TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2024;39(2):234–243
doi: 10.5505/tjo.2024.4285

REVIEW

Genetic Alterations in Lung Cancer

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SUMMARY

Lung cancer is the leading cause of cancer-related deaths worldwide. Due to the prevalence of late-stage diagnoses, treatment options are frequently constrained. Molecular profiling of lung cancer is crucial for the clinical management and successful therapy of the disease because lung cancer originates from a multilayered carcinogenesis consisting of multiple genetic and epigenetic abnormalities. The potential of anomalies involved in carcinogenesis as biomarkers that can be used in the diagnosis and treatment of lung cancer has begun to be evaluated due to the development of new generation sequencing methods and their more frequent application in the clinic. This review presents information regarding the genetic alterations responsible for the malignant transformation of lung cells. The article highlights the predominant gene mutations that are specific to a particular subtype of lung cancer, their impact on the clinical progression of the disease, and the response to treatment. However, in summarizing all genetic features, the latest information from the NCCN v2.2024 guide was taken into account.

Keywords: Epidemiology of lung cancer; genetic alterations; lung cancer; molecular pathology; targeted therapy.

INTRODUCTION

Globally, lung cancer is the primary cause of cancer-related mortality, claiming the lives of over a million people annually. The 2022 report from the World Health Organization (WHO) revealed that lung cancer ranked as the sixth leading cause of death, accounting for 1.8% of all deaths.[1] The report, covering the period from 2019 to 2022 and issued by the Turkish Statistical Institute (TUIK), indicates that the number of deaths attributed to malignant lung tumors was 24,326 in 2019, which decreased to 22,546 by 2022 (Fig. 1).[2] This decline in lung cancer incidence in general is related to the number of male patients. While the number of cases in men decreases, there is an increase in women. This issue has been correlated with the increase in smoking prevalence among women in recent years.[1] Although there have been significant advancements in the diagnosis and treatment of lung cancer, its 5-year survival rate remains only 17%, making it the second most unfavorable cancer prognosis following pancreatic cancer.[3] The primary factor contributing to this issue is delayed diagnosis. In the early stages, lung cancer might either exhibit no symptoms at all or present signs that resemble respiratory disorders like the flu. Consequently, 85% of pa-

Received: February 14, 2024
Revised: February 25, 2024
Accepted: February 26, 2024
Online: March 05, 2024

Accessible online at:
www.onkder.org

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tients are diagnosed at an advanced metastatic stage. The challenges in the treatment of lung cancer arise from its complexity as a disease, which develops due to a series of genetic changes throughout oncogenesis and progression. Lung cancers are divided into subtypes that differ according to their location within the lung, growth rate, response to treatment, and genetic profile. As these subtypes exhibit distinct genetic alterations, they manifest through different molecular pathways. Selecting an appropriate treatment plan begins with identifying the lung cancer's histological subtypes.[4] Lung cancer is primarily categorized into two categories based on the histology of the cells: non-small cell lung cancer (NSCLC), representing around 85% of lung cancer cases, and small cell lung cancer (SCLC), representing approximately 15%.[5] NSCLC is further categorized into three distinct subtypes: adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma (Fig. 2).

Adenocarcinoma originates from lung cells that produce mucus. It is a slowly developing subtype that is most common in non-smokers, especially women.[6] Adenocarcinomas account for 40% of all lung cancer cases.[7]

Squamous cell carcinomas, accounting for 20–30% of cases of NSCLC, originate from the pleural cells that line the airways. It is commonly associated with genetic susceptibility within families and smoking. Mutation profiles differ from adenocarcinoma.[8]

Approximately 9–10% of all lung cancer cases consist of large cell carcinomas, which are characterized by poor differentiation and have an unfavorable prognosis. It is frequently visible as a big mass with a necrotic center in adults over the age of 60 and typically follows an aggressive course.[9]

SCLC is histologically characterized by the presence of small cells with enlarged nuclei. Neuroendocrine-derived SCLC, which accounts for just 10% of lung cancer cases, has a poor clinical course due to the tumor cells' rapid division potential, early metastasis, and high recurrence rate.[10] Among individuals with a substantial smoking background, the maximum 5-year survival rate is about 5%, reflecting a high rate of somatic tumor burden, especially bi-allelic deletion of tumor suppressor genes.[11]

Changes in the genetic and biological processes that govern the growth, specialization, and stability of healthy lung cells lead to the development of cancerous characteristics in these cells.[12] A series of genetic anomalies acquired following the development of the primary tumor cause the formation of invasive cancer. This mechanism, along with the escalation in mutation load, leads to the invasive tumor developing into a metastatic form that is resistant to treatment.

The identification of distinct genetic alterations that are unique to lung cancer is crucial for the timely and precise detection of the disease. Recently, the adoption of advanced sequencing technology in medical practice has enabled more frequent examination of individuals with lung cancer and the detection of genetic abnormalities. Analysis of the genetic characteristics of patients allowed the detection of oncogenic transformation processes resulting from a number of genetic changes such as driver mutations, gene amplifications, translocations, etc.[13]

The genomic profile of lung cancer patients has revealed several types of genetic alterations, including point mutations, insertions-deletions, copy number variations, fusions, and rearrangements.[14] The genetic abnormalities may vary based on the specific subtype of lung cancer. While there is no exact limit, *EGFR* and *KRAS* mutations that cause tyrosine kinase activity are typically found in NSCLC patients, whereas mutations that cause loss of function in the *TP53* and *RB1* tumor suppressor genes are typically seen in SCLC patients. The most common gene mutations associated with lung cancer formation are shown in Table 1, along with the cellular processes affected by these mutations. Additional detailed information about these genes is provided in the subsequent section. These genes are the primary targets of developing anti-cancer therapeutic techniques since they are the foundation for the development of cancer.

METHODS

This review was conducted through a comprehensive analysis of original articles, systematic reviews, meta-analyses, case reports, and summaries published in English between the years 2010 and 2023. A total of 53,437 studies were retrieved when the literature was searched in the PubMed, PMC, Google Scholar, and Scopus databases using the keywords "lung cancer," "genetics," "NSCLC," and "SCLC." These studies were evaluated following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies that did not meet the parameters of the review or did not contain current information were excluded from the literature review. Finally, the findings were summarized and presented to the readers under the NCCN_2024 guideline.

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doi: 10.5505/tjo.2024.4285

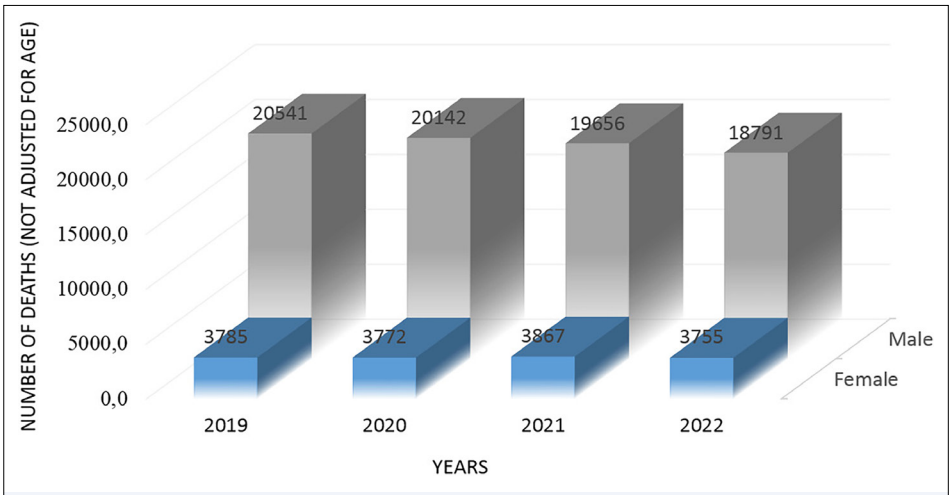

Fig. 1. Number of deaths caused by lung malignancy, according to TUIK-2022.[2].

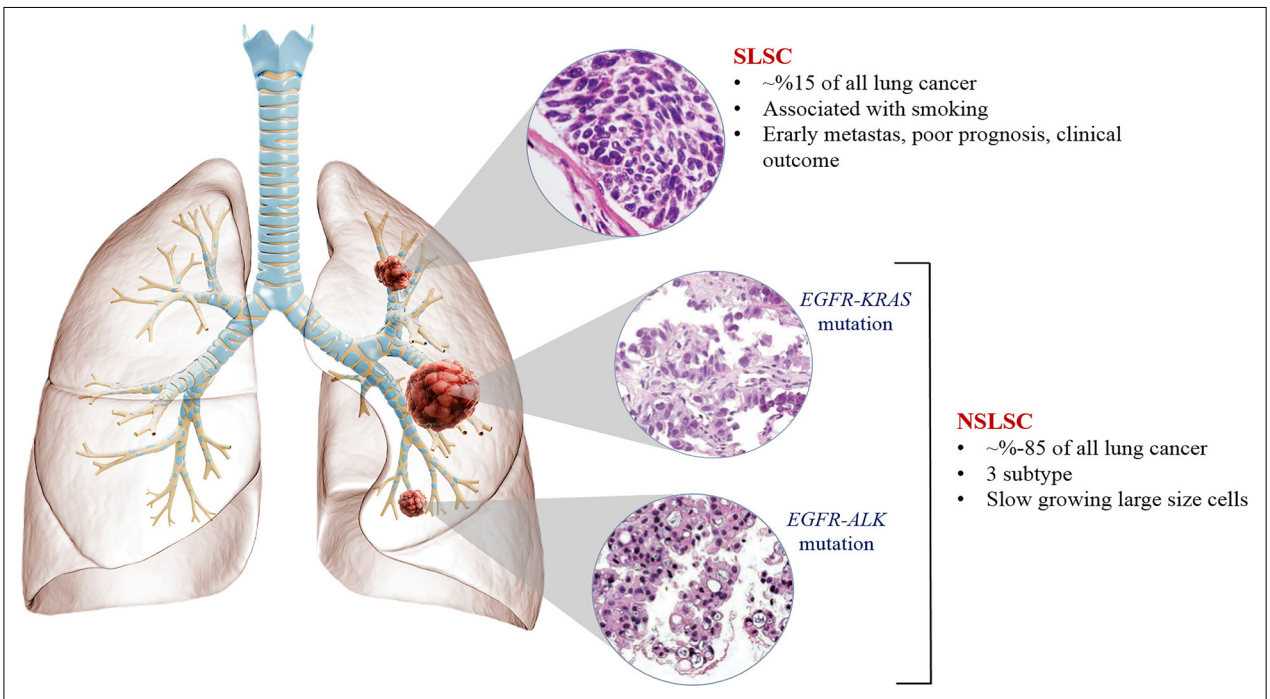

Fig. 2. Histopathological classification and characteristic features of lung cancer.

GENETIC LANDSCAPE OF NSCLC

***KRAS* Gene:** The first mutation identified in adenocarcinomas, the first type of lung cancer to be evaluated genetically, was *KRAS*. Additionally, *KRAS* is the most commonly mutated gene in NSCLC, occurring in approximately 30% of cases.[15] The *KRAS* gene, belonging to the RAS family, codes for a protein that exhibits GTPase activity and is involved in critical intracellular processes such as cell survival, proliferation, and regulation of the cytoskeleton. *KRAS*, which is stimulated by GTPase-activating proteins (GAPs) through its binding to GTP, initiates the downstream MAPK/ERK, PI3K/AKT/mTOR C1 signaling pathways and induces cell proliferation. Genetic mutations in the *KRAS* gene prevent the process of GTP hydrolysis, resulting in persistent activation of the protein.[16]

The majority (95%) of *KRAS* mutations consist of single nucleotide alterations in codons 12 and 13, resulting in variants such as G12D, G12V, and G12C.

These genetic alterations cause the loss of GTPase activity. Non-smoking patients typically exhibit G12D and G12V mutations, whereas smokers commonly have the G12C mutation.[17] While the exact prognostic significance of *KRAS* mutations in NSCLC remains uncertain, they have been linked to a reduced response to chemotherapy and increased resistance to *EGFR* inhibitors, particularly. The FDA (The U.S. Food and Drug Administration) approved Sotorasib in May 2021 as the initial treatment for patients with locally advanced or metastatic NSCLC whose tumors have *KRAS* G12C mutations.[18] Ongoing clinical studies are assessing the efficacy of Adagrasib (MRTX849), an alternative tyrosine kinase inhibitor (TKI), in patients harboring the *KRAS* G12C mutation.[19] On the other side, there are ongoing treatment trials that target different molecules in the gene's downstream signaling pathway.

The creation of mRNA vaccines is another therapeutic approach that targets cells that have *KRAS* mutations. The objective of the Phase I clinical trial is to assess the safety and tolerability of the combination treatment of mRNA-5671/V941 and Pembrolizumab in patients with NSCLC, colorectal cancer, and pancreatic cancer who have the *KRAS* mutation. The latest update on the study findings indicated that the immune response was stimulated in animal models.[20]

***EGFR* Gene:** Epidermal growth factor receptor (*EGFR*) belongs to a family of tyrosine kinase receptors consisting of four members. *EGFR* modulates crucial cellular processes including proliferation, cell migration, cell death, and adhesion. The receptor involves dimerization and activation of tyrosine kinase activity by autophosphorylation in response to the binding of particular ligands. This stimulation leads to subsequent activation of the *EGFR*-associated PI3K-AKT-mTOR pathway, JNK pathway, and MAPK/ERK pathways.[21]

EGFR gene mutations in NSCLC are restricted to exons 18–21, which are specifically associated with the tyrosine kinase activity of the protein. The majority (90%) of the mutations consist of microdeletions occurring in exon 19 (Del19) and exon 21 (Del21). These two mutations, which are classified as the prevalent mutation of *EGFR*, result in comparable alterations in the ATP binding domain of the protein. The mutations G719X in exon 18, S768I in exon 20, and L861Q in exon 21 are infrequent variants of the *EGFR* gene. *EGFR* mutations in precancerous neoplasms inhibit apoptosis, triggering angiogenesis and metastatic progression.[22]

EGFR mutation prevalence rates differ among various ethnic populations. The prevalence of *EGFR* mutation in NSCLC patients is 78–90% in the East Asian population, but drops to 16% in Europe and 12% in Atlantic and Mediterranean populations. The cause of this phenomenon remains unknown.[23]

EGFR mutation is associated with poor prognosis. Nevertheless, individuals with *EGFR* mutation exhibit a favorable response to TKI therapy, with a success rate ranging from 55% to 78%. TKI is primarily administered as the initial treatment for patients with metastatic lung cancer. Gefitinib or Erlotinib, which have been approved by the FDA for patients with *EGFR* mutations initially, exhibit a progression-free survival (PFS) rate that is about twice as high as that of conventional chemotherapy (11.0 months versus 5.6 months). Fatinib, Dacomitinib, and Osimertinib are the other three TKIs approved for lung cancer patients with *EGFR* mutations.[24] It has been demonstrated that Osimertinib is especially effective in preventing secondary mutations from developing during treatment.[25]

***BRAF* Gene:** The *BRAF* gene is responsible for producing the *BRAF* protein, which is a member of the RAF kinase family and functions as a serine-threonine kinase. When activated, this protein forms homo- and heterodimers and plays a role in the regulation of the MAPK/ERK signaling pathway. Oncogenic mutations in the *BRAF* gene cause phosphorylation of MEK in the MAPK/ERK pathway, thus causing downstream activation of this pathway. This stimulus triggers cellular proliferation and ensures its viability.[26]

BRAF mutations are prevalent in various forms of cancer, including colorectal, thyroid, and melanomas. The presence of *BRAF* mutation is observed in 5–8% of NSCLC adenocarcinomas. The V600E mutant variation accounts for 90% of all *BRAF* mutations. The prevalence of this mutation variant in cases of lung cancer is approximately 20–30%.[26] This mutation leads to activation of the MAPK/ERK pathway independent of RAS proteins. The existence of the *BRAF* V600E mutation has been associated with the advancement of aggressive tumors and poor clinical outcomes. Furthermore, whereas the occurrence of axillary lymph node involvement is detected in only 0.6% of individuals with lung cancer, this percentage has been demonstrated to rise significantly to around 15% in patients who have the *BRAF* mutation.[27]

Vemurafenib and Dabrafenib are *BRAF* inhibitors specifically designed for the therapeutic management of several cancer types, including lung cancer. Research has demonstrated that a combination of MEK inhibitors with them results in a 33% to 42% enhancement in the response rate for lung cancer.[28]

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doi: 10.5505/tjo.2024.4285

Encorafenib and Binimetinib in combination therapy was approved by the FDA on October 11, 2023, for adult patients with metastatic NSCLC with *BRAF* V600E mutation.[18]

***ALK* Gene:** The *ALK* (anaplastic lymphoma kinase) gene encodes a transmembrane protein that belongs to the insulin receptor family of tyrosine kinase receptors. This gene is prone to form fusion genes with different genes such as *GCC2, STRN, PTPN3, TPR, HIP1, PHACTR1, DCTN1*. However, the fusion gene variation generated by the *EML4* (Echinoderm microtubule-associated protein-like 4) gene is the first and most commonly detected fusion gene in NSCLC. This gene abnormality accounts for 80% of all gene fusions in NSCLC patients and is present in about 7% of cases of the disease. Based on differences in the breakpoint, 15 different variants of the *ALK*-EML4 gene fusions have been found in NSCLC.[29] The most common of these are the fusion variants between exon 20 of the *ALK* gene and exon 13 (v1), exon 20, and exon 6 (v3) of *EML4* gene. Compared to v1, tumors containing a v3 translocation exhibit a more aggressive course and a lower response rate to TKIs.[30]

The *ALK*-EML4 gene fusion produces a chimeric protein with higher tyrosine kinase activity. This protein, which has developed an oncogenic function, promotes the development of cancer by increasing metabolism, stimulating cell division, and preventing apoptosis.[29]

Crizotinib, an *ALK* inhibitor, is used therapeutically to treat lung cancer with *ALK* fusions. Crizotinib-treated patients have an increased PFS rate and 57–74% inhibitor sensitivity. Nevertheless, specific genetic alterations, such as L1196M, F1174L, and C1156Y, occurring in the kinase domain of EML4-*ALK*, result in patients acquiring resistance to Crizotinib. Novel *ALK* inhibitors of the second generation, namely Alectinib and Ceritinib, are now under development with the aim of specifically targeting secondary mutations in patients with *ALK*-positive NSCLC. Lorlatinib, a third-generation TKI, has demonstrated a PFS efficacy of 72% in patients with *ALK* mutations.[31]

Other Gene Mutations Observed in NSCLC: Different types of mutations, such as point mutations, insertion/deletions, and amplifications, have been identified in the *ERBB2* gene in NSCLC as well as in many other cancers. The most common mutations in this gene are often found in the exon 20 region, involving insertions or duplications. Additionally, point mutations leading to single or double nucleotide changes in *ERBB2* are frequently observed. However, unlike insertion/duplication mutations, comprehensive genomic studies have shown that these mutations do not exhibit activating oncogenic effects. *ERBB2* mutations have been associated with a positive response to anti-HER2 targeted therapy.[32]

Another targetable molecule in lung cancer is the *NTRK1/2/3* (neurotrophic tyrosine receptor kinase) gene fusions. These gene fusions result in increased tyrosine kinase activity. Among the NRTK genes, with numerous fusion partners identified, the most common ones are *MPRIP-NTRK1* and *CD74-NTRK1* fusions, which have demonstrated oncogenic effects. Point mutations in *NTRK1/2/3* are also common, although their activating effects have not been demonstrated. Targeted therapies associated with these mutations have not been extensively studied.[33]

Gene rearrangements of *RET*, a tyrosine kinase receptor (rearrangement during transfection), are observed in 1–2% of NSCLC cases. Fusions of this gene result in dysregulated and increased signaling in the RET-i kinase domain. Although numerous fusion partners have been reported, the most common ones are *KIF5B, CCDC6*, and *NCOA4*. Fusion of this gene is typically associated with a positive response to tyrosine kinase inhibitors (TKIs). Selpercatinib, Pralsetinib, and Cabozantinib are FDA-approved TKIs for *RET* rearrangements.[34]

Information on the first-line and subsequent treatment following the gene mutations detected in NSCLC according to the NCCN Guidelines v2.2024 is given in Table 1.

GENETIC LANDSCAPE OF SCLC

Compared to NSCLC, comprehensive whole genome studies of oncogenic driver mutations for SCLC are progressing slowly due to the limited number of patient samples available for research. Therefore, our understanding of the pathways influencing oncogenesis is incomplete. Oncogenesis has been suggested to be initiated by the simultaneous inactivation of *RB1* and *TP53* genes in pulmonary neuroendocrine cells, which leads to tumor growth. Subsequent clinical studies have revealed that epithelial cells (basal and type II alveolar cells) as well as neuroendocrine cells may be the source of SCLC. The following section provides information about the tumor suppressor *TP53*, *RB1* gene mutation, and *MYC* amplification, which are the most common gene alterations found in SCLC patients.

Comprehensive whole genome investigations of oncogenic driver mutations for SCLC are not as advanced as those for NSCLC since there are fewer patient samples available for study. Consequently, our understanding of the pathways influencing oncogenesis is incomplete. Oncogenesis is believed to be initiated by the simultaneous inactivation of *RB1* and *TP53* genes in pulmonary

neuroendocrine cells, which leads to tumor growth. Subsequent clinical studies have shown that SCLC may arise from epithelial cells, such as basal and type II alveolar cells, as well as neuroendocrine cells.[35]

The following section provides more detailed information on the most common gene changes in SCLC patients, such as biallelic loss of tumor suppressors such as *TP53, RB1*, and *MYC* amplification.[35]

***TP53* Gene:** Under conditions of intracellular stress, such as hypoxia, aging of cells, or damage to DNA, the tumor suppressor gene *TP53* is activated, arresting the cell cycle, controlling genomic stability, and inducing apoptosis. When this gene is inactive, the cell loses its ability to regulate its responses, which leads to a loss of genomic stability and malignant transformation. Most mutations in the *TP53* gene occur in the area responsible for binding to DNA. *TP53* mutation is correlated with poor survival and poor clinical outcome. The five most common and clinically significant mutation variants of *TP53*, which have extremely different and numerous mutations in SCLC, have been identified. These mutations cause the formation of R249M, Y220C, M237I, R273L, and R248W substitutions in the p53 protein.[36]

Smoking is commonly associated with *TP53* mutations. Approximately three times as many smokers as nonsmokers have this mutation. The *TP53* mutation profile of these groups also varies. G>C or G>A transversions are prevalent in individuals who have never smoked, whereas the G>T mutation is typically found among smokers.[37]

Genome sequencing conducted on samples from 110 patients with SCLC revealed somatic mutations in TP73, another member of the p53 family. This finding reaffirms the involvement of *TP53* family genes in the progression of SCLC.[38]

***RB1* Gene:** The *RB1* gene, together with RBL1 and RBL2, forms the pocket protein family and is a tumor suppressor first identified in retinoblastoma but commonly encountered in many malignancies, including prostate and breast cancer. *RB1* is responsible for cell cycle regulation and cell proliferation.[38] Transcriptome analyses have shown that other mutation variants, such as insertion/deletion seen in the *RB1* gene, cause incorrect protein formation since they are generally seen at splicing points. The *RB1* gene also regulates the activation of transcription factors such as Sox2 and Oct4. It is known that when this gene is silenced, cells gain pluripotent properties and exhibit aggressive tumor formation as a result of excessive activation of these transcription factors.[39] It has also been shown that loss of *RB1* causes overexpression of the *EZH2* gene, which is associated with tumor development in lung cancer. These results support the role of mutations in the *RB1* gene in SCLC formation and tumor development.[38]

In comprehensive genomic studies, biallelic loss of *RB1* and *TP53* genes has been found at a rate of 93% and 100% respectively in patients, and this has come to be recognized as the hallmark of SCLC carcinogenesis. Since both genes are crucial for controlling the cell cycle, losing one of them means losing control over the cell cycle. In addition, inhibition of other kinases such as *CHK1* and *ATR*, which are involved in the cell cycle, is also triggered. The resulting genomic instability continues with DNA damage, activation of the PI3K-AKT-mTOR pathway, resistance to apoptosis, and results in the cell gaining malignant transformation.[40]

Both *TP53* and *RB1* are not therapeutically targetable.[41]

***MYC* Gene:** The *MYCL, MYCN*, and *MYC* genes, which have different functions but strong structural homology, make up the *MYC* gene family. In 20% of cases of SCLC, the *MYC* gene is overexpressed. This gene's amplification has been linked to chemotherapy resistance and poor clinical outcomes.[42] However, the mechanisms of action of these gene family members have not been fully determined. While experiments with mice have shown that loss of the *MYCN* and *MYCL* genes stops tumor development, the same is not true for the *MYC* gene.[43] These genes also differ in sensitivity to aurora kinase inhibitors. In fact, the *MYC* gene showed hypersensitivity, while *MYCL* and *MYCN* showed a very mild response.[44]

Other Gene Mutations Observed in SCLC: The *PTEN* gene, situated on chromosome 10, functions as a tumor suppressor gene and governs the AKT/PKB pathway. The prevalence of these genetic abnormalities in patients with SCLC is 9%. However, its role in the development of lung cancer is not completely understood. Suppressing the expression of this gene in mice models has been reported to expedite the advancement of SCLC. In another study, it was reported that biallelic inactivation of this gene triggered the transformation of adenocarcinomas into neuroendocrine carcinoma.[45]

Located on chromosome 8 and consisting of 24 exons, the fibroblast growth factor receptor (FGFR) gene is a member of the fibroblast growth factor (FGF) family. Mutation of this gene is observed in 8% of SCLC patients. Gene amplification typically leads to overexpression, which is primarily observed during the early stages of carcinogenesis. Although there have been suggestions on the potential of TKIs to inhibit FGFR1 activity, there have not been enough studies done due to the small patient population.[46]

Table 1 The most common gene mutations in lung cancer, their prevalence, and FDA-approved drug formulations targeting these genes (according NCCN v2.2024)

Type of lung cancer	Gene	Mutation	FDA approved targeted agent		Frequency	Reference
			First-line therapy	Subsequent therapy		
NSCLC	*KRAS*	G12C mutation	–	Sotorasib Adagrasib	30%	[47]
	EGFR	Exon 19 Deletion	Afatinib Erlotinib	Osimertinib Amivantamab-vmjw+ carboplatin+pemetrexed (nonsquamous)	15% (Western patients) 78–90% (Asia population)	[48] [49]
		L858R Mutation in Exon 21	Dacomitinib Gefitinib Osimertinib Osimertinib+pemetrexed+(cisplatin or carboplatin) (nonsquamous) Erlotinib+ramucirumab Erlotinib+bevacizumab (nonsquamous)			
		G719X Mutation in Exon 18	Afatinib Erlotinib	Osimertinib Amivantamab-vmjw+ carboplatin+pemetrexed (nonsquamous)		
		S768I Mutation in Exon 20	Dacomitinib Gefitinib Osimertinib			
		L861Q Mutation in Exon 21				
		Exon 20 Insertion	Amivantamab-vmjw+carboplatin+ pemetrexed (nonsquamous)	Amivantamab-vmjw		
	BRAF	V600E Mutation	Dabrafenib/trametinib Encorafenib/binimetinib Dabrafenib Vemurafenib	Dabrafenib/trametinib Encorafenib/binimetinib	5–8%	[50]
	ALK	Rearrangement	Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib	Alectinib Brigatinib Ceritinib Lorlatinib	5–7%	[51]
	MET	Exon 14 skipping mutation	Capmatinib Crizotinib Tepotinib	Capmatinib Crizotinib Tepotinib	5%	[49]
	ERBB2	Gene mutations	–	Fam-trastuzumab deruxtecan-nxki	1–3%	[32]

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doi: 10.5505/tjo.2024.4285

Table 1 Cont.

Type of lung cancer	Gene	Mutation	FDA approved targeted agent		Frequency	Reference
			First-line therapy	Subsequent therapy		
HER2			Ado-trastuzumab emtansine			
	NTRK	Gene fusion	Larotrectinib	Larotrectinib	<1%	[33]
	1/2/3		Entrectinib	Entrectinib		
	RET	Rearrangementd	Selpercatinib	Selpercatinib	1–2%	[34]
			Pralsetinib	Pralsetinib		
			Cabozantinib	Cabozantinib		
SCLC	*RB1*	Lost of gene	–	–	65%	[38]
	TP53	Lost of gene	–	–	78–90%	[36]
	MYC	Gene mutations	–	–	50%	[52]
	PTEN	Gene mutations	–	–	4–9%	[45]
	FGRF1	Gene mutations	–	–	8%	[46]

FDA: The U.S. Food and Drug Administration; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer

CONCLUSION

Significant advancements in the early diagnosis and treatment of cancer have been made in recent years due to developments in genomic techniques, non-invasive diagnostic methods such as liquid biopsy, the capacity to obtain genetic data at the single-cell level, and the ability for bioinformatics analysis. Nevertheless, lung cancer has a poor prognosis and a challenging course of therapy. Patients have a high rate of relapse and resistance to treatment. Therefore, there is a need to identify predictive and targetable markers that will enable early diagnosis, overcome drug resistance, improve survival and quality of life of cancer patients, and be used in personalized treatment. To achieve this, a comprehensive understanding of the molecular pathology of these tumors is essential. Lung cancer treatment requires multi-parameter consideration due to its strong tumor immunity, intralesion heterogeneity, and multiple genetic and epigenetic alterations. Therefore, today lung cancer treatment is designed to include the treatment goals of both pathologists, molecular oncologists, and clinical oncologists. If a few decades ago, patients were treated with one treatment, today, with the appearance of targeted therapy and immunotherapy, personalized treatment is applied. However, since current treatments are inadequate, understanding the genetic mechanisms underlying lung cancer formation, progression, drug resistance, and recurrence will lead to the development and improvement of treatment options. Consequently, further research is required to eradicate the notoriety associated with this tumor.

Conflict of Interest: All authors declared no conflict of interest.

Use of AI for Writing Assistance: All authors declare that they did not use AI while preparing the review article.

Financial Support: None declared.

Peer-review: Externally peer-reviewed.

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