Genetic vs. Environmental Factors in Lung Cancer Development

Ryan Le

Abstract

Lung cancer remains a prominent cause of cancer-related mortality worldwide and is characterized by numerous genetic predispositions and environmental factors. This review will highlight how mutations in genes that are components of critical molecular processes influence the development of lung cancer. It will also highlight environmental influences, such as smoking, air pollution and age. Genetic predispositions can significantly increase susceptibility, while environmental exposures can often act as triggers or amplifiers of genes that ultimately result in cancer. Given the substantial impact of lung cancer on human health, understanding how genetic and environmental factors contribute to the development of lung cancer is crucial for advancing personalized medicine and improving population health outcomes.

Introduction

Cancer is a major health problem worldwide and is responsible for being the second leading cause of death in the United States. Lung cancer, being the most frequent cause of cancer deaths, leads to over 1.5 million deaths each year worldwide. Depending on the disease stage, the 5-year survival rate of lung cancer ranges from 4-17% [1]. Cancer incidence, especially in lung cancer, increases with age, with the median age of diagnosis being 70 years old. However, individuals below the age of 55 make up to 10% of the lung cancer population within the United States. In recent years, the number of young adults who develop lung cancer has increased, and is speculated to be the result of certain environmental factors. Research regarding young-onset lung cancer is still being refined, and researchers are still gathering data on its complex nature [2].

Often when discussing the development of lung cancer, researchers consider the impact of nature vs nurture. Smoking and other environmental factors contribute to the “nurture” aspect regarding the development of lung cancer. These environmental factors can influence the occurrence of genetic and epigenetic events [1]. These events/processes as well as the genetic predispositions within an individual comprise the “nature” aspect when it comes to lung cancer development. Essentially, nature refers to the inherent features/characteristics of an individual while nurture focuses on how one’s environment influences these features.

When it comes to treating lung cancer, doctors use various approaches depending on the subtype of lung cancer. The two major subtypes being non-small cell lung cancer and small cell lung cancer. Non-small cell lung cancer, the most common subtype, is usually approached with chemotherapy and thoracic radiotherapy [1]. Though in recent years, patients with advanced NSCLC have been treated with molecular targeted therapy. Molecular targeted therapy uses high-throughput sequencing technology and has been advanced for younger patients with lung adenocarcinoma, a classification of NSCLC [1].

Genetic Factors Related to the Development of Lung Cancer

Lung cancer is a complex disease driven by a series of genetic and molecular alterations that disrupt normal cellular processes. When mutated, genes play a crucial role in cancer development since they disrupt various molecular processes within the body. These commonly include regulation of cell growth, division, and survival [2]. Some gene mutations commonly found in non-small cell lung cancer include *TP53, KRAS,* and *EGFR* (Figure 2). By

understanding the genetic factors and their corresponding molecular process, scientists are able to uncover mechanisms of cancer and hope to develop further treatments.

At the heart of cancer development are alterations in specific genes responsible for controlling critical cellular functions. These genes can be broadly categorized into two types: oncogenes and tumor suppressor genes. Oncogenes, when mutated or overexpressed, drive cancer by promoting excessive cell growth and survival [3]. For example, when the *EGFR* gene undergoes mutations or changes in its structure, leading to a change in the frequency in which it carries out its function, ultimately leading to uncontrolled cell proliferation [3].

In contrast, tumor suppressor genes, such as TP53, produce proteins that inhibit cell division between cells that may develop into cancerous tumors. Mutations in these genes can impair their regulatory functions, allowing cells with damaged DNA to continue dividing and accumulating further mutations, an indicator of cancer. These genetic changes disrupt key molecular processes, including cell cycle regulation, apoptosis, and genomic stability, leading to the initiation and overall development of cancer [4].

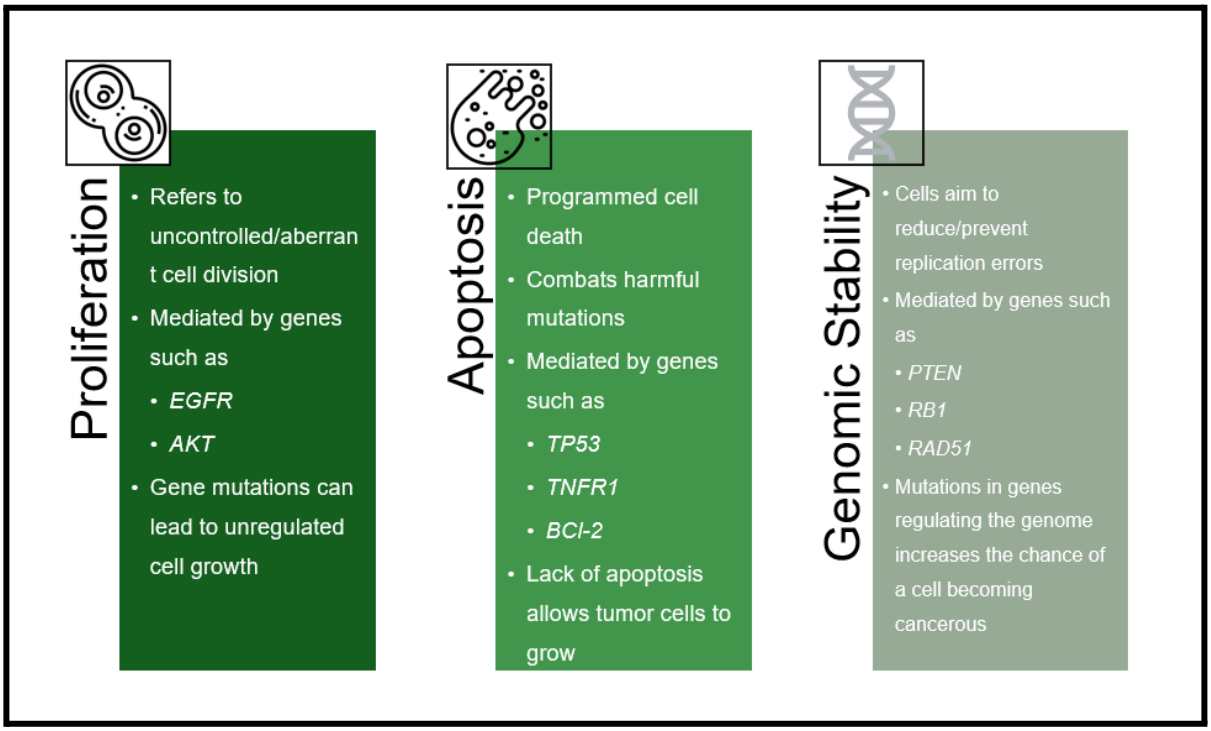

Figure 1. Key molecular processes dysregulated in lung cancer. This is not an exhaustive list of molecular processes dysregulated in lung cancer, but these are the processes this review will focus on.

Proliferation

Proliferation is the rapid and repeated production of masses of cells by a rapid succession of cell divisions. In order to begin the process of cell division, cells receive signals produced by genes involved in proliferation. Epidermal growth factor receptor (*EGFR*) plays a prominent role in regulating cell proliferation [3]. While essential for proliferation, mutations of *EGFR* can lead to the development of lung cancer tumors. Mutations as well as overexpression of *EGFR* have appeared in 43-89% of non-small cell lung cancer cases [5]. In young-onset

NSCLC, the most common gene mutation lies in *EGFR*, which ranges from 20%-57% of cases [2]. *EGFR* mutations activate the *EGFR*-signaling pathway, further promoting cell proliferation and deceiving cells into thinking they require more frequent signals from functional EGFR for survival [3]. Out of the various mutations affecting *EGFR*, the two most common include: 1) short in-frame deletions of exon 19 which appear in 45-50% of mutations 2) point mutation of CTG to CGG in exon 21 [3]. These mutations appear frequently in NSCLC cases, especially in patients who have never smoked.

Apoptosis

Apoptosis, also known as programmed cell death, is an effective physiological process that removes redundant or damaged cells from tissues. Apoptosis can proceed through 2 main pathways: extrinsic and intrinsic [6]. Inhibition of apoptosis is a famous hallmark of cancer since cells that can accumulate oncogenic events are given the opportunity to accumulate, which is a crucial component of tumor development [4]. The *TP53* gene is noted for its role as tumor suppressor that oversees the cell cycle, apoptosis, and regulating genomic stability. It is also well studied due to it being the most mutated gene found in human cancers. After IMPACT sequencing of 240 NSCLC tumor/normal pairs, *TP53* mutations were discovered in 58.8% of cases [7]. When dysregulation of the P53 protein occurs, the development of various cancers often follow. [8]. Mutations or loss of P53 disrupt the protein's function of regulating the cell cycle and facilitating DNA repair, potentially causing cells with DNA damage to avoid undergoing apoptosis and initiate tumorigenesis. Following this, mutated P53 can also induce metastasis, which enhances the migratory and invasive properties of tumor cells [8].

Genomic Stability

Genomic stability is an organism's ability to maintain and pass on genetic material from one generation to the next during cell division while preventing genetic changes. As cell divisions occur, various genes work to monitor and regulate cell growth. Tumor suppressing genes such as *P53, Rb1*, and *PTEN* play crucial roles in maintaining genomic stability and ultimately preventing the development of cancer [8]. *PTEN* is one of the most prominent tumor suppressor genes involved in cancer since a decrease in its expression is found in numerous cancer tumors. *PTEN* is responsible for fundamental anti-oncogenic tasks, including but not limited to: maintenance of chromosomal stability and ensuring DNA repair through regulation of *RAD51*, a DNA repair protein. This allows it to play a prominent role in maintaining genomic integrity [9]. Loss of *PTEN* expression was found in 24-44% of non-small cell lung cancer cases. It was found that 24% of early NSCLC cases lack *PTEN* expression due to hypermethylation regarding *PTEN*'s promoter. Additionally, it was found that 69% of NSCLC cell lines contained a *PTEN* promoter that had undergone methylation. When cells are not being regulated by a tumor suppressing gene as important as *PTEN*, complications with cell division occur since any DNA damage that has occurred in the process is not being regulated correctly and ultimately leads to tumorigenesis [10]

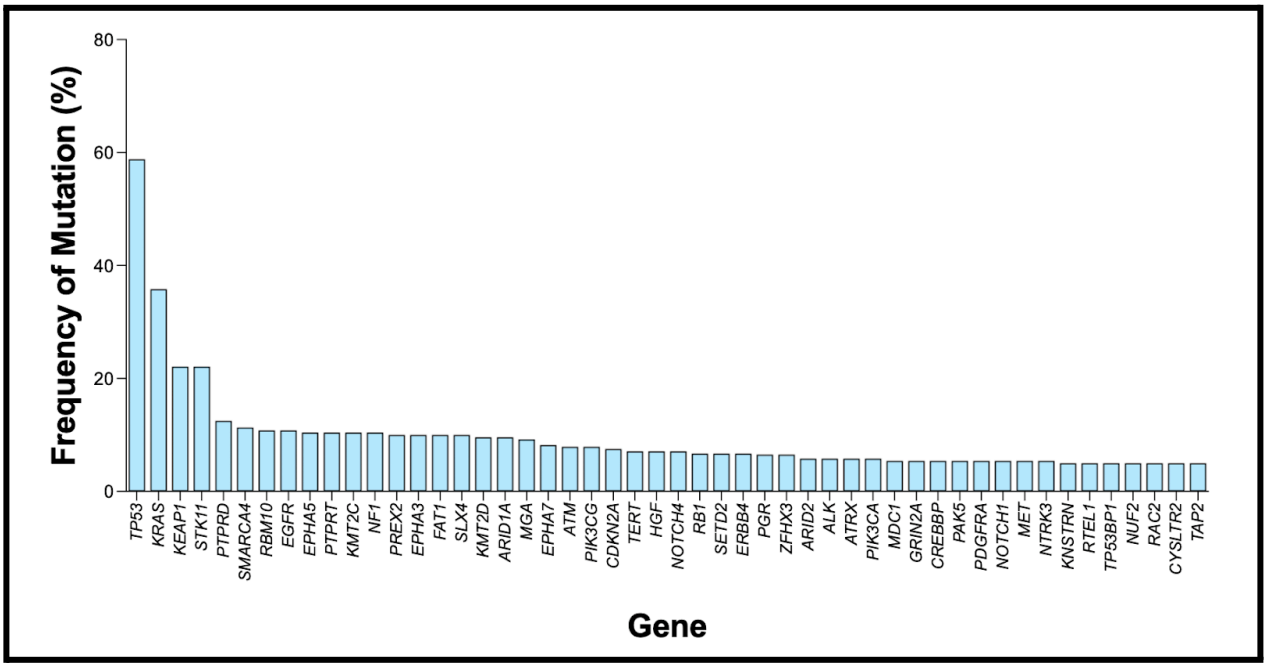

Figure 2. Frequency of gene mutations in non-small cell lung cancer. Data from (Rizvi et al., 2018). Data downloaded from cBioPortal. The 50 most mutated genes in NSCLC from a study of 240 samples are shown.

Environmental Factors

The development of lung cancer is influenced by a variety of environmental factors. Most commonly, these factors involve chemicals that when traveling through the respiratory system, are exposed to the lungs and increase the risk of lung cancer. Factors such as exposure to tobacco smoke, air pollution, and radon gas have been identified as major risk elements. By exploring these influences, we can hope to further address and emphasize the risk of these factors to ultimately improve public health from diseases as harmful as lung cancer.

In the 1950's, scientists first discovered epidemiologic evidence connecting tobacco smoking and lung cancer. Since then, scientists have frequently identified tobacco to be the primary risk factor for lung cancer, with it being responsible for 85% of lung cancer cases [2]. Containing over 4000 detectable substances, cigarette smoking is one of the most common forms of tobacco usage and is responsible for 6 million deaths every year through its role in cardiovascular disease and lung cancer development [11]. Modeling projections from Jeon et al. (2018) suggests that amongst US adults (30-84 years old), reduced tobacco smoking prevented 800,000 lung cancer deaths between 1975–2000 [12]. Commonly found in tobacco products, nicotine can be tumor promoting. Nitrosamine NNN and NNK are nicotine derivatives that act through the β receptor family, which induces signaling pathways and ultimately leads to mutations in *KRAS* and *TP53*. Tobacco smoking as well as the nicotine within many tobacco processes generate an increased risk for mutations regarding a variety of genes [11]. These genes include a variety of growth factor genes as well as tumor suppressing genes. These mutations are most commonly involved in a decrease in apoptosis, proliferation of tumor cells, and/or genomic stability.

In recent decades, air pollution in populated areas has been found to play a role in the increase in lung cancer cases. In early studies regarding air pollution and lung cancer, lung

cancer rates of urban and rural areas were compared. Majority of studies found that urban areas had a 30-40% higher occurrence of lung cancer compared to rural areas and that non-smokers made up a higher portion of these findings [13]. This is due to the mutagenic and carcinogenic properties of combustion-source air pollution such as diesel exhaust, which is common within urban areas [14]. Several lines of epidemiologic evidence also suggest that exposure to outdoor air pollution increases the rate of lung cancer.

Primarily found in the ground, where it can seep through old house floors and cracks, radon is among the top four environmental risks to public health in the United States. Radon-222 is a radioactive gas that is a decay product of uranium-238, which is found naturally throughout the Earth's crust [15]. The World Health Organization states that radon may account for 3–14% of lung cancer cases, which would make it the second leading cause of lung cancer in tobacco smokers and the leading cause in non-smokers [16]. Initial evidence of radon influencing lung cancer development was found when numerous miners in uranium mines died of lung cancer. Through experimental studies with animals, it has been discovered that radon inhalation does generate an increase in risk of lung cancer development. Mechanisms such as base mutations and chromosomal breaks are just two instances of radon-induced cytogenetic damage [15]. The European pooling study by Darby et al. (2004) analyzed 13 European case-controlled studies and discovered a statistically significant and linear increase of 5%-31% of lung cancer risk 100 becquerels (Bq/m^3) of indoor radon. By composing and analyzing 17 case-controlled studies from various countries, Pavia et. al (2003) determined that indoor radon gas increased the risk of lung cancer in patients exposed to more than 150 Bq/m^3 by 24% and an odds ratio of 1.24 [16].

Epigenetic events are known to alter gene expression without changing the DNA sequence itself [1]. Two notable epigenetic events are DNA methylation and histone modification which can trigger genetic changes in various ways. DNA methylation is capable of helping enhance the binding of carcinogens. It also is able to silence tumor suppressor genes and DNA repair genes facilitating tumorigenesis such as *TP53, BRCA1* and *BRCA2* (Herceg et al., 2011). Smoking tobacco can have a strong influence on the methylation levels of various genes. Herceg et al. (2011) observed a strong association between MTHFR hypermethylation in lung cancer and tobacco smoking [18]. *MTHFR* is a gene that is crucial for DNA synthesis and repair. *MGMT* is another crucial DNA repair protein and is commonly silenced when involved in carcinogenesis. It was observed that *MGMT* promoter hypermethylation is a frequently occurring event [1].

Future Directions

The future of lung cancer treatment and prevention lies in the increased use of personalized medicine and innovative biotechnologies. Depending on a patient's identified genetic mutation, medication with specific agents tailored to the mutation should be prescribed. Emerging biotechnologies such as Amivantamab could help treat cases of lung cancer. Amivantamab, a bispecific antibody that recognizes *EGFR* and *MET*, has been treating NSCLC cases through *EGFR* exon 20 insertions. This prevents ligand binding to *EGFR* and the dimerization of the receptors suppressing the downstream signal transduction [19]. Currently, the only way to prevent lung cancer is to avoid exposure to lung carcinogens. Even though lung cancer continues to develop in individuals who have never smoked, through awareness regarding the dangers of carcinogens, numerous cases of lung cancer have been prevented. Overall, the promising future of lung cancer treatment relies on the emerging biotechnological innovations,

which will not only treat cases of lung cancer, but prevent them through proactive measures tailored to individual risk profiles.

Conclusion

In conclusion, with lung cancer as a leading cause of cancer-related mortality globally, it is important to understand both the genetic and environmental factors playing pivotal roles in its development. Advances in molecular biology will continue to deepen our understanding of the specific gene mutations that provide the foundation for this disease, and shed light on the complex interactions between genetics and environmental exposures such as smoking, air pollution, and radon gas. As research progresses, the ability to identify these mutations with precision and efficiency is proving to be vital for the development of personalized treatment strategies. Tailoring treatments to an individual's specific genetic makeup through methods such as targeted therapies or immunotherapy, holds great promise in improving treatment outcomes and preventing escalation of any cancer. Furthermore, future therapeutic approaches may find themselves relying on integrating genetic screening with a background on an individual's exposure to environmental factors, to more accurately predict and devise individualized prevention and treatment plans. This personalized approach will not only enhance the effectiveness of lung cancer treatments but overall improve population health by emphasizing the unique genetic and environmental profiles that contribute to the disease.

References

[1] Shi, Yuan-Xiang, De-Qiao Sheng, Lin Cheng, and Xin-Yu Song. 2019. "Current Landscape of Epigenetics in Lung Cancer: Focus on the Mechanism and Application." *Journal of Oncology* 2019 (December):1–11. https://doi.org/10.1155/2019/8107318.

[2] Laguna, Juan Carlos, Marco Tagliamento, Matteo Lambertini, James Hiznay, and Laura Mezquita. 2024. "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. https://doi.org/10.1200/EDBK_432488.

[3] Antonicelli, Alberto, Stefano Cafarotti, Alice Indini, Alessio Galli, Andrea Russo, Alfredo Cesario, Filippo Maria Lococo, et al. 2013. "EGFR-Targeted Therapy for Non-Small Cell Lung Cancer: Focus on EGFR Oncogenic Mutation." *International Journal of Medical Sciences* 10 (3): 320–30. https://doi.org/10.7150/ijms.4609.

[4] Lowe, Scott W., and Athena W. Lin. 2000. "Apoptosis in Cancer." *Carcinogenesis* 21 (3): 485–95. https://doi.org/10.1093/carcin/21.3.485.

[5] Bethune, Gillian, Drew Bethune, Neale Ridgway, and Zhaolin Xu. 2010. "Epidermal Growth Factor Receptor (EGFR) in Lung Cancer: An Overview and Update." *Journal of Thoracic Disease* 2 (1): 48–51.

[6] Fridman, Jordan S, and Scott W Lowe. 2003. "Control of Apoptosis by P53." *Oncogene* 22 (56): 9030–40. https://doi.org/10.1038/sj.onc.1207116.

[7] Rizvi, Hira, Francisco Sanchez-Vega, Konnor La, Walid Chatila, Philip Jonsson, Darragh Halpenny, Andrew Plodkowski, et al. 2018. "Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing." *Journal of Clinical Oncology: Official Journal of the*

American Society of Clinical Oncology 36 (7): 633–41. https://doi.org/10.1200/JCO.2017.75.3384.

[8] Benitez, Dixan A., Guadalupe Cumplido-Laso, Marcos Olivera-Gómez, Nuria Del Valle-Del Pino, Alba Díaz-Pizarro, Sonia Mulero-Navarro, Angel Román-García, and Jose Maria Carvajal-Gonzalez. 2024. "P53 Genetics and Biology in Lung Carcinomas: Insights, Implications and Clinical Applications." *Biomedicines* 12 (7): 1453. https://doi.org/10.3390/biomedicines12071453.

[9] Gkountakos, Anastasios, Giulia Sartori, Italia Falcone, Geny Piro, Ludovica Ciuffreda, Carmine Carbone, Giampaolo Tortora, et al. 2019. "PTEN in Lung Cancer: Dealing with the Problem, Building on New Knowledge and Turning the Game Around." *Cancers* 11 (8): 1141. https://doi.org/10.3390/cancers11081141.

[10] Milella, Michele, Italia Falcone, Fabiana Conciatori, Ursula Cesta Incani, Anais Del Curatolo, Nicola Inzerilli, Carmen M. A. Nuzzo, et al. 2015. "PTEN: Multiple Functions in Human Malignant Tumors." *Frontiers in Oncology* 5 (February). https://doi.org/10.3389/fonc.2015.00024.

[11] Condoluci, Adalgisa, Calogero Mazzara, Alice Zoccoli, Aldo Pezzuto, and Giuseppe Tonini. 2016. "Impact of Smoking on Lung Cancer Treatment Effectiveness: A Review." *Future Oncology* 12 (18): 2149–61. https://doi.org/10.2217/fon-2015-0055.

[12] Jeon, Jihyoun, Theodore R. Holford, David T. Levy, Eric J. Feuer, Pianpian Cao, Jamie Tam, Lauren Clarke, John Clarke, Chung Yin Kong, and Rafael Meza. 2018. "Smoking and Lung Cancer Mortality in the US from 2015-2065: A Comparative Modeling Approach." *Annals of Internal Medicine* 169 (10): 684–93. https://doi.org/10.7326/M18-1250.

[13] Cohen, A J. 2000. "Outdoor Air Pollution and Lung Cancer." *Environmental Health Perspectives* 108 (suppl 4): 743–50. https://doi.org/10.1289/ehp.00108s4743.

[14] Cohen, A J, and C A Pope. 1995. "Lung Cancer and Air Pollution." *Environmental Health Perspectives* 103 (suppl 8): 219–24. https://doi.org/10.1289/ehp.95103s8219.

[15] Sethi, Tarsheen K., Moataz N. El-Ghamry, and Goetz H. Kloecker. 2012. "Radon and Lung Cancer." *Clinical Advances in Hematology & Oncology: H&O* 10 (3): 157–64.

[16] Riudavets, Mariona, Marta Garcia De Herreros, Benjamin Besse, and Laura Mezquita. 2022. "Radon and Lung Cancer: Current Trends and Future Perspectives." *Cancers* 14 (13): 3142. https://doi.org/10.3390/cancers14133142.

[17] Darby, S., D. Hill, A. Auvinen, J. M. Barros-Dios, H. Baysson, F. Bochicchio, H. Deo, et al. 2005. "Radon in Homes and Risk of Lung Cancer: Collaborative Analysis of Individual Data from 13 European Case-Control Studies." *BMJ (Clinical Research Ed.)* 330 (7485): 223. https://doi.org/10.1136/bmj.38308.477650.63.

[18] Herceg, Zdenko, and Thomas Vaissière. 2011. "Epigenetic Mechanisms and Cancer: An Interface between the Environment and the Genome." *Epigenetics* 6 (7): 804–19. https://doi.org/10.4161/epi.6.7.16262.

[19] Petrini, Iacopo, and Giuseppe Giaccone. 2022. "Amivantamab in the Treatment of Metastatic NSCLC: Patient Selection and Special Considerations." *OncoTargets and Therapy* 15 (October):1197–1210. https://doi.org/10.2147/OTT.S329095.