural support. Moreover, cancer cell metabolic reprogramming, characterized by processes such as the Warburg Effect and miscellaneous lipid metabolism, promotes rapid cell division, energy production, and adaptation to stress, and in turn contributes to (Balta et al., 2021; Bagaev et al., 2021; Baghy et al., 2023; Kundu et al., 2024; Li et al., 2023; Dzobo et al., 2023; Xie et al., 2023; Chen et al., 2022; Sadhukhan et al., 2023; Shin et al., 2022; Raju et al., 2022).

2.2 Mechanisms of Immune Evasion

The way cancer cells evade detection and destruction by the vulnerable system loses an immune evasive foundation or sits and it enables them to flourish and spread. And there are several ways to do that. First, to block T cell-mediated attack against cancer cells, they exploit checkpoints such as PD-1/PD-L1 and CTLA-4. New checkpoint molecules like Pause 3 and TIM-3 are being considered for cancer treatment (as shown in Table 2). Immune checkpoint inhibitors can block these relationships, reactivating T cells to target cancer cells.(Malinga et al., 2022; Ziogas et al., 2023; Mimura et al., 2021; Mollavelioglu et al., 2022; Shiravand et al., 2022; Catalano et al., 2022; Kuzevanova et al., 2022; Hussain et al., 2024; El Halabi et al., 2021; Jin et al., 2023).

Table 2. Immune Checkpoints

Checkpoint	Ligand	Function in Immune Evasion	Targeted Therapy (Status)
PD-1	PD-L1/ PD-L2	Inhibits T cell activation, promotes T cell exhaustion	Nivolumab, Pembrolizumab (FDA-approved)
CTLA-4	B7-1/B7-2	Inhibits early T cell priming	Ipilimumab (FDA-approved)
TIM-3	Galectin-9	Suppresses Th1 responses, promotes T cell dysfunction	Clinical trials ongoing
LAG-3	MHC Class II	Limits T cell proliferation and cytokine production	Clinical trials ongoing
TIGIT	CD155	Suppresses NK and T cell cytotoxicity	Clinical trials ongoing

Second, malignant cells store molecules with immune suppression, including cytokines (TGF-β and IL-10, for example) and enzymes (IDO, for example), that inhibit successful cell activity and generate a milieu permissive to evolution (see Table 3). (Abdul-Rahman et al., 2024; Accogli et al., 2021; Lopresti et al., 2024; Khalaf et al., 2021; Soleimani Mamalo et al., 2025).

Table 3. Secretion of Immunosuppressive Molecules

Secretion of Immunosuppressive Molecules	Description
Cytokines (e.g., TGF-β, IL-10)	Suppresses immune cell activity and promotes an immunosuppressive environment.
Enzymes like IDO	IDO depletes tryptophan, which is essential for T cell function, suppressing immune responses.
Prostaglandin E2 (PGE2)	Promotes immune cell suppression, supports regulatory T cell expansion, and enhances angiogenesis.
Adenosine	Accumulates in the TME and binds to A2A receptors on immune cells, leading to suppression of cytotoxic T cell activity.

Third, they slow the elimination of immunosuppressive cells such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and Tumor-associated macrophages (TAMs), that promote excrescence growth and an immune susceptible response (Table 4). (Li et al., 2022; Pietrobon & Marincola, 2021; Qureshi et al., 2021).

Table 4. Immunosuppressive Cells

Immunosuppressive Cells	Function
Regulatory T Cells (Tregs)	suppress killer T cells, creating a calm and restrained immune system.
Myeloid-Derived Suppressor Cells (MDSCs)	Dampen T cell activity and encourage tumor growth with cytokines and enzymes.
Tumor-Associated Macrophages (TAMs)	Encourage the growth of tumors, the formation of new blood vessels (angiogenesis), and immune suppression.

Ultimately, they then mutate major histocompatibility complex (MHC) molecules and downregulate antigen presentation, rendering the already vulnerable system less capable of recognizing and attacking cancer cells. (Dhatchinamoorthy et al., 2021; Yang et al., 2023; Jhunjhunwala et al., 2021; Algarra et al., 2021) Combined, these mechanisms allow cancer cells to avoid the vulnerable system and play a role in the growth of excrescences.

2.3 Implications for Therapy

Targeting the tumor microenvironment (TME) includes creative methods for increasing the efficiency of standard treatments. TME-targeted curatives can be mentioned, such as anti-angiogenic agents (e.g., bevacizumab) and ECM modifiers (e.g., hyaluronidase), which respectively aim to inhibit angiogenesis and ECM formation in the pro-tumorigenic TME in the tumor progression (Huang et al.,

2022). They consist of binding to cancer-associated fibroblasts (CAFs), modifying the extracellular matrix (ECM), and blocking pro-tumorigenic signaling pathways (Ma et al., 2023). Immunotherapy strategies have reinvigorated the cancer-resistant system to a great extent. Immune checkpoint inhibitors activate T cells to attack cancer cells, targeting PD-1, PD-L1, and CTLA-4 checkpoints (Wang et al., 2023). Oncolytic viruses (OV), either in line or reconstituted through lyophilized injection, are designed to infect and kill bacterial cells directly, all the while stimulating a vulnerable response to exosome-specific antigens. (Ghafouri-Fard et al., 2022) Auto T cell therapy involves re-engineering a patient's T cells to express excellent antigen receptors that target specific excrescence antigens, resulting in direct cancer cell elimination (Hou et al., 2022). It is possible to overcome resistance and increase treatment efficacy by combining immunotherapy with conventional therapies like chemotherapy, radiation, and targeted curatives (Sun et al., 2023). These combination curatives work the strengths of different modalities to achieve synergistic goods and address multiple mechanisms of resistance. relating and exercising biomarkers like PD-L1 expression, exome mutational burden (TMB), and other molecular signatures help guide treatment decisions. biomarkers play a crucial role in predicting and covering responses to immunotherapy (Dong et al., 2022). For illustration, PD-L1 expression situations can inform the use of PD-1/PD-L1 inhibitors, while TMB may prognosticate response to vulnerable checkpoint inhibitors (Zhao et al., 2022). Cancer treatment still faces obstacles and limitations, such as treatment resistance, patient response variability, and the need for better biomarkers. Understanding the TME and vulnerable evasion mechanisms shown in Table 5, coming up with new treatments, and solving patient problems with backed drugs are the primary focuses of ongoing research. The objectives of these studies are to address the issues that exist right now, illustrated in Figure 4, and open the way for more efficient cancer treatments in the future (Zhang et al., 2023).

Table 5. Immune Evasion Mechanisms

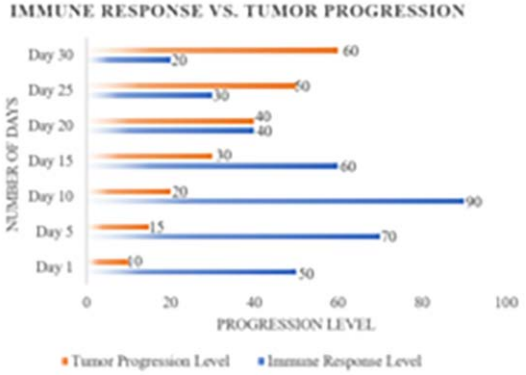
Immune Evasion Mechanism	Description
Immune Checkpoint Inhibition	Cancer cells upregulate inhibitory molecules like PD-L1 to suppress T-cell activity.
Secretion of Immunosuppressive Cytokines	Tumor cells release factors such as TGF-β and IL-10 to inhibit immune responses.
Tumor-Induced Immune Cell Dysfunction	Tumors can alter the function of immune cells, leading to reduced anti-tumor activity.
Recruitment of Regulatory T Cells (Tregs)	Tumors attract Tregs that suppress the activity of other immune cells.

continued on following page

Table 5. Continued

Immune Evasion Mechanism	Description
Alteration of Antigen Presentation	Tumor cells can downregulate antigen-presenting molecules, making them less recognizable to T cells.
Expression of Immune Checkpoints	Tumor cells express molecules like CTLA-4 to inhibit immune cell activation and proliferation.
Metabolic Competition	Tumor cells consume nutrients and produce waste products, creating an inhospitable environment for immune cells.
Induction of Immune Cell Apoptosis	Tumor cells can induce apoptosis (programmed cell death) in immune cells through various mechanisms.

Figure 4. Immune Response Vs. Tumor Progression



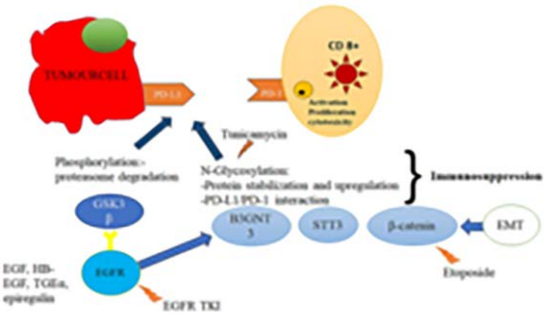
3. GENETIC MUTATIONS AND MOLECULAR SUBTYPES OF NSCLC

3.1 Genetic Mutations in NSCLC

1. Genetic research has changed drastically as a result of inheritable exploration. Treatment of Non-Small Cell Lung Cancer Genes such as EGFR, KRAS, ALK, ROS1, and BRAF drives cancer, illustrated in Figure 5 (NSCLC molecular pathways). Select the appropriate treatment. Take the novel TKI-otinib and its many indications in EGFR-mutated NSCLC. These medicines block dangerous signals to treat cases (Lei et al., 2022). And two ALK inhibitors, crizotinib and alectinib, benefit some patients with ALK mutations (Passaro et al., 2021). This problem was significantly addressed with the introduction of newer KRAS

G12C inhibitors (e.g., Sotorasib) (;;)They treat mutations that were previously difficult to treat. Alternatively, new targeted therapies that target the PD-1/PD-L1 pathways have transformed the medical treatment of the condition, extending some cases to long-term remission (Tan et al., 2022). Improved liquid necropsies that test for ctDNA in the complaint give crooks the ability to monitor the effectiveness of the treatment in real time and provide a more precise diagnosis of the problem (Pop-Bica et al., 2022). Croakers must overcome drug resistance to extend the lives of NSCLC patients. Gene specialists, medical experimenters, and laboratory scientists continue to collaborate in the creation of new medicines and the integration of various treatments (Liu et al., 2025).

Figure 5. NSCLC molecular pathways



3.2 Clinical Relevance of Genetic Mutations in NSCLC

These tailored approaches have led to the discovery of several targetable mutations in non-small-cell lung cancer (NSCLC), including mutations affecting EGFR, TP53, KRAS, MET, ALK, ROS1, and BRAF.(Koenig et al., 2021; Pruis, 2021) Erlotinib, Gefitinib, and Osimertinib are highly effective for those with EGFR mutations, found in 10–15% of NSCLC patients (eg, adenocarcinoma, especially in Asian women and nonsmokers) (Tada et al., 2022; Tsuboi et al., 2023), but resistance mutations (eg, T790M) will undermine any future combination therapy efforts. (Blaquier et al., 2023). Recent development of treatment options for TP53 mutations, which have an impact on proteins that prevent excretion (Canale et al., 2022). Both of these treatments have negative side effects. Specifics like sotorasib have improved the prognosis for KRAS mutations, which occur in 25 to 30 cases, primarily in smokers; however, the prognosis is still not as good as it is for EGFR or ALK mutations (Koenig et al., 2021). Capmatinib and other inhibitors are being

developed to treat cancer and poor health in order to investigate MET mutations that have been linked to aggressive diseases (Koenig et al., 2021). Specific treatments like sotorasib have shown promise for KRAS mutations, which affect approximately 25 to 30 cases, most of which are smokers; however, the prognosis is still not as good as it is for EGFR or ALK mutations (Koenig et al., 2021). Medicines like Crizotinib, Alectinib, and Lorlatinib, which improve survival and quality of life, have seen transformative success with ALK mutations, which are found in 3 to 5 cases (mostly in young, nonsmoking cases) (Fabbri et al., 2023). Capmatinib and other inhibitors are being developed to study MET mutations, which have been linked to aggressive cancers and poor health (Koenig et al., 2021). Besides, targeted curatives such as Dabrafenib and Trametinib are superior in the survival index than conventional chemotherapies for ROS1 mutations, which appear in about one to two cases (predominantly, young nonsmokers) (Dziadziuszko et al., 2021; Fabbri et al., 2023). It's a good disease to have if you have to have one — eventually, crizotinib and entrectinib work well to treat BRAF mutations, seen in one to three cases in smokers and nonsmokers alike (Koenig et al., 2021; Dziadziuszko et al., 2021). The importance of these treatments substantiates the need for ongoing exploration of resistance mechanisms and evidence-based treatment to mitigate the long-term problems posed by NSCLC cases (Yue et al., 2025; Diaz-Jimenez et al., 2024; Oya et al., 2025; Yuan et al., 2024).

3.3 Future Directions and Recent Findings:

Key inheritable mutations EGFR, KRAS, ALK, ROS1, and BRAF that have transformed non-small cell lung cancer (NSCLC) treatment via evidence-based cures have been identified by scientists (Koenig et al., 2021). Tyrosine kinase inhibitors (TKIs) such as Erlotinib, Gefitinib, and Osimertinib specifically target EGFR mutations, thus improving patient outcomes significantly, whereas medications such as Crizotinib and Alectinib have changed the landscape of care for ALK mutations (Herrera-Juárez et al., 2023). The case has been buoyed by the launch of the advanced KRAS G12C asset, Sotorasib, which has offered a new stopgap of sorts in the management of preliminarily recalcitrant cases, and by immunotherapies that target PD-1/PD-L1 pathways still yield durable outcomes (Rodak et al., 2021). Innovations such as liquid autopsies for real-time excrescence shadowing of DNA, oncolytic contagion curatives, and Auto-T cell treatments have an amazing potential to propel cancer treatment (Pezzuto et al., 2023). Continued imaging technologies and the growing cooperation between experimenters, oncologists, and inventors of specifics in medicine enhance the energy evolution that leads to the discovery of new specifics and adjusted curatives based on inheritable biographies (Pan et al., 2021). This heuristic matrix type, which appears in the NSCLC Inherited Muta-

tions Overview table, emphasizes the high influence of targeted treatments aimed at increasing NSCLC patients' quality of life and survival rates (Karagiannakos et al., 2022; Dan et al., 2024; Cognigni et al., 2022; Parvaresh et al., 2024; Gemelli et al., 2024)

Table 6. NSCLC Inheritable Mutations

Mutation	Prevalence (%)	Population	Prognosis	Therapies	References
EGFR	10–15	Non-smokers, Asian women	Improved with TKIs	Erlotinib, Gefitinib, Osimertinib	Koenig et al. (2021); Pezzuto et al. (2023a)
KRAS	25–30	Smokers	Challenging but improving	Sotorasib (KRAS G12C)	Rodak et al. (2021); Pan et al. (2021)
MET	~5	Aggressive cases	Poor prognosis	MET inhibitors in development	Karagiannakos et al. (2022); Dan et al. (2024)
ALK	3–5	Younger, nonsmokers	Favorable with targeted therapies	Crizotinib, Alectinib, Lorlatinib	Cognigni et al. (2022); Parvaresh et al. (2024)
ROS1	1–2	Younger, nonsmokers	Positive with targeted therapies	Crizotinib, Entrectinib	Herrera-Juárez et al. (2023); Rodak et al. (2021)
BRAF	1–3	Smokers, nonsmokers	Improved with BRAF inhibitors	Dabrafenib, Trametinib	Gemelli et al. (2024)

Other mutations:

Infrequently heritable mutations like MET amplifications, RET rearrangements, and HER2 mutations indicate non-small cell lung cancer (NSCLC), paving the way for largely adapted treatments. MET amplifications, for illustration, constantly reduce the efficacy of EGFR inhibitors but can be managed with MET blockers like Capmatinib (Lee et al., 2024; Dagogo-Jack et al., 2023). Also, RET rearrangements, seen in 1 – 2 of NSCLC cases, are effectively treated with targeted antidotes analogous to Selpercatinib and Pralsetinib, offering an expedient for better outcomes (Ali et al., 2022; Syed et al., 2022; Russo et al., 2024; Novello et al., 2023). Advanced treatments like fam-trastuzumab deruxtecan-nxki and ado-trastuzumab emtansine are effective, even though HER2 mutations disrupt cell signaling and proliferation in two to four instances (Olmedo et al., 2022; Lo et al., 2023; Clark et al., 2023). These mutations and their treatments are epitomized in Table 7, Rare heritable Mutations in NSCLC, which highlights their frequency, impact, and the targeted antidotes used (Ghosh et al., 2024; LoPiccolo et al., 2024).

Table 7. Rare Genetic Mutations in NSCLC

Mutation Type	Prevalence in NSCLC	Impact	Targeted Therapy (Examples)	References
MET Amplifications	Associated with resistance to EGFR inhibitors	Continuous activation of the MET pathway	Capmatinib	Lee et al. (2024); Dagogo-Jack et al. (2023)
RET Rearrangements	1–2% of cases	Production of abnormal proteins driving cancer progression	Selpercatinib, Pralsetinib	Ali et al. (2022); Syed (2022); Russo et al. (2024); Novello et al. (2023)
HER2 Mutations	2–4% of cases	Abnormal cell signaling and proliferation	Fam-trastuzumab deruxtecan-nxki, Ado-trastuzumab emtansine	Olmedo et al. (2022); Lo & Lindeman (2023); Clark et al. (2023); Ghosh et al. (2024); LoPiccolo et al. (2024)

3.4 Molecular Subtypes

Treatment plans are heavily influenced by the molecular subtypes of NSCLC, such as adenocarcinoma, gauged cell carcinoma, large cell carcinoma, and mixed-lineage excrescences. Adenocarcinoma, which accounts for roughly 40% of cases, is presently among nonsmokers and responds effectively to targeted therapies, chemotherapy, and immunotherapy (Sen et al., 2024). On the other hand, scaled cell melanoma, explosively linked to smoking and comprising 30% of cases, frequently requires chemotherapy and radiation but generally presents a poorer outlook (Wang et al., 2025). Large cell melanoma, seen in 15 of NSCLC cases, is aggressive and inadequately discerned, challenging individualized approaches that combine targeted and vulnerable curatives (Grilli, 2022; Friedlaender et al., 2024). Incipiently, mixed-lineage excrescences, characterized by features of multiple subtypes, demand acclimatized treatments grounded on their dominant molecular profile (Munteanu et al., 2023; Sulewska et al., 2023). These subtype details are epitomized in Table 8, Molecular Subtypes of NSCLC, which outlines the frequency, characteristics, and treatment strategies for each subtype (Meira, 2023; Wunderlich et al., 2024; Winge et al., 2023; Stanganelli et al., 2022; Sun et al., 2022; Palma et al., 2022; Hyytiäinen et al., 2023; De Jong et al., 2022; Zhu et al., 2024; Koroulakis & Agarwal, 2024).

Table 8. Molecular Subtypes of NSCLC

Subtype	Prevalence (%)	Characteristics	Treatment Strategies	References
Adenocarcinoma	~40	Most common; occurs in both smokers and non-smokers	Targeted therapies, chemotherapy, and immunotherapy	Sen et al. (2024); Friedlaender et al. (2024); Munteanu et al. (2023)
Squamous cell carcinoma	~30	Linked to smoking, it arises in the central airways	Chemotherapy, radiation therapy, and targeted therapies	Wang et al. (2025); Stanganelli et al. (2022); Sun et al. (2022)
Large cell carcinoma	~15	Poorly differentiated; aggressive	Chemotherapy, targeted therapies, and immunotherapy	Sulewska et al. (2023); Palma et al. (2022); De Jong et al. (2022)
Mixed-lineage tumor cells	Varies	Features of multiple subtypes	Treatment based on predominant subtype: chemotherapy, targeted therapies, and immunotherapy	Wunderlich et al. (2024); Winge et al. (2023); Koroulakis & Agarwal (2024)

3.5 Immune Subtypes

Immunological subtypes of non-small cell lung cancer (NSCLC) are separable by molecular entities and infiltration of susceptible cells. Immunotherapy works whenever the lesion has lots of vulnerable cells, when it improves the body's ability to find and count cancer cells (Lei et al., 2022). NOTE: PD-L1 expression and Tumor Mutational Burden (TMB) are both good predictors of treatment efficacy because tumors that have high PD-L1 expression or TMB are typically responsive to susceptible checkpoint inhibitors (Xie et al., 2024; Mamdani et al., 2022; Xing et al., 2022). Table 9 Immunological subtypes of NSCLC, their significance as prognostic factors, and the biomarkers associated with them are presented in Subtypes of NSCLC (Yang et al., 2022; Iglesias-Escudero et al., 2023; Taefehshokr et al., 2022).

Table 9. Immunological Subtypes of NSCLC

Subtype	Definition and Characteristics	Prognostic Significance and Response	Biomarkers	References
Immune Infiltration and Molecular Clustering	Presence of immune cells within the tumor and specific molecular traits	High immune infiltration leads to better immunotherapy responses	PD-L1 expression, Tumor Mutational Burden (TMB)	Lei et al. (2022); Xie et al. (2024); Mamdani et al. (2022)
Prognostic Significance and Response to Immunotherapy	Tumors with high immune infiltration tend to respond better to immunotherapy	Improved outcomes with high immune infiltration	PD-L1 expression, TMB	Xing et al. (2022); Yang et al. (2022); Iglesias-Escudero et al. (2023)
Biomarkers for Predicting Outcomes	Biomarkers such as PD-L1 expression and TMB guide immunotherapy decisions	Better response with high PD-L1 and TMB	PD-L1 expression, TMB	Taefehshokr et al. (2022)

3.6 Prognostic and Predictive Biomarkers

Biomarkers are useful tools for understanding and treating conditions because they give pivotal insight into the progression of complaints and the applicable course of action. Regardless of the treatment, prognostic biomarkers prognosticate the likely course of a condition, such as the likelihood of rushing or overall survival (Tarighati et al., 2023). Predictive biomarkers, on the other hand, help in determining which treatments are most applicable for a given circumstance, ensuring that treatments are acclimatized to the case's condition (Zhang et al., 2023). These natural pointers empower croakers to customize care, relating cases that admit targeted antidotes that meliorate issues, extend survival, and avoid gratuitous or potentially dangerous treatments (Al-Tashi et al., 2023). Personalized medicine is revolutionized by directly relating and using these biomarkers, paving the way for more effective and supported case care (Li et al., 2022; Li et al., 2022; Zhang et al., 2023; Ding et al., 2022; Rosellini et al., 2023; Veyssière et al., 2022; Cao et al., 2022; Su et al., 2023; Győrffy, 2023; Iida et al., 2022).

4 ADVANCED DIAGNOSTIC APPROACHES IN NSCLC

Advanced imaging methods must help in portraying the anatomy of the body organs and their functionality, and also need to detect diseases like non-small cell lung cancer (NSCLC). CT, PET, and MRI are three of the most commonly used

imaging modalities; each has its underlying principles, advantages, and drawbacks. CT scans use X-rays to create and generate their slice-by-slice output, the true 3D image of the body. CT scans are a vital part of many medical specialties, including emergency medicine, cardiology, and oncology, as they are very good at early detection of internal bleeding, tumors, and fractures. CT scans are not just fast, mundane, and cheap, but are also going to be a source of radiation exposure for patients and, therefore, are less effective at visualizing soft tissues. Contrast dyes are also uncomfortable for patients with renal disease. PET scans use radioactive tracers, such as fluorodeoxyglucose (FDG), to mark the cellular metabolism of the areas involved. PET is discovered to provide the best optimal outcomes in the diagnosis of brain diseases such as Alzheimer's, cancer diagnosis, tracking cancer growth, and heart disease diagnosis (Nooreldeen et al., 2021; Jin et al., 2023).

Although PET scans may be most useful for cancer detection, they are labor-intensive, difficult to locate, and low in radiation. The heart, brain, joints, and other soft parts of the body are depicted with superior picture quality and detail in MRI scans, which use a strong magnetic field and radio waves. MRIs are needed more for 3D imaging of ligaments and tissues, brain tumors, and scars of multiple sclerosis. MRIs aren't ionizing, but they are much more expensive, take a lot of time, and aren't good for people with heart devices or metal implants, as shown in Table 10, the features of CT, PET, and MRI like imaging modalities (Tan et al., 2025; Pradhan et al., 2023).

Table 10. The features of imaging modalities

Feature	CT (Computed Tomography)	PET (Positron Emission Tomography)	MRI (Magnetic Resonance Imaging)	References
Principle	Separating components based on differential partitioning between stationary and mobile phases, analyzed using computational methods.	Detecting gamma rays from positron annihilation to create detailed images of metabolic activity.	Hydrogen nuclei emit signals when exposed to a strong magnetic field and radiofrequency pulses, producing detailed images.	Rolfo et al. (2021); Abdayem & Planchard (2021); Tomasik et al. (2023)
Best For	Detecting bone fractures, tumors, and internal bleeding.	Assessing metabolic activity, cancer detection, heart disease, and brain disorders.	Imaging soft tissues, brain, spinal cord, and joints.	Qi et al. (2025); Di Capua et al. (2021); Cucchiara et al. (2021)
Radiation	Yes	Yes	No	Smolle et al. (2021); Jin et al. (2023); Nooreldeen & Bach (2021)

continued on following page

Table 10. Continued

Feature	CT (Computed Tomography)	PET (Positron Emission Tomography)	MRI (Magnetic Resonance Imaging)	References
Procedure Time	5-30 minutes	30-60 minutes	15-90 minutes	Malapelle et al. (2021); Ning et al. (2021); Bazhenova et al. (2021)
Contrast Agent	Sometimes required	Required	Sometimes required	Guo et al. (2022); Gandhi et al. (2023); Huang et al. (2023)
Cost	Moderate	High	High	Sharma et al. (2022); Qi et al. (2021); Spira et al. (2021)
Availability	Widely available	Less widely available	Widely available	Pisapia et al. (2022); Liu et al. (2021); Rodrigues et al. (2022)

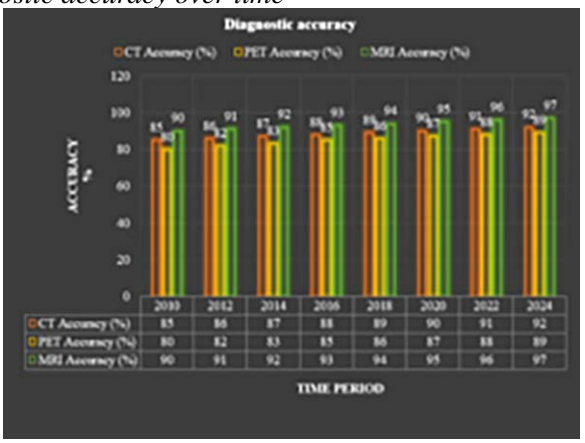
Advancements in diagnostic technologies have been on the incremental side that resulting in an increase in accuracy over time. The visual representation has been carefully done according to this change, where CT scans have been consistently on the rise, making them the best in anatomical imaging, PET scans have been the first in functional imaging, and MRIs still have the best imaging ability in soft tissue. These methods together are a must for medical professionals to diagnose a situation properly and in the most accurate way that is possible.

Despite having all those imaging technologies, the fact still stands that the new diagnosis of NSCLC was revolutionized by liquid biopsies and molecular profiling. Molecular profiling, which is the analysis of changes in the DNA, RNA, and proteins of cells, is commonly done with methods such as WGS and RNA-Seq. The cross-referencing of the most efficient targetable cancer-causing mutations (for example, EGFR, KRAS, and BRAF) can assist medical professionals in the formulation of a more individualized therapy plan (Spira et al., 2021; Bazhenova et al., 2021). To name one, the identification of cancer cells in blood (CTCs) and circulating tumor DNA (ctDNA) may be carried out through a liquid biopsy, which is a less invasive and more patient-friendly procedure than the conventional body fluid testing, like blood and plasma. The use of ddPCR and NGS, among other methods, can be a potential tool to constantly survey patients and hence have a better chance of providing the necessary treatments while at the same time drastically lowering the number

of cancer-causing mutations to the level of sensitivity that is safe for the patients (Rolfo et al., 2021; Tomasik et al., 2023; Qi et al., 2025).

This combination shows that the processes above are an important part of the progress that has been made in NSCLC detection. While, at the same time, they also give us the confidence of more precision, enhanced patient care, and the continued development in the medical field, as shown in Figure 6 (Cucchiara et al., 2021; Malapelle et al., 2021; Liu et al., 2021).

Figure 6. Diagnostic accuracy over time



5 SYSTEMIC THERAPIES FOR NSCLC: CHEMOTHERAPY, TARGETED THERAPY, AND IMMUNOTHERAPY

The largest number of cases was set up to be non-small cell lung cancer (NSCLC), which accounts for around 85% of all lung cancers. In late-stage cancers with metastatic diseases, treatment mainly involves the use of drugs falling under the classes of systemic therapy for NSCLC. They can all be taken as immunotherapy, targeted therapy, or cytotoxic chemotherapy. With efficacy and actions being variable, their differences compose each one specific to the specialty of the respective tumor are shown in Table 14& 15 and survival rate variation between therapy is graphically illustrated in Figure 9 (Massafra et al., 2021; Godoy et al., 2023; Lahiri et al., 2023).

5.1 Chemotherapy Mechanisms

Chemotherapy has been used to differentiate some forms of non-small cell lung cancer, or NSCLC. Chemotherapy, on the other hand, causes problems because it affects both cancerous and healthy cells within its range during treatment. This non-selectivity generally results in other side effects, including myelosuppression, nausea, and neuropathy in tumors with particular driver mutations, restricting the overall effect and patient tolerance. As revealed in the following table, the action mechanisms of some reputable chemotherapy agents- Cisplatin, Pemetrexed, Paclitaxel, and Etoposide- are different and attach to cancer cells in their own special way. All these drugs attack specific weaknesses to stop the tumor from growing while killing the cells. The mechanisms of action for the major chemotherapy categories, discussed in Table 11 (Ying et al., 2024; Li et al., 2024; Wang et al., 2024; Xi et al., 2025; Huang et al., 2024; Sito et al., 2024).

i. Platinum-Based Doublet Therapy (Cisplatin)

Chemotherapy places chemical bonds-intrastrand and interstrand cross-links-at DNA-targeted cancer cells. Those bonds cause the deformities in the original structure, which don't let the strands separate in two vital processes for the growth and function of cells-transcription and replication, therefore, don't let the cell develop. The majority of damaged cells trigger a repair process; however, the weight of damage exceeds the capability of these processes and leads to cell cycle arrest and apoptosis (inducement of programmed cell death). The action of cisplatin, which is useful in NSCLC tumors, targets the dividing cells for attack. As shown in the table, this treatment prevents tumor growth through DNA cross-links and the death of cancer cells (Umar et al., 2024; Zou et al., 2024; Lee et al., 2024; Sito et al., 2024; Xi et al., 2025; Wang et al., 2024).

ii. Pemetrexed antimetabolites

Several folate-requiring enzymes involved in the synthesis of DNA and RNA intermediates utilized by the proliferating cancer cells are inhibited by this class of anticancer drugs. In particular, the targets for this drug are thymidylate synthase for the thymidine synthesis, dihydrofolate reductase to sustain folate pool for other generation of DNA precursors, glycinamide ribonucleotide formyl transferase; so upon interference, Pemetrexed could readily stop the S cell cycle, which is utilized for the replication of DNA, leading to cell death. It does a good job of fighting the various subtypes of non-squamous NSCLC, which rely a lot on this kind of metabolic activity to grow faster. Pemetrexed performs one of these interferences in

nucleotide synthesis, which will essentially affect tumor survival, as shown in this table (Nardin et al., 2024; Hendriks et al., 2024; Molinaro et al., 2024; Heymach et al., 2025; Nagy et al., 2024).

iii. Taxanes (Paclitaxel)

Paclitaxel involves the cell microtubule structure in the target cells, where the microtubules generate resistance, rigidity, and help in chromosome separation during mitosis (cell division). The mitotic spindles are very effective stabilizers of microtubules because they induce mitotic arrest when paclitaxel is added to the cultures. This causes a metaphase arrest of the cell when paclitaxel stabilizes the microtubules within the spindle. When this checkpoint is prolonged, it results in what is called mitotic catastrophe, which is a cell death mechanism where the divisions go wrong. This artificiality of formation during mitosis uses paclitaxel to kill extensively dividing cancer cells most effectively. - As highlighted in the table, paclitaxel's therapeutic action was ascribed to the stabilization of microtubules and cellular propagation processes within cancer cells (Díaz et al., 2024).

iv. Topoisomerase Inhibitors (Etoposide)

This chemotherapeutic drug works by inhibiting topoisomerase II, an enzyme that resolves DNA supercoiling during transcription and replication. Etoposide stabilizes the intermediate enzyme-DNA complex that prevents DNA strands from religating, causing the cell to accumulate DNA breaks (Jang et al., 2025). The cumulative effect of these breaks affects the replication and transcription processes in the cell. This initiates apoptotic pathways because neither damage repair nor replication can continue (Huang et al., 2024). Etoposide selectively kills cancer cells that are rapidly dividing and that need a functional DNA repair mechanism for survival. In the table, etoposide's therapeutic action involves the disruption of DNA and killing cancer cells by blocking topoisomerase II (Özkaya Gül et al., 2025).

Table 11. Mechanism of action of chemotherapeutic agents

Chemotherapeutic Category	Agents	Mechanism of Action	References
Platinum-Based Doublet Therapy	Cisplatin	Causes DNA cross-links, inducing apoptosis.	Umar et al. (2024); Sito et al. (2024); Zou et al. (2024)
Antimetabolites	Pemetrexed	Inhibits folate-requiring enzymes, disrupting DNA synthesis (effective in non-squamous NSCLC).	Nardin et al. (2024); Hendriks et al. (2024); Molinaro et al. (2024)
Taxanes	Paclitaxel	Stabilizes microtubules, blocking cell division and causing mitotic catastrophe.	Lahiri et al. (2023); Xi et al. (2025); Huang et al. (2024)
Topoisomerase Inhibitors	Etoposide	Inhibits topoisomerase II, preventing DNA repair and replication.	Jang et al. (2025); Huang et al. (2024); Özkaya Gül et al. (2025)

5.2 Targeted Therapy

Targeted therapies are highly specific drug treatments that block one molecular abnormality in cancer cells to promote their growth and spread. This method of treating NSCLC is a refined therapy. The mechanism of targeted therapy is illustrated in Figure 7. Targeted therapy for cancer cells blocks specific signals, whereas chemotherapy is cytotoxic to proliferating cells. As a result, the treatment is expected to have a more specific effect and fewer potentially harmful side effects (Mina et al., 2025). Nearly all of the targeted therapy drugs are oral agents, providing a convenient way for patients to self-treat. Utilizing cancer-targeting medications with minimal off-target toxicity in genetically determined subgroups that the various mutations should reflect within cells is the best way to achieve the best results (Mina et al., 2025). Targeted treatments are, nonetheless, constrained by several limitations such as limited distribution geographically in some areas, treatment costs being prohibitive, occurrence of mutations leading to resistance (Zhao et al., 2024), and overall poor response rate of 20-30% among patients, prompting the necessity for additional research in this area (Mina et al., 2025). The modes of action of major classes of targeted treatment, such as EGFR inhibitors, ALK inhibitors, ROS1 inhibitors, MET inhibitors, and KRAS inhibitors, are described in Table 12.

1. EGFR inhibitors

The inhibition of EGFR with its inhibitors smothers the essential signals needed for the growth of cancer cells and leading to their proliferation. Consequently, these cancer cells ultimately die, and there is no mechanism for them to reproduce

any further (Hawash, 2024; Wang et al., 2024). This is the most targeted approach toward types with cancer-potential possessing EGFR mutations (since these mutations are the actual growth inhibitors among the tumor bulk). For instance, if you unplug a light source that doesn't have a cord to plug in, so it doesn't have any energy, just like mutant types' work is likely cut short.

2. ALK Inhibitors

Anaplastic lymphoma kinase (ALK) proteins inhibit the cell-to-cell communication that contributes to the spread of cancer cells. EML4-ALK and other ALK fusion proteins aid in the growth and development of cancer cells. At the same time, ALK inhibitors stop these processes from passing and make it harder for the Interference with the means of communication among the cancer cells greatly stunts their growth, compared to severing the connection of the cancer cells from the network by turning off a Wi-Fi router .

3. ROS1 Inhibitors

The ROS1 inhibitors are designed to disrupt ROS1 gene rearrangement that leads to uncontrollable growth of cancer cells. The cessation of tumor growth by these compounds has prevented or even reversed cancer development (Stanzione et al., 2023; Desilets et al., 2025; Zhao et al., 2024). This approach is aimed at tumors with ROS1 rearrangement, inflicting minimal damage on surrounding normal cells. Picture a road that gets closed to cancer cells, so their passage gets wary and the disease fails to spread.

4. MET Inhibitors

Mutations in the MET gene lead to abnormal, uncontrolled growth of cancer cells, and so-called MET inhibitors aim to address these mutations. By inhibiting MET exon 14 skipping mutations, the drugs bring the equilibrium back to the situation, therefore restraining tumor growth and keeping the cancer in check (Dong et al., 2022; Rosas et al., 2024). It is then that the MET inhibitors directly reverse the aberrant signaling pathways initiated by these mutations and shine. Imagine going and repairing a jammed thermostat: that act prevents the room (or cancer cells) from overheating and getting out of control.

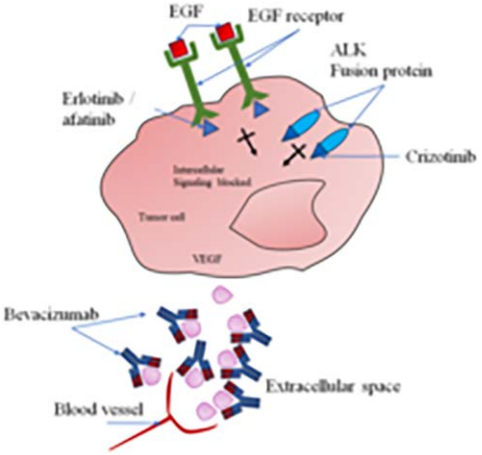
5. KRAS Inhibitors

The mutations in the KRAS gene disrupt normal function, acting like a stuck accelerator that pushes cancer cell growth and tumor formation forward. As a result, KRAS inhibitors slow down this acceleration, effectively stopping the cancer cells' uncontrolled growth (Skoulidis et al., 2021; Singhal et al., 2024). Because it targets only the KRAS G12C mutation, this new class of drugs represents a paradigm shift in how tumors along this pathway have been treated. If one applies the brakes to a speeding car, it would come to a halt. The car won't move, and the cancer cells will die if the brakes work.

Table 12. Targeted Therapy Mechanism

Drug Category	Agents	Target/Mechanism	References
EGFR Inhibitors	Erlotinib, Gefitinib, Osimertinib	Block mutations in EGFR, shutting down growth signals	Hawash, (2024);Wang et al., (2024); Rosas et al. (2024)
ALK Inhibitors	Crizotinib, Alectinib, Lorlatinib	Inhibit ALK fusion proteins (e.g., EML4-ALK)	Tao et al., (2022); Rosas et al. (2024); Mina et al. (2025)
ROS1 Inhibitors	Crizotinib, Entrectinib	Target ROS1 gene rearrangements	Stanzione et al., (2023) ; Desilets et al. (2025); Zhao et al. (2024)
MET Inhibitors	Capmatinib, Tepotinib	Block MET exon 14 skipping mutations	Dong et al., (2022); Rosas et al. (2024); Adamopoulos et al. (2024)
KRAS Inhibitors	Sotorasib	Target KRAS G12C mutation, halting accelerated growth	Skoulidis et al. (2021); Singhal et al. (2024); Wang et al. (2025)

Figure 7. Mechanism of targeted therapy



5.3 Immunotherapy

Immunotherapy is the most recent treatment for non-small cell lung cancer, into which the immune-checkpoint stimulators essentially mobilize the quality of the human immune system from delusions, letting it identify and finally engulf the cancer cells. Immunotherapy strikes pathways that are usually exploited by malignant tumors to escape the immune defense—and hence the T-cells, considered to be the warriors of the immune system, aiming to attack the tumors (Cheng et al., 2024). Therefore, in most cases, adjuvant treatments in advanced and early stages of NSCLC treatment are most beneficial to patients with PD-1-positive tumors, with expression greater than 50 percent. The therapy is usually given first alone or in combination with chemotherapy in cases of low-level PD-L1 expression. Some of the advantages include long-standing therapeutic effects, probably being the cause of remissions; comparatively lower systemic toxicity than chemotherapy, and efficacy against most subtypes of NSCLC. However, challenges remain: 20-30 patient efficacy at times shows adverse effects in the form of immune-related toxicities such as colitis, pneumonitis, and endocrinopathies; it is very costly and not widely available (Zhao et al., 2025). Almost all the common immunotherapies are PD-1, PD-L1, and CTLA-4 inhibitors, with their mechanisms of action discussed in Table 13 and illustrated below in Figure 8 (Sharma et al., 2024).

i. PD-1 Inhibitors

The mechanism of action of PD-1 inhibitors is binding to the PD-1 receptor that is expressed by cancer cells to evade immunity. PD-1 serves as a 'shield' and prevents T-cells from the immune system soldiers from recognizing and killing cancer cells. Such drugs act to prevent PD-1, just like taking down that protective shield and exposing the cancer cells to their immunological attackers. The prompt release of this 'shield' will activate the action of T-cells to fight against the cancer cells and restore immunity toward tumor growth. PD-1 inhibitors are highly effective in treating patients with lung cancers that carry marked expression of PD-L1, a related protein (Shen et al., 2024).

ii. PD-L1 Inhibitors

PD-L1 inhibitors intercept a tumor-promoting signaling pathway that is restively expressed by malignant cells-many times. PD-L1 acts as a “disguise” that enables the cancer cells to escape detection from T-cells. These drugs strip the disguise by blocking the activity of PD-L1, allowing the immune system to now view the cancer and destroy it. Once the immune cells identify the cancer, this knowledge broadens and deepens their ability to prosecute the sustained massacre of the tumor (Zabeti Touchaei & Vahidi, 2024). PD-L1 inhibitors work best for patients who have tumors positive for high expression of PD-L1 and represent a powerful arm against cancer evasion mechanisms by bolstering the immune response (Habib, 2024).

iii. CTLA-4 Inhibitors

CTLA-4 blockade releases some brakes on the operation of the immune system. By blocking T-cell activation, CTLA-4 prevents these immune cells from getting overexcited in their reactions. But cancer cells have put a loop in this system, whereby they can manipulate T-cells so that they can no longer become potent against these relentless enemies. Ipilimumab inhibits CTLA-4, making the brakes dysfunctional, thus enabling T-cells to act in full force. Therefore, under these circumstances of optimal strength from T-cells, the latter can unleash an attack against that cancer cell, which ultimately destroys it (Wang, Cheng et al., 2024). CTLA-4 inhibitors are also generally employed together with other therapies, such that victory over NSCLC may ensue with all forces on high gear (Wang, Liu et al., 2024).

Table 13. Common Immunotherapeutic Agents

Inhibitor Type	Agents	Mechanism of Action	References
Programmed Death-1 (PD-1)	Pembrolizumab, Nivolumab	Inhibit PD-1, reactivating T-cell function against cancer cells	Cheng et al. (2024); Zhao et al. (2025); Shen et al. (2024)
Programmed Death-Ligand 1 (PD-L1)	Atezolizumab, Durvalumab	Inhibit PD-L1, preventing tumor immune evasion	Sharma et al. (2024); Zabeti Touchaei & Vahidi (2024); Wang et al. (2024)
CTLA-4 Inhibitors	Ipilimumab	Enhance T-cell priming and activation, boosting the immune response	Habib et al. (2024); Yadav et al. (2024); Ruan et al. (2024)

Figure 8. Mechanism of immunotherapy

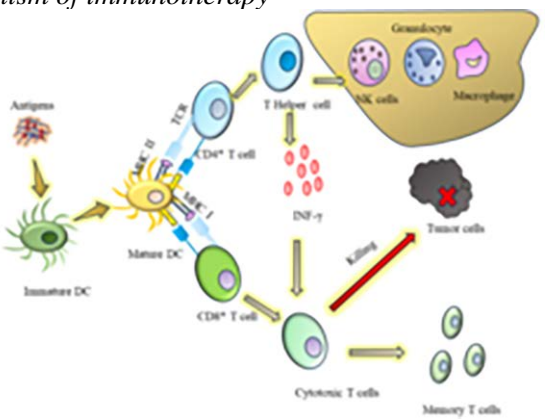


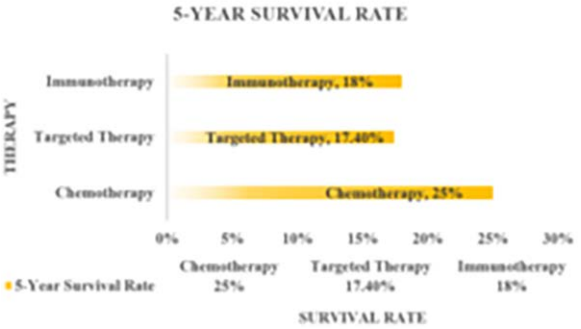
Table 14. outcomes vs therapy types

Treatment Type	Outcomes
Chemotherapy	Effective across various cancer types; significant side effects due to non-selectivity; used as a standard treatment for many cancers.
Targeted Therapy	High specificity for cancer cells; fewer side effects; effectiveness depends on genetic mutations; used for cancers with specific biomarkers.
Immunotherapy	Durable responses with potential long-term remission; less systemic toxicity; effective in certain cancers like melanoma and NSCLC; risk of immune-related toxicities.

Table 15. Survival rates for NSCLC patients

Therapy Type	5-Year Survival Rate	Key Points
Chemotherapy	~25%	Standard treatment; lower survival rates for advanced stages.
Targeted Therapy	~17.4%	Effective for specific genetic mutations; better outcomes for early-stage diagnosis.
Immunotherapy	~18%	Improved survival rates, especially for PD-L1-positive patients.

Figure 9. Patient survival rates by therapy type



6 EMERGING INNOVATIVE THERAPIES: CAR T CELL THERAPY AND EXPERIMENTAL TREATMENTS

6.1 CAR T Cell Therapy

The overall end of immunotherapy is to use vulnerable checkpoint inhibitors (ICIs) to spark the immune system so that it can attack cancer cells and interfere with the signals that typically inhibit T-cells from being activated (Joy et al., 2024; Gómez-Melero et al., 2025). Ipilimumab, for illustration, enhances T-cell priming and activation by inhibiting CTLA-4 (Yang et al., 2024). In the cancer battle, PD-1 asset pembrolizumab and PD-L1 asset durvalumab both help prevent excrescences from escaping the vulnerable system (Socinski et al., 2021). Immunotherapy typically employs all of these drugs as shown in Figure 10. As a first-line treatment in PD- PD-L1-positive NSCLC (expression of 50 or further), immunotherapy has a part in clinical practice in the form of an adjuvant for advanced NSCLC as well as early NSCLC. In those with low PD-L1 expression, chemotherapy is generally combined with immunotherapy. Immunotherapy can have sustained benefits and

grant sustained remission, which is one benefit over chemotherapy. It also has lower systemic toxicity and is effective for most NSCLC subtypes (Nadal et al., 2023). One thing to note, still, is that only 20 to 30 percent of cases will find it salutary. It is also extremely valuable, not always readily available, and it can affect vulnerability-mediated side effects like endocrinopathies, colitis, and pneumonitis described in Table 16, challenges, and proposed solutions (Hu et al., 2024).

Figure 10. CAR -T cell therapy process

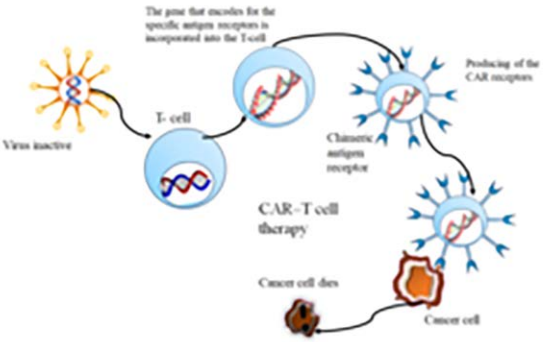


Table 16. Challenges and Proposed Solutions for CAR-T CELL THERAPY

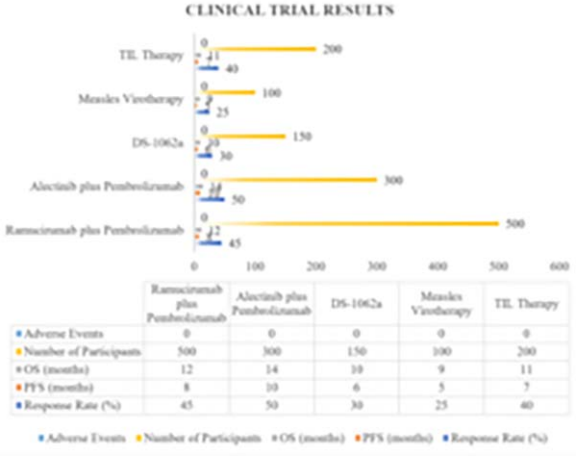
Challenge	Description	Solution	References
Tumor Microenvironment	The immunosuppressive tumor environment can reduce CAR-T cell efficacy.	Combining CAR-T therapy with other immunotherapies or using cytokine support to boost T-cell activity.	Joy et al. (2024); Gómez-Melero et al. (2025); Hu et al. (2024)
On-Target/Off-Tumor Toxicity	CAR-T cells may inadvertently attack healthy cells with low antigen expression.	Developing dual CAR designs or incorporating safety switches to regulate CAR-T cell activity.	Lodka et al. (2024); Huo et al. (2024); Schett et al. (2024)
Neurological Toxicity	Some patients experience severe neurological side effects.	Close monitoring and early intervention with corticosteroids or other supportive care.	Zhang et al. (2023); Chen et al. (2024); Cwynarski et al. (2025)

6.2 Experimental Therapies in NSCLC

New therapies for metastatic or advanced non-small cell lung cancer (NSCLC) are demonstrating true potential in clinical trials (Zhang et al., 2022; Chen et al.,

2024). One of them, DS-1062a, is an experimental drug class known as TROP2 that is often found on cancer cells. Designed as an attack on the cancer without harming healthy tissues, it transmits a potent medicine directly to a tumor. Another exciting approach is measles virotherapy, leveraging a safe, modified measles virus that infects and kills cancer cells and enhances the body's immune response (Li et al., 2022). The drug nivolumab helps immune cells fight the disease by stripping the cancer of its ability to hide. Finally, there's tumor-infiltrating lymphocyte (TIL) therapy, a rarefied treatment in which physicians extract immune cells from the patient's tumor, supercharge them in a lab, and then reinject them into the cancer-killing body (Zhang, Wang & Wang, 2023). These ground-breaking treatments taken together offer patients with advanced NSCLC new hope for improved outcomes, as shown in Figure 11, which illustrates clinical trial results for emerging therapies (Cwynarski et al., 2025).

Figure 11. Clinical trial results for emerging therapies



6.3 Future Directions

Researchers are investigating several promising strategies for advancing Auto T cell therapy and innovative treatments to push them forward (Huo, 2024; Lodka et al., 2024). It aims to deliver individualized treatment based on the peculiar genetic and molecular characteristics of a person to maximize efficacy while reducing adverse effects (Zhang & Wang, 2024). Combination therapies seek to bring together several types of therapies to bond into more synergistic properties against more complex problems to solve and enhance outcomes (Li et al., 2022). So-called ef-

forts to defeat treatment resistance are also accelerating, focusing on the ways that cancer escapes therapies (Zhang, Wang & Wang, 2023; Schett et al., 2024). This is an attempt to guarantee long-term effectiveness and sustain consistent patient responses over time, paving the way for cancer care solutions that are more long-lasting and efficient (Ohno & Nakamura, 2024; National Cancer Institute, 2024).

7 PUBLIC HEALTH PERSPECTIVES AND PREVENTION OF NSCLC

Public health initiatives, environmental protections, and smoking cessation programs comprise a large portion of strategies to decrease the burden of non-small cell lung cancer (NSCLC) (Karim et al., 2025). In previous decades, comprehensive tobacco control programs have helped to reduce smoking rates due to lower incidence of NSCLC (Kazerooni et al., 2024). Reducing exposure to tobacco and other environmental pollutants (i.e., air pollution and second-hand smoke) to low or no risk has also produced an increased risk reduction (Cuttano et al., 2024). In addition, maintaining safety in the workplace and occupational exposure to carcinogens continues to be an effective NSCLC prevention measure (Garg et al., 2024).

Figure 12. Diagram of prevention strategies for NSCLC

For example, as seen in Figure12, screening programs such as Low-Dose Computed Tomography (LDCT) provide early detection and have been shown to lower the death rate due to NSCLC (Pillay et al., 2024). Public education campaigns also add another layer of protection against lung cancer by inform individuals of the risks involved, discouraging smoking use, and encouraging healthy lifestyle behaviours (Liu et al., 2024).

Policy and regulation have been a particularly important catalyst for prevention. International frameworks (the WHO Framework Convention on Tobacco Control) and national policy approaches (i.e. taxation of tobacco; plain packaging; and restrictions on marketing) have, and will continue to, constrain tobacco consumption by households and populations around the globe.

Further policies to improve the quality of indoor air, provided there is clean energy source and transition to lower exposure to biomass as a fuel source, are also significant risk factors in many low- and middle-income settings.

At the level of individuals and communities, lifestyle and behaviour change are also very important. Eating a range of foods that are balanced in terms of risk, being physically active and reducing alcohol intake all contribute to reducing cancer risk overall. Smoking cessation programs for specific individuals, particularly adolescents or marginalized populations is a special consideration. Technology is increasingly supporting these programs, with mobile health applications and personalized, AI-assisted smoking cessation programs developed to be individually appropriate and broadly available to help support quitting.

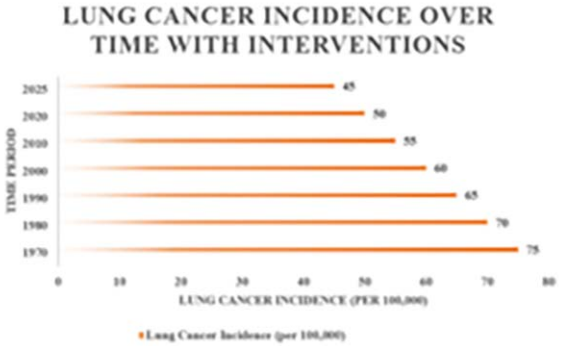
Screening and early detection are crucial to saving lives. A recent study of LDCT scans showed that lung cancer could be detected at an earlier stage, but even with evidence for LDCT screening, there are still obstacles, such as false positives, risk of radiation, and whether screening is worth the cost. Research is also exploring various emerging biomarkers including liquid biopsy and circulating tumor DNA, which may one day provide safer, more accurate, non-invasive alternatives. In the meantime, guidelines that identify high-risk populations at the highest risk, and rank populations by risk, also help us to monitor the utilization of LDCT screening resources.

But we also need to work towards equity in prevention. Disparities in access to healthcare often mean that rural areas and low-income populations are usually not privy to either LDCT screening or resources/ supports to successfully quit. Economic barriers, and barriers related to awareness including problem and knowledge of the resources for smoking cessation help keep the divide as wide as it is, particularly for low-income populations and especially indigenous communities. Developing programs that reflect cultural sensitivity and help us begin to reach vulnerable populations & indigenous populations, and work towards equitable prevention strategies.

Looking ahead, we should be excited about what innovation has to offer. The role of electronic cigarettes and vaping devices in tobacco control and as harm reduction products is still controversial and in need of appropriate regulation, but still contribute to the ever-changing tobacco landscape. New developments in genetic risk profiling and artificial intelligence-driven predictive modelling will inevitably bring us to a point of individual prevention strategies. Even public health campaigns

are changing, developing new campaigns and using social media and influencer-led initiatives to engage young people to prevent smoking before it starts.

Figure 13. Lung cancer incidence over time with interventions



Finally, prevention technologies should be monitored and evaluated at all times. Continuous and longitudinal monitoring of smoking prevalence, air quality indicators, and lung cancer incidence rates is important to evaluate what is working and what should be modified. Japan, Australia and the UK show us that sustained modalities reduce lung cancer incidence. Furthermore, preventative measures—particularly quitting smoking—have considerably bigger health and financial benefits than treatment, according to cost-effectiveness studies. The prevalence of lung cancer has already begun to gradually fall as a result of concerted measures, as seen in Figure 13.

8 CHALLENGES AND FUTURE DIRECTIONS IN NSCLC RESEARCH AND TREATMENT

8.1 Innovations in Research

To address these challenges, exploration is focusing on new strategies including substantiated drugs, immunotherapy, Auto-T cell therapy, oncolytic viruses, and neoadjuvant therapy (Bertolaccini et al., 2024; Li et al., 2025; Tahayneh et al., 2025). Individualized drug leverages inheritable profiling to design acclimatized treatments grounded on specific mutations, while immunotherapy advances aim to enhance excrescence responses through vulnerable checkpoint inhibitors and combination rules. Auto-T cell curatives target NSCLC-specific antigens to ameliorate efficacy and safety. With a high degree of specificity, oncolytic contagions infect and destroy cancer cells in large numbers. Neoadjuvant therapy, involving systemic treatments

administered before surgery, helps shrink excrescences and enhances surgical outcomes. These advancements are captured in the Table 17 below.

Table 17. Advancements and their impacts

Future Research Focus	Description	Impact	References
Personalized Medicine	Tailored treatments via genetic profiling.	More effective and less toxic therapies.	Bertolaccini et al., 2024
Immunotherapy	Enhanced immune checkpoint inhibitors and combinations.	Greater tumor response and immune activity.	Li et al., 2025
CAR-T Cell Therapy	Targeting NSCLC-specific antigens.	Increased precision and reduced toxicity.	Tahayneh et al., 2025
Oncolytic Viruses	Viruses are designed to infect and kill cancer cells.	Improved cancer selectivity and potency.	Li et al., 2025; Tahayneh et al., 2025
Neoadjuvant Therapy	Systemic therapy before surgery.	Shrinks tumors and enhances outcomes.	Bertolaccini et al., 2024

8.2 Comprehensive Overview

Non-Small Cell Lung Cancer (NSCLC) exploration and treatment face multiple challenges and opportunities for advancement (Bertolaccini et al., 2024; Li et al., 2025; Tahayneh et al., 2025). Medicine resistance, driven by inheritable mutations, indispensable signaling pathways, and changes in medicine targets, frequently leads to treatment failure and disease progression. Excrescence diversity, encompassing inheritable and phenotypic variations, complicates treatment issues and enables the emergence of resistant subclones. Excretion diversity and the complex progression of cancer make it difficult to identify reliable biomarkers, which are essential for individualized drug development. Additionally, restricted access to advanced curative treatments caused by nonsupervisory, logistical, and financial barriers exacerbates care disparities. The major aspects of these challenges are epitomized in Table 18 below.

Table 18. Challenges in various aspects

Aspect	Description	Impact
Drug Resistance	Genetic mutations, alternative pathways, and changes in drug targets.	Leads to treatment failure and disease progression.
Tumor Heterogeneity	Variations in genetic and cell behaviour and microenvironment interactions.	Causes inconsistent treatment responses and the emergence of resistant clones.
Biomarker Identification	Difficulty in finding sensitive, specific biomarkers due to tumor diversity.	Crucial for improving personalized treatment outcomes.
Access to Treatments	Regulatory and cost-related barriers limit the availability of therapies.	Restricts access to innovative and life-saving treatments.

8.3 Emerging Therapies

Emerging treatment paradigms emphasize the integration of advanced technologies and multidisciplinary collaboration. Precision drug is acclimatizing curatives to individual inheritable biographies, while combination curatives aim to overcome resistance mechanisms. Advanced imaging and biomarker technologies are influenced by prior discovery strategies to identify cancer at earlier, more treatable stages. As demonstrated, global businesses aim to increase the availability of these treatments by reducing costs and improving healthcare structures, as described in Table 19.

Table 19. Emerging therapies

Emerging Paradigm	Description	Impact
Precision Medicine	Treatments tailored to individual genetic profiles.	Enhanced efficacy and reduced side effects.
Combination Therapies	Synergistic use of drugs or modalities.	Overcomes resistance and improves outcomes.
Early Detection	Use of biomarkers and imaging for early diagnosis.	Higher treatment success rates and survival.
Multidisciplinary Care	Collaboration among specialists.	Comprehensive and personalized care.
Global Access	Expanding availability and affordability.	Broader access to innovative treatments.

8.4 Clinical Trials and Future Projections

Active clinical trials are crucial to understanding and perfecting NSCLC treatment approaches. Trials like the ALCHEMIST Trial, targeted radiation studies, and

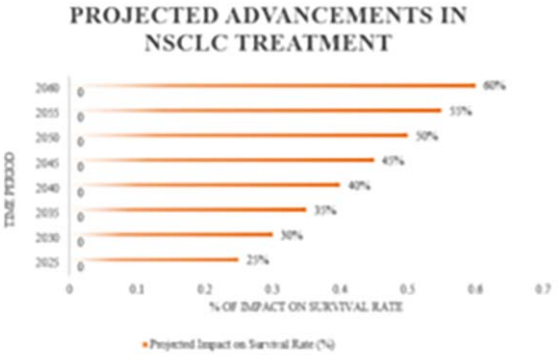
virotherapy exploration are being conducted to identify the most effective strategies for managing NSCLC (Sorin et al., 2024; Hu, 2024; Franceschini et al., 2024; Thomas et al., 2024). A summary of ongoing clinical trials is as follows

Table 20. Clinical trials related to NSCLC

Trial Name	Description	Location	References
ALCHEMIST Trial	Test pembrolizumab with chemotherapy for surgically removed stage IIA-IIIB NSCLC.	1,068 locations worldwide	Sorin et al. (2024)
High Dose, Targeted Radiation Trial	Combines stereotactic body radiation therapy (SBRT) with usual treatment for inoperable NSCLC.	Multiple locations	Hu et al. (2024); Franceschini et al. (2024)
Durvalumab vs Placebo Following SBRT	Evaluates durvalumab's effectiveness post-SBRT in early-stage NSCLC patients.	Rochester, MN	Thomas et al. (2024)
Oraxol and Pembrolizumab	Study oral paclitaxel (Oraxol) with pembrolizumab for advanced solid tumors, including NSCLC.	Scottsdale, AZ; Jacksonville, FL; Rochester, MN	Chen et al. (2025)
Measles Virotherapy with Nivolumab	Phase 1 trial combining measles virus with nivolumab in metastatic NSCLC.	Rochester, MN	Amemiya et al. (2025)
Genome Sequencing for Multifocal Cancers	Assess genome sequencing in treating multifocal lung cancer.	Rochester, MN	Zou et al. (2025)
PT-112 with Avelumab	Studies PT-112 combined with anti-PD-L1 antibody avelumab for advanced solid tumors.	Multiple U.S. locations	Zou et al. (2025)

Projected advancements in treatments like Auto-T remedy, oncolytic contagions, and early discovery methods are anticipated to mainly ameliorate survival rates for NSCLC cases. By 2060, survival rates are projected to increase from 25 in 2025 to 60, driven by inventions in perfect drugs, combination curatives, and a global access enterprise (Chen et al., 2025; Amemiya et al., 2025; Zou et al., 2025). This progress is visually represented in the Graph of Projected Advancements in NSCLC Treatment, pressing a promising future for cases worldwide.

Figure 14. Projected advancements in NSCLC treatment



REFERENCES

Abdayem, P., & Planchard, D. (2021). Update on molecular pathology and role of liquid biopsy in nonsmall cell lung cancer. *European Respiratory Review : an Official Journal of the European Respiratory Society*, *30*(161), 200286. DOI: 10.1183/16000617.0294-2020 PMID: 34289984

Abdul-Rahman, T., Ghosh, S., Badar, S. M., Nazir, A., Bamigbade, G. B., Aji, N., Roy, P., Kachani, H., Garg, N., Lawal, L., Bliss, Z. S., Wireko, A. A., Atallah, O., Adebusoye, F. T., Teslyk, T., Sikora, K., & Horbas, V. (2024). The paradoxical role of cytokines and chemokines at the tumor microenvironment: A comprehensive review. *European Journal of Medical Research*, *29*(1), 124. DOI: 10.1186/s40001-024-01711-z PMID: 38360737

Accogli, T., Bruchard, M., & Végran, F. (2021). Modulation of CD4 T cell response according to tumor cytokine microenvironment. *Cancers (Basel)*, *13*(3), 373. DOI: 10.3390/cancers13030373 PMID: 33498483

Al-Tashi, Q., Saad, M. B., Muneer, A., Qureshi, R., Mirjalili, S., Sheshadri, A., Le, X., Vokes, N. I., Zhang, J., & Wu, J. (2023). Machine learning models for the identification of prognostic and predictive cancer biomarkers: A systematic review. *International Journal of Molecular Sciences*, *24*(9), 7781. DOI: 10.3390/ijms24097781 PMID: 37175487

Alduais, Y., Zhang, H., Fan, F., Chen, J., & Chen, B. (2023, February 22). Non-small cell lung cancer (NSCLC): A review of risk factors, diagnosis, and treatment. *Medicine*, *102*(8), e32899. DOI: 10.1097/MD.0000000000032899 PMID: 36827002

Algarra, I., Garrido, F., & Garcia-Lora, A. M. (2021). MHC heterogeneity and response of metastases to immunotherapy. *Cancer and Metastasis Reviews*, *40*(2), 501–517. DOI: 10.1007/s10555-021-09964-4 PMID: 33860434

Ali, F., Neha, K., & Chauhan, G. (2022). Pralsetinib: Chemical and therapeutic development with FDA authorization for the management of RET fusion-positive non-small-cell lung cancers. *Archives of Pharmacal Research*, *45*(5), 309–327. DOI: 10.1007/s12272-022-01385-3 PMID: 35598228

Amemiya, K., Hirotsu, Y., Iimuro, Y., Tajiri, R., Oyama, T., Obi, S., Mochizuki, H., & Omata, M. (2025). Decoding Genomic Diversity to Guide Tumor Lesion-Specific Treatment of Multifocal Hepatocellular Carcinoma. *Cancer Medicine*, *14*(7), e70814. DOI: 10.1002/cam4.70814 PMID: 40145314

Bagaev, A., Kotlov, N., Nomie, K., Svekolkin, V., Gafurov, A., Isaeva, O., Osokin, N., Kozlov, I., Frenkel, F., Gancharova, O., Almog, N., Tsiper, M., Ataullakhanov, R., & Fowler, N. (2021). Conserved pan-cancer microenvironment subtypes predict response to immunotherapy. *Cancer Cell*, *39*(6), 845–865. DOI: 10.1016/j.ccell.2021.04.014 PMID: 34019806

Bagaev, A., Kotlov, N., Nomie, K., Svekolkin, V., Gafurov, A., Isaeva, O., Osokin, N., Kozlov, I., Frenkel, F., Gancharova, O., Almog, N., Tsiper, M., Ataullakhanov, R., & Fowler, N. (2021). Conserved pan-cancer microenvironment subtypes predict response to immunotherapy. *Cancer Cell*, *39*(6), 845–865. DOI: 10.1016/j.ccell.2021.04.014 PMID: 34019806

Baghy, K., Ladányi, A., Reszegi, A., & Kovalszky, I. (2023). Insights into the tumor microenvironment—Components, functions and therapeutics. *International Journal of Molecular Sciences*, *24*(24), 17536. DOI: 10.3390/ijms242417536 PMID: 38139365

Balta, E., Wabnitz, G. H., & Samstag, Y. (2021). Hijacked immune cells in the tumor microenvironment: Molecular mechanisms of immunosuppression and cues to improve T cell-based immunotherapy of solid tumors. *International Journal of Molecular Sciences*, *22*(11), 5736. DOI: 10.3390/ijms22115736 PMID: 34072260

Bazhenova, L., Minchom, A., Viteri, S., Bauml, J. M., Ou, S. H. I., Gadgeel, S. M., Trigo, J. M., Backenroth, D., Li, T., Londhe, A., Mahadevia, P., & Girard, N. (2021). Comparative clinical outcomes for patients with advanced NSCLC harboring EGFR exon 20 insertion mutations and common EGFR mutations. *Lung Cancer (Amsterdam, Netherlands)*, *162*, 154–161. DOI: 10.1016/j.lungcan.2021.10.020 PMID: 34818606

Bertolaccini, L., Casiraghi, M., Uslenghi, C., Maiorca, S., & Spaggiari, L. (2024). Recent advances in lung cancer research: Unravelling the future of treatment. *Updates in Surgery*, *76*(6), 2129–2140. DOI: 10.1007/s13304-024-01841-3 PMID: 38581618

Blaquier, J. B., Ortiz-Cuaran, S., Ricciuti, B., Mezquita, L., Cardona, A. F., & Recondo, G. (2023, September 15). Tackling Osimertinib Resistance in EGFR-Mutant Non–Small Cell Lung Cancer. *Clinical Cancer Research*, *29*(18), 3579–3591. DOI: 10.1158/1078-0432.CCR-22-1912 PMID: 37093192

Bożyk, A., Wojas-Krawczyk, K., Krawczyk, P., & Milanowski, J. (2022). Tumor microenvironment—A short review of cellular and interaction diversity. *Biology (Basel)*, *11*(6), 929. DOI: 10.3390/biology11060929 PMID: 35741450

Canale, M., Andrikou, K., Priano, I., Cravero, P., Pasini, L., Urbini, M., Delmonte, A., Crinò, L., Bronte, G., & Ulivi, P. (2022, February 23). The role of TP53 mutations in EGFR-mutated non-small-cell lung cancer: Clinical significance and implications for therapy. *Cancers (Basel)*, *14*(5), 1143. DOI: 10.3390/cancers14051143 PMID: 35267450

Cao, Y., Haring, C. T., Brummel, C., Bhambhani, C., Aryal, M., Lee, C., Heft Neal, M., Bhangale, A., Gu, W., Casper, K., Malloy, K., Sun, Y., Shuman, A., Prince, M. E., Spector, M. E., Chinn, S., Shah, J., Schonewolf, C., McHugh, J. B., & Brenner, J. C. (2022). Early HPV ctDNA kinetics and imaging biomarkers predict therapeutic response in p16+ oropharyngeal squamous cell carcinoma. *Clinical Cancer Research*, *28*(2), 350–359. DOI: 10.1158/1078-0432.CCR-21-2338 PMID: 34702772

Catalano, M., Shabani, S., Venturini, J., Ottanelli, C., Voltolini, L., & Roviello, G. (2022). Lung cancer immunotherapy: Beyond common immune checkpoints inhibitors. *Cancers (Basel)*, *14*(24), 6145. DOI: 10.3390/cancers14246145 PMID: 36551630

Chen, K., Liu, A., Wang, C., Hu, C., Chen, C., Yang, F., Chen, H., Shen, H., Zhang, H., Liu, H., Xiong, J., Wang, J., Zhang, L., Xu, L., Wang, L., Zhao, M., Li, Q., Song, Q., Zhou, Q., & Wang, J. (2025). Multidisciplinary expert consensus on diagnosis and treatment of multiple lung cancers. *Med (New York, N.Y.)*, *6*(4), 100643. DOI: 10.1016/j.medj.2025.100643 PMID: 40220743

Chen, R., Li, Q., Xu, S., Ye, C., Tian, T., Jiang, Q., Shan, J., & Ruan, J. (2022). Modulation of the tumour microenvironment in hepatocellular carcinoma by tyrosine kinase inhibitors: From modulation to combination therapy targeting the microenvironment. *Cancer Cell International*, *22*(1), 73. DOI: 10.1186/s12935-021-02435-4 PMID: 35148789

Chen, T., Wang, M., Chen, Y., & Liu, Y. (2024). Current challenges and therapeutic advances of CAR-T cell therapy for solid tumors. *Cancer Cell International*, *24*(1), 133. DOI: 10.1186/s12935-024-03315-3 PMID: 38622705

Cheng, W., Kang, K., Zhao, A., & Wu, Y. (2024). Dual blockade immunotherapy targeting PD-1/PD-L1 and CTLA-4 in lung cancer. *Journal of Hematology & Oncology*, *17*(1), 54. DOI: 10.1186/s13045-024-01581-2 PMID: 39068460

Clark, L., Fisher, G., Brook, S., Patel, S., & Arkenau, H. T. (2023). Selective RET Inhibitors (SRIs) in Cancer: A Journey from Multi-Kinase Inhibitors to the Next Generation of SRIs. *Cancers (Basel)*, *16*(1), 31. DOI: 10.3390/cancers16010031 PMID: 38201460

Cognigni, V., Pecci, F., Lupi, A., Pinterpe, G., De Filippis, C., Felicetti, C., Cantini, L., & Berardi, R. (2022). The landscape of ALK-rearranged non-small cell lung cancer: A comprehensive review of clinicopathologic, genomic characteristics, and therapeutic perspectives. *Cancers (Basel)*, *14*(19), 4765. DOI: 10.3390/cancers14194765 PMID: 36230686

Cucchiara, F., Petrini, I., Romei, C., Crucitta, S., Lucchesi, M., Valleggi, S., Scavone, C., Capuano, A., De Liperi, A., Chella, A., Danesi, R., & Del Re, M. (2021). Combining liquid biopsy and radiomics for personalized treatment of lung cancer patients: State of the art and new perspectives. *Pharmacological Research*, *169*, 105643. DOI: 10.1016/j.phrs.2021.105643 PMID: 33940185

Cuttano, R., Mazzarelli, F., Afanga, K. M., Bianchi, F., & Dama, E. (2024). MicroRNAs and the Mediterranean diet: A nutri-omics perspective for lung cancer. *Journal of Translational Medicine*, *22*(1), 632. DOI: 10.1186/s12967-024-05454-7 PMID: 38972997

Cwynarski, K., Iacoboni, G., Tholouli, E., Menne, T., Irvine, D. A., Balasubramaniam, N., Wood, L., Shang, J., Xue, E., Zhang, Y., Basilico, S., Neves, M., Raymond, M., Scott, I., El-Kholy, M., Jha, R., Dainton-Smith, H., Hussain, R., Day, W., & Pule, M. (2025). TRBC1-CAR T cell therapy in peripheral T cell lymphoma: A phase 1/2 trial. *Nature Medicine*, *31*(1), 137–143. DOI: 10.1038/s41591-024-03326-7 PMID: 39528665

Dagogo-Jack, I., Kiedrowski, L. A., Heist, R. S., Lin, J. J., Meador, C. B., Krueger, E. A., Do, A., Peterson, J., Sequist, L. V., Gainor, J. F., Lennerz, J. K., & Digumarthy, S. R. (2023). Efficacy and tolerability of ALK/MET combinations in patients with ALK-rearranged lung cancer with acquired MET amplification: A retrospective analysis. *JTO Clinical and Research Reports*, *4*(8), 100534. DOI: 10.1016/j.jtocrr.2023.100534 PMID: 37533439

Dan, A., Burtavel, L. M., Coman, M. C., Focsa, I. O., Duta-Ion, S., Juganaru, I. R., Zaruha, A.-G., Codreanu, P.-C., Strugari, I.-M., Hotinceanu, I.-A., Bohiltea, L.-C., & Radoi, V. E. (2024). Genetic Blueprints in Lung Cancer: Foundations for Targeted Therapies. *Cancers (Basel)*, *16*(23), 4048. DOI: 10.3390/cancers16234048 PMID: 39682234

De Jong, E., Lammerts, M. U. P. A., Genders, R. E., & Bouwes Bavinck, J. N. (2022). Update of advanced cutaneous squamous cell carcinoma. *Journal of the European Academy of Dermatology and Venereology*, *36*(S1), 6–10. DOI: 10.1111/jdv.17728 PMID: 34855246

Desai, S. A., Patel, V. P., Bhosle, K. P., Nagare, S. D., & Thombare, K. C. (2025). The tumor microenvironment: Shaping cancer progression and treatment response. *Journal of Chemotherapy (Florence, Italy)*, *37*(1), 15–44. DOI: 10.1080/1120009X.2023.2300224 PMID: 38179655

Desilets, A., Repetto, M., Yang, S. R., & Drilon, A. (2025). Targeting ROS1 rearrangements in non–small cell lung cancer: Current insights and future directions. *Cancer*, *131*(S1), e35784. DOI: 10.1002/cncr.35784 PMID: 40171848

Dhatchinamoorthy, K., Colbert, J. D., & Rock, K. L. (2021). Cancer immune evasion through loss of MHC class I antigen presentation. *Frontiers in Immunology*, *12*, 636568. DOI: 10.3389/fimmu.2021.636568 PMID: 33767702

Di Capua, D., Bracken-Clarke, D., Ronan, K., Baird, A. M., & Finn, S. (2021). The liquid biopsy for lung cancer: State of the art, limitations and future developments. *Cancers (Basel)*, *13*(16), 3923. DOI: 10.3390/cancers13163923 PMID: 34439082

Díaz, M. A., Fusco, M., Benítez, C. A., Gayet, F., García, L., Victoria, L., Jaramillo, S., Bayo, J., Zubieta, M. R., Rizzo, M. M., Piccioni, F., & Malvicini, M. (2024). Targeting hyaluronan metabolism-related molecules associated with resistant tumor-initiating cells potentiates chemotherapy efficacy in lung cancer. *Scientific Reports*, *14*(1), 16803. DOI: 10.1038/s41598-024-66914-0 PMID: 39039104

Diaz-Jimenez, A., Shuldiner, E. G., Somogyi, K., Gonzalez, O., Akkas, F., Murray, C. W., ... EML4-ALK variant-specific genetic interactions shape lung tumorigenesis. bioRxiv. 2024 Aug 27:2024-08.

Ding, L., Gosh, A., Lee, D. J., Emri, G., Huss, W. J., Bogner, P. N., & Paragh, G. (2022). Prognostic biomarkers of cutaneous melanoma. *Photodermatology, Photoimmunology & Photomedicine*, *38*(5), 418–434. DOI: 10.1111/phpp.12770 PMID: 34981569

Dong, Y., Xu, J., Sun, B., Wang, J., & Wang, Z. (2022). MET-targeted therapies and clinical outcomes: A systematic literature review. *Molecular Diagnosis & Therapy*, *26*(2), 203–227. DOI: 10.1007/s40291-021-00568-w PMID: 35266116

Dziadziuszko, R., Krebs, M. G., De Braud, F., Siena, S., Drilon, A., Doebele, R. C., Patel, M. R., Cho, B. C., Liu, S. V., Ahn, M.-J., Chiu, C.-H., Farago, A. F., Lin, C.-C., Karapetis, C. S., Li, Y.-C., Day, B., Chen, D., Wilson, T. R., & Barlesi, F. (2021, April 10). Updated integrated analysis of the efficacy and safety of entrectinib in locally advanced or metastatic ROS1 fusion–positive non–small-cell lung cancer. *Journal of Clinical Oncology*, *39*(11), 1253–1263. DOI: 10.1200/JCO.20.03025 PMID: 33646820

Dzobo, K., Senthebane, D. A., & Dandara, C. (2023). The tumor microenvironment in tumorigenesis and therapy resistance revisited. *Cancers (Basel)*, *15*(2), 376. DOI: 10.3390/cancers15020376 PMID: 36672326

El Halabi, L., Adam, J., Gravelle, P., Marty, V., Danu, A., Lazarovici, J., Ribrag, V., Bosq, J., Camara-Clayette, V., Laurent, C., & Ghez, D. (2021). Expression of the immune checkpoint regulators LAG-3 and TIM-3 in classical Hodgkin lymphoma. *Clinical Lymphoma, Myeloma & Leukemia*, *21*(4), 257–266. DOI: 10.1016/j.clml.2020.11.009 PMID: 33277223

El-Tanani, M., Rabbani, S. A., Babiker, R., Rangraze, I., Kapre, S., Palakurthi, S. S., Alnuqaydan, A. M., Aljabali, A. A., Rizzo, M., El-Tanani, Y., & Tambuwala, M. M. (2024, April 16). Unraveling the tumor microenvironment: Insights into cancer metastasis and therapeutic strategies. *Cancer Letters*, *591*, 216894. DOI: 10.1016/j.canlet.2024.216894 PMID: 38626856

Escobedo-Calvario, A., Chávez-Rodríguez, L., Simoni-Nieves, A., Souza-Arroyo, V., Miranda-Labra, R. U., Gomez-Quiroz, L. E., & Gutiérrez-Ruíz, M. C. (2022). Tumor immune microenvironment modulation by cholesterol in hepatocellular carcinoma. *Exploration of Digestive Diseases*, *1*, 21–39. DOI: 10.37349/edd.2022.00003

Fabbri, L., Di Federico, A., Astore, M., Marchiori, V., Rejtano, A., Seminerio, R., Gelsomino, F., & De Giglio, A. (2023, December 25). From development to place in therapy of Lorlatinib for the treatment of ALK and ROS1 rearranged non-small cell lung cancer (NSCLC). *Diagnostics (Basel)*, *14*(1), 48. DOI: 10.3390/diagnostics14010048 PMID: 38201357

Farc, O., & Cristea, V. (2021). An overview of the tumor microenvironment, from cells to complex networks. *Experimental and Therapeutic Medicine*, *21*(1), 96. DOI: 10.3892/etm.2020.9528 PMID: 33363607

Franceschini, D., Franzese, C., Comito, T., Ilieva, M. B., Spoto, R., Marzo, A. M., Dominici, L., Massaro, M., Bellu, L., Badalamenti, M., Mancosu, P., & Scorsetti, M. (2024). Definitive results of a prospective non-randomized phase 2 study on stereotactic body radiation therapy (SBRT) for medically inoperable lung and liver oligometastases from breast cancer. *Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology*, *195*, 110240. DOI: 10.1016/j.radonc.2024.110240 PMID: 38522597

Friedlaender, A., Perol, M., Banna, G. L., Parikh, K., & Addeo, A. (2024). Oncogenic alterations in advanced NSCLC: A molecular super-highway. *Biomarker Research*, *12*(1), 24. DOI: 10.1186/s40364-024-00566-0 PMID: 38347643

Gandhi, Z., Gurram, P., Amgai, B., Lekkala, S. P., Lokhandwala, A., Manne, S., Mohammed, A., Koshiya, H., Dewaswala, N., Desai, R., Bhopalwala, H., Ganti, S., & Surani, S. (2023). Artificial intelligence and lung cancer: Impact on improving patient outcomes. *Cancers (Basel)*, *15*(21), 5236. DOI: 10.3390/cancers15215236 PMID: 37958411

Ganti, A. K., Klein, A. B., Cotarla, I., Seal, B., & Chou, E. (2021, December 1). Update of incidence, prevalence, survival, and initial treatment in patients with non–small cell lung cancer in the US. *JAMA Oncology*, *7*(12), 1824–1832. DOI: 10.1001/jamaoncol.2021.4932 PMID: 34673888

Garg, P., Singhal, S., Kulkarni, P., Horne, D., Malhotra, J., Salgia, R., & Singhal, S. S. (2024). Advances in non-small cell lung cancer: Current insights and future directions. *Journal of Clinical Medicine*, *13*(14), 4189. DOI: 10.3390/jcm13144189 PMID: 39064229

Gemelli, M., Albini, A., Catalano, G., Incarbone, M., Cannone, M., Balladore, E., Ricotta, R., & Pelosi, G. (2024). Navigating resistance to ALK inhibitors in the lorlatinib era: A comprehensive perspective on NSCLC. *Expert Review of Anticancer Therapy*, *24*(6), 347–361. DOI: 10.1080/14737140.2024.2344648 PMID: 38630549

Ghosh, D. D., McDonald, H., Dutta, R., Krishnan, K., Thilakan, J., Paul, M. K., Arya, N., Rao, M., & Rangnekar, V. M. (2024). Prognostic Indicators for Precision Treatment of Non-Small Cell Lung Carcinoma. *Cells*, *13*(21), 1785. DOI: 10.3390/cells13211785 PMID: 39513892

Godoy, L. A., Chen, J., Ma, W., Lally, J., Toomey, K. A., Rajappa, P., Sheridan, R., Mahajan, S., Stollenwerk, N., Phan, C. T., Cheng, D., Knebel, R. J., & Li, T. (2023). Emerging precision neoadjuvant systemic therapy for patients with resectable non-small cell lung cancer: Current status and perspectives. *Biomarker Research*, *11*(1), 7. DOI: 10.1186/s40364-022-00444-7 PMID: 36650586

Gómez-Melero, S., Hassouneh, F., Vallejo-Bermúdez, I. M., Agüera-Morales, E., Solana, R., & Caballero-Villarraso, J. (2025). Tandem CAR-T cell therapy: Recent advances and current challenges. *Frontiers in Immunology*, *16*, 1546172. DOI: 10.3389/fimmu.2025.1546172 PMID: 40092990

. Grilli, G. (2022). Molecular target therapy and immunotherapy of rare lung tumors.

Guo, Q., Liu, L., Chen, Z., Fan, Y., Zhou, Y., Yuan, Z., & Zhang, W. (2022). Current treatments for non-small cell lung cancer. *Frontiers in Oncology*, *12*, 945102. DOI: 10.3389/fonc.2022.945102 PMID: 36033435

Győrffy, B. (2023). Discovery and ranking of the most robust prognostic biomarkers in serous ovarian cancer. *GeroScience*, *45*(3), 1889–1898. DOI: 10.1007/s11357-023-00742-4 PMID: 36856946

. Habib, P. (2024). Review of immunotherapy in non-small cell lung cancer: mechanisms, clinical applications, and future prospects.

Hawash, M. (2024). Advances in cancer therapy: A comprehensive review of CDK and EGFR inhibitors. *Cells*, *13*(19), 1656. DOI: 10.3390/cells13191656 PMID: 39404419

Hendriks, L. E., Remon, J., Faivre-Finn, C., Garassino, M. C., Heymach, J. V., Kerr, K. M., Tan, D. S. W., Veronesi, G., & Reck, M. (2024). Non-small-cell lung cancer. *Nature Reviews. Disease Primers*, *10*(1), 71. DOI: 10.1038/s41572-024-00551-9 PMID: 39327441

Herrera-Juárez, M., Serrano-Gómez, C., Bote-de-Cabo, H., & Paz-Ares, L. (2023). Targeted therapy for lung cancer: Beyond EGFR and ALK. *Cancer*, *129*(12), 1803–1820. DOI: 10.1002/cncr.34757 PMID: 37073562

Heymach, J. V., Yu, H. A., Besse, B., Cheng, Y., Tan, D. S., Wei, L., Wacheck, V., & Nishio, M. (2025). REZILIENT3: Randomized phase III study of first-line zipalertinib plus chemotherapy in patients with EGFR exon 20 insertion-mutated NSCLC. *Future Oncology (London, England)*, *21*(5), 549–556. DOI: 10.1080/14796694.2025.2457294 PMID: 39957151

Hu, C. (2024). Stereotactic Body Radiotherapy for Medically Inoperable Early-Stage Non–Small Cell Lung Cancer. *JAMA Oncology*, *10*(11), 1576–1577. DOI: 10.1001/jamaoncol.2024.2905 PMID: 39298175

Hu, D., Yang, R., Wang, G., Li, H., Fan, X., & Liang, G. (2024). Emerging strategies to overcome current CAR-T therapy dilemmas—Exosomes derived from CAR-T cells. *International Journal of Nanomedicine*, *19*, 2773–2791. DOI: 10.2147/IJN.S445101 PMID: 38525009

Huang, J., Zhang, J., Sun, C., Yang, R., Sheng, M., Hu, J., Kai, G., & Han, B. (2024). Adjuvant role of Salvia miltiorrhiza bunge in cancer chemotherapy: A review of its bioactive components, health-promotion effect and mechanisms. *Journal of Ethnopharmacology*, *318*, 117022. DOI: 10.1016/j.jep.2023.117022 PMID: 37572929

Huang, R., Chen, H., Pi, D., He, X., Yu, C., & Yu, C. (2024). Preparation of etoposide liposomes for enhancing antitumor efficacy on small cell lung cancer and reducing hematotoxicity of drugs. *European Journal of Pharmaceutics and Biopharmaceutics*, *198*, 114239. DOI: 10.1016/j.ejpb.2024.114239 PMID: 38452907

Huang, S., Yang, J., Shen, N., Xu, Q., & Zhao, Q. (2023, February). Artificial intelligence in lung cancer diagnosis and prognosis: Current application and future perspective. *Seminars in Cancer Biology*, *89*, 30–37. DOI: 10.1016/j.semcancer.2023.01.006 PMID: 36682439

Huo, T. (2024). Next-gen CAR-T therapy: Innovations, challenges and future directions. BioTechniques. Retrieved from https://www.biotechniques.com/cancer-research/next-gen-car-t-therapy-innovations-challenges-and-future-directions/

Hussain, F. H., & Raza, A. (2024). Immune checkpoint inhibitors in cancer immunotherapy. In *Critical Developments in Cancer Immunotherapy* (pp. 123–156). IGI Global., DOI: 10.4018/979-8-3693-3976-3.ch004

Hyytiäinen, A., Mroueh, R., Peltonen, J., Wennerstrand, P., Mäkitie, A., Al-Samadi, A., Ventelä, S., & Salo, T. (2023). Prognostic histological markers in oral tongue squamous cell carcinoma patients treated with (chemo) radiotherapy. *APMIS*, *131*(4), 142–151. DOI: 10.1111/apm.13298 PMID: 36695633

Iglesias-Escudero, M., Arias-González, N., & Martínez-Cáceres, E. (2023). Regulatory cells and the effect of cancer immunotherapy. *Molecular Cancer*, *22*(1), 26. DOI: 10.1186/s12943-023-01714-0 PMID: 36739406

Iida, H., Tani, M., Komeda, K., Nomi, T., Matsushima, H., Tanaka, S., Ueno, M., Nakai, T., Maehira, H., Mori, H., Matsui, K., Hirokawa, F., Kaibori, M., & Kubo, S. (2022). Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. *HPB : The Official Journal of the International Hepato Pancreato Biliary Association*, *24*(1), 101–115. DOI: 10.1016/j.hpb.2021.06.414 PMID: 34244053

Jang, J. Y., Kim, D., Im, E., & Kim, N. D. (2025). Etoposide as a key therapeutic agent in lung cancer: Mechanisms, efficacy, and emerging strategies. *International Journal of Molecular Sciences*, *26*(2), 796. DOI: 10.3390/ijms26020796 PMID: 39859509

Jhunjhunwala, S., Hammer, C., & Delamarre, L. (2021). Antigen presentation in cancer: Insights into tumour immunogenicity and immune evasion. *Nature Reviews. Cancer*, *21*(5), 298–312. DOI: 10.1038/s41568-021-00339-z PMID: 33750922

Jin, S., Shang, Z., Wang, W., Gu, C., Wei, Y., Zhu, Y., Yang, C., Zhang, T., Zhu, Y., Zhu, Y., Wu, J., & Ye, D. (2023). Immune co-inhibitory receptors CTLA-4, PD-1, TIGIT, LAG-3, and TIM-3 in upper tract urothelial carcinomas: A large cohort study. *Journal of Immunotherapy*, *46*(4), 154–159. DOI: 10.1097/CJI.0000000000000466 PMID: 37017991

Jin, Y., Yang, F., & Chen, K. (2023). An overview of current development and barriers on liquid biopsy in patients with early-stage non-small-cell lung cancer. *Holistic Integrative Oncology.*, *2*(1), 43–49. DOI: 10.1007/s44178-023-00066-5

Joy, R., Phair, K., O'Hara, R., & Brady, D. (2024). Recent advances and current challenges in CAR-T cell therapy. *Biotechnology Letters*, *46*(1), 115–126. DOI: 10.1007/s10529-023-03461-0 PMID: 38150098

Karagiannakos, A., Adamaki, M., Tsintarakis, A., Vojtesek, B., Fåhraeus, R., Zoumpourlis, V., & Karakostis, K. (2022). Targeting oncogenic pathways in the era of personalized oncology: A systemic analysis reveals highly mutated signaling pathways in cancer patients and potential therapeutic targets. *Cancers (Basel)*, *14*(3), 664. DOI: 10.3390/cancers14030664 PMID: 35158934

Karim, N. A., Rabea, A. M., Mack, P. C., Subramanian, J., Khalil, E., Sherif, M., Marawan, R., Gaafar, T., Shash, L., Suzuki, K., Ahluwalia, M., Wahba, H., Aboelela, S., Al Ahmadi, A., Al Husaini, H., Mohsen, N., Khaled, R., Kassem, N., Khaled, H., & Sen, T. (2025). State of Lung Cancer in Egypt: Moving Towards Improved Guidelines for Prevention, Screening, Treatment, and Clinical Care Programs. *JTO Clinical and Research Reports*, *6*(1), 100776. DOI: 10.1016/j.jtocrr.2024.100776 PMID: 39790369

Kazerooni, E. A., Wood, D. E., Rosenthal, L. S., & Smith, R. A. (2024). The American Cancer Society National Lung Cancer Roundtable strategic plan: Introduction. *Cancer*, *130*(23), 3948–3960. DOI: 10.1002/cncr.35385 PMID: 39302215

Khalaf, K., Hana, D., Chou, J. T., Singh, C., Mackiewicz, A., & Kaczmarek, M. (2021). Aspects of the tumor microenvironment involved in immune resistance and drug resistance. *Frontiers in Immunology*, *12*, 656364. DOI: 10.3389/fimmu.2021.656364 PMID: 34122412

Koenig, D., Savic Prince, S., & Rothschild, S. I. (2021, February 15). Targeted therapy in advanced and metastatic non-small cell lung cancer. An update on treatment of the most important actionable oncogenic driver alterations. *Cancers (Basel)*, *13*(4), 804. DOI: 10.3390/cancers13040804 PMID: 33671873

Koroulakis, A., & Agarwal, M. (2024). Laryngeal cancer. In *StatPearls* [Internet]. StatPearls Publishing.

Kundu, M., Butti, R., Panda, V. K., Malhotra, D., Das, S., Mitra, T., Kapse, P., Gosavi, S. W., & Kundu, G. C. (2024). Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. *Molecular Cancer*, *23*(1), 92. DOI: 10.1186/s12943-024-01990-4 PMID: 38715072

Kuzevanova, A., Apanovich, N., Mansorunov, D., Korotaeva, A., & Karpukhin, A. (2022). The features of checkpoint receptor–ligand interaction in cancer and the therapeutic effectiveness of their inhibition. *Biomedicines*, *10*(9), 2081. DOI: 10.3390/biomedicines10092081 PMID: 36140182

Laguna, J. C., Tagliamento, M., Lambertini, M., Hiznay, J., & Mezquita, L. (2024, June). Tackling non–small cell lung cancer in young adults: From risk factors and genetic susceptibility to lung cancer profile and outcomes. *American Society of Clinical Oncology Educational Book*, *44*(3), e432488. DOI: 10.1200/EDBK_432488 PMID: 38788188

Lahiri, A., Maji, A., Potdar, P. D., Singh, N., Parikh, P., Bisht, B., Mukherjee, A., & Paul, M. K. (2023). Lung cancer immunotherapy: Progress, pitfalls, and promises. *Molecular Cancer*, *22*(1), 40. DOI: 10.1186/s12943-023-01740-y PMID: 36810079

Lee, J. Y., Bhandare, R. R., Boddu, S. H., Shaik, A. B., Saktivel, L. P., Gupta, G., Negi, P., Barakat, M., Singh, S. K., Dua, K., & Chellappan, D. K. (2024). Molecular mechanisms underlying the regulation of tumour suppressor genes in lung cancer. *Biomedicine and Pharmacotherapy*, *173*, 116275. DOI: 10.1016/j.biopha.2024.116275 PMID: 38394846

Lei, Y., Wang, K., Liu, Y., Wang, X., Xiang, X., Ning, X., Ding, W., Duan, J., Li, D., Zhao, W., Li, Y., Zhang, F., Luo, X., Shi, Y., Wang, Y., Huang, D., Bai, Y., & Zhang, H. (2022). Various subtypes of EGFR mutations in patients with NSCLC define genetic, immunologic diversity and possess different prognostic biomarkers. *Frontiers in Immunology*, *13*, 811601. DOI: 10.3389/fimmu.2022.811601 PMID: 35265073

Li, C. L., Yuan, X., & Yi, P. (2025). The role of immunotherapy in lung cancer treatment: Current strategies, future directions, and insights into metastasis and immune microenvironment. *Current Gene Therapy*, *25*(4), 453–466. DOI: 10.2174/0115665232340926241105064739 PMID: 39779552

Li, Q., Guo, C., Cao, B., Zhou, F., Wang, J., Ren, H., Li, Y., Wang, M., Liu, Y., Zhang, H., & Ma, L. (2024). Safety and efficacy evaluation of personalized exercise prescription during chemotherapy for lung cancer patients. *Thoracic Cancer*, *15*(11), 906–918. DOI: 10.1111/1759-7714.15272 PMID: 38462754

Li, W., Li, T., Sun, C., Du, Y., Chen, L., Du, C., Shi, J., & Wang, W. (2022). Identification and prognostic analysis of biomarkers to predict the progression of pancreatic cancer patients. *Molecular Medicine (Cambridge, Mass.)*, *28*(1), 43. DOI: 10.1186/s10020-022-00467-8 PMID: 35428170

Li, X., Gulati, M., Larson, A. C., Solheim, J. C., Jain, M., Kumar, S., & Batra, S. K. (2022). Immune checkpoint blockade in pancreatic cancer: Trudging through the immune desert. In *Seminars in Cancer Biology* (Vol. 86, pp. 14–27). Academic Press., DOI: 10.1016/j.semcancer.2022.08.009

Li, X. Y., Zhao, Z. J., Wang, J. B., Shao, Y. H., You, J. X., & Yang, X. T. (2022). m7G methylation-related genes as biomarkers for predicting overall survival outcomes for hepatocellular carcinoma. *Frontiers in Bioengineering and Biotechnology*, *10*, 849756. DOI: 10.3389/fbioe.2022.849756 PMID: 35620469

Li, Y., Liu, X., & Wang, Y. (2022). CAR-T cell combination therapy: The next revolution in cancer treatment. *Cancer Cell International*, *22*(1), 1–15. DOI: 10.1186/s12935-022-02778-6 PMID: 34980127

Li, Y. R., Fang, Y., Lyu, Z., Zhu, Y., & Yang, L. (2023). Exploring the dynamic interplay between cancer stem cells and the tumor microenvironment: Implications for novel therapeutic strategies. *Journal of Translational Medicine*, *21*(1), 686. DOI: 10.1186/s12967-023-04575-9 PMID: 37784157

Li, Z., Li, J., Bai, X., Huang, X., & Wang, Q. (2024, September 28). Tumor microenvironment as a complex milieu driving cancer progression: A mini review. *Clinical & Translational Oncology*, *27*(5), 1–0. DOI: 10.1007/s12094-024-03697-w PMID: 39342061

Lin, H. L., Lin, Q. Y., Feng, J. N., Zheng, W. E., Yang, C., & Yuan, S. F. (2024, September 18). Plasma fatty acid levels and risk of non-small cell lung cancer: A large-scale prospective cohort study. *Frontiers in Nutrition*, *11*, 1462300. DOI: 10.3389/fnut.2024.1462300 PMID: 39376792

Liu, J., Wang, H., Aggarwal, A., Ortiz-Ruiz, M. J., Zapatero-Solana, E., Lallena, M. J., Peregrina, S., del Hoyo, G. M., Velasco, S., Ebert, P. J., Gong, X., Hossain, A. M., & Estrem, S. T. (2025). Survival benefit from abemaciclib in non–small cell lung cancer by Kirsten rat sarcoma–mutation gene expression subtype: Retrospective analysis from the JUNIPER Trial. *Frontiers in Oncology*, *15*, 1461530. DOI: 10.3389/fonc.2025.1461530 PMID: 40231258

Liu, L., Bai, H., Wang, C., Seery, S., Wang, Z., Duan, J., Li, S., Xue, P., Wang, G., Sun, Y., Du, X., Zhang, X., Ma, Z., & Wang, J. (2021). Efficacy and safety of first-line immunotherapy combinations for advanced NSCLC: A systematic review and network meta-analysis. *Journal of Thoracic Oncology*, *16*(7), 1099–1117. DOI: 10.1016/j.jtho.2021.03.016 PMID: 33839365

Liu, M., Liu, L., Lv, Z., Mao, Y., & Liu, Y. (2024). Investigating the determinants of fear of cancer recurrence in patients with early-stage non-small cell lung cancer: Insights from a restricted cubic spline model. *Cancer Medicine*, *13*(12), e7406. DOI: 10.1002/cam4.7406

Lo, Y. C., & Lindeman, N. I. (2023). Molecular Pathology of Lung Tumors. In *Molecular Surgical Pathology* (pp. 231–245). Springer International Publishing. DOI: 10.1007/978-3-031-35118-1_9

Lodka, D., Zschummel, M., Bunse, M., Rousselle, A., Sonnemann, J., Kettritz, R., Höpken, U. E., & Schreiber, A. (2024). CD19-targeting CAR T cells protect from ANCA-induced acute kidney injury. *Annals of the Rheumatic Diseases*, *83*(4), 499–507. DOI: 10.1136/ard-2023-224875 PMID: 38182404

LoPiccolo, J., Gusev, A., Christiani, D. C., & Jänne, P. A. (2024). Lung cancer in patients who have never smoked—An emerging disease. *Nature Reviews. Clinical Oncology*, *21*(2), 121–146. DOI: 10.1038/s41571-023-00844-0 PMID: 38195910

Lopresti, L., Tatangelo, V., Baldari, C. T., & Patrussi, L. (2024). Rewiring the T cell-suppressive cytokine landscape of the tumor microenvironment: A new frontier for precision anti-cancer therapy. *Frontiers in Immunology*, *15*, 1418527. DOI: 10.3389/fimmu.2024.1418527 PMID: 39281678

Malapelle, U., Leprieur, E. G., Kamga, P. T., Chiasseu, M. T., & Rolfo, C. (2021). Emerging biomarkers for NSCLC: Recent advances in diagnosis and therapy. *Frontiers in Oncology*, *11*, 694578. DOI: 10.3389/fonc.2021.694578 PMID: 34055656

Malinga, N. Z., Siwele, S. C., Steel, H. C., Kwofie, L. L., Meyer, P. W., Smit, T., Anderson, R., Rapoport, B. L., & Kgokolo, M. C. (2022). Systemic levels of the soluble co-inhibitory immune checkpoints, CTLA-4, LAG-3, PD-1/PD-L1 and TIM-3 are markedly increased in basal cell carcinoma. *Translational Oncology*, *19*, 101384. DOI: 10.1016/j.tranon.2022.101384 PMID: 35255355

Mamdani, H., Matosevic, S., Khalid, A. B., Durm, G., & Jalal, S. I. (2022). Immunotherapy in lung cancer: Current landscape and future directions. *Frontiers in Immunology*, *13*, 823618. DOI: 10.3389/fimmu.2022.823618 PMID: 35222404

Massafra, M., Passalacqua, M. I., Gebbia, V., Macrì, P., Lazzari, C., Gregorc, V., & Santarpia, M. (2021). Immunotherapeutic advances for NSCLC. *Biologics*, ●●●, 399–417. PMID: 34675481

Meira, D. D. (2023). de Castro e Caetano. *Lung Cancer (Amsterdam, Netherlands)*, *24*, 26.

Mimura, K., Kua, L. F., Xiao, J. F., Asuncion, B. R., Nakayama, Y., Syn, N., Fazreen, Z., Soong, R., Kono, K., & Yong, W. P. (2021). Combined inhibition of PD-1/PD-L1, LAG-3, and TIM-3 axes augments antitumor immunity in gastric cancer–T cell coculture models. *Gastric Cancer*, *24*(3), 611–623. DOI: 10.1007/s10120-020-01151-8 PMID: 33611641

Mina, S. A., Shanshal, M., Leventakos, K., & Parikh, K. (2025). Emerging Targeted Therapies in Non-Small-Cell Lung Cancer (NSCLC). *Cancers (Basel)*, *17*(3), 353. DOI: 10.3390/cancers17030353 PMID: 39941723

Molinaro, M., Skrodzki, D., & Pan, D. (2024). Chemoradiotherapy and nanomedicine: Drug mechanisms and delivery systems. *Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology*, *16*(4), e1984. DOI: 10.1002/wnan.1984 PMID: 39109509

Mollavelioglu, B., Cetin Aktas, E., Cabioglu, N., Abbasov, A., Onder, S., Emiroglu, S., Tükenmez, M., Muslumanoglu, M., Igci, A., Deniz, G., & Ozmen, V. (2022). High co-expression of immune checkpoint receptors PD-1, CTLA-4, LAG-3, TIM-3, and TIGIT on tumor-infiltrating lymphocytes in early-stage breast cancer. *World Journal of Surgical Oncology*, *20*(1), 349. DOI: 10.1186/s12957-022-02810-z PMID: 36271406

Munteanu, R., Tomuleasa, C., Iuga, C. A., Gulei, D., & Ciuleanu, T. E. (2023). Exploring therapeutic avenues in lung cancer: The epigenetic perspective. *Cancers (Basel)*, *15*(22), 5394. DOI: 10.3390/cancers15225394 PMID: 38001653

Nadal, E., Saleh, M., Ponce Aix, S., Ochoa-de-Olza, M., Patel, S. P., Antonia, S., Zhao, Y., Gueorguieva, I., Man, M., Estrem, S. T., Liu, J., Avsar, E., Lin, W. H., Benhadji, K. A., Gandhi, L., Guba, S. C., & Ales Diaz, I. (2023). A phase Ib/II study of galunisertib in combination with nivolumab in solid tumors and non-small cell lung cancer. *BMC Cancer*, *23*(1), 11153. Advance online publication. DOI: 10.1186/s12885-023-11153-1 PMID: 37507657

Nagy, A., Börzsei, D., Hoffmann, A., Török, S., Veszelka, M., Almási, N., Varga, C., & Szabó, R. (2024). A comprehensive overview on chemotherapy-induced cardiotoxicity: Insights into the underlying inflammatory and oxidative mechanisms. *Cardiovascular Drugs and Therapy*, ●●●, 1–15. DOI: 10.1007/s10557-024-07574-0 PMID: 38492161

Nardin, S., Sacco, G., Lagodin D'Amato, A., Barcellini, L., Rovere, M., Santamaria, S., Marconi, S., Coco, S., & Genova, C. (2024). Updates in pharmacotherapy for non-small cell lung cancer: A focus on emerging tubulin inhibitors. *Expert Opinion on Pharmacotherapy*, *25*(8), 1051–1069. DOI: 10.1080/14656566.2024.2369196 PMID: 38935538

Naser, R., Fakhoury, I., El-Fouani, A., Abi-Habib, R., & El-Sibai, M. (2022). Role of the tumor microenvironment in cancer hallmarks and targeted therapy. *International Journal of Oncology*, *62*(2), 23. DOI: 10.3892/ijo.2022.5471 PMID: 36579669

National Cancer Institute. (2024). CAR T cells: Engineering patients' immune cells to treat their cancers. Retrieved from https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

Ning, J., Ge, T., Jiang, M., Jia, K., Wang, L., Li, W., Chen, B., Liu, Y., Wang, H., Zhao, S., & He, Y. (2021). Early diagnosis of lung cancer: Which is the optimal choice? *Aging (Albany NY)*, *13*(4), 6214–6229. DOI: 10.18632/aging.202504 PMID: 33591942

Nooreldeen, R., & Bach, H. (2021). Current and future development in lung cancer diagnosis. *International Journal of Molecular Sciences*, *22*(16), 8661. DOI: 10.3390/ijms22168661 PMID: 34445366

Novello, S., Califano, R., Reinmuth, N., Tamma, A., & Puri, T. (2023). RET fusion-positive non small cell lung cancer: The evolving treatment landscape. *The Oncologist*, *28*(5), 402–413. DOI: 10.1093/oncolo/oyac264 PMID: 36821595

Ohno, R., & Nakamura, A. (2024, May). Advancing autoimmune rheumatic disease treatment: CAR-T Cell Therapies—Evidence, safety, and future directions. In *Seminars in Arthritis and Rheumatism* (p. 152479). WB Saunders. DOI: 10.1016/j.semarthrit.2024.152479

Olmedo, M. E., Cervera, R., Cabezon-Gutierrez, L., Lage, Y., de la Fuente, E. C., Rueda, A. G., & Couñago, F. (2022). New horizons for uncommon mutations in non-small cell lung cancer: BRAF, KRAS, RET, MET, NTRK, HER2. *World Journal of Clinical Oncology*, *13*(4), 276–286. DOI: 10.5306/wjco.v13.i4.276 PMID: 35582653

Oya, Y., Tanaka, I., & Soo, R. A. (2025, April 8). Integration of Liquid Biopsy for Optimal Management of NSCLC. *Tuberculosis and Respiratory Diseases*. Advance online publication. DOI: 10.4046/trd.2024.0146

Özkaya Gül, S., Şimşek, B., Yıldız, F., & Aydemir, E. (2025). Cytotoxic effect of escitalopram/etoposide combination on etoposide-resistant lung cancer. *Pharmaceuticals (Basel, Switzerland)*, *18*(4), 531. DOI: 10.3390/ph18040531 PMID: 40283966

Palma, D. A., Prisman, E., Berthelet, E., Tran, E., Hamilton, S., Wu, J., Eskander, A., Higgins, K., Karam, I., Poon, I., Husain, Z., Enepekides, D., Hier, M., Sultanem, K., Richardson, K., Mlynarek, A., Johnson-Obaseki, S., Odell, M., Bayley, A., & Nichols, A. C. (2022). Assessment of toxic effects and survival in treatment deescalation with radiotherapy vs transoral surgery for HPV-associated oropharyngeal squamous cell carcinoma: The ORATOR2 phase 2 randomized clinical trial. *JAMA Oncology*, *8*(6), 845–851. DOI: 10.1001/jamaoncol.2022.0615 PMID: 35482348

Pan, D., Hu, A. Y., Antonia, S. J., & Li, C. Y. (2021). A gene mutation signature predicting immunotherapy benefits in patients with NSCLC. *Journal of Thoracic Oncology*, *16*(3), 419–427. DOI: 10.1016/j.jtho.2020.11.021 PMID: 33307194

Parvaresh, H., Roozitalab, G., Golandam, F., Behzadi, P., & Jabbarzadeh Kaboli, P. (2024). Unraveling the potential of ALK-targeted therapies in non-small cell lung cancer: Comprehensive insights and future directions. *Biomedicines*, *12*(2), 297. DOI: 10.3390/biomedicines12020297 PMID: 38397899

Passaro, A., Attili, I., Rappa, A., Vacirca, D., Ranghiero, A., Fumagalli, C., Guarize, J., Spaggiari, L., de Marinis, F., Barberis, M., & Guerini-Rocco, E. (2021). Genomic characterization of concurrent alterations in Non-Small Cell Lung Cancer (NSCLC) harboring actionable mutations. *Cancers (Basel)*, *13*(9), 2172. DOI: 10.3390/cancers13092172 PMID: 33946519

Pezzuto, F., Hofman, V., Bontoux, C., Fortarezza, F., Lunardi, F., Calabrese, F., & Hofman, P. (2023a). The significance of co-mutations in EGFR-mutated non-small cell lung cancer: Optimizing the efficacy of targeted therapies? *Lung Cancer (Amsterdam, Netherlands)*, *181*, 107249. DOI: 10.1016/j.lungcan.2023.107249 PMID: 37244040

Pietrobon, V., & Marincola, F. M. (2021). Hypoxia and the phenomenon of immune exclusion. *Journal of Translational Medicine*, *19*(1), 9. DOI: 10.1186/s12967-020-02667-4 PMID: 33407613

Pillay, J., Rahman, S., Klarenbach, S., Reynolds, D. L., Tessier, L. A., Thériault, G., Persaud, N., Finley, C., Leighl, N., McInnes, M. D. F., Garritty, C., Traversy, G., Tan, M., & Hartling, L. (2024). Screening for lung cancer with computed tomography: Protocol for systematic reviews for the Canadian Task Force on Preventive Health Care. *Systematic Reviews*, *13*(1), 88. DOI: 10.1186/s13643-024-02506-3 PMID: 38493159

Pisapia, P., Pepe, F., Baggi, A., Barberis, M., Galvano, A., Gristina, V., Mastrilli, F., Novello, S., Pagni, F., Pasini, S., Perrone, G., Righi, D., Russo, A., Troncone, G., & Malapelle, U. (2022). Next generation diagnostic algorithm in non-small cell lung cancer predictive molecular pathology: The KWAY Italian multicenter cost evaluation study. *Critical Reviews in Oncology/Hematology*, *169*, 103525. DOI: 10.1016/j.critrevonc.2021.103525 PMID: 34813925

Pop-Bica, C., Ciocan, C. A., Braicu, C., Haranguș A., Simon, M., Nutu, A., Pop, L. A., Slaby, O., Atanasov, A. G., Pirlog, R., Al Hajjar, N., & Berindan-Neagoe, I. (2022). Next-generation sequencing in lung cancer patients: A comparative approach in NSCLC and SCLC mutational landscapes. *Journal of Personalized Medicine*, *12*(3), 453. DOI: 10.3390/jpm12030453 PMID: 35330454

Pradhan, K. S., Chawla, P., & Tiwari, R. (2023). HRDEL: High ranking deep ensemble learning-based lung cancer diagnosis model. *Expert Systems with Applications*, *213*, 118956. DOI: 10.1016/j.eswa.2022.118956

. Pruis M. Genotype-guided anti-cancer therapy: development, associated diagnostics and clinical applications: From mutation to patient.

Qi, S. A., Wu, Q., Chen, Z., Zhang, W., Zhou, Y., Mao, K., Li, J., Li, Y., Chen, J., Huang, Y., & Huang, Y. (2021). High-resolution metabolomic biomarkers for lung cancer diagnosis and prognosis. *Scientific Reports*, *11*(1), 11805. DOI: 10.1038/s41598-021-91276-2 PMID: 34083687

Qi, W., Tian, L., Xu, J., Li, Z., & Wang, T. (2025). Multimodal framework in lung cancer management: Integrating liquid biopsy with traditional diagnostic techniques. *Cancer Management and Research*, *17*, 461–481. DOI: 10.2147/CMAR.S506630 PMID: 40060704

Qin, Y., Mo, Y., Li, P., Liang, X., Yu, J., & Chen, D. (2025, April 16). Concurrent immunotherapy improves progression-free survival but increases toxicity in unresectable stage III NSCLC. *Lung Cancer (Amsterdam, Netherlands)*, *203*, 108544. DOI: 10.1016/j.lungcan.2025.108544 PMID: 40253944

Qureshi, M., Afridi, H. I., & Unar, A. (n.d.). [-dioxygenase in primary biliary cholangitis: A comprehensive review of its role, clinical applications, and regulatory mechanisms.]. *Indoleamine*, *2*, 3.

Raju, G. S., Pavitra, E., Varaprasad, G. L., Bandaru, S. S., Nagaraju, G. P., Farran, B., Huh, Y. S., & Han, Y.-K. (2022). Nanoparticles mediated tumor microenvironment modulation: Current advances and applications. *Journal of Nanobiotechnology*, *20*(1), 274. DOI: 10.1186/s12951-022-01476-9 PMID: 35701781

Raju, G. S., Pavitra, E., Varaprasad, G. L., Bandaru, S. S., Nagaraju, G. P., Farran, B., Huh, Y. S., & Han, Y.-K. (2022). Nanoparticles mediated tumor microenvironment modulation: Current advances and applications. *Journal of Nanobiotechnology*, *20*(1), 274. DOI: 10.1186/s12951-022-01476-9 PMID: 35701781

Rakaee, M., Tafavvoghi, M., Ricciuti, B., Alessi, J. V., Cortellini, A., Citarella, F., Nibid, L., Perrone, G., Adib, E., Fulgenzi, C. A., Hidalgo Filho, C. M., Di Federico, A., Jabar, F., Hashemi, S., Houda, I., Richardsen, E., Rasmussen Busund, L.-T., Donnem, T., Bahce, I., & Kwiatkowski, D. J. (2025, February 1). Deep Learning Model for Predicting Immunotherapy Response in Advanced Non– Small Cell Lung Cancer. *JAMA Oncology*, *11*(2), 109–118. DOI: 10.1001/jamaoncol.2024.5356 PMID: 39724105

Rodak, O., Peris-Díaz, M. D., Olbromski, M., Podhorska-Okołów, M., & Dzięgiel, P. (2021, September 20). Current landscape of non-small cell lung cancer: Epidemiology, histological classification, targeted therapies, and immunotherapy. *Cancers (Basel)*, *13*(18), 4705. DOI: 10.3390/cancers13184705 PMID: 34572931

Rodrigues, A., Chauhan, J., Sagkriotis, A., Aasaithambi, S., & Montrone, M. (2022). Understanding the lived experience of lung cancer: A European social media listening study. *BMC Cancer*, *22*(1), 475. DOI: 10.1186/s12885-022-09505-4 PMID: 35490223

Rolfo, C., Mack, P., Scagliotti, G. V., Aggarwal, C., Arcila, M. E., Barlesi, F., Bivona, T., Diehn, M., Dive, C., Dziadziuszko, R., Leighl, N., Malapelle, U., Mok, T., Peled, N., Raez, L. E., Sequist, L., Sholl, L., Swanton, C., Abbosh, C., & Gandara, D. (2021). Liquid biopsy for advanced NSCLC: A consensus statement from the International Association for the Study of Lung Cancer. *Journal of Thoracic Oncology*, *16*(10), 1647–1662. DOI: 10.1016/j.jtho.2021.06.017 PMID: 34246791

Rosas, D., Jones, C., Akinbobuyi, O., Yee Theik, N. W., & Alvarez-Pinzon, A. (2024). Molecular Targeting in Non-Small Cell Lung Cancer: Advances in EGFR, ROS1, ALK, and MET Pathways. *Journal of Oncology Research and Therapy*, *9*, 10214.

Rosellini, M., Marchetti, A., Mollica, V., Rizzo, A., Santoni, M., & Massari, F. (2023). Prognostic and predictive biomarkers for immunotherapy in advanced renal cell carcinoma. *Nature Reviews. Urology*, *20*(3), 133–157. DOI: 10.1038/s41585-022-00676-0 PMID: 36414800

Russo, G. L., Bironzo, P., Bennati, C., Bonanno, L., Catino, A., Metro, G., Petrini, I., Russano, M., & Passaro, A. (2024). Clinical evidence and adverse event management update of patients with RET-rearranged advanced non-small-cell lung cancer (NSCLC) treated with pralsetinib. *Critical Reviews in Oncology/Hematology*, *194*, 104243. DOI: 10.1016/j.critrevonc.2023.104243 PMID: 38135019

Sadhukhan, P., & Seiwert, T. Y. (2023). The role of macrophages in the tumor microenvironment and tumor metabolism. *Seminars in Immunopathology*, *45*(2), 187–201. DOI: 10.1007/s00281-023-00988-2 PMID: 37002376

Scheffler, M., Ihle, M. A., Hein, R., Merkelbach-Bruse, S., Scheel, A. H., Siemanowski, J., Brägelmann, J., Kron, A., Abedpour, N., Ueckeroth, F., Schüller, M., Koleczko, S., Michels, S., Fassunke, J., Pasternack, H., Heydt, C., Serke, M., Fischer, R., Schulte, W., & Wolf, J. (2019). K-ras mutation subtypes in NSCLC and associated co-occurring mutations in other oncogenic pathways. *Journal of Thoracic Oncology*, *14*(4), 606–616. DOI: 10.1016/j.jtho.2018.12.013 PMID: 30605727

Schett, G., Müller, F., Taubmann, J., Mackensen, A., Wang, W., Furie, R. A., Gold, R., Haghikia, A., Merkel, P. A., Caricchio, R., D'Agostino, M.-A., Locatelli, F., June, C. H., & Mougiakakos, D. (2024). Advancements and challenges in CAR T cell therapy in autoimmune diseases. *Nature Reviews. Rheumatology*, *20*(9), 531–544. DOI: 10.1038/s41584-024-01139-z PMID: 39107407

Sen, T., Takahashi, N., Chakraborty, S., Takebe, N., Nassar, A. H., Karim, N. A., Puri, S., & Naqash, A. R. (2024). Emerging advances in defining the molecular and therapeutic landscape of small-cell lung cancer. *Nature Reviews. Clinical Oncology*, *21*(8), 610–627. DOI: 10.1038/s41571-024-00914-x PMID: 38965396

Sharma, A., Shambhwani, D., Pandey, S., Singh, J., Lalhlenmawia, H., Kumarasamy, M., Singh, S. K., Chellappan, D. K., Gupta, G., Prasher, P., Dua, K., & Kumar, D. (2022). Advances in lung cancer treatment using nanomedicines. *ACS Omega*, *8*(1), 10–41. DOI: 10.1021/acsomega.2c04078 PMID: 36643475

Sharma, K., Saini, K., Chimaniya, P., Sahu, S., Gantayat, D., Sharma, R., & Shilpi, S. (2024). Lung Cancer Therapy: Synergistic Potential of PD-1/PD-L1 and CTLA-4 Inhibitors. In *Immunotherapy Against Lung Cancer: Emerging Opportunities and Challenges* (pp. 297–316). Springer Nature Singapore. DOI: 10.1007/978-981-99-7141-1_15

Shen, S., Hong, Y., Huang, J., Qu, X., Sooranna, S. R., Lu, S., Li, T., & Niu, B. (2024). Targeting PD-1/PD-L1 in tumor immunotherapy: Mechanisms and interactions with host growth regulatory pathways. *Cytokine & Growth Factor Reviews*, *79*, 16–28. DOI: 10.1016/j.cytogfr.2024.08.001 PMID: 39179486

Shin, S.. (2022, April 1). Tumor microenvironment modulating functional nanoparticles for effective cancer treatments. *Tissue Engineering and Regenerative Medicine*, ●●●, 1–5. PMID: 34674182

Shiravand, Y., Khodadadi, F., Kashani, S. M., Hosseini-Fard, S. R., Hosseini, S., Sadeghirad, H., Ladwa, R., O'Byrne, K., & Kulasinghe, A. (2022). Immune checkpoint inhibitors in cancer therapy. *Current Oncology (Toronto, Ont.)*, *29*(5), 3044–3060. DOI: 10.3390/curroncol29050247 PMID: 35621637

Shiravand, Y., Khodadadi, F., Kashani, S. M. A., Hosseini-Fard, S. R., Hosseini, S., Sadeghirad, H., Ladwa, R., O'Byrne, K., & Kulasinghe, A. (2022). Immune checkpoint inhibitors in cancer therapy. *Current Oncology (Toronto, Ont.)*, *29*(5), 3044–3060. DOI: 10.3390/curroncol29050247 PMID: 35621637

Singhal, A., Li, B. T., & O'Reilly, E. M. (2024). Targeting KRAS in cancer. *Nature Medicine*, *30*(4), 969–983. DOI: 10.1038/s41591-024-02903-0 PMID: 38637634

Sito, H., Sharzehan, M. A. K., Islam, M. A., & Tan, S. C. (2024). Genetic variants associated with response to platinum-based chemotherapy in non-small cell lung cancer patients: A field synopsis and meta-analysis. *British Journal of Biomedical Science*, *81*, 11835. DOI: 10.3389/bjbs.2024.11835 PMID: 38450253

Sito, H., & Tan, S. C. (2024). Genetic polymorphisms as potential pharmacogenetic biomarkers for platinum-based chemotherapy in non-small cell lung cancer. *Molecular Biology Reports*, *51*(1), 102. DOI: 10.1007/s11033-023-08915-2 PMID: 38217759

Skoulidis, F., Li, B. T., Dy, G. K., Price, T. J., Falchook, G. S., Wolf, J., & Riely, G. J. (2021). Sotorasib for lung cancers with KRAS p.G12C mutation. *The New England Journal of Medicine*, *384*(25), 2371–2381. DOI: 10.1056/NEJMoa2103695 PMID: 34096690

Smolle, E., Taucher, V., Lindenmann, J., Pichler, M., & Smolle-Juettner, F. M. (2021). Liquid biopsy in non-small cell lung cancer—Current status and future outlook: A narrative review. *Translational Lung Cancer Research*, *10*(5), 2237–2252. DOI: 10.21037/tlcr-21-3 PMID: 34164273

Socinski, M. A., Özgüroğlu, M., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., Gray, J. E., Park, K., Vincent, M., Mann, H., Newton, M., Dennis, P. A., & Antonia, S. J. (2021, November 1). Durvalumab after concurrent chemoradiotherapy in elderly patients with unresectable stage III non–small–cell lung cancer (PACIFIC). *Clinical Lung Cancer*, *22*(6), 549–561. DOI: 10.1016/j.cllc.2021.05.009 PMID: 34294595

Soleimani Mamalo, A., Pashaei, M., Valilo, M., & Ojarudi, M. (2025). Cytokine-mediated regulation of immune cell metabolic pathways in the tumor microenvironment. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *398*(9), 1–9. DOI: 10.1007/s00210-025-04133-8 PMID: 40220026

Sorin, M., Prosty, C., Ghaleb, L., Nie, K., Katergi, K., Shahzad, M. H., Dubé, L.-R., Atallah, A., Swaby, A., Dankner, M., Crump, T., Walsh, L. A., Fiset, P. O., Sepesi, B., Forde, P. M., Cascone, T., Provencio, M., & Spicer, J. D. (2024). Neoadjuvant chemoimmunotherapy for NSCLC: A systematic review and meta-analysis. *JAMA Oncology*, *10*(5), 621–633. DOI: 10.1001/jamaoncol.2024.0057 PMID: 38512301

Spira, A. I., Tu, H., Aggarwal, S., Hsu, H., Carrigan, G., Wang, X., Ngarmchamnanrith, G., Chia, V., & Gray, J. E. (2021). A retrospective observational study of the natural history of advanced non–small-cell lung cancer in patients with KRAS p.G12C mutated or wild-type disease. *Lung Cancer (Amsterdam, Netherlands)*, *159*, 1–9. DOI: 10.1016/j.lungcan.2021.05.026 PMID: 34293517

Stanganelli, I., Spagnolo, F., Argenziano, G., Ascierto, P. A., Bassetto, F., Bossi, P., Donato, V., Massi, D., Massone, C., Patuzzo, R., Pellacani, G., Quaglino, P., Queirolo, P., Zalaudek, I., & Palmieri, G. (2022). The multidisciplinary management of cutaneous squamous cell carcinoma: A comprehensive review and clinical recommendations by a panel of experts. *Cancers (Basel)*, *14*(2), 377. DOI: 10.3390/cancers14020377 PMID: 35053539

Stanzione, B., Del Conte, A., Bertoli, E., De Carlo, E., Revelant, A., Spina, M., & Bearz, A. (2023). Therapeutical options in ROS1-rearranged advanced non-small cell lung cancer. *International Journal of Molecular Sciences*, *24*(14), 11495. DOI: 10.3390/ijms241411495 PMID: 37511255

Su, K., Huang, W., Li, X., Xu, K., Gu, T., Liu, Y., Song, J., Qian, K., Xu, Y., Zeng, H., Yang, Y., Guo, L., & Han, Y. (2023). Evaluation of lactate dehydrogenase and alkaline phosphatase as predictive biomarkers in the prognosis of hepatocellular carcinoma and development of a new nomogram. *Journal of Hepatocellular Carcinoma*, *10*, 69–79. DOI: 10.2147/JHC.S398632 PMID: 36685113

Sulewska, A., Pilz, L., Manegold, C., Ramlau, R., Charkiewicz, R., & Niklinski, J. (2023). A systematic review of progress toward unlocking the power of epigenetics in NSCLC: Latest updates and perspectives. *Cells*, *12*(6), 905. DOI: 10.3390/cells12060905 PMID: 36980246

Sun, Z., Sun, X., Chen, Z., Du, J., & Wu, Y. (2022). Head and neck squamous cell carcinoma: Risk factors, molecular alterations, immunology and peptide vaccines. *International Journal of Peptide Research and Therapeutics*, *28*(1), 1–18. DOI: 10.1007/s10989-021-10334-5 PMID: 34903958

Syed, Y. Y. (2022). Pralsetinib: A review in advanced RET fusion-positive NSCLC. *Drugs*, *82*(7), 811–816. DOI: 10.1007/s40265-022-01720-4 PMID: 35587858

Tada, H., Mitsudomi, T., Misumi, T., Sugio, K., Tsuboi, M., Okamoto, I., Iwamoto, Y., Sakakura, N., Sugawara, S., Atagi, S., Takahashi, T., Hayashi, H., Okada, M., Inokawa, H., Yoshioka, H., Takahashi, K., Higashiyama, M., Yoshino, I., & Nakagawa, K. (2022, January 20). Randomized phase III study of gefitinib versus cisplatin plus vinorelbine for patients with resected stage II-IIIA non–small-cell lung cancer with EGFR mutation (IMPACT). *Journal of Clinical Oncology*, *40*(3), 231–241. DOI: 10.1200/JCO.21.01729 PMID: 34726958

Taefehshokr, S., Parhizkar, A., Hayati, S., Mousapour, M., Mahmoudpour, A., Eleid, L., Rahmanpour, D., Fattahi, S., Shabani, H., & Taefehshokr, N. (2022). Cancer immunotherapy: Challenges and limitations. *Pathology, Research and Practice*, *229*, 153723. DOI: 10.1016/j.prp.2021.153723 PMID: 34952426

Tahayneh, K., Idkedek, M., & Abu Akar, F. (2025). NSCLC: Current evidence on its pathogenesis, integrated treatment, and future perspectives. *Journal of Clinical Medicine*, *14*(3), 1025. DOI: 10.3390/jcm14031025 PMID: 39941694

Tan, A. C., Saw, S. P., Chen, J., Lai, G. G., Oo, H. N., Takano, A., Lau, D. P. X., Yeong, J. P. S., Tan, G. S., Lim, K. H., Skanderup, A. J., Chan, J. W. K., Teh, Y. L., Rajasekaran, T., Jain, A., Tan, W. L., Ng, Q. S., Kanesvaran, R., Lim, W.-T., & Tan, D. S. W. (2022). Clinical and genomic features of HER2 exon 20 insertion mutations and characterization of HER2 expression by immunohistochemistry in east Asian non–small-cell lung cancer. *JCO Precision Oncology*, *6*(6), e2200278. DOI: 10.1200/PO.22.00278 PMID: 36240473

Tan, S. L., Selvachandran, G., Paramesran, R., & Ding, W. (2025). Lung cancer detection systems applied to medical images: A state-of-the-art survey. *Archives of Computational Methods in Engineering*, *32*(1), 343–380. DOI: 10.1007/s11831-024-10141-3

Tao, Y., Zhou, Y., Tang, L., Chen, H., Feng, Y., & Shi, Y. (2022). Toxicity profile of anaplastic lymphoma kinase tyrosine kinase inhibitors for patients with non-small cell lung cancer: A systematic review and meta-analysis. *Investigational New Drugs*, *40*(4), 831–840. DOI: 10.1007/s10637-022-01242-6 PMID: 35435628

Tarighati, E., Keivan, H., & Mahani, H. (2023). A review of prognostic and predictive biomarkers in breast cancer. *Clinical and Experimental Medicine*, *23*(1), 1–16. PMID: 35031885

Thomas, Q. D., Chaabouni, M., Al Herk, A., Lefevbre, C., Cavaillon, S., Sinoquet, L., Pouderoux, S., Viala, M., Roca, L., & Quantin, X. (2024). Exploring the Efficacy of Pembrolizumab in Combination with Carboplatin and Weekly Paclitaxel for Frail Patients with Advanced Non-Small-Cell Lung Cancer: A Key Investigative Study. *Cancers (Basel)*, *16*(5), 992. DOI: 10.3390/cancers16050992 PMID: 38473356

Tiwari, A., Trivedi, R., & Lin, S. Y. (2022). Tumor microenvironment: Barrier or opportunity towards effective cancer therapy. *Journal of Biomedical Science*, *29*(1), 83. DOI: 10.1186/s12929-022-00866-3 PMID: 36253762

Tomasik, B., Skrzypski, M., Bieńkowski, M., Dziadziuszko, R., & Jassem, J. (2023). Current and future applications of liquid biopsy in non-small-cell lung cancer—A narrative review. *Translational Lung Cancer Research*, *12*(3), 594–608. DOI: 10.21037/tlcr-22-742 PMID: 37057121

Tsuboi, M., Herbst, R. S., John, T., Kato, T., Majem, M., Grohé, C., Wang, J., Goldman, J. W., Lu, S., Su, W.-C., de Marinis, F., Shepherd, F. A., Lee, K. H., Le, N. T., Dechaphunkul, A., Kowalski, D., Poole, L., Bolanos, A., Rukazenkov, Y., & Wu, Y.-L. (2023, July 13). Overall survival with osimertinib in resected EGFR-mutated NSCLC. *The New England Journal of Medicine*, *389*(2), 137–147. DOI: 10.1056/NEJMoa2304594 PMID: 37272535

Umar, H., Wahab, H. A., Attiq, A., Amjad, M. W., Bukhari, S. N. A., & Ahmad, W. (2024). Platinum-based targeted chemotherapies and reversal of cisplatin resistance in non-small cell lung cancer (NSCLC). *Mutation Research. Fundamental and Molecular Mechanisms of Mutagenesis*, *828*, 111856. DOI: 10.1016/j.mrfmmm.2024.111856 PMID: 38520879

Veyssière, H., Bidet, Y., Penault-Llorca, F., Radosevic-Robin, N., & Durando, X. (2022). Circulating proteins as predictive and prognostic biomarkers in breast cancer. *Clinical Proteomics*, *19*(1), 25. DOI: 10.1186/s12014-022-09362-0 PMID: 35818030

Wang, B., Shen, C., Liu, D., Dong, Z., Lin, X., & Liao, H. (2025). A Comprehensive Review of Advances in Molecular Mechanisms and Targeted Therapies for the Specific Type of Cystic Lung Cancer. *OncoTargets and Therapy*, *18*, 211–224. DOI: 10.2147/OTT.S495018 PMID: 39959914

Wang, H., Cheng, X., Yang, F., Chen, L., Zhang, A., Zhong, L., Long, H., Zhu, B., & Wang, Z. (2024). Subsequent strategies and underlying mechanism of acquired resistance to PD-1 axis inhibitors in advanced non-small cell lung cancer. *Chinese Medical Journal*, *137*(7), 880–882. DOI: 10.1097/CM9.0000000000003015 PMID: 38494340

Wang, Q., Li, H., Wu, T., Yu, B., Cong, H., & Shen, Y. (2024). Nanodrugs based on co-delivery strategies to combat cisplatin resistance. *Journal of Controlled Release*, *370*, 14–42. DOI: 10.1016/j.jconrel.2024.04.020 PMID: 38615892

Wang, S., Liu, C., Yang, C., Jin, Y., Cui, Q., Wang, D., Ge, T., He, G., Li, W., Zhang, G., Liu, A., Xia, Y., Liu, Y., & Yu, J. (2024). PI3K/AKT/mTOR and PD-1/CTLA-4/CD28 pathways as key targets of cancer immunotherapy. *Oncology Letters*, *28*(6), 567. DOI: 10.3892/ol.2024.14700 PMID: 39390982

Wang, Y., Hu, J., Fleishman, J. S., Li, Y., Ren, Z., Wang, J., Feng, Y., Chen, J., & Wang, H. (2024). Inducing ferroptosis by traditional medicines: A novel approach to reverse chemoresistance in lung cancer. *Frontiers in Pharmacology*, *15*, 1290183. DOI: 10.3389/fphar.2024.1290183 PMID: 38855750

Wang, Y. T., Yang, P. C., Zhang, J. Y., & Sun, J. F. (2024). Synthetic routes and clinical application of representative small-molecule EGFR inhibitors for cancer therapy. *Molecules (Basel, Switzerland)*, *29*(7), 1448. DOI: 10.3390/molecules29071448 PMID: 38611728

Winge, M. C., Kellman, L. N., Guo, K., Tang, J. Y., Swetter, S. M., Aasi, S. Z., Sarin, K. Y., Chang, A. L. S., & Khavari, P. A. (2023). Advances in cutaneous squamous cell carcinoma. *Nature Reviews. Cancer*, *23*(7), 430–449. DOI: 10.1038/s41568-023-00583-5 PMID: 37286893

Wunderlich, K., Suppa, M., Gandini, S., Lipski, J., White, J. M., & Del Marmol, V. (2024). Risk factors and innovations in risk assessment for melanoma, basal cell carcinoma, and squamous cell carcinoma. *Cancers (Basel)*, *16*(5), 1016. DOI: 10.3390/cancers16051016 PMID: 38473375

Xi, Z., Dai, R., Ze, Y., Jiang, X., Liu, M., & Xu, H. (2025). Traditional Chinese medicine in lung cancer treatment. *Molecular Cancer*, *24*(1), 57. DOI: 10.1186/s12943-025-02245-6 PMID: 40001110

Xie, M., Vuko, M., Rodriguez-Canales, J., Zimmermann, J., Schick, M., O'Brien, C., Paz-Ares, L., Goldman, J. W., Garassino, M. C., Gay, C. M., Heymach, J. V., Jiang, H., Barrett, J. C., Stewart, R. A., Lai, Z., Byers, L. A., Rudin, C. M., & Shrestha, Y. (2024). Molecular classification and biomarkers of outcome with immunotherapy in extensive-stage small-cell lung cancer: Analyses of the CASPIAN phase 3 study. *Molecular Cancer*, *23*(1), 115. DOI: 10.1186/s12943-024-02014-x PMID: 38811992

Xie, Z., Zhou, Z., Yang, S., Zhang, S., & Shao, B. (2023). Epigenetic regulation and therapeutic targets in the tumor microenvironment. *Molecular Biomedicine*, *4*(1), 17. DOI: 10.1186/s43556-023-00126-2 PMID: 37273004

Xie, Z., Zhou, Z., Yang, S., Zhang, S., & Shao, B. (2023). Epigenetic regulation and therapeutic targets in the tumor microenvironment. *Molecular Biomedicine*, *4*(1), 17. DOI: 10.1186/s43556-023-00126-2 PMID: 37273004

Xing, S., Hu, K., & Wang, Y. (2022). Tumor immune microenvironment and immunotherapy in non-small cell lung cancer: Update and new challenges. *Aging and Disease*, *13*(6), 1615. DOI: 10.14336/AD.2022.0407 PMID: 36465180

Yang, K., Halima, A., & Chan, T. A. (2023). Antigen presentation in cancer—Mechanisms and clinical implications for immunotherapy. *Nature Reviews. Clinical Oncology*, *20*(9), 604–623. DOI: 10.1038/s41571-023-00789-4 PMID: 37328642

Yang, M., Cao, H., Wang, C., Yu, C., & Sun, P. (2024). Incidence of thromboembolic events in non-small cell lung cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis. *Journal of Cancer Research and Therapeutics*, *20*(2), 509–521. DOI: 10.4103/jcrt.jcrt_1031_23 PMID: 38687920

Yang, T., Xiong, Y., Zeng, Y., Wang, Y., Zeng, J., Liu, J., Xu, S., & Li, L. S. (2022). Current status of immunotherapy for non-small cell lung cancer. *Frontiers in Pharmacology*, *13*, 989461. DOI: 10.3389/fphar.2022.989461 PMID: 36313314

Ying, Q., Fan, R., Shen, Y., Chen, B., Zhang, J., Li, Q., & Shi, X. (2024). Small cell lung cancer—An update on chemotherapy resistance. *Current Treatment Options in Oncology*, *25*(8), 1112–1123. DOI: 10.1007/s11864-024-01245-w PMID: 39066852

Yuan, W., Shi, X., & Lee, L. T. (2024, April 24). RNA therapeutics in targeting G protein-coupled receptors: Recent advances and challenges. *Molecular Therapy. Nucleic Acids*, *35*(2), 102195. DOI: 10.1016/j.omtn.2024.102195 PMID: 38741614

Zabeti Touchaei, A., & Vahidi, S. (2024). MicroRNAs as regulators of immune checkpoints in cancer immunotherapy: Targeting PD-1/PD-L1 and CTLA-4 pathways. *Cancer Cell International*, *24*(1), 102. DOI: 10.1186/s12935-024-03293-6 PMID: 38462628

Zhang, C., Wang, Y., & Wang, Y. (2023). Antigen escape in CAR-T cell therapy: Mechanisms and overcoming strategies. *European Journal of Cancer*, *180*, 1–10. DOI: 10.1016/j.ejca.2023.10.001

Zhang, L., Feng, J., Kuang, T., Chai, D., Qiu, Z., Deng, W., Dong, K., Zhao, K., & Wang, W. (2023). Blood biomarkers predict outcomes in patients with hepatocellular carcinoma treated with immune checkpoint inhibitors: A pooled analysis of 44 retrospective studies. *International Immunopharmacology*, *118*, 110019. DOI: 10.1016/j.intimp.2023.110019 PMID: 36933492

Zhang, L., Ma, W., Qiu, Z., Kuang, T., Wang, K., Hu, B., & Wang, W. (2023). Prognostic nutritional index as a prognostic biomarker for gastrointestinal cancer patients treated with immune checkpoint inhibitors. *Frontiers in Immunology*, *14*, 1219929. DOI: 10.3389/fimmu.2023.1219929 PMID: 37545502

Zhang, Y., & Wang, Y. (2024). Advancements and future directions of dual-target chimeric antigen receptor T-cell therapy. *Journal of Immunology Research*. PMID: 39844819

Zhang, Z., Wang, T., Wang, X., Zhang, Y., Song, S., & Ma, C. (2022). Improving the ability of CAR-T cells to hit solid tumors: Challenges and strategies. *Pharmacological Research*, *175*, 106003. DOI: 10.1016/j.phrs.2021.106036 PMID: 34920118

Zhao, H., Huang, S., Wu, J., Lu, Y., Zou, Y., Zeng, H., Li, C., Wang, J., Zhang, X., Duan, S., & Liang, W. (2025). Efficacy and safety of first-line PD-1/PD-L1 inhibitor in combination with CTLA-4 inhibitor in the treatment of patients with advanced non-small cell lung cancer: A systemic review and meta-analysis. *Frontiers in Immunology*, *16*, 1515027. DOI: 10.3389/fimmu.2025.1515027 PMID: 39981238

Zhao, X., Zhang, X., Chen, H., Bao, H., Wu, X., Wang, H., Bao, H., Pang, J., Wang, S., & Wang, J. (2024). Mechanisms of resistance to tyrosine kinase inhibitors in ROS1 fusion-positive nonsmall cell lung cancer. *Clinical Chemistry*, *70*(4), 629–641. DOI: 10.1093/clinchem/hvae008 PMID: 38416709

Zhu, J., Lu, H., Wang, K., Liu, B., & Yan, J. (2024). Tertiary lymphoid structures in head and neck squamous cell carcinoma. *Translational Oncology*, *44*, 101949. DOI: 10.1016/j.tranon.2024.101949 PMID: 38583352

Ziogas, D. C., Theocharopoulos, C., Lialios, P. P., Foteinou, D., Koumprentziotis, I. A., Xynos, G., & Gogas, H. (2023). Beyond CTLA-4 and PD-1 inhibition: Novel immune checkpoint molecules for melanoma treatment. *Cancers (Basel)*, *15*(10), 2718. DOI: 10.3390/cancers15102718 PMID: 37345056

Ziogas, D. C., Theocharopoulos, C., Lialios, P.-P., Foteinou, D., Koumprentziotis, I.-A., Xynos, G., & Gogas, H. (2023). Beyond CTLA-4 and PD-1 inhibition: Novel immune checkpoint molecules for melanoma treatment. *Cancers (Basel)*, *15*(10), 2718. DOI: 10.3390/cancers15102718 PMID: 37345056

Zou, J. X., Chang, M. R., Kuznetsov, N. A., Kee, J. X., Babak, M. V., & Ang, W. H. (2025). Metal-based immunogenic cell death inducers for cancer immunotherapy. *Chemical Science (Cambridge)*, *16*(15), 6160–6187. DOI: 10.1039/D4SC08495K PMID: 40160356

Zou, T., Liu, J. Y., Liu, Z. Q., Xiao, D., & Chen, J. (2024). The role of ADCY1 in regulating the sensitivity of platinum-based chemotherapy in NSCLC. *Pharmaceuticals (Basel, Switzerland)*, *17*(9), 1118. DOI: 10.3390/ph17091118 PMID: 39338283