# A Review on Recent Advances in Drugs for Lung Cancer Treatment

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
BRAC University
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## Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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# Approval

The thesis titled “A Review on Recent Advances in Drugs for Lung Cancer Treatment” submitted by Fouzia Noor (19146045), of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on February, 2023.

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## Ethics Statement

The study does not involve any kind of animal and human trial.

## Abstract

One of the predominant reasons for cancer-related fatalities worldwide is lung cancer. Existing drugs in the therapeutic landscape though beneficial are linked with various limitations. Overcoming these posed a major challenge. However, significant progress has been made in the development of novel drugs to treat lung cancer in recent years. The advancements can be attributed to development of newer agents in existing classes of drugs and targeting new aberrations in genes associated with particularly non-small cell lung cancer that was previously impossible. They have improved treatment outcomes and prolonged survival in patients. Regardless, they are also associated with their own set of limitations. To this date, development of drugs that can target specific genetic changes for small cell lung cancer is deemed to be arduous. This review has delineated information related to the existing drugs in use, the novel agents and the combination drugs in use during the recent years.

**Keywords:** Lung cancer; recent advances; drugs; resistance; mechanism of action

# Dedication

***Dedicated to my amazing parents, teachers and friends who have been with me every step of the way.***

## Acknowledgement

I am thankful to the almighty Allah for infinite blessing and mercy. All praise to Him for allowing me to interact with some truly inspiring individuals throughout my time in School of Pharmacy.

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## List of Acronyms

| | |
|---|---|
| ADCC | Antibody-dependent Cell-mediated Cytotoxicity |
| ADCP | Antibody-dependent Cellular Phagocytosis |
| ADCR | Antibody-dependent Cytokine Release |
| ADCT | Antibody-dependent Cellular Trogocytosis |
| AKT | Protein kinase B |
| ALK | Anaplastic Lymphoma Kinase |
| ASCL1 | Achaete-scute Homolog 1 |
| BBB | Blood-brain barrier |
| BER | Base Excision Repair |
| BRAF | B-Raf Proto-oncogene, Serine/Threonine Kinase |
| CCL2 | C-C motif Chemokine Ligand 2 |
| CDK4 | Cyclin-dependent Kinase 4 |
| CXCL8 | C-X-C motif Chemokine Ligand 8 |
| DAPK | Death-associated Protein Kinase |
| DDR2 | Discoidin Domain Receptor Kinase 2 |
| DHFR | Dihydrofolate Reductase |
| DoR | Duration of Response |
| EGFR | Epidermal Growth Factor Receptor |

| | |
|---|---|
| EML4 | Echinoderm Microtubule-Associated Protein-like 4 |
| ErbB | Erythroblastic Leukemia Viral Oncogene Homologue |
| ERK | Extracellular Signal-regulated Kinase |
| ES-SCLC | Extensive-stage Small Cell Lung Cancer |
| FGFR | Fibroblast Growth Factor Receptor |
| GARFT | Glycinamide Ribonucleotide Formyltransferase |
| HER | Human Epidermal Growth Factor Receptor |
| IGF-1R | Insulin-like Growth Factor 1 |
| IL-6 | Interleukin-6 |
| ILD | Interstitial Lung Disease |
| IRC | Independent Review Committee |
| IRR | Infusion Related Reaction |
| JAK | Janus Kinase |
| KIF5B | Kinesin Family Member 5B |
| KRAS | Kirsten Rat Sarcoma |
| LKB1 | Liver Kinase B1 |
| LVEF | Left Ventricular Ejection Fraction |
| MAPK | Mitogen-activated Protein Kinase |
| MET | Mesenchymal Epithelial Transition |
| MKI | Multiple Kinase Inhibitor |

| | |
|---|---|
| MGMT | O6-methylguanine-DNA methyltransferase |
| MPS | Mononuclear Phagocyte System |
| mTOR | Mammalian target of rapamycin |
| NER | Nucleotide Excision Repair |
| NeuroD1 | Neuronal Differentiation 1 |
| NF1 | Neurofibromatosis type 1 |
| NFIB | Nuclear Factor I/B |
| NF-κB | Nuclear factor kappa B |
| NSCLC | Non-small Cell Lung Cancer |
| OR | Overall Survival |
| ORR | Overall Response Rate |
| PARP1 | Poly (ADP-ribose) Polymerase 1 |
| p16INK4a | Cyclin-dependent kinase inhibitor 2A |
| PD-1 | Programmed cell death protein 1 |
| PDL-1 | Programmed cell death ligand 1 |
| PFS | Progression Free Survival |
| PI3K | Phosphatidylinositol-3 kinase |
| PTEN | Phosphatase and Tensin Homolog |
| QoL | Quality of Life |
| RAF | Rapidly Accelerated Fibrosarcoma |

| | |
|---|---|
| RalA | Ras like Proto-Oncogene A |
| RalB | Ras like Proto-Oncogene B |
| RALGDS | Ral Guanine nucleotide Dissociation Stimulator |
| RAS | Rat Sarcoma |
| RASSF1A | Ras association domain family 1A |
| RB | Retinoblastoma |
| RTK | Receptor Tyrosine Kinase |
| SCC | Squamous cell carcinoma |
| SCLC | Small Cell Lung Cancer |
| S-IIP | Switch-II pocket |
| STAT | Signal Transducer and Activator of Transcription |
| STK-11 | Serine/Threonine Kinase 11 |
| TAM | Tumor-associated Macrophages |
| TF | Transcription Factors |
| TopoII | Topoisomerase II |
| TS | Thymidylate Synthase |
| VEGF | Vascular Endothelial Growth Factor |
| VGFR | Vascular Endothelial Growth Factor Receptor |

# Chapter 1

# Introduction

## 1.1 Background

The process of lung cancer involves the cells in the respiratory epithelium to undergo oncogenesis where there is unrestricted multiplication of these cells and metastasis occurs to distant parts of the body. Various factors can lead to this disease which include first-hand and second-hand smoking, exposure to air pollution, asbestos and radon gas, genes and infection (Thandra et al., 2021). These can result in acquired genetic and epigenetic aberrations like alterations in KRAS, HER2, MEK, BRAF, and PI3K, transforming rearrangement in ALK, ROS1 and RET, amplifications in MET, FGFR1 and DDR2, reduced expression of tumor suppressor genes, DNA methylation, histone code changes and many more (Langevin et al., 2014; Lemjabbar-Alaoui et al., 2015). In 2022, this cancer was the second leading cause of death from tumorigenesis (Doumat et al., 2023). Although there have been improvements in treatment options, survival rate of five years for this disease is just around 16% (Huang et al., 2017). Treatment strategies that are commonly used in therapeutic setting include surgery, radiotherapy, chemotherapeutic drugs, and concurrent use of radiotherapy and chemotherapeutic drugs (Doumat et al., 2023). Currently, drugs that provide targeted therapies for specific oncogenic mutations and drugs providing immunotherapy are also available (Doumat et al., 2023; Mayekar & Bivona, 2017). The biomarkers in tumors can be detected with minimally invasive approaches that involve identification through blood or urine samples as a substitute for biopsies (Ruiz-Ceja & Chirino, 2017).

Drugs that have been in use over the past 2 decades successfully provided therapeutic benefits. However, major challenges of targeting tumorigenic biomarker KRAS, MET, RET and EGFR with exon 20 alteration, targeting epigenetic mutations that allow for tumor cell

proliferation other than RTKs, emerging resistance to available drugs, low specificity for targets, achieving increased survival rates and overcoming aggressive adverse effects remain (Halliday et al., 2019; Ruiz-Ceja & Chirino, 2017). These strengthen the search for innovative drugs that will be able to overcome this conundrum.

## 1.2 Rationale of Study

It is essential that the agents used for treatment provide promising outcomes for the patient in terms of tolerability, efficacy, and good improvement in PFS and OS. Otherwise, patients suffer from the drawbacks of hazards linked to the available agents. Currently, available drugs for NSCLC are associated with various challenges of resistance to tyrosine kinase inhibitor drugs that can happen due to numerous oncogenic alterations that produce them, severe toxicities, and many more (Wu et al., 2022). Determining particular mutations associated with the tumor will result in developing drugs that are highly specific for the targets (Ruiz-Ceja & Chirino, 2017). However, the predominant challenge linked to SCLC is the identification of therapeutic targets that will be efficacious as most are undruggable (Wu et al., 2022). For these reasons, more effective and novel drugs are urgently required for combating lung tumorigenesis. The goal of this research was to compile and critically examine key data on emerging drugs that are used in the treatment of this disease.

## 1.3 Aim and Objectives of the Study

The aim of this study "A Review on Recent Advances in Drugs for Lung Cancer Treatment" is to provide an unparalleled opportunity to attain a better understanding of the emerging drugs that could pave the way for finding the ultimate curative options.

The objectives of the review:

- To discuss the limitations of existing drugs
- To provide details of the knowledge on pharmacokinetics for the novel drugs

- To address the mechanism of actions of the individual agents
- To delineate the advantages and limitations of the innovative agents
- To provide an overview and mechanism of action of combination drugs

# Chapter 2

# Methodology

The current study has been initially started with a thorough evaluation of the scholarly articles from authentic sources that is relevant to the aforementioned topic. All the vital information for this review has been collected from reliable online search engines and journal databases. These include Google Scholar, ScienceDirect, PubMed, ACS publications, Wiley Online Library and many more. Professional websites were also referred to in order to accumulate topic-specific knowledge. After identifying all the vital and required information, an outline was developed. For this to happen, it was important to first determine all the emerging drugs to combat lung cancer in the recent past. Moreover, a further literature search was conducted to find the mode of activity, benefits and limitations associated with the selected agents. The use of accurate and well-grounded information was given first and foremost consideration. Additionally, proper citation of applicable literation for the review was ensured.

# Chapter 3

# Lung Cancer

This denotes tumors that are malignant and is associated with unrestricted growth and division of cells. Distant sites of metastasis include the brain, liver, adrenal glands, etc. It is associated with high fatality rates as it is challenging to detect the disease when it is in the early stage (Sato et al., 2007). Symptoms that frequently accompany smokers with lung cancer are cough, wheezing, shortness of breath and hemoptysis (Cersosimo, 2002). To examine the lungs for any physical abnormalities, an x-ray of the chest can be performed. Moreover, CT scans, PET scans and MRI scans also be used for the identification of the disease (American Cancer Society, 2022).

## 3.1 Factors that Cause Lung Cancer

### Tobacco Smoke

Major contribution to lung cancer can be attributed to smoking and this leads to about 80% deaths (American Cancer Society, 2023). 20- to 50- fold increase in risk can be observed in people who smoke frequently compared to those who are non-smokers. Cigars, pipes, local tobacco products of different countries all have similar carcinogenic effects like cigarette smoking (Malhotra et al., 2016). The probability of acquiring the disease elevates with the factors such as the quantity of cigarettes pack smoked and the length of time one smokes (Zappa & Mousa, 2016). Nicotine which is a constituent of cigarette smoke is able to modify the gene expression which will ultimately promote dependence by upregulating its receptors. In addition, it also contributes to advancing the lung tumors that are already present. The risk of lung cancer can be further increased when menthol cigarettes are smoked. These allow for smoke to be deeply inhaled and also causes upregulation of nicotinic receptors that leads to enhanced addiction and decreased potential to quit smoking (de Groot et al., 2018).

## Second-hand Smoke

People who live in close proximity to smokers have a higher probability of developing the disease as a result of inhaling the cigarette smoke that those smokers produce**.** 20% to 30 % rise in cancer is observed when the non-smoker lives in the same household as the smoker (Zappa & Mousa, 2016). Moreover, an estimated 7000 people die from lung cancer as a consequence of involuntary smoking (American Cancer Society, 2023).

## Radon Gas

The second most prevalent factor that raises the risk of lung cancer is radon. This naturally radioactive gas originates when uranium in the earth's crust decays, and over time, this releases alpha particles that eventually will transform into polonium and bismuth. Radon levels out in the environment is so low that it is unlikely to pose a threat however more concentration of it is found indoors like in the building's lower levels and the basements (de Groot et al., 2018). Consequently, small doses of the gas can enter the lungs during normal breathing and this in turn can increase the possibility of having the disease (American Cancer Society, 2023).

## Asbestos

An estimated 5% to 10% of lung cancers can occur due to exposure to the carcinogen asbestos in the workplace like mines, textile industries, mills, and others (American Cancer Society, 2023; de Groot et al., 2018). In this situation, there is 5 times greater probability of the cancer occurring. Mortality due to lung cancer is deemed to be strongly correlated with the size of asbestos fibers (Zappa & Mousa, 2016). Additionally, workers who concurrently smoke and undergo exposure to asbestos face higher risk of the cancer (American Cancer Society, 2023).

## Air Pollution

Production of carcinogens when fossil fuels are burned and fine particulate presence in the air is the primary issue affecting the air quality both indoors and outdoors. Emissions containing polycyclic aromatic hydrocarbons, sulphur dioxide and trace metals are different forms of carcinogens that can be found in the outside air. Exposure to these compounds over a prolonged period of time in a working environment increases the risk of acquiring this disease (de Groot et al., 2018). Moreover, mortality by lung cancer from any other causes is 8% more likely in presence of air pollution (Zappa & Mousa, 2016). Air pollution can occur in the indoor environment due to the use of soft coal and biomass fuels and is linked to elevating the risk of cancer primarily in developing nations. There is possibility of non-smokers in some parts of Asia facing a greater likelihood of acquiring the disease because of this (de Groot et al., 2018).

## Genes

Each person's chance of acquiring the disease is different, depending on factors such as their personal history and family history. Certain genes and chromosomes have been linked to a higher likelihood of the disease. Acquiring lung cancer is three-fold more likely in smokers who also have germline TP53 mutations than never smokers. According to research, a marker on chromosome 15 is also linked to lung cancer which encompasses three genes for nicotinic receptors. When nicotine binds to these receptors, alterations in cells takes place. Certain genes and chromosomes have been linked to a higher likelihood of the disease. The chance of developing the disease increases by 30% for each additional copy of the marker. However, the danger rises by 70% to 80% when there are two copies (Zappa & Mousa, 2016). Risk of acquiring cancer is significantly linked with the genetic regions 5p15, 15q25-26, and 6q21. Telomerase reverse transcriptase is encoded by 5p15 and is linked to forming

adenocarcinomas in those who smoke and never smoke. Moreover, risk of the cancer and nicotine dependency both are significantly associated with alternations in 15q25-26. Under normal circumstances, G-protein signaling is mediated by 6p21. However, mutations in this locus can greatly elevate the risk in never smokers (de Groot et al., 2018).

### Infection

Carcinogenesis is linked to severe complications of the lung due to affliction with infection and inflammation. A greater prevalence of lung cancer is observed in people with HIV infection that is not associated with AIDS. Additionally, approximately 30% of deaths occurring in HIV-positive patients are due to cancer. Lung cancer incidence is correlated with diminishing CD4 levels. Irrespective of whether they smoke or not, people with HIV have a 2.5-fold higher chance of developing the disease. In comparison to the general people, patients who have both lung cancer and HIV are detected at more progressive stages and have shorter survival rates (de Groot et al., 2018).

## 3.2 Prevalence of Lung Cancer

According to Global Cancer Observatory, there were 2,206,771 number of incident cases and 1,796,144 mortality cases of lung cancer worldwide including all sexes and ages in 2020. It was anticipated that about 1.9 million individuals will be diagnosed with cancer in the United States in 2022, and 609,360 will lose their lives to the disease. On average, 350 people lose their lives to lung cancer every single day. Of the 130,180 deaths from this disease, 105,840 are directly attributable to smoking. Additionally, 3650 fatalities will be contributed to second-hand smoke. Between the years of 2009 to 2018, lung cancer occurrence reduced by 1% per year for females and 3% per year for males. In contrast to men, women started smoking in substantial quantities in recent time periods. Hence, they quit smoking more gradually so reductions in smoking happened later for them. There were optimized outcomes

for lung cancer patients due to increased availability of patient care. The percentage of people who survived for a minimum of 3 years following detection of the disease increased from 19% to 31% from 2001 to 2015-2017 respectively (Siegel et al., 2022). The survival rate of five years for people with disease spreading to distant body parts was 5%, while the rates for those with disease to localized and regional sites were 33% and 60%, respectively. Death rates from the disease fell by 56% for males and 32% for women between 1990 and 2019 (Sung et al., 2021). According to Global Cancer Observatory, there were an anticipated 156775 new cases and 108990 deaths from the disease in Bangladesh in 2020.

## 3.3 Lung Cancer Types

The prevalent types are the small cell lung cancer and the non- small cell lung cancer. 10% to 15% of the cases are due to SCLC whereas the remainder 80% to 85% are due to the NSCLC (American Cancer Society, 2023).

### 3.3.1 Small Cell Lung Cancer

This disease is triggered by a malignant epithelial tumor that forms in the airway's submucosa (van Meerbeeck et al., 2011). It is associated with small cells with almost no cytoplasm, no granular chromatin, and no clear cell border (Wang et al., 2020). Certain crucial genetic features are associated with SCLC. These include autocrine growth loops recognition, depletion or deactivation of tumour-suppressor genes and activation of proto-oncogene. Higher incidence of recurrent mutations is observed in TP53 which results in decline of apoptosis inducing action. This decline occurs during the SCLC tumour formation stage and consequently stimulates aggressive disease with prompt growth of the tumour and high rate of metastasis occurring at an early stage to lymph nodes, liver, brain and other distant areas (van Meerbeeck et al., 2011). Two categories of SCLC can be found which include limited

stage and extensive stage. Tobacco smoking is the predominant cause of it. In addition, poor prognosis is observed in SCLC with a low survival rate (Kalemkerian, 2016).

### 3.3.2 Non-Small Cell Lung Cancer

This refers to any subtype of the disease that develops in the epithelium other than the SCLC (National Cancer Institute, 2020). Its classification is given below:

Adenocarcinomas: Origination of adenocarcinomas can be from the type II cells of the alveoli that normally secrete mucus and are found in the miniature epithelial tissue of the airways. Their anatomic site is the periphery of the lungs. This is attributed to the fact that smoke particles of enormous size are blocked from invading the lungs by the presence of filters in cigarettes (Zappa & Mousa, 2016). In addition, they are capable of spreading by creating atelectasis of the entire lobe of the lung and pneumonitis (Lemjabbar-Alaoui et al., 2015). Adenocarcinomas account for 40% of all malignant tumours of the lung. They are equally common in men and women of all ages and smoking and non-smoking backgrounds (Zappa & Mousa, 2016).

Squamous cell carcinomas: Flat squamous cells lining the interior of the main bronchi give rise to these tumours, which spread to the lung's carina. Between 25 and 30 per cent of all lung cancers can be attributed to them (Lemjabbar-Alaoui et al., 2015). Cigarette smoking is the primary factor in the demise of these cells. As a result of the injury, these cells keratinize and develop intracellular junctions between them (Sabbula et al., 2022).

Large cell carcinomas: Unlike the other carcinomas that occur in the lung, these tumours are weakly differentiated and lack glandular and squamous maturation. They can be diagnosed by eliminating the possibility of other lung carcinomas. This type of carcinoma accounts for 5-10% of all tumorigenesis in the lungs cancer and tobacco use is the major cause. These can develop in any lung region. Consequently, they progress to regions like the lymph nodes,

chest walls and other tissues that are located at distant sites in the body (Zappa & Mousa, 2016).

## 3.4 Molecular Pathogenesis of Lung Cancer

Genetic and epigenetic changes are linked to the onset and progression of this disease. Tumour formation occurs due to growth promoting pathways involving KRAS, EGFR, BRAF, ALK, HER2, MET, RET, PI3K/AKT/mTOR pathway etc. Moreover, abnormalities of the tumour suppressor pathways involving the P53, PTEN, LKB-1, p16INK4a–Cyclind1-CDK4-RB pathway, etc. are also found in the NSCLC tumorigenesis (W. A. Cooper et al., 2013). Switching an amino acid at the sites of 12, 13 or 61 results in a genetic alteration like missense mutation which is associated with mutated oncogene like KRAS. Here, single mutations involving G1 and G2 amino acids are usually observed. Mutations in the EGFR receptor led to uncontrolled cell growth which is a hallmark of lung cancer. In the exons 18 to 21 are sites of frequent alterations for EGFR. Large proportion of these changes result from deletions in exon 19 and the L858R change in exon 21 (Zappa & Mousa, 2016). The proto-oncogene BRAF is associated with cell generation and survival. Mutations in BRAF for adenocarcinomas takes place at a different kinase domain compared to breast cancer. The alterations of V600E and D594G are found in exon 15 and alteration of G469A in exon 11 are examples of the BRAF abnormalities that can occur (Cooper et al., 2013; Zappa & Mousa, 2016). ALK mutations are commonly seen in people with an average age of 49. Transforming rearrangement of ALK gene very frequently results in EML-4-ALK fusion gene. This is the most prevalent kind of rearrangement observed for the ALK gene. The 5' end and the 3' end of EML-4 and ALK respectively will be fused together. Not only that, but this combination occurs on chromosome 2p23 (Zappa & Mousa, 2016). Gene overexpression, activating alterations, and an increase in the number of copies all contribute to HER2 activation in a subset of patients. Frame-shift mutation of insertions in exon 20 of

three to twelve base pairs are responsible for the activating alterations. Overexpression of MET is the outcome of alterations caused by the amplification of the MET gene. This consequently activates cascade involving the PI3K, AKT, and mTOR, cascade involving RAS, RAF, MEK, and ERK and pathway involving c-SRC. Few patients have the chromosomal translocation that activates RET. The kinase domain associated with RET is capable of combining with KIF5B-RET which is situated on chromosome 10 and is 10 Mb from the RET gene. This is seen in 1 to 2% of adenocarcinomas. In PI3K/AKT/mTOR pathway, PI3Ks subsequent effector is AKT. Activation of this AKT leads to tumorigenesis. Lack or reduction of PTEN activity leads to AKT pathway activation in lung cancer. Moreover, active AKT targets the downstream molecule mTOR (Sato et al., 2007). In 90% of SCLC and 65% of NSCLC, there is inactivation of TP53 which is associated with the deletion of the chromosome 17p13. When it comes to smoking-related lung cancer, base substitution of guanine to thymine is more common than guanine to cytosine. Furthermore, in non-smoking related tumours, higher frequency of G to A base substitution occurs at CpG dinucleotides. When the tumour suppressing ability of PTEN is inhibited then this leads to AKT/protein kinase B overactivation. Due to inactivity of LKB1 by diverse forms of alterations in the gene gives rise to shortened proteins. This is observed in 11 to 30% of adenocarcinomas (Cooper et al., 2013). For the pathway involving $p16^{INK4a}$, Cyclind1, CDK4 and RB, changes in all four constituents can be observed. Due to alterations in coding site, loss of both alleles of a gene and hypermethylation of promoter, there will be inhibition of $p16^{INK4a}$. This absence of activity in $p16^{INK4a}$ gives rise to lack of activity in RB. Tumour suppressor RB protein can also be inactivated due excess expression of the proteins CDK4 or Cyclin D1. During this situation, cells are unable to pass the G1/S checkpoint and continue replicating (Sato et al., 2007). While the exact causes of SCLC are still unclear, the tumour suppressor genes TP53 and RB1 almost always lose their ability to function. Recent studies

have shown additional recurrent genetic changes and signal transduction pathways activation involved with the disease. Among these include PTEN loss, activating alterations in PI3K, suppression of the NOTCH pathway, amplification of MYC and activation of aurora kinase. Additionally, it appears that elevated levels of PARP1, FGFR1 amplification, and activation of the Hedgehog pathway participate in the formation of tumours (Tsoukalas et al., 2018). Epigenetic pathways are both heritable and changeable. Hypermethylation of promoter is one instance of DNA methylation that can occur. Hypermethylation of RASSF1A, MGMT, DAPK, and $p16^{INK4a}$ are examples. MicroRNA are non-coding RNA molecules that are relatively short in size. Lung cancer is usually associated with a deregulated expression of microRNA. Specifically, miR-196a and miR-200b are overexpressed at abnormally high levels. Another epigenetic modification that dampens gene activity is histone deacetylation (Langevin et al., 2014).

# Chapter 4

# Existing Drugs for Lung Cancer Treatment and their Limitations

The FDA has approved a plethora of drugs for treatment of this disease between 2000 and 2015. Though they have bought immense benefit to the care for patients, however they do come with their own set of risks.

## 4.1 EGFR Inhibitors

Gefitinib and erlotinib belonging to first-generation, afatinib belonging to second-generation and osimertinib belonging to third-generation are all the existing agents of this class. They can target deletion of exon 19 or point alteration of exon 21. They are associated with limitation of dermatologic toxicities due to the absence of epithelial barrier when EGFR undergoes inhibition (Thomas et al., 2019). These effects include like acneiform eruption, pruritis, xerosis, and many more (Kozuki, 2016). However, with osimertinib they are milder in nature (Chu et al., 2018). These can worsen to the point that they become critical, making management challenging and even necessitating therapy withdrawal to preserve the patient's general wellbeing. The administration of these drugs must be discontinued due to the serious toxicity of ILD and stomatitis. Drug-specific significant risks which can also hamper the wellbeing of patients include gastrointestinal perforation for erlotinib and gefitinib, lengthy QT interval and cardiomyopathy for osimertinib (Shah & Shah, 2019). Additionally, acquired resistance to these agents is also observed. For first-generation drugs, a crucial mechanism of resistance occurs via T970M alteration in the EGFR gene (Singh & Jadhav, 2018). Other mechanisms include Met overactivation, HGF overexpression, activation of IGF-1R, activating alterations in AKT, absence of PTEN, and many more (Morgillo et al., 2016). For the second-generation agent, an additional EGFR T790M mutation contributes to its acquired

resistance (Tanaka et al., 2017). Moreover, resistance to osimertinib can occur via 2 pathways. One of them involves EGFR alterations like C797S, L792H/V, G796S/C, G719A, etc. The other pathway involves amplification of MET and HER2, alterations in NRAS and PI3KCA, ALK fusion, RET fusion, etc. For NSCLC with EGFR exon 20 alterations, none of these drugs has proven to be very effective (Schmid et al., 2020).

Necitumumab is a monoclonal antibody belonging to this class. It is not efficacious in the treatment of lung adenocarcinomas (Brinkmeyer & Moore, 2016). Discontinuation of the agent can occur if there are frequent toxic events observed. These include electrolyte imbalance like hypomagnesemia, dermatologic toxicity like dermatitis or acneiform rash, and life-threatening IRR. The packing of the drug includes a black box warning for cardiopulmonary arrest, unanticipated death and hypomagnesemia (Brinkmeyer & Moore, 2016).

## 4.2 Folic Acid Antagonist

Pemetrexed resistance can be seen in non- squamous NSCLC. The factors contributing to this are a surge in the efflux of the drug, deficiency in polyglutamylation, epithelial-to-mesenchymal transition pathway activation, overexpression of TTF-1 and target proteins, erroneous DNA repair involving BER and NER system, and others (Liang et al., 2019). This agent produces dose-limiting toxicity like myelosuppression with the manifestation of thrombocytopenia and neutropenia. Additionally, the adverse effect is linked to high levels of homocysteine in plasma before treatment with pemetrexed (Chen et al., 2014). It is not recommended for squamous cell carcinoma as it is associated with poor response in individuals.

## 4.3 Microtubule Inhibitor

Therapy with paclitaxel is frequently associated with peripheral neuropathy. This limits its usage in high doses during monotherapy or combination therapy with antitumor drugs like cisplatin (Scripture et al., 2006). Resistance due to elevated expression of MDR1 encoded P-glycoprotein which is involved with the efflux of the drug from the tumour cells can occur. Hence, reduction in drug accumulation and tumour cell proliferation denotes failure of therapy with the drug (Ruiz-Ceja & Chirino, 2017). Even after four repeated regimens of paclitaxel therapy, tumour suppression does not occur and also within 6 months tumour renewal is observed again (Huang et al., 2017).

## 4.4 Angiogenesis Inhibitor

Existing drug in this class includes bevacizumab. When monotherapy with bevacizumab capable of VEGF-A inhibition is used, it has the limitation of not producing efficacy in treatment of lung adenocarcinoma and needs to be used in combination setting (Haibe et al., 2020). It did not prolong overall survival when given together with chemotherapeutic drugs like cisplatin and gemcitabine (Kurkjian & Kim, 2011). Moreover, no improvement in OS occurred when bevacizumab is given with etoposide and cisplatin for ES-SCLC (Montanino et al., 2021). Moreover, there is higher incidence of hemorrhage, proteinuria and hypertension when treatment is done with Bevacizumab in advanced NSCLC (Lai et al., 2016). Resistance to the agent occurs however complete understanding of its mechanism has yet to be determined (Ruiz-Ceja & Chirino, 2017).

## 4.5 PD-1 Inhibitor

Drug that is currently in use for this class include nivolumab. Compared to chemotherapy drugs, there was no prolongation in PFS when used for patients with no prior therapy and

who has NSCLC that has metastasized or which reoccurs observed with this agent (Carbone et al., 2017). In addition, no good predictive biomarker for instance PD-L1 expression for the agent can be found (Zago et al., 2016). This does not allow for proper selection of patients to be treated with nivolumab. Moreover, immunotherapy with this drug improves the condition of a limited number of patients (Morgensztern & Herbst, 2016). Pneumonitis is the most frequent immune related adverse effect associated with this agent that can lead to discontinuation of treatment (Zago et al., 2016).

## 4.6 TKI Targeting ALK or ROS1

An existing drug belonging to this class is crizotinib. It does not substantially prolong OS when treating patients with NSCLC who has abnormalities in ALK or ROS1 in contrast to chemotherapy drugs (Shen et al., 2020); Solomon et al., 2014). Another limitation is treatment-related toxicity. These include severe visual deficiency, liver abnormality associated with enhanced levels of total bilirubin and alanine transaminase, lengthy QT interval, GI toxicity and pneumonitis (O'Bryant et al., 2013; Sahu et al., 2013). Consequently, they can result in the discontinuation of treatment. More common are the GI toxicities and the visual deficiency adverse effects. Patients have the potential to develop resistance to the medication within the first year of starting treatment. The L1196 mutation, L1152R mutation, C1156Y mutation, G1202R mutation, S1206C/Y mutation, and many more are all examples of ALK alterations that can cause resistance. (Wu et al., 2022). The ROS1 alterations of G2032R, D2033R, S1986Y/F, L2026M, and L1951R are the most common ones that lead to resistance (D'Angelo et al., 2020). Moreover, the drug does not have any activity towards metastases in the brain as it is incapable of penetrating the blood-brain barrier (Rocco et al., 2019).

## 4.7 ALK Inhibitors

Second-generation medications from this class include ceritinib and alectinib.

A limitation associated with ceritinib is that it does not have prolonged OS or PFS in comparison to first-generation crizotinib (Hoang et al., 2020). When adverse effects like liver abnormalities, pneumonitis, the elevation of QT interval, abnormally slow heart rate and hyperglycemia that cannot be regulated by antihyperglycemics occur then discontinuation of the agent in possible (Cooper et al., 2014). Moreover, resistance can be the result of amplification of the ALK gene, as well as changes in its kinase domain, which can lead to the progression of disease (Shaw et al., 2014). The mutations include G1202R, C1156Y, L1152P, 1151Tins and F1174C/L/V (Wu et al., 2022).

Alectinib is associated with adverse events which include extremely low heart rate, hepatic dysfunction, hemolytic anemia, severe myalgia and severe renal toxicity (Dziadziuszko et al., 2022). More common are liver abnormalities and musculoskeletal adverse effects. Patients can acquire resistance to the drug due to ALK mutations like L1196M, G1202R, V1180L and I1171T/N/S (Wu et al., 2022).

*Table 1: List of Existing Drugs with the Type of Lung Cancer Treated and their Mechanism of Action*

| Name of drug | Type of lung cancer treated | Mechanism of action | Reference |
|---|---|---|---|
| Gefitinib | Metastatic NSCLC | Prevents interaction of ATP with its binding site. Inhibition of mutant EGFR occurs. No receptor phosphorylation occurs. No PI3K/Akt pathway and MAPK/Erk pathway | (Ruiz-Ceja & Chirino, 2017) (Araki et |

| | | | |
|---|---|---|---|
| | | activation. This, in turn, causes apoptosis and a decrease of the proliferation of tumour cells. | al., 2012) |
| Erlotinib | Metastatic NSCLC | Competes with ATP and inhibits the binding site it occupies within EGFR. No activation of pathway involving Ras, Raf, MEK and ERK, pathway involving Jak2 and STAT3 and pathway involving PI3K and Akt pathway. No tumour cell generation and ultimately cell death. | (Schettino et al., 2008) |
| Afatinib | Metastatic NSCLC particularly squamous cell carcinoma | Inhibition of EGFR, HER2, HER3, and HER4 occurs in an irreversible manner. Specifically, it inhibits signaling by ErbB family homodimers and heterodimers. Competes with ATP and forms covalent bonds with Cysteine-773 by Michael addition to inactivate kinase domain. No activation of cascade involving Ras, Raf, MEK, and ERK1/2, phospholipase C pathway and cascade involving PI3K and AKT. | (Hirsh, 2017) (Xu et al., 2017) |
| Osimertinib | Metastatic NSCL | Irreversible binding of C797 amino acid of drug with the T790M, L858R and exon 19 deletion alterations of EGFR. Inhibition in | (H. Zhang, 2016) |

| | | | |
|---|---|---|---|
| | | pathway involving PI3K and AKT, pathway involving RAS, RAF, MEK and ERK pathway occurs. There is a lack of DNA synthesis and the formation of tumour cells. | |
| Necitumumab | Squamous cell carcinomas | Inhibition of domain III in EGFR which overlays the site for binding of EGF ligands. Inhibition of ligand binding occurs. No MAPK kinase activation occurs which prevents tumour cell survival and proliferation. | (Ruiz-Ceja & Chirino, 2017) (Wu et al., 2022) |
| Pemetrexed | Lung adenocarcinoma that is locally advanced or has metastasized | Inhibits enzymes thymidylate synthase, DHFR and GARFT. Major inhibition of thymidylate is observed as no conversion of dUMP to dTMP to DNA occurs. Also synthesizing purines from the other two pathways are also inhibited. No DNA replication in tumour cells. | (Ruiz-Ceja & Chirino, 2017) (Velez et al., 2012) |
| Paclitaxel | Locally advanced NSCLC or NSCLC that has metastasized | Binds and phosphorylates β-tubulin. Induces stability of microtubules and enhances their polymerization. There is a lack of DNA synthesis and the formation of tumour cells. | (Ruiz-Ceja & Chirino, 2017) (Jiménez-López et al., 2021) |
| Bevacizumab | Lung adenocarcinoma | Binds to VEGF and prevents receptor dimerization. Subsequently, there is no | (Ruiz-Ceja & Chirino, |

| | | | |
|---|---|---|---|
| | that is locally advanced or that metastasized | autophosphorylation of the receptor. This leads to tyrosine kinase domain of receptor to not get activated. MAPK, phospholipase C and PI3K-AKT pathways are not activated. Blocks the formation of new blood vessels and endothelial cells, so starving tumors of the nutrients they need to grow. Tumour tissues receives restricted blood flow. | 2017) (Planchard, 2014) |
| Nivolumab | NSCLC that has metastasized | High affinity interaction with PD-1 receptor that is expressed by T-cell that are active. This, in turn, prevents PD-L1 and PD-L2 from attaching to their targets. Consequently, there will be an enhanced immune response due to T cell proliferation. These are specific for tumour antigens. | (Ruiz-Ceja & Chirino, 2017) (Guo et al., 2017) |
| Crizotinib | Metastatic NSCLC | Inhibits tyrosine kinase of ALK and ROS1. By binding to ALK and ROS1 protein, it inhibits the pathway involving RAS and MAPK, pathway involving PI3K and AKT and pathway involving JAK and STAT. No G1 to S phase progression and apoptosis occurs. | (Ruiz-Ceja & Chirino, 2017) (Poon & Kelly, 2017) (Sahu et al., 2013) |

| | | | |
|---|---|---|---|
| Ceritinib | Metastatic NSCLC | Interaction and blocking of ALK protein<br>Competes with ATP for binding site<br>No activation of the PI3/AKT pathway, RAS/MAPK pathway and JAK/STAT pathway. No G1 to S phase progression and apoptosis occur. | (Ruiz-Ceja & Chirino, 2017)<br>(Poon & Kelly, 2017)<br>(Rocco et al., 2019) |
| Alectinib | Metastatic NSCLC | Competitively blocks ATP binding site of ALK tyrosine kinase domain<br>No ATP binding occurs and no ALK phosphorylation. Downstream pathways like STAT3 and PI3K/AKT are not activated. Cell death occurs. | (Ruiz-Ceja & Chirino, 2017)<br>(Herden & Waller, 2018) |

# Chapter 5

# Emerging Drugs for Lung Cancer Treatment

Based on the FDA approvals, novel drugs that have become available between the years of 2016 and 2022, are categorized into their respective classes.

## 5.1 KRAS Inhibitors

### 5.1.1 Sotorasib

Sotorasib is first agent to be approved in class of KRAS inhibitors (Parums, 2022). It provides targeted therapy by specifically inhibiting $KRAS^{G12C}$ by an irreversible mechanism in NSCLC that is locally advanced or metastasized to distant organs as second line treatment. (Hong et al., 2020).

#### 5.1.1.1 Pharmacokinetics

Non-linear and time dependent pharmacokinetics are observed for this agent across the daily dosing limit of 180 to 960 mg. There is an average value of 0.56 for the accumulation ratio which demonstrated that there is no discernible accumulation of the drug in the body. Over the span of 22 days, the agent's concentration will reach steady state levels. At steady state, it is found to have an average of volume of distribution of 211 liters and apparent clearance of 26.2L/h. Moreover, sotorasib takes an hour to reach its $C_{max}$ as well as has a plasma protein binding of 89% (Blair, 2021). It also has a terminal elimination half-life with an average value of 5 hours (Lee, 2022). When a patient is given an individual dose of the drug at 960 mg along with food that contains high fat and calorie content then the $AUC_{0–24h}$ will be elevated by 25% as opposed to when the patient was fasting. The biotransformation process of the drug includes oxidative process by CYP3As and non-enzymatic conjugation process. Additionally, reduction in the drug's AUC and $C_{max}$ was observed when it was given with

proton pump inhibitor like omeprazole, H2 blocker like famotidine and frequent doses of CYP3A4 inhibitor like rifampicin (Blair, 2021).

### 5.1.1.2 Mechanism of Action

KRAS belongs to RAS family and encodes a GTPase. It is the oncogene that undergoes mutation recurringly in 13% of aggressive cancer like NSCLC. In order to control downstream cellular signal transduction, the GTPase will alternate between its active and inactive conformations. These are KRAS being bound to GTP and GDP respectively. Single point mutations of glycine to cysteine takes place in codon 12 which results in $KRAS^{G12C}$ alterations. This primarily diminishes the GTP hydrolysis and consequently results in GTP bound KRAS oncoprotein which leads to increased tumour cell generation (Hong et al., 2020). Sotorasib has reactive functional groups that will rapidly create covalent bond formation with the cysteine 12 of $KRAS^{G12C}$. Moreover, isopropyl pyridine substituent will form another different bond with the P2 pocket on the S-IIP that contains H95, Y96 and Q99. As the presence of S-IIP is only found in the GDP bound KRAS in inactivated form hence sotorasib will permanently confine the GDP bound KRAS protein in its inactivated state (S. S. Zhang & Nagasaka, 2021). This suppresses the RALGDS-RalA/B pathway, pathway involving Raf, MEK and ERK and pathway involving PI3K, AKT, and mTOR. Therefore, tumor cell growth inhibition and apoptosis occur (Corral de la Fuente et al., 2022). (Figure 1)

### 5.1.1.3 Advantages and Limitations

It has been reported from CodeBreak100 clinical trial that this agent diminished the size of tumours in 36% of patients and this improvement in condition continued for an average period of 10 months. This benefit superseded general therapy that could only reduce tumour size for a transitory period in less than 20% of patients. Moreover, it has been observed that an estimated 51% of patients who were under targeted therapy with sotorasib lived for a year

and estimated 33% of patients lived for 2 years after initiation of treatment (National Cancer Institute, 2021). Patients treated with sotorasib benefited better in terms of PFS and QoL than those treated with docetaxel, according to results from the phase 3 clinical trial CodeBreak200.

With sotorasib, PFS had an average value 5.6 months while average value of 4.5 months was observed with docetaxel. PFS of one year was observed in 25% patients getting sotorasib therapy versus 10% of patients getting docetaxel therapy (Parikh et al., 2022). Additionally, in a study it was observed that those patients who had mutations in both KRAS and STK-11 performed better with sotorasib therapy. They had and average PFS of 11-month and average OS of 15.3 months (Herdeis et al., 2021).

Limitation include discontinuation of sotorasib due to elevated aspartate aminotransferase, alanine aminotransferase, liver injury due to drug use, interstitial lung disease or pneumonitis (Lee, 2022). Emergence of resistance to sotorasib is also prevalent as a risk as it will result in unrestricted tumour cell proliferation. Acquiring heterogeneous alterations in RTKs, EGFR, secondary RAS, NF1, PTEN, MET and combination of oncogenes involving RET, ALK, BRAF, RAF1 and FGFR3 can lead to resistance associated with the drug (Lee, 2022; Liu et al., 2021). From preclinical data, secondary KRAS alterations that lead to resistance are Y96D, R68M, A59T and A59S. In addition, when EMT gets induced, sotorasib resistance is observed (Liu et al., 2021). For instance, RTKs can elevate the activity of KRAS through SOS 1 or 2 which in turn will cycle KRAS back to its GTP bound state which is activated and will not respond to sotorasib and divide uncontrollably. Furthermore, by activating the signaling PI3K-AKT-mTOR pathway which is independent of KRAS, it is possible to evade KRAS inhibition by the drug (Lee, 2022).

### 5.1.2 Adagrasib

It provides targeted therapy by specifically inhibiting $KRAS^{G12C}$ by an irreversible mechanism. It is used in treating individuals who have NSCLC that has spread to nearby tissues or lymph nodes or has metastasized to distant organs as second line treatment. This dug is administered via the oral route.

#### 5.1.2.1 Pharmacokinetics

$C_{max}$ and $AUC_{0\text{-}12h}$ increases in a proportional manner with the dose across the daily dosing limit of 400 to 600 mg. It takes an average value of 6 hours to reach $C_{max}$ and the average volume of distribution is observed to be 942 L. From in vitro results, it is observed that plasma protein binding occurs and is found to be 98%. The $t_{1/2}$ is found to be 23 hours and a value of 37 L/h is observed for the apparent clearance of the drug. The biotransformation of tepotinib primarily occurs by CYP3A4. Additionally, 4.5% of the drug was excreted in urine and 75% was excreted in faeces when provided with an individual dose of radiolabeled drug via the oral route. When individual 200 mg dose of adagrasib is concurrently given with a powerful inhibitor of CYP3A like itraconazole, there is elevation of $C_{max}$ and AUC by 2.4 times and 4 times respectively than the values observed at 600 mg. However, concurrent administration of individual 600 mg dose of the drug with strong inducer of CYP3A like rifampin causes a reduction of $C_{max}$ and AUC by 88% and 95% respectively (Mann, 2023).

#### 5.1.2.2 Mechanism of Action

It irreversibly blocks the oncogenic RAS GTPase which is the KRAS G12C. When the mutant receptor will be in the inactive state (GDP bound KRAS) then in adjacent P2 pocket, the aberrant cysteine will be located. Adagrasib is capable of binding with the P2 pocket and hence will permanently confine the GDP bound KRAS in its inactivated state (Mann, 2023). This in turn suppresses the RALGDS-RalA/B pathway, pathway involving the Raf, MEK and

ERK pathway and pathway involving PI3K, AKT and mTOR (Corral de la Fuente et al., 2022). Consequently, there will be no tumour cell movement, growth and division, survival, and cell death will occur. (Figure 1)

### 5.1.2.3 Advantages and Limitations

According to the KRYSTAL1 trial results, the average PFS value was 6.5 months and median OS value was 12.6 months. This was observed for patients who received the medication as a second-line option. However, the general second line option is docetaxel. It showed significantly shorter PFS and OS which were average of 3 months and 9.1 months respectively (Tian et al., 2022). This denotes adagrasib has the potential of substantial benefit in late-stage NSCLC. Moreover, compared to sotorasib, it showed comparable efficacy without any new safety signal (Jänne et al., 2022).

Limitation includes frequent adverse reactions of gastrointestinal related events, liver toxicity, renal impairment, edema, dyspnea, and many more. Treatment discontinuation can occur with severe ILD/pneumonitis, elongation of QT interval, liver toxicity and gastrointestinal related events (Mann, 2023). Moreover, from preclinical and clinical trial reports, the possible KRAS secondary mutations are Y96D, Q99L, R68S and A59S. The possible off-target mechanism for resistance is MET amplification and BRAF V600E mutations. One process of off-target resistance is associated with conversion of adenocarcinoma of the lung to SCC (Blaquier et al., 2021).

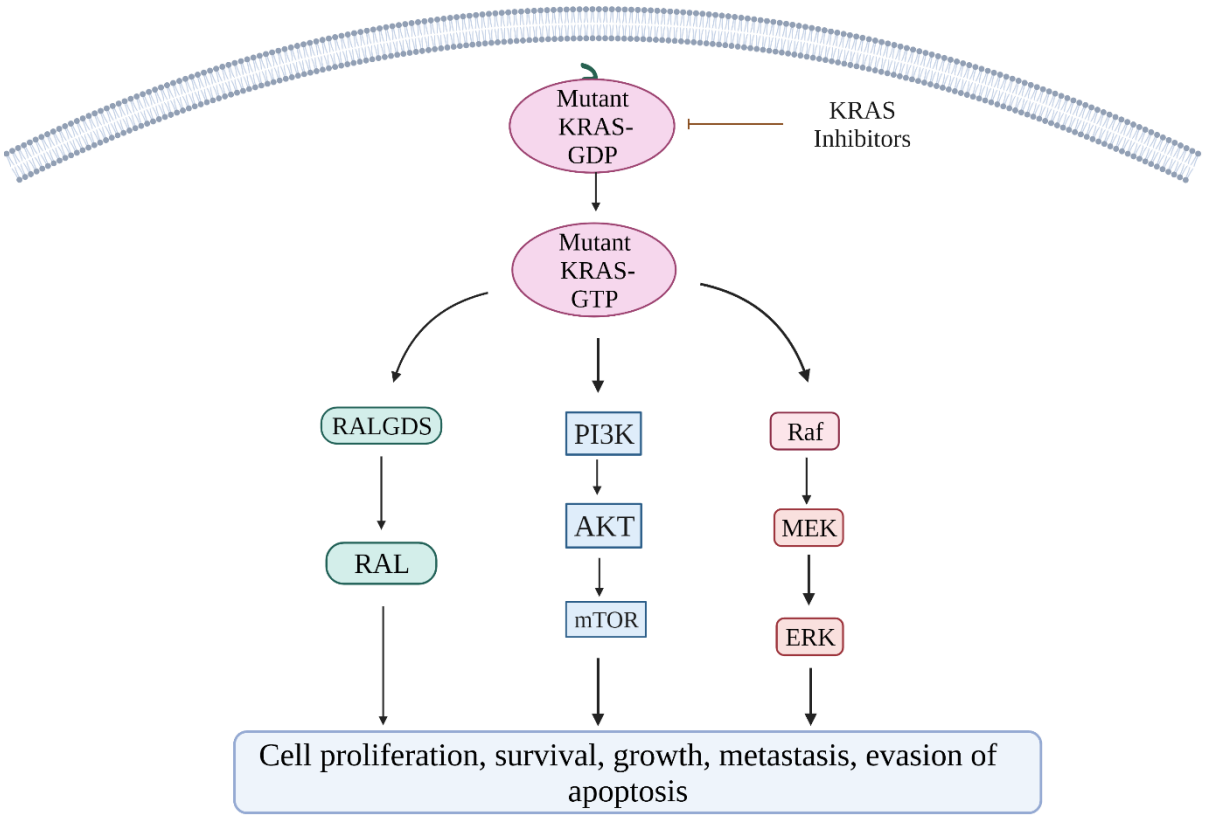



*Figure 1: Mechanism of Action of KRAS Inhibitors*

## 5.2 EGFR Inhibitors Targeting Exon 20 mutation

### 5.2.1 Amivantamab

It is a bispecific antibody that is first in its class to be approved for NSCLC with alteration in EGFR of exon 20 insertion that is locally advanced or has metastasized following cancer progression after treatment with platinum-based chemotherapeutic agents. It is to be administered as intravenous infusion.

#### 5.2.1.1 Pharmacokinetics

Within the dosing limit of 350 mg to 1750 mg, linear pharmacokinetics has been observed for this bispecific antibody. By the time infusion of this agent was taken for the 9$^{th}$ time, steady state has been reached and the value for accumulation ratio was 2.4. It had an average value

for $V_D$ of 5.13 L and daily clearance of 360 mL. Moreover, it had a value of 11.3 days for its terminal half-life (Brazel & Nagasaka, 2021; Vyse & Huang, 2022).

### 5.2.1.2 Mechanism of Action

There are two arms on amivantamab which allows it to concurrently bind and inhibit EGFR and MET. This bispecific antibody is capable of interacting with the extracellular domains that are present in EGFR and MET. This blocks the binding between EGF and EGFR. The blocking also prevents HGF binding (Brazel & Nagasaka, 2021). Consequently, this receptor will not be activated and hence its phosphorylation will not take place, Ultimately, pathway involving PI3K and AKT and pathway involving RAS, RAF, MEK and ERK will not be activated (Cho et al., 2022; Vyse & Huang, 2022). Hence, no cell growth and division and survival occur. Another potential mechanism is amivantamab bound receptors will get enveloped by the membrane of the cell, undergo internalization and move to lysosomes. These lysosomes will then degrade the complex of antibody-receptor. Additionally, the Fc portion of the agent has the potential to bind to the Fcγ receptors that are on the immune cells of the body. This results in activation of the immune cells that will then perform actions like ADCC that can cause discharge of cytotoxic granules to kill tumour cells, ADCP which can form an envelope around the tumour cell and damage it, ADCR which can release chemokines and cytokines to trigger killing of tumour cells or cause activation of other immune cells and ADCT which can shift the agent attached to tumour cell surface to the immune cells in order to destroy tumor cells (Cho et al., 2022). (Figure 2)

### 5.2.1.3 Advantages and Limitations

In comparison to general treatment with chemotherapy agents, currently available EGFR TKIs, and immune checkpoint inhibitors, a key benefit of this agent is significantly prolonged PFS and OS. These values for them include 8.3 months and 22.8 months respectively

(Minchom et al., 2022). It is able to show activity against resistance to EGFR inhibitors in spite of the type of resistance alterations (Nagasaka et al., 2022). It has a manageable safety profile (Vyse & Huang, 2022).

Limitation includes frequent adverse events like infusion related reactions, rash, stomatitis, and paronychia (Vyse & Huang, 2022). Another probable limitation can be related to its enormous size, which limits its ability to cross the blood-brain barrier and function against the secondary brain tumors (Petrini & Giaccone, 2022).

### 5.2.2 Mobocertinib

Mobocertinib is an approved agent to provide targeted therapy for NSCLC is locally advanced or has metastasized following cancer progression after treatment with platinum-based chemotherapeutic agents through selective inhibition of EGFR exon 20 mutations by an irreversible mechanism (Campello et al., 2022; Zhang & Zhu, 2021). It is to be administered via the oral route.

#### 5.2.2.1 Pharmacokinetics

Time dependent and nonlinear pharmacokinetics that is efficiently denoted by a two-compartmental model are observed for this drug. Mobocertinib is a class 1 agent under Biopharmaceutics Classification System as it has both high solubility and permeability (Gupta et al., 2022). Moreover, it takes an average time of four hours to reach $C_{max}$ and after administration of a single dose, it has an average elimination half-life of 18 hours. The absolute bioavailability of the agent is found to be 37% and it has a volume of distribution of 3509 L. CYP3A4/5 controlled biotransformation of mobocertinib occurs to produce AP32960 and AP32914. These are active metabolites which is generated by oxidative N-demethylation taking place on the ethylenediamine side chain that is found on the right aniline ring and on the 1-methylindole. $IC_{50}$ value against exon 20 insertion alteration for AP32960 is found to be

2.4 to 12 nM and for AP32914 is found to be 7.1 to 41 nM. Moreover, these two products also contribute to mobocertinib's effectiveness in lung cancer treatment. There is possibility of inducing CYP3A enzymes by the drug which consequently causes autoinduction of metabolism (Wang et al., 2022). As a result, there will minimal accumulation of the drug in the body when frequent doses of the drug are given. Excretion of drug happens in minute quantities via the renal route. When mobocertinib is concurrently given with a powerful inhibitor of CYP3A like itraconazole, there is elevation of $AUC_{0-\infty}$ by 527%. However, concurrent administration of the drug with strong inducer of CYP3A like rifampin causes a reduction of $AUC_{0-\infty}$ by 95% (Gupta et al., 2022).

### 5.2.2.2 Mechanism of Action

EGFR has a kinase domain. Within this, the active site is found and this is enclosed by various intrinsic attributes that includes a hinge residue M793, P-loop, "gatekeeper" residue of T790, A-loop, C-helix, and C797 found at the periphery of the cleft of active site. Mutation in exon 20 of EGFR takes place via frame insertion of 3 to 21 base pairs and this consequently leads to alterations in shape of EGFR that will give rise to a structure that nearly mirrors the wild type EGFR's active conformation. Ultimately this results in cancer cell survival and proliferation. Mobocertinib has an aniline ring in its structure where at 5-position there is presence of α, β-unsaturated acrylamide group. This group is capable of functioning as a Michael receptor which will undergo Michael addition by forming covalent bond with the thiol group that is found in C797. Creation of non-covalent bond also occurs like hydrogen bonds. There is presence of N-H bond in M793 residue that is located in hinge region and the N1 of the pyrimidine core of the drug. These two facilitates formation of an individual hydrogen bond. Additionally, there is presence of 2-positon N-H of the pyrimidine core of the drug and oxygen of carbonyl group of M793 residue. Another hydrogen bonding occurs between these two positions. The formation of these non-covalent bonds as well as

precise configuration of the drug when it interacts with the tyrosine kinase of EGFR allows for strengthening the covalent bond formation. There is high structural compatibility between mobocertinib and EGFR tyrosine kinase. This is only possible as the pyrimidine core of the drug contains C5-carboxylate isopropyl side chain which is capable of binding and utilizing a selectivity pocket found in the near vicinity of "gatekeeper" residue of T790. This inhibits the tyrosine units from being phosphorylated in the kinase domain. The pathway involved with Ras, Raf, MEK and ERK and the pathway involved with PI3K, AKT and mTOR will not be activated (Wang et al., 2022). Hence, tumour cell survival, growth and division, metastasis are inhibited and cell death occurs. (Figure 2)

### 5.2.2.3 Advantages and Limitations

According to the evaluations made by the independent review committee from NCT02716116 trial, treatment with mobocertinib had a value of 28% for ORR, 7.3 months for PFS, 17.5 months for average DoR and 24 months for OS (Gupta et al., 2022). This shows mobocertinib treatment is advantageous over the currently available EGFR TKIs, immune checkpoint inhibitors and platinum based chemotherapeutic drugs. The reason is that these existing treatments for the metastatic NSCLC has an estimated low chance of recovery with the EGFR exon 20 insertion alterations. Moreover, the drug has a substitution of isopropyl ester on the pyrimidine ring which allows for binding with a selectivity pocket that is present beside T790 (Wang et al., 2022). This provides greater selectivity, binding affinity and kinase activity blocking which results in elevated potency of the drug (Gonzalvez et al., 2021). The major benefit of mobocertinib use was major symptoms elevation within 2 months of starting treatment. The improvement continued as the treatment proceeded and was also observed in patients who are difficult to treat (Campello et al., 2022).

Limitation includes termination of patient treatment with the agent due to occurrence of serious adverse effects. These include lengthy QT interval particularly Torsade's de Pointes,

pulmonary toxicities particularly pneumonitis/ILD, cardiotoxicity particularly heart failure, embryo-fetal toxicity and gastrointestinal toxicity (Wang et al., 2022). Emergence of resistance to mobocertinib is also prevalent in patients. This could be attributed to mutations in EGFR C797S. In addition, reports from some preclinical studies established that alterations like T790M/C797S and L858R/C797S in EGFR were not susceptible to mobocertinib (Wang et al., 2022).

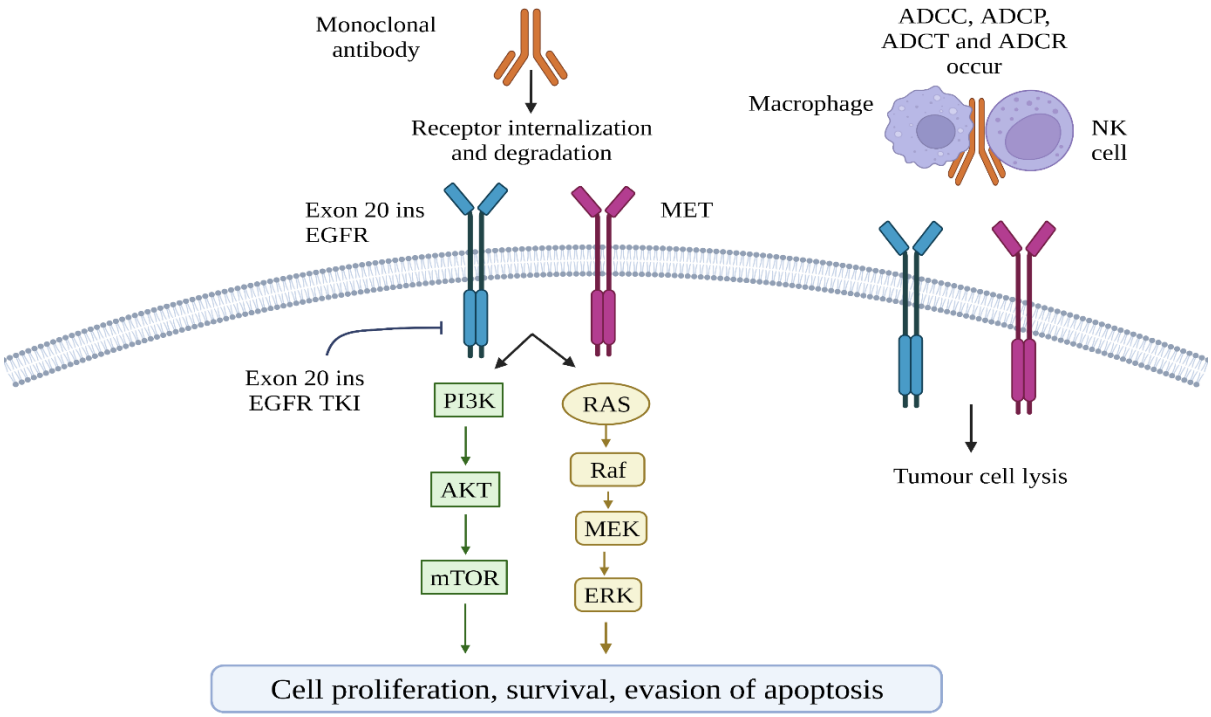



*Figure 2: Mechanism of Action of EGFR Inhibitors Targeting Exon 20 Mutation*

## 5.3 MET Inhibitors

### 5.3.1 Capmatinib

Capmatinib is the first approved drug to provide targeted therapy by specifically acting against the mutation MET exon 14 skipping found in metastatic NSCLC (Nogueira & de Souza, 2021). It is to be administered via the oral route.

### 5.3.1.1 Pharmacokinetics

Linear pharmacokinetics is observed for the drug as $C_{max}$ and $AUC_{0\text{-}12h}$ increases across the daily dosing limit of 200 to 400 mg. This drug undergoes quick absorption and takes an estimated average value of 1 to 2 hours to reach $C_{max}$. More than 70% of the administered drug will be absorbed. When the drug is given twice a day, steady state can be reached within 3 days and the $V_D$ is observed to be 164 L. Moreover, accumulation ratio can be deduced to have a value of 1.5 and the apparent clearance is 24 L/h at steady state. Regardless of the drug level in the body, protein binding of the drug in plasma occurs and it is found to be 96%. The biotransformation of the drug predominantly occurs by aldehyde oxidase and CYP3A4. In addition, the effective elimination half-life has a value of 6.5 hours. When capmatinib is concurrently given with a potent CYP3A inhibitor like itraconazole, there will be increase in $AUC_{0\text{-}\infty}$ and $C_{max}$ by 42%. This will lead to prevalence of severe adverse drug reactions. Furthermore, concurrent administration of the drug with a CYP3A4 inducer like rifampicin will lead decrease in $AUC_{0\text{-}\infty}$ by 67% and decrease in $C_{max}$ by 56%. The consequence of this is reduction in activity of the drug towards tumour growth (Dhillon, 2020).

### 5.3.1.2 Mechanism of Action

When alterations like MET exon 14 skipping occurs then it results in a truncated receptor which does not possess the juxtamembrane domain. Regardless, the MET receptor remains capable of blocking the ligand HGF and decrease its negative regulation. As a consequence of this, the receptor will begin to assemble itself on the outer membrane of the tumor cell, and persistent receptor activity will be detected as a result of HGF binding. There is also activation of the downstream pathways that is involved with the HGF-MET signal and leads to tumorigenesis (Nogueira & de Souza, 2021). Capmatinib has a central aromatic ring which is capable of interacting with the phenol group present in $MET^{Y1230}$ residue via a pi-stacking

interactions. Furthermore, there is formation of a salt bridge between $MET^{k1110}$ and $MET^{D1228}$ residues which contributes to the stabilize the interaction between Y1230 and capmatinib (Brazel et al., 2022; Wu et al., 2022). Capmatinib binds to ATP binding site found in MET and decreases HGF interaction with the receptor. This prevents dimerization of the MET receptor and in the catalytic domain there is no autophosphorylation of Y1235 and Y1234 tyrosine residues. Consequently, in MET's intracellular portion there will be blocking of autophosphorylation of the Y1349 and Y1356 which are found close to the COOH terminal. This will lead to blocking of MAPK, PI3K, STAT and NFκ-B pathways (Nogueira & de Souza, 2021). There will be no more tumour growth, survival and ultimately death of cells. (Figure 3)

#### 5.3.1.3 Advantages and Limitations

Major advantage of the drug is that it is capable of forming stable interaction with Y1230 which results in it causing a highly selective and potent blocking of the MET (Brazel et al., 2022). It had potency that is 30 times greater than that of crizotinib and five times greater than tepotinib as detected by biochemical vitro testing (Wu et al., 2022). Moreover, it is capable of altering the outcomes associated with the activation of MET in the EGFR pathways and HER2 pathways. Capmatinib also alters the resistance to EGFR inhibitor that is dependent on MET (Vansteenkiste et al., 2019). Based on the findings of the GEOMETRY mono-1 study, it was discovered that the ORR for patients who had never had treatment for NSCLC in the past was 68%, and the average DoR was 12.6 months. Whereas, existing treatment options for NSCLC with exon 14 skipping like combination of platinum based-chemotherapy drugs with PD-L1 inhibitor produced ORR of 48% to 58% and average DoR of 7.2 to 11.2 months (Mathieu et al., 2022). This showed that capmatinib is capable of producing substantial antitumor action (Wolf et al., 2020).

Limitation includes discontinuity in treatment with capmatinib due to ILD/pneumonitis, liver toxicity, peripheral edema, nausea and fatigue. From Ba/F3 cell line analysis and patient clinical reports, it was found alterations of METD1228 and METY1230 leads to resistance to the drug. Other prospective ways of acquiring resistance could be through KRAS and PIK3CA mutations and MET amplification (Brazel et al., 2022).

### 5.3.2 Tepotinib

Tepotinib is an approved drug to provide targeted therapy by specifically acting against the mutation MET exon 14 skipping found in NSCLC that has metastasized. The recommended method of administration for this agent is by mouth.

#### 5.3.2.1 Pharmacokinetics

$C_{max}$ and $AUC_{0\text{-}12h}$ increases in a proportional manner across the daily dosing limit of 27 to 450 mg (U.S. Food & Drug Administration, 2022). It takes an average value of 8 hours to reach $C_{max}$ and in the fed state, the absolute bioavailability is considered to be 71.6%. After having a high-fat meal, $AUC_{0\text{-}INF}$ is considered to be elevated by 1.6-fold and the $C_{max}$ is considered to be elevated by 2-fold. Moreover, the average volume of distribution is observed to be 1038 L and regardless of the drug levels in the body, protein binding of the drug occurs in the plasma and is found to be 98%. The $t_{1/2}$ is found to be 32 hours and a value of 23.8 L/h is observed for the apparent clearance of the drug. The biotransformation of tepotinib primarily occurs by CYP2C8 and CYP3A4 (Mathieu et al., 2022). Additionally, 13.6 % of the drug was excreted in urine and 85% was excreted in faeces when provided with a 450 mg of a radiolabeled dose via the oral route (U.S. Food & Drug Administration, 2022).

### 5.3.2.2 Mechanism of Action

This agent possesses the ability to form a U-shaped configuration in order to bind to MET. This utilized attachment to both activation loop and hinge residue of Y1230 to inhibit ATP binding to its site (Brazel et al., 2022). This will also inhibit activation sites in the intracellular domain and not allow phosphorylation of the tyrosine kinase of MET. Moreover, it will impair ligand HGF binding to MET and prevent the receptor's dimerization. The Y1234 and Y1235 residues located within kinase domain in the receptor will not be phosphorylated (Fujino et al., 2021). These in turn will inhibit the signaling via pathways involving JAK and STAT, and PI3K, Akt and mTOR and RAS, RAF, MEK and ERK (Puccini et al., 2019). Hence, there will be no tumour cell survival, no tumour cell growth or division and cell death will occur. (Figure 3)

### 5.3.2.3 Advantages and Limitations

It allows for selective inhibition of the receptor in NSCLC due to the hydrogen bonding with the drug's pyrimidine nitrogen and the MET1160 of hinge region and due strong CH-π interaction that occurs in between the pyrimidine of the drug and Tyr1159 residue (Schadt & Blaukat, 2017). According to the findings of the VISION trial, per IRC, the ORR for patients who were not previously treated for the disease was determined to be 46%, and the average PFS was 8.5 months (Dong et al., 2022). Whereas, existing treatment options for NSCLC with exon 14 skipping like chemotherapeutic drugs produced average ORR of 26.5% and average PFS of 4.5 months (Reuther et al., 2022). This showed that tepotinib is capable of producing substantial antitumor action for patients.

A limitation of the drug is that it is 5 times less potent compared to capmatinib. From in vitro results, it is observed that the drug shares majority of the MET alterations that induce resistance to capmatinib. This gives indication that the agent is not a viable option to

overcome the resistance associated with capmatinib (Wu et al., 2022). Additionally, discontinuity in treatment with the drug can occur due to severe pneumonitis, liver toxicity, edema, pleural effusion and dyspnea (Mathieu et al., 2022).

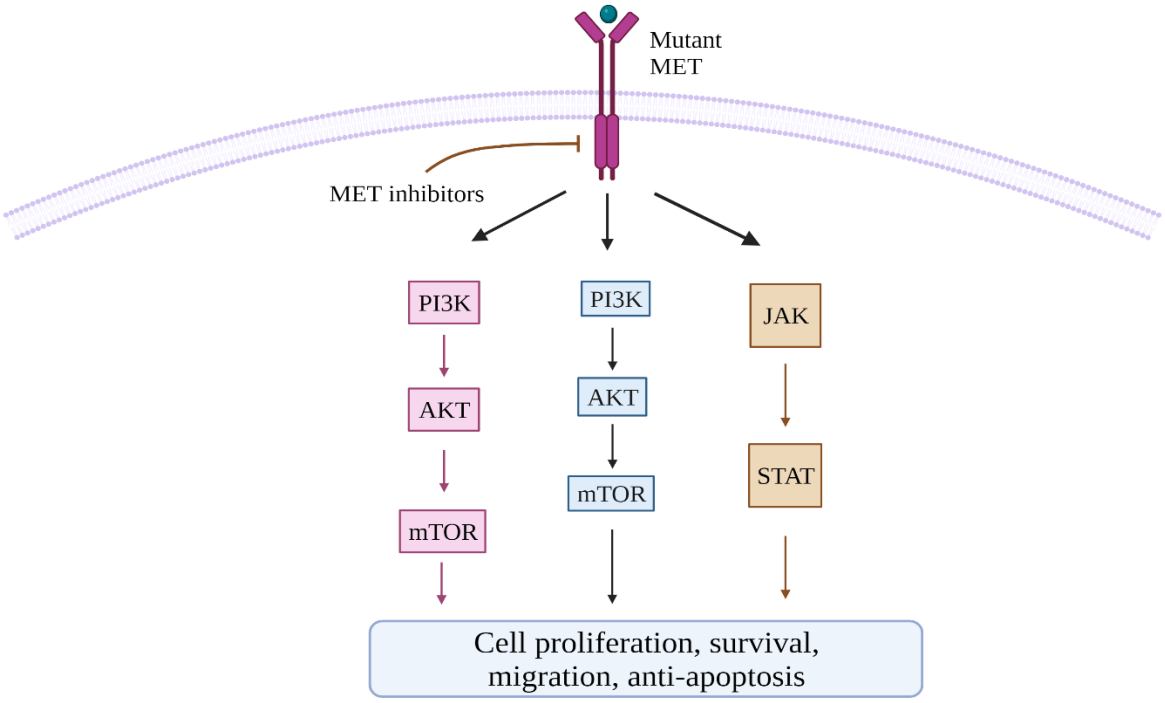



*Figure 3: Mechanism of Action of MET Inhibitors*

## 5.4 RET Inhibitors

### 5.4.1 Selpercatinib

It is the first drug that has been approved for locally advanced NSCLC and for NSCLC that has metastasized that has a RET gene rearrangement. It is to be administered via oral route.

#### 5.4.1.1 Pharmacokinetics

At steady state, $C_{max}$ and AUC for the drug will be elevated in a manner that is marginally more than dose proportionate across the daily dosing limit of 20 to 240 mg taken twice a day.

When the drug is given twice a day, steady state can be reached after approximately 7 days and the average value for $AUC_{0\text{-}24h}$ and $C_{max}$ can be found to be 52600 ng·h/mL and 2980 ng/mL respectively (Markham, 2020). Moreover, the accumulation ratio can be observed to be increased by 3.4-fold and it takes a mean value of 2 hours to reach $C_{max}$ at steady state. 73% of the administered drug gets absorbed and a value of 191 L is observed to be the $V_D$. There is high protein binding of the drug observed in the plasma at a value of 96% (U.S. Food & Drug Administration, 2020). In addition, the $t_{1/2}$ is found to be 32 hours and the apparent clearance has a value of 6L/h. The biotransformation of the drug majorly occurs by CYP3A4. 4% and 69% of the drug is excreted in urine and faeces respectively when provided with 160 mg of radiolabeled dose. Furthermore, when selpercatinib is concurrently given with many doses of itraconazole which is a potent CYP3A inhibitor then elevation in $C_{max}$ and $AUC_{0\text{-}INF}$ occurs by 30% and 133% respectively. Administering the drug with may doses of rifampin which is a potent CYP3A inducer results in a reduction of $C_{max}$ and $AUC_{0\text{-}INF}$ by 70% and 40% respectively (Markham, 2020).

### 5.4.1.2 Mechanism of Action

RET is a gene that has the potential to express a transmembrane tyrosine kinase receptor. This protein contains intracellular, transmembrane and extracellular domains (Cascetta et al., 2021). This drug is capable of blocking the non-mutated RET and many RET mutant variants. These include the KIF5B-RET, CCDC6, V804M, V804L and M918T. Moreover, VEGFR1, VEGFR3 and VEGFR2 are also inhibited by the drug although less inhibition is seen for VEGFR2. This agent is capable of blocking the mutant RET by not allowing the formation of homodimers. In turn, this inhibits tyrosine residues located in kinase unit of receptor from getting phosphorylated. Thus, pathway involving RAS, RAF, MEK and ERK, pathway involving JAK and STAT3, and pathway involving PI3K/AKT are all

downregulated. Consequently, there is inhibition of these signaling pathways (Nogueira & de Souza, 2021). This prevents tumour cell survival, production and growth. (Figure 4)

### 5.4.1.3 Advantages and Limitations

A major advantage of treatment with Selpercatinib is that it is more selective and efficacious than the multiple kinase inhibitors as it is not associated with potent blocking of the non-RET targets like VEGFR2. Consequently, it does not produce toxicities like proteinuria, hand-foot skin reaction and hypertension (Choudhury & Drilon, 2020). In comparison to MKI cabozantinib, which had a PFS of 3.6 months with patients who had prior chemotherapy, selpercatinib had PFS of 18.4 months (Choudhury & Drilon, 2020). This denotes it has positive and durable responses. This drug is capable of being active against the alteration of $RET^{V804M/L}$ which was associated with multiple kinase inhibitors (Wu et al., 2022).

A major limitation includes the $RET^{G810C/S}$ alterations, MET amplifications and KRAS amplifications that leads to resistance to the drug (Lin et al., 2020). Discontinuity of treatment with the agent can be observed when adverse events like hypertension, ILD/pneumonitis, liver dysfunction, severe bleeding and lengthy QT interval (U.S. Food & Drug Administration, 2020).

## 5.4.2 Pralsetinib

Pralsetinib is a drug approved for RET altered NSCLC that has metastasized. It is to be administered via the oral route as capsules.

### 5.4.2.1 Pharmacokinetics

$C_{max}$ and AUC elevation for the drug was erratic across the dosing limit of 60 to 600 mg. For this dosing limit, the average time to reach $C_{max}$ was 2 to 4 hours. When the drug is given once a day, the accumulation ratio is observed to be an estimated 2-fold. Moreover, achieving

steady state takes a time period of 3 to 5 days and the oral clearance was deduced to be 9.1 L/h (Markham, 2020). The average volume of distribution is 303 L and regardless of the drug levels in the body, plasma protein binding of it occurs and it is found to be 97.1% (U.S. Food & Drug Administration, 2020). Moreover, when an individual dose of the drug is administered, $t_{1/2}$ was found to be 14.7 hours and when many doses of the drug is given $t_{1/2}$ was found to be 22.2 hours. Biotransformation of the drug majorly occurred by CYP3A4 and minorly occurred by CYP2D6 and CYP1A2. 6% and 73% of the drug is excreted in urine and faeces respectively when provided with an individual dose of 310 mg of drug that has been radiolabeled. Additionally, when only 200 mg of drug is given as an individual dose concurrently with itraconazole which is a potent CYP3A inhibitor then elevation in $AUC_{0\text{-}INF}$ and $C_{max}$ occurs by 251% and 84% respectively. Administering the 400 mg drug as a single dose with rifampin which is a potent CYP3A inducer results in reduction of $AUC_{0\text{-}INF}$ and $C_{max}$ by 68% and 30% respectively (Markham, 2020).

### 5.4.2.2 Mechanism of Action

RET is a gene that has the potential to express a transmembrane tyrosine kinase receptor. This protein contains intracellular, transmembrane and extracellular domains (Cascetta et al., 2021). This drug is capable of blocking the non-mutated RET and many RET mutant variants. These include the KIF5B-RET, CCDC6-RET, V804M, V804L, M918T and V804E which has been recently determined. Moreover, VEGFR1, VEGFR3 and VEGFR2 are also inhibited by the drug although less inhibition is seen for VEGFR2. This agent is capable of blocking the mutant RET by not allowing the formation of homodimers. This blocking would not occur if the ligand GDNF interacts with the extracellular domain of the receptors. In turn, this inhibits tyrosine residues located in kinase domain of receptor from getting phosphorylated. Thus, pathway involving RAS, RAF, MEK and ERK, pathway involving

JAK and STAT3, and pathway involving PI3K/AKT are all downregulated (Nogueira & de Souza, 2021). This prevents tumour cell survival, production and growth. (Figure 4)

### 5.4.2.3 Advantages and Limitations

A major advantage of treatment with pralsetinib is that it is more selective and efficacious than the multiple kinase inhibitors as it is not associated with potent blocking of the non-RET targets like VEGFR2. Consequently, it does not produce toxicities like proteinuria, hand-foot skin reaction and hypertension (Choudhury & Drilon, 2020). In comparison to MKI cabozantinib which had a PFS of 5.5months with patients who had prior chemotherapy, pralsetinib had PFS of 16.5 months (Choudhury & Drilon, 2020; Griesinger et al., 2022). This signifies it had positive and durable responses. The agent is also capable of being active against the alteration of $RET^{V804M/L}$ which was associated with multiple kinase inhibitors (Wu et al., 2022). Moreover, the chances of prolonged QT interval warning that comes with selpercatinib is not present for pralsetinib (U.S. Food & Drug Administration, 2020).

A major limitation includes the $RET^{G810C/S}$ alterations, MET amplifications and KRAS amplifications that leads to resistance to the drug (Lin et al., 2020). Discontinuity of treatment with the agent can be observed when adverse events like hypertension, ILD/pneumonitis, liver dysfunction and severe bleeding (U.S. Food & Drug Administration, 2020).

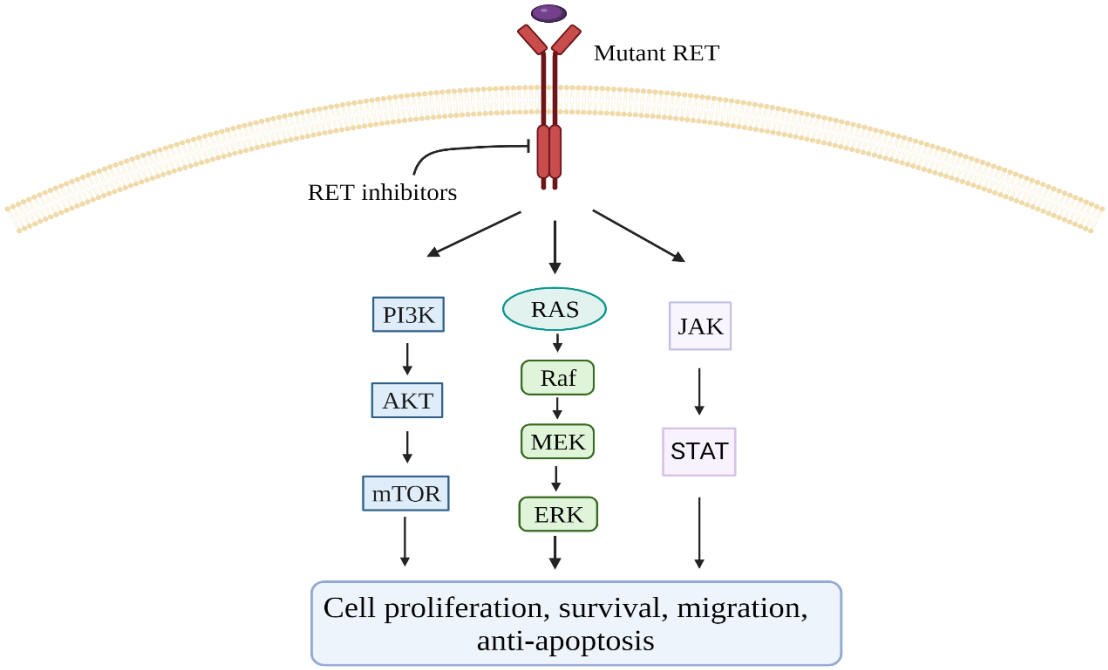



*Figure 4: Mechanism of Action of RET Inhibitors*

## 5.5 DNA Alkylating Agent

### 5.5.1 Lurbinectedin

This is a drug that is approved for individuals with SCLC that has spread to distant sites in the body. It is to be used as second line option and is given as infusion intravenously (Patel et al., 2021).

#### 5.5.1.1 Pharmacokinetics

The dose approved for the drug is 3.2 $mg/m^2$ and no accumulation was observed after treatment was done every three weeks. The values of 551 µg·h/L and 107 µg/L were deduced for the geometric means of $AUC_{0\text{-}inf}$ and $C_{max}$ respectively. At steady state, lurbinectedin is found to have a $V_D$ of 504 L (Markham, 2020). Albumin and alpha-1-acid glycoprotein accounts for roughly 99% of the protein binding of the drug (U.S. Food & Drug

Administration, 2020). In addition, $t_{1/2}$ is found to be 51 hours and the total clearance has a value of 11L/h. From in vitro studies, it has been determined that the drug is predominantly biotransformed by CYP3A4. 6% and 89% of the drug is excreted in urine and faeces respectively when provided with a single radiolabeled dose of the drug. Additionally, clearance was reduced by 30% when lurbinectedin was concurrently given with CYP3A4 inhibitors according to a population pharmacokinetic research (Markham, 2020).

### 5.5.1.2 Mechanism of Action

There is formation of adducts that is capable of creating breaks in both strands of DNA. This occurs when lurbinectedin attaches to the guanine residues that are located within the minor groove of DNA (Patel et al., 2021). There is stabilization of the breaks that takes place when nucleotides on the complementary strands interact through van der Waals forces and a minimum of one hydrogen bond. This elicits a series of events that causes advancement through the S phase to be delayed and hence cell cycle progression will be stopped in G2/M phase leading to cell death. Moreover, CG- rich sequences are found in the promoter sites of genes coding for proteins. The drug will block the transcription process for RNA by specifically binding to these sequences and also prevent phosphorylation of the RNA polymerase II which leads to their degradation. Furthermore, XPF endonucleases will create an assembly of double stranded breaks in DNA which will ultimately lead to tumour cell destruction and death. This drug can also contribute to segregating ASCL1, NFIB and NeuroD1 from their promoters and blocks the creation of CCL2, IL-6, CXCL8 and VEGF. In this way, this agent is able to reduce the functioning ability of the MPS like TAMs which results in the tumour cells not being provided with their inflammatory microenvironment and ultimately inhibit tumorigenesis (Nogueira & de Souza, 2021). (Figure 5)

#### 5.5.1.3 Advantages and Limitations

A major advantage of lurbinectedin is that it can be used in treatment of platinum-resistant SCLC and platinum-sensitive SCLC. However, the only approved drug as second line option for over two decades was topotecan which was only valuable for platinum sensitive SCLC (S. Singh et al., 2021). Lurbinectedin is considered to be more effective and associated with less toxicity compared to topotecan (Patel et al., 2021). Reports from a phase II trial deduced that lurbinectedin has a value of 9.3 months for OS, 3.5 months for PFS and 35.2% for ORR. Whereas, with topotecan, OS was 7.8 months, PFS was 4.2 months and ORR was 16.9% (Toublanc et al., 2022). Additionally, with lurbinectedin repeated administration was not required. It could be infused once every 21 days. However, with topotecan frequent administration was required like 5 subsequent days of infusion in one 21-day cycle (Singh et al., 2020).

Limitation includes discontinuation of the drug due to severe bone marrow suppression, liver dysfunction, extravasation that leads to tissue death and rhabdomyolysis (U.S. Food & Drug Administration, 2020).

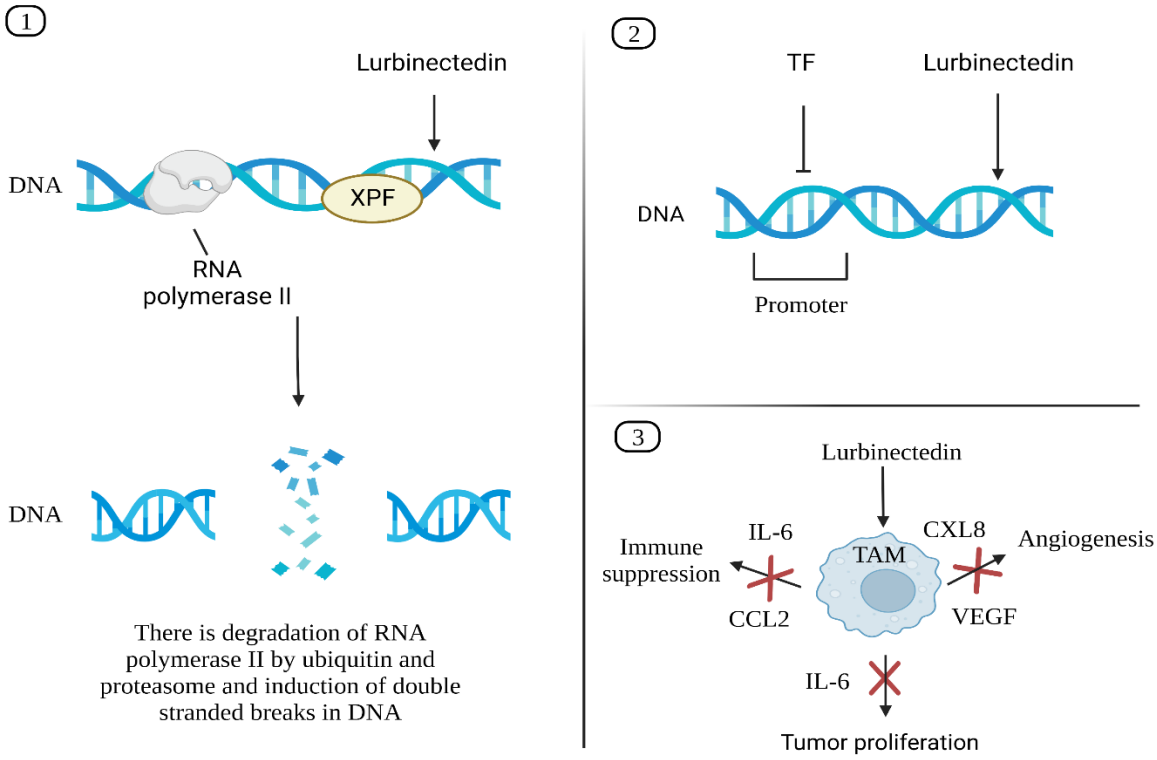



*Figure 5: Mechanism of Action of DNA Alkylating Agent*

## 5.6 ALK Inhibitors

### 5.6.1 Brigatinib

It is a third-generation drug approved for ALK-positive NSCLC that has metastasized. It is administered via the oral route as tablets.

#### 5.6.1.1 Pharmacokinetics

For the doses of 90 and 180 mg, drug's $C_{max}$ can be found to 552 and 1452 ng/mL respectively. $AUC_{0\text{-}Tau}$ was found to be 8165 and 20276 ng·h/mL for the same dose limits. Across the daily dosing range of 60 to 240 mg, brigatinib's systemic exposure was found to increase proportionately with the dose. The accumulation ratio had an average value of 1.9 to 2.4 after administration of multiple doses (Spencer et al., 2019). Moreover, when an

individual dose of the drug is administered, $t_{max}$ was found to be within 1 and 4 hours. 66% of protein binding for the drug is observed in the plasma and the average value for $V_D$ at steady state is deduced to be 153 L. The biotransformation of the drug majorly occurred by CYP3A4 and CYP2C8. On average, the drug had a value of 12.7 L/h for clearance and a value of 25 hours for $t_{1/2}$ during steady state. 25% and 65% of the drug is excreted in urine and faeces respectively when provided with a single dose of approximately 180 mg of radiolabeled dose (Markham, 2017). Additionally, when only a single dose of 90 mg drug is concurrently given with two times a day regimen of 200 mg itraconazole which is a potent CYP3A inhibitor then elevation in $AUC_{0\text{-}INF}$ and $C_{max}$ occurs by 101% and 21% respectively. Administering the 180 mg drug as a single dose with two times a day regimen of 600 mg rifampin which causes potent induction of CYP3A results in reduction of $AUC_{0\text{-}INF}$ and $C_{max}$ by 80% and 60% respectively (Spencer et al., 2019).

### 5.6.1.2 Mechanism of Action

This tyrosine kinase inhibitor is capable of blocking IGF-1R, ROS1, FLT-3, EGFR along with its approved site of ALK (Markham, 2017). Brigatinib utilizes a U-shaped ligand structure to interact with ALK via its ATP binding site. There is a pyrimidine core in the drug that is capable of being bound to the ALK's adenosine region. The methoxy group of drug attaches to the hinge region of ALK. There will be interaction of the dimethylphosphine oxide aniline of the drug and the DFG regions found in ALK. It also prevents interaction of phosphate group to ALK (Spencer et al., 2019). Consequently, there is inhibition of phosphorylation of the signaling proteins. These include ERK1/2, STAT3 and AKT. Ultimately, there will be no tumour cell growth and division, no metastasis, no cell movement and cell death will occur (Markham, 2017). (Figure 6)

### 5.6.1.3 Advantages and Limitations

A major advantage of brigatinib is that it can provide potent and selective inhibition of ALK due to presence of a structural characteristic of phosphine oxide that is distinguishing for it (Spencer et al., 2019). It is able to show activity against the ALK alterations of C1156Y, V1180L, L1196M, L1152R/P, I1171S/T and many more. However, these mutations are linked to the development of resistance to ALK inhibitors of prior generations. When the cancer progresses owing to resistance to crizotinib, brigatinib is very effective at preventing the development of brain metastases (Ali et al., 2019). Moreover, from ALTA-1L phase 3 study, it is reported that the drug is associated with higher 3-year PFS (43%) than crizotinib (19%) (Camidge et al., 2021). According to ALTA trial findings, this drug was associated with a PFS that was 9 to 10 months longer than crizotinib. Additionally, the average PFS for Brigatinib was 7 to 8 months longer than alectinib (Reckamp et al., 2018). This agent is also less prone to having resistance ALK alterations and it is considered to have a reasonable safety profile (Ali et al., 2019).

Limitations

Brigatinib discontinuation can occur due to severe ILD/pneumonitis, extreme slow heart rate, severe hypertension, severe visual impairment and hyperglycemia (Spencer et al., 2019). There is probability of resistance to the drug occurring due to ALK alterations of E1210K, S1206Y/C, D1203N and G1202R (Wu et al., 2022).

## 5.6.2 Lorlatinib

It is a third-generation agent that is approved for $ALK^+$ NSCLC that has metastasized. It is to be administered via oral route as tablets.

### 5.6.2.1 Pharmacokinetics

Within the daily dosing limit of 10 to 200 mg taken once a day, $C_{max}$ and AUC for the drug will be elevated in a manner that is dose proportionate and marginally lower than dose proportionate respectively. This is observed at steady state. Moreover, $t_{max}$ has a value of 1.2 hours after administration of an individual 100 mg dose and has a value of 2 hours when the individual 100 mg drug dose is given every day. As opposed to an intravenous dose, the average value of 81% is observed for absolute bioavailability when the drug is given via the oral route. 66% of protein binding for the drug is observed in the plasma and the average value for $V_D$ at steady state is deduced to be 305 L. The biotransformation of the drug majorly occurred by UGT1A4 and CYP3A4. The value for $t_{1/2}$ was found to be 24 hours and the value for clearance elevated from 11 to 18 L/h at steady state. 48% and 41% of the drug is excreted in urine and faeces respectively when provided with an individual dose of approximately 100 mg of radiolabeled drug (Syed, 2019). Furthermore, when an individual 100 mg of the drug is concurrently given with itraconazole which is a potent CYP3A inhibitor then elevation in $C_{max}$ and $AUC_{0\text{-}INF}$ occurs by 24% and 42% respectively. Administering the drug on day 8 with once a day 600 mg dose of rifampin which is a potent CYP3A inducer following an 8-day regimen results in reduction of $C_{max}$ and $AUC_{0\text{-}INF}$ by 76% and 85% respectively (U.S. Food & Drug Administration, 2018).

### 5.6.2.2 Mechanism of Action

ALK constitutes of the extracellular, transmembrane and intracellular units. An individual peptide can be found in the amino-terminal which precedes the extracellular unit and the intracellular unit is found at the carboxyl-terminal (Brenner & Gunnes, 2021). Aberrations of the ALK is found in many tumour cells which predominantly include combination of ALK gene with other genes like EML4 to form EML4-ALK fusion which activates several

pathways leading to tumorigenesis. The kinase unit has C-terminal and N-terminal lobes between which the crevice of the hinge site can be found. ATP binding pocket is located within this region. This drug will compete with ATP to occupy the pocket (Brenner & Gunnes, 2021; Yang & Gong, 2019). The macrocycle structure of the drug consists of the aminopyridine component and the hinge site has Glu1197 and Met1199 residues. Hydrogen bonding occurs between these components (Liang et al., 2021). This does not allow Y1282, Y1283 and Y1278 residues found within the kinase unit to be phosphorylated. Consequently, there is no activation of the signaling pathways which are mediated by ALK. These include pathway associated with RAS, RAF, MEK and ERK, pathway associated with JAK and STAT, and pathway associated with PI3K, AKT and mTOR pathway (Brenner & Gunnes, 2021). Thus, there will be no tumour cell survival, no tumour cell growth and division, no metastasis, no cell movement and cell death will occur. (Figure 6)

### 5.6.2.3 Advantages and Limitations

As the drug is able to target the leucine at position 1198 of the kinase unit, it is considered a more powerful and selective inhibitor. This residue is only found in 26% of kinases. Lorlatinib provides superior PFS benefit compared to crizotinib and ceritinib and prolonged PFS compared to brigatinib (Ma et al., 2021; Yu et al., 2022). However, no significant differences in PFS exist compared to alectinib. Given its potent capacity to cross the BBB, it is regarded as superior to earlier generations of ALK inhibitors in terms of treating secondary brain tumors (Basit et al., 2017; Ye et al., 2021)). Moreover, it has activity against the known ALK resistant alterations particularly the common G1202R alterations associated with both the first- and second-generation drugs (Wu et al., 2022).

Limitation includes compound mutations that result in resistance to the drug. These alterations include the C1156Y+L1198F, I1171N+L1256F, I1171N+L1198F and G1202R+L1196M (Mizuta et al., 2021). This medication is linked to greater incidence of

severe adverse outcomes after ceritinib (Peng et al., 2021). These include hypercholesterolemia, peripheral neuropathy, CNS effects hypertension, weight gain, hypertriglyceridemia, edema, and gastrointestinal effects (Bauer et al., 2019). Consequently, they can result in treatment discontinuation.

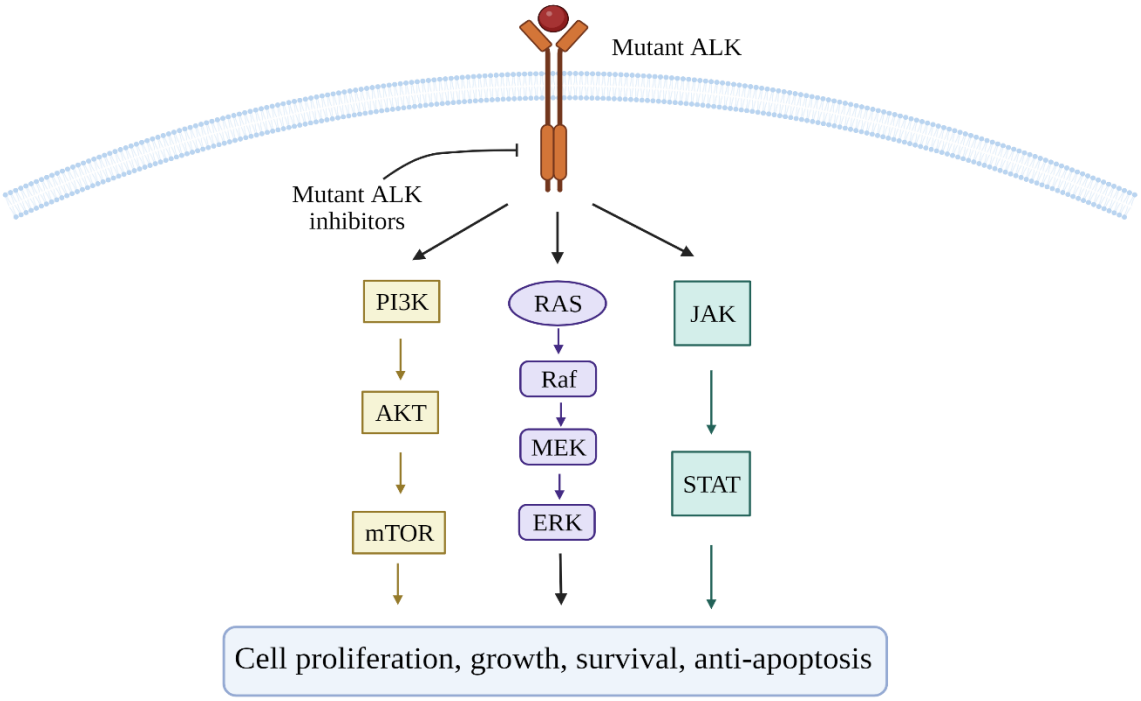



*Figure 6: Mechanism of Action of ALK Inhibitors*

## 5.7 EGFR Inhibitors Targeting Exon 19 Deletion or Exon 21 Substitution

### 5.7.1 Dacomitinib

It is a second-generation drug that has been approved for the treatment of NSCLC that has spread to other parts of the body and has deletion of exon 19 or substitution in exon 21 of L858R in EGFR. It is administered via the oral route as tablets.

### 5.7.1.1 Pharmacokinetics

Linear pharmacokinetics are observed for this agent across the daily dosing limit of 2 to 60 mg taken once a day. Within this daily dosing limit $C_{max}$ and AUC for the drug will be elevated in a manner that is dose proportionate at steady state. Over the span of 14 days, the drug's concentration will reach steady state levels and the average accumulation ratio will have a value of 5.7. Moreover, $t_{max}$ has a value of 6 hours after administration of an individual 45 mg dose. The average value of 80% is observed for absolute bioavailability when the drug is given via the oral route. 99% of protein binding for the drug is observed in the plasma and the average value for $V_D$ at steady state is deduced to be 1889 L. This large value denotes that there is substantial penetration of the drug into the body tissues. The biotransformation of dacomitinib occurs via oxidation process and the glutathione conjugation process. *O*-desmethyl dacominitib which the active metabolite of the drug was formed predominantly by the action of CYP2D6. The value for $t_{1/2}$ was found to be 70 hours and 24.9 L/h was observed for the clearance. 79% and 3% of the drug is excreted in faeces and urine respectively when provided with an approximate 45 mg individual dose of radiolabeled drug (Shirley, 2018). Furthermore, when an individual 45 mg of the drug is concurrently given with many doses rabeprazole which is a PPI then reduction in $C_{max}$ and $AUC_{0\text{-}96h}$ occurs by 51% and 39% respectively. Giving an individual dose of 45 mg of the drug with dextromethorphan which is a CYP2D6 substrate results in elevation of $C_{max}$ and $AUC_{last}$ by 9.7-fold and 9.6-fold respectively (U.S. Food & Drug Administration, 2018).

### 5.7.1.2 Mechanism of Action

EGFR contains extracellular, transmembrane and the intracellular units (Patel et al., 2019). Their activation can be achieved through ligand binding and the subsequent homodimerization and heterodimerization of these receptors which can result in

autophosphorylation of the intracellular domain. Moreover, mutations can result in autophosphorylation of the tyrosine kinase domain (Brzezniak et al., 2013). All these can activate signaling pathways that result in tumour cell growth, expansion and survival. It is possible for dacomitinib to inhibit the EGFR, as well as HER2 and HER4, respectively. However, in comparison to the other receptors, it possesses a significantly higher capacity for inhibiting the activity of mutant EGFR. It inhibits cellular signaling through all the homodimers and heterodimers of the ErbB family (Shah & Lester, 2020). There is presence of Cys797 near the binding pocket of ATP in the receptor. Through a Michael addition process, this agent has the potential to create a covalent bond with the Cys797 (Ayati et al., 2020; H. M. Patel et al., 2019). This provides strong irreversible binding affinity for the ATP binding site. This prevents ATP binding and makes the kinase inactive. In turn, there will be no phosphorylation of the kinase unit and hence, the pathway associated with RAS, RAF, MEK and ERK, pathway associated PI3K and AKT, and pathway associated with JAK and STAT will not be activated (Bergonzini et al., 2020; H. M. Patel et al., 2019). Thus, there will be no tumour cell survival, no tumour cell growth and division, and no angiogenesis. (Figure 7)

#### 5.7.1.3 Advantages and Limitations

A major advantage compared to the first-generation agent gefitinib is that dacomitinib produced greater potent blocking of EGFR which contributed to its enhanced efficacy. According to the findings of phase III study reports, average values for PFS and OS were 14.2 and 34.1 months with this drug whereas with gefitinib, the average values of 9.2 and 26.8 months respectively were observed. This demonstrated that dacomitinib performed significantly better in extending PFS and OS than the older agent (Karachaliou et al., 2019).

Comparable values for average PFS and OS were achieved when the drug does was reduced due to adverse effects and the initial dose of drug used during preliminary treatment. The

values were 16.6 and 36.7 months for average PFS and OS respectively are observed for patients taking reduced doses. Hence, modifying dose is helpful to prevent adverse events and maintain effectiveness rather than permanently discontinuing the drug (Corral et al., 2019).

A limitation of the agent includes higher toxicity compared to the first-generation agents due to its irreversible mode of action which creates a lasting effect even on normal body cells (Bergonzini et al., 2020). Adverse events that occur more frequently with the use of this agent is dermatitis acneiform, diarrhea, stomatitis and paronychia (X. Wang et al., 2022). These can result in treatment discontinuation along with ILD (Shah & Lester, 2020). From preclinical reports, it is deduced that resistance to the drug is associated with secondary alterations of T790M or C797S (Kobayashi et al., 2018). Moreover, it does not have any efficacy for alteration of exon 20 insertion in EGFR (Wang et al., 2022).

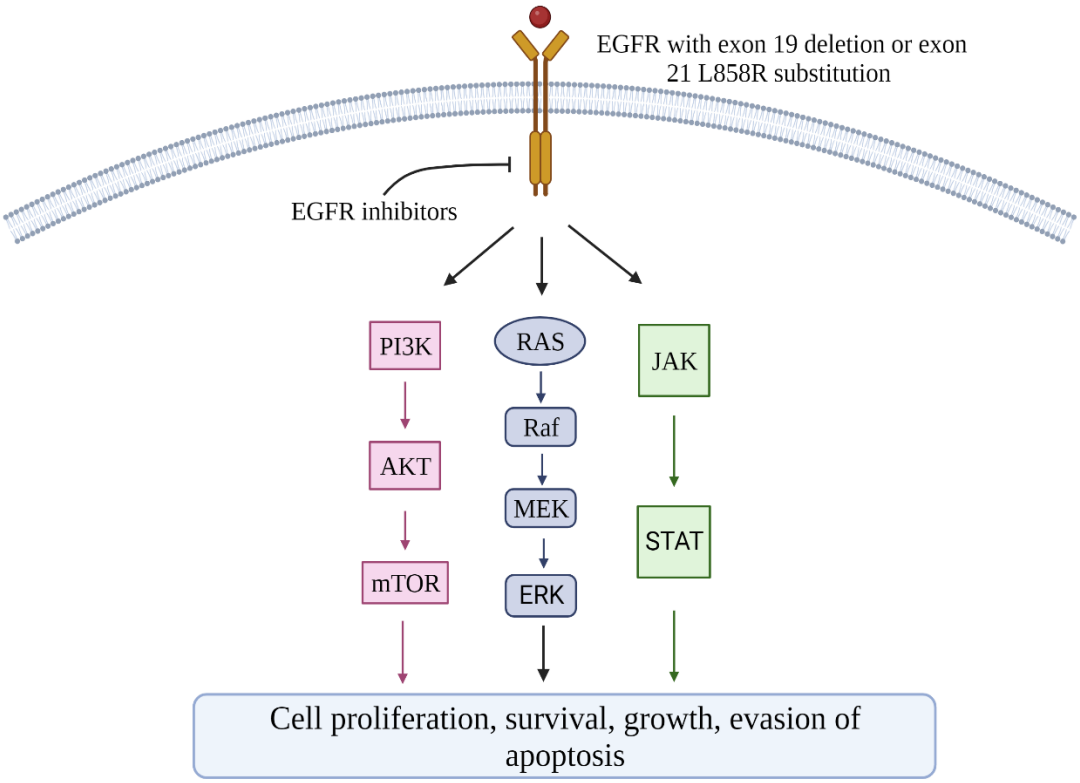



*Figure 7: Mechanism of Action of EGFR Inhibitors Targeting Exon 19 Deletion or Exon 21 Substitution*

## 5.8 ROS1 Inhibitor

### 5.8.1 Entrectinib

This drug is approved for $ROS1^{+}$ NSCLC that has metastasized. It is administered via the oral route as capsules.

#### 5.8.1.1 Pharmacokinetics

It shows linear, time and dose-independent pharmacokinetics. Over the span of one week with daily intake of the drug, the drug's concentration will reach steady state levels. $T_{max}$ has a value of 4 to 6 hours after administration of an individual 600 mg dose. 99% of protein binding for the drug is observed in the plasma and the approximate value for $V_D$ is deduced to

be 551 L. The biotransformation of dacomitinib occurs predominantly via CYP3A4 and the primary active metabolite is M5. The value for $t_{1/2}$ was found to be 20 hours and the value for clearance was 19.6 L/h (Frampton, 2021). 3% and 83% of the drug is excreted in urine and faeces respectively when provided with an individual oral dose. Furthermore, when an individual 100 mg of the drug is concurrently given with itraconazole which is a potent CYP3A inhibitor then elevation in $C_{max}$ and $AUC_{0\text{-}INF}$ occurs by 1.7 times and 6 times respectively. Administering a 600 mg dose of the drug with rifampin which is a potent CYP3A inducer results in a decrease of $C_{max}$ and $AUC_{0\text{-}INF}$ by 56% and 77% respectively (U. S. Food & Drug Administration, 2019).

### 5.8.1.2 Mechanism of Action

ROS1 protein is associated with an extracellular, transmembrane and the intracellular units (Araujo et al., 2021). The ROS1 rearrangements that are associated with NSCLC are the CD74-ROS1 which is the most frequent, EZR-ROS1, SLC34A2-ROS1 and the SDC4-ROS1. These ROS1 fusions are the real oncogenic drivers and they allow for catalytic action without ligand binding. There will be interaction between entrectinib and the DGF-in configuration of the kinase unit of the receptor. This inactivates ROS1 and there is no autophosphorylation of tyrosine residues like Y2114, Y2274, Y1923, Y2110, Y2115 and Y2334. As a result, pathway associated with RAS, RAF, MEK and ERK, pathway involving PI3K, AKT and mTOR and pathway involving JAK and STAT3 are not activated. Ultimately no tumour cell survival, no tumour cell growth and division take place (Drilon et al., 2020). (Figure 8)

### 5.8.1.3 Advantages and Limitations

A major advantage of entrectinib over the first approved ROS1 inhibitor crizotinib is that it is 30 times more potent. Because it is a poor target for P-glycoprotein, this pump will not cause efflux of the drug (Wu et al., 2022). Consequently, it is able to achieve greater CNS

concentration and effective in treating brain metastases (Chawla et al., 2021; Wu et al., 2022). It is well tolerated and has a toxicity profile that is manageable as rate of discontinuation of drug owing to adverse events was low (Sartore-Bianchi et al., 2020).

A prevalent limitation of this drug is that it does not have any activity towards the resistance imparting alterations of L2026M, G2032R, and D2033N associated with crizotinib that results in disease to progress. Resistance to entrectinib also occur due to F2004C/I and G2032R substitutions (García-Pardo & Calles, 2021). The frequent adverse reactions associated with this drug includes edema, dysgeusia, dyspnea, thinking impairment, weight gain, vision impairment, arthralgia and many more. Treatment discontinuation can occur due to elongation of QT interval, congestive heart failure, CNS effects and liver dysfunction (U. S. Food & Drug Administration, 2019).

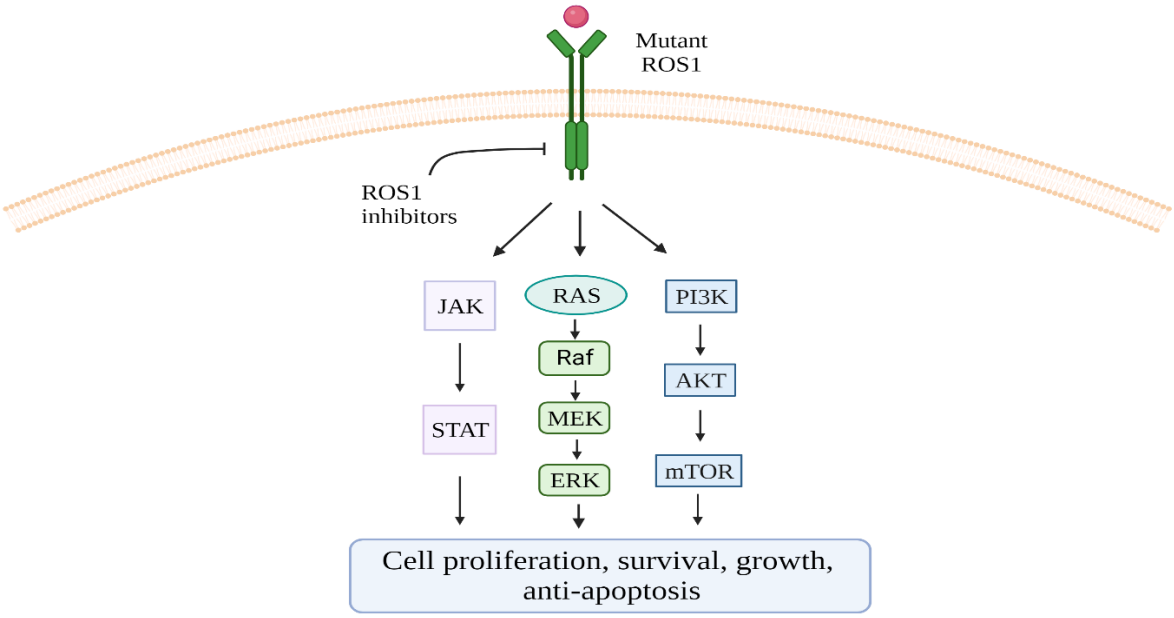



*Figure 8: Mechanism of Action of ROS1 Inhibitors*

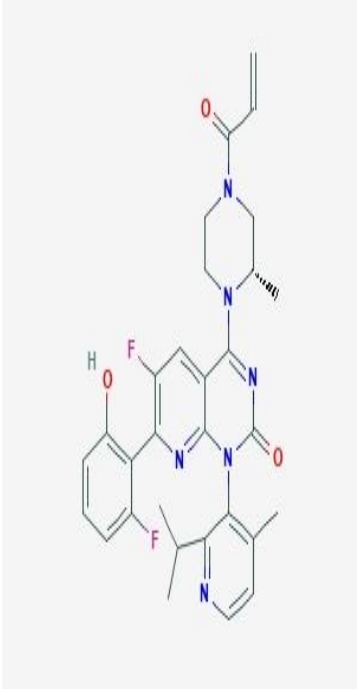
*Table 2: List of Emerging Drugs with the Type of Lung Cancer Treated and their Mechanism of Action*

| **Name of drug** | **Type of lung cancer treated** | **Mechanism of action** | **Reference** |
|---|---|---|---|
| Sotorasib | NSCLC that is locally advanced or has metastasized | Interacts with inactive GDP bound KRAS Locks the receptor in inactive state. Suppresses the RALGDS-RalA/B pathway, pathway involving Raf-MEK-ERK, and pathway associated with PI3K, AKT, and mTOR. | (Corral de la Fuente et al., 2022) (Zhang & Nagasaka, 2021) |
| Adagrasib | NSCLC that is locally | Binds with the P2 pocket. Permanently lock the GDP bound KRAS in its | (Corral de la Fuente et al., |

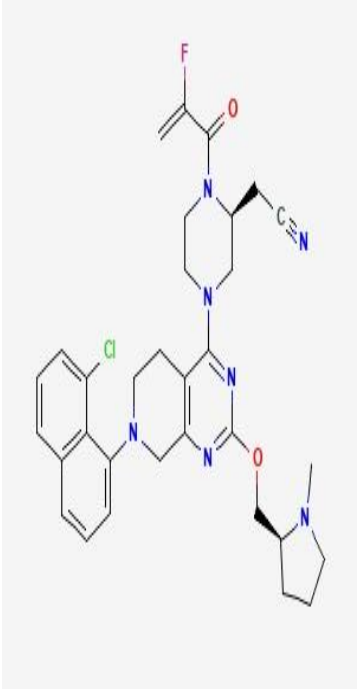
| | | | |
|---|---|---|---|
| | advanced or has metastasized | inactivated state. This in turn suppresses the RALGDS-RalA/B pathway, pathway associated with RAF, MEK and ERK pathway and pathway involved with PI3K/AKT/mTOR. | 2022)<br>(Mann, 2023) |
| Amivantamab | NSCLC that is locally advanced or has metastasized | Prevents attachment of the ligands to EGFR and to MET. No activation of pathway involving PI3K and AKT and pathway involving RAS, RAF, MEK and ERK. Internalization occurs then complex moves to lysosomes and degrades. There is activation of the immune cells that will then perform actions like ADCC, ADCP, ADCR and ADCT. | (Cho et al., 2022)<br>(Vyse & Huang, 2022) |
| Mobocertinib | NSCLC that is locally advanced or has metastasized | Irreversibly interacts with the binding pocket of ATP in mutant EGFR. No activation of Ras-Raf-MEK-ERK pathway and PI3K/AKT/mTOR pathway. | (Wang et al., 2022) |
| Capmatinib | Metastatic NSCLC | Blocks interaction of ATP and its binding pocket. Decreases HGF and MET attachment. Inhibition of the signaling via MAPK, PI3K, STAT and NFκ-B pathways. | (Nogueira & de Souza, 2021) |

| | | | |
|---|---|---|---|
| Tepotinib | Metastatic NSCLC | Competes with ATP for the binding site of MET. Inhibits HGF and MET attachment. Inhibition of the signaling via pathway involved with Ras, Raf, MEK and ERK, pathway associated with JAK and STAT3 and pathway involved with PI3K, Akt, and mTOR. | (Brazel et al., 2022) (Fujino et al., 2021) (Puccini et al., 2019) |
| Selpercatinib | NSCLC that is locally advanced or has metastasized | ATP-competitive blocking of mutant RET. Blocking of pathway involved with RAS, RAF, MEK and ERK, pathway associated with PI3K and AKT and pathway associated with JAK and STAT3. | (Nogueira & de Souza, 2021). |
| Pralsetinib | Metastatic NSCLC | Competes with ATP for binding site in mutant RET. Blocking of pathway involved with RAS, RAF, MEK and ERK, pathway associated with PI3K and AKT and pathway associated with JAK and STAT3. | (Nogueira & de Souza, 2021). |
| Lurbinectedin | Metastatic SCLC | Interacts with CG-rich segments which are located nearby promoters. There is permanent blocking of RNA Pol II elongation. Their particular degradation occurs by ubiquitin/proteasome. Double stranded breaks occur in DNA and ultimately tumour cell death occur. | (Nuñez et al., 2016) |

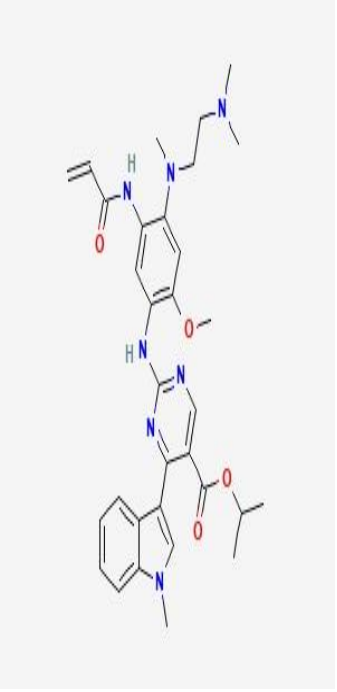
| | | | |
|---|---|---|---|
| Brigatinib | Metastatic NSCLC | Blocks ATP binding site in ALK. Prevents interaction of phosphate group to ALK. No phosphorylation of signaling proteins like ERK1/2, STAT3 and AKT. | (Spencer et al., 2019) (Markham, 2017). |
| Lorlatinib | Metastatic NSCLC | Competitively blocks ATP binding site of ALK tyrosine domain. Pathway involved with RAS, RAF, MEK and ERK, pathway associated with PI3K and AKT and pathway associated with JAK and STAT3 not activated. | (Brenner & Gunnes, 2021) (Yang & Gong, 2019) (S. Liang et al., 2021) |
| Dacomitinib | Metastatic NSCLC | Bond forms with cys797 near ATP binding pocket. Inhibit mutant EGFR. Pathway involved with RAS, RAF, MEK and ERK, pathway associated with PI3K and AKT and pathway associated with JAK and STAT3 not activated. | (Shah & Lester, 2020) (Ayati et al., 2020) (Bergonzini et al., 2020) |
| Entrectenib | Metastatic NSCLC | Inactivation of ROS1. Pathway involved with RAS, RAF, MEK and ERK, pathway associated with PI3K and AKT and pathway associated with JAK and STAT3 not activated. | (Drilon et al., 2020) |



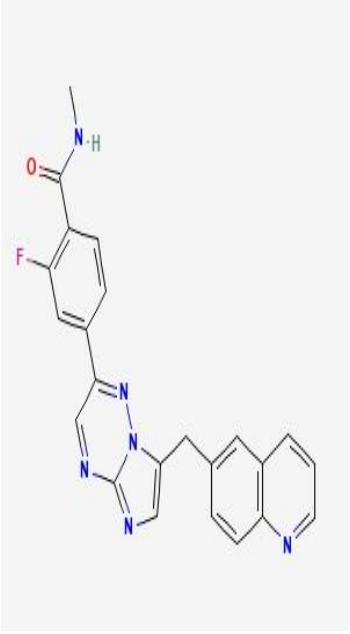
Sotorasib



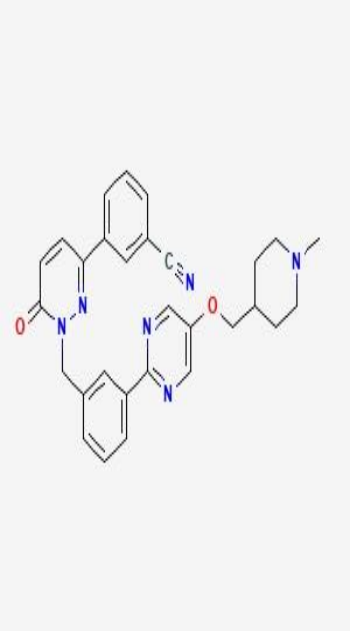
Adagrasib



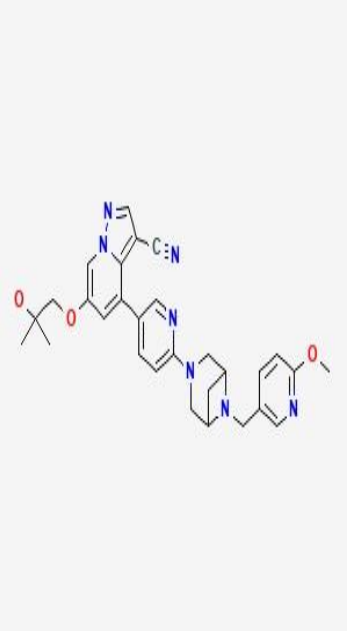
Mobocertinib



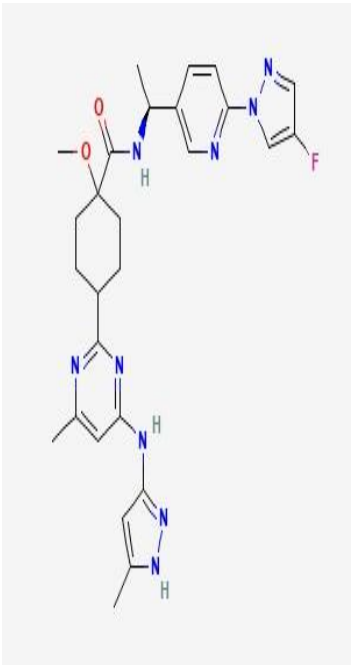
Capmatinib



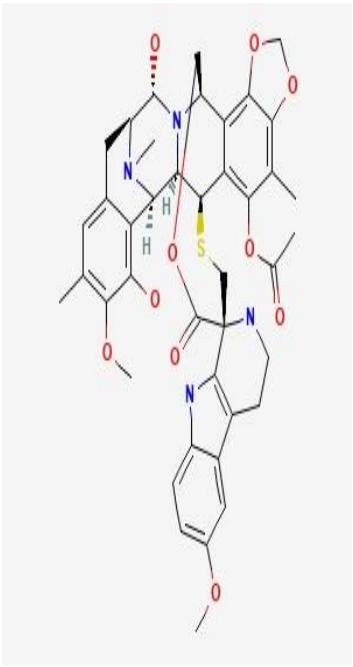
Tepotinib



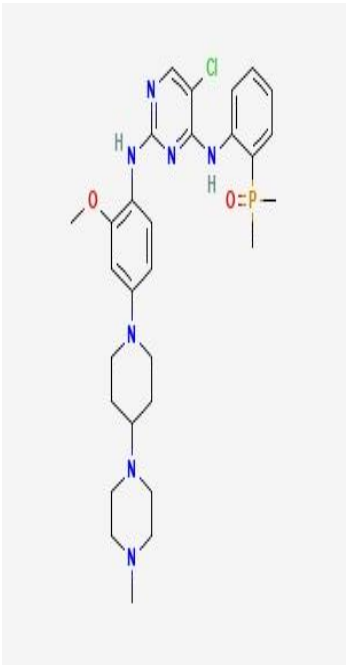
Selpercatinib



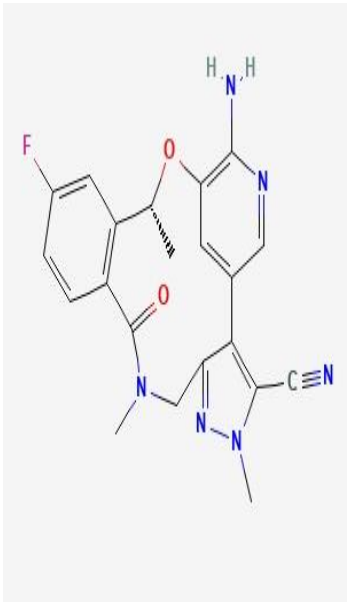
Pralsetinib



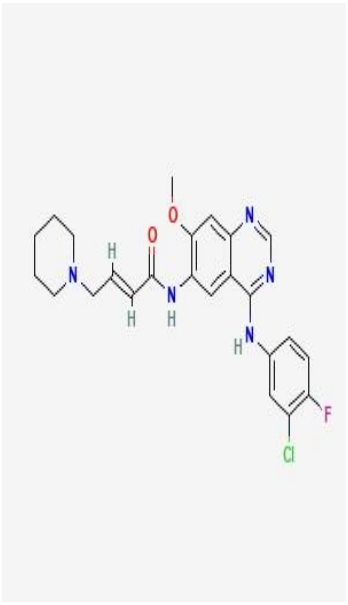
Lurbinectedin



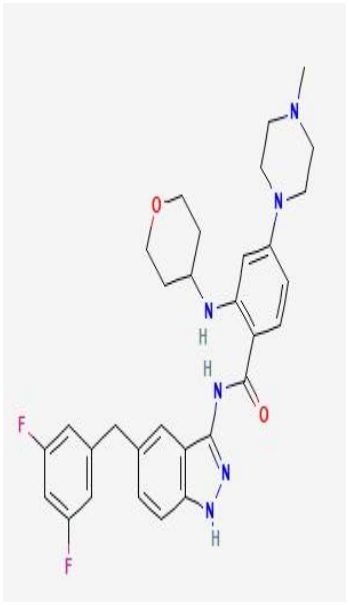
Brigatinib



Lorlatinib



Dacomitinib



Entrectinib

*Figure 9: Chemical Structures of Emerging Drugs (Adapted from National Center for Biotechnology Information, 2023)*

# Chapter 6

# Combination Drugs for Lung Cancer Treatment

## 6.1 BRAF Inhibitor with MEK Inhibitor

### 6.1.1 Overview

This combination includes Dabrafenib which is a BRAF inhibitor with Trametinib which is a MEK inhibitor. It is recommended for individuals with NSCLC that has spread to distant body parts and where tumors have an alteration of V600E in BRAF gene (Khunger et al., 2018).

Significant improvement in efficacy is observed for this combination compared to dabrafenib monotherapy as its activity is limited. Results from BRF113928 trial deduced that the drug combination had an average value of 9.7 and 18.2 months for PFS and OS respectively for patients who received prior treatment. Whereas, for the individuals who received only dabrafenib monotherapy, average values of 5.5 and 12.7 months for PFS and OS respectively were observed. Average PFS and OS values in patients who had not been treated before were 10.9 and 24.6, respectively. Moreover, the acquired resistance to dabrafenib is associated with MAPK pathway reactivation. When trametinib is added to therapy then it is able to hinder the emergence of resistance to dabrafenib by inhibiting the ERK signaling (Sforza et al., 2022).

Several adverse events that occur frequently associated with this combination of drugs include the pyrexia, rash, chills, dry skin, edema, dyspnea and many more. Adverse events that can lead to treatment discontinuation include cutaneous events, severe pyrexia, hemorrhage, uveitis and reduced left ventricular ejection fraction (Chalmers et al., 2019).

### 6.1.2 Mechanism of Action

V600M alteration of BRAF results in activity of the MAPK pathway without ligand binding to RTKs. Dabrafenib will compete with the ATP for its binding site in BRAF which is a component of MAPK pathway. This results in BRAF adopting a DGF-in structure and gets inactivated. In the active site of BRAF there is Asp594 and Phe595 residues which binds to the sulphonamide group of the drug Singh et al., 2021). This prevents dimerization of BRAF and there will be no phosphorylation of MEK1/2 which further will not phosphorylate or activate ERK. Trametinib binds to the allosteric site found in MEK that is next to the binding site for ATP and inactivates it. This inactivation prevents phosphorylation of ERK in the MAPK pathway. Hence, ERK will not move into the nucleus to interact and phosphorylate factors of transcription. In turn, tumour cell will not progress through G1 phase of cell cycle and cell death will occur (Khunger et al., 2018).

## 6.2 VEGFR2 Inhibitor with EGFR Inhibitor

### 6.2.1 Overview

Ramucirumab, a VEGFR2 inhibitor, is used in combination with erlotinib, an EGFR inhibitor. It is recommended for individuals with NSCLC that was spread to distant body parts and where tumors have deletion of exon 19 alteration of L858R in exon 21.

Compared to erlotinib monotherapy, the combination therapy appears to be more efficacious. Results from RELAY trial deduced that the prolonged PFS of 19.4 months on average is obtained with the combination whereas PFS of 12.4 months is obtained with erlotinib in patients who were not previously treated for the disease. When ramucirumab is added to therapy, it is able to hinder the emergence of resistance to erlotinib. This is due to the fact that tumours containing alterations in EGFR results in enhanced EGFR signaling which in turn results in elevated VEGF levels through hypoxia independent pathways. This increased

VEGF is associated with the development of resistance which is mediated through addition of ramucirumab (Le et al., 2021).

The toxicity associated with ramucirumab which includes severe hypertension, proteinuria and bleeding which usually comprise the significant PFS improvement associated with the combination drugs (Boussageon et al., 2021).

### 6.2.2 Mechanism of Action

Antigen-binding fragment (Fab) of ramucirumab binds selectively with VEGFR-2's extracellular domain. This binding happens at the end of domain 3, which is close to the receptor's N-terminal end. Consequently, VEGF-A, VEGF-C, and VEGF-D which are the ligands cannot bind to the receptor (Cobo et al., 2017). Moreover, receptors conformation gets changes which further facilitates blocking the ligand attachment. This does not allow receptor to get phosphorylated and this in turn does not activate pathway associated with PI3K and AKT and pathway involving RAS, RAF, MEK and ERK (Smyth et al., 2014). Ultimately, there is suppression of endothelial cell growth and division, survival, migration and angiogenesis. Erlotinib blocks the interaction of ATP with its binding pocket in the kinase unit found in EGFR. In turn, the receptor does not get phosphorylated. Pathways involving PI3K and AKT, RAS, RAF, MEK and ERK and Jak2 and STAT3 are blocked. Hence, no tumour cell growth and division, no metastasis, no angiogenesis and ultimately cell death occurs (Schettino et al., 2008).

## 6.3 PD-L1 Inhibitor with Topoisomerase II Inhibitor and Alkylating Agent

### 6.3.1 Overview

This combination includes atezolizumab which is a PD-L1 inhibitor with carboplatin which is an alkylating agent and etoposide which is a topoisomerase II inhibitor. Approval has been

granted for its use as a frontline therapy in individuals with SCLC which has spread extensively.

Improvement in efficacy is observed for this combination of drugs in contrast to using only the other two chemotherapy drugs together. According to the findings of the Impower133 trials, individuals who have never been treated for cancer have an average PFS and OS of 5.2 and 12.3 months respectively when treated with this combination. This is higher compared to the average PFS and OS of 4.3 and 10.3 months respectively when treated with the chemotherapy drugs alone (Horn et al., 2018). Despite the excellent initial response rates, patients eventually experience chemoresistance and recurrence of the disease when they are given the combination of chemotherapeutic drug only. However, immune response by the T-cells is reactivated by the addition atezolizumab to therapy which results in long-lasting tumour shrinkage. For this combination, no new adverse events have been detected except for the ones that are already associated with the individual drugs of this combination (Frampton, 2020).

Several adverse events related to this treatment that occur frequently include neutropenia, anemia, thrombocytopenia, leukopenia and infusion related reactions (Frampton, 2020).

### 6.3.2 Mechanism of Action

Lung tumor cells overexpress PD-L1, which binds to T cell PD-1 receptors to inactivate them and avoid T-cell immunological responses. Atezolizumab will block PD-L1 and block its interaction with PD-1 (Reck et al., 2020). This rejuvenates suppressed T cells and reactivates the anti-tumour immune response without ADCC. This reverses PD-L1 and PD-1's immunosuppression. In turn, there is destruction of the tumour cells.

Carboplatin is first up taken by the tumour cells and undergoes aquation by acquiring two molecules of water and losing two chloride ions. Inside the cell, it is able to bind to the N7 positions found in the guanosine and adenosine of the DNA as it is the nucleophilic site. This

results in DNA lesions. This includes formation of monoadducts when only a molecule of water is lost from carboplatin. Moreover, DNA adducts will further react to give rise to crosslinks. Greater amount of intrastrand crosslinks is produced of which 1,2-d(GpG) crosslinks are predominant. Interstrand crosslinks are also formed. All these crosslinks lead to deformation of the DNA double helix (Rabik & Dolan, 2007). RNA polymerases stop at the cross-linked sites during transcription. At this point, the transcription-coupled repair mechanism is called into action. In the event that the repair machinery is ineffective, the cell will initiate apoptosis (Johnstone et al., 2014).

Topoisomerase II is involved in creation of double stranded breaks in DNA and causes re-ligation of the strands during the DNA replication process. Etoposide forms a binding interaction with the complex of the enzyme and the DNA, which prevents the strands from resealing. This results in permanent double-stranded breaks and when there is accumulation of these breaks, it will inevitably lead to apoptosis (van den Borg et al., 2019).

## 6.4 PD-1 Inhibitor with Folic Acid Antagonist and Alkylating Agent

### 6.4.1 Overview

This combination includes pembrolizumab which is a PD-1 inhibitor with pemetrexed which is a folic acid antagonist and carboplatin which is an alkylating agent. It is the recommended therapy for individuals with non-squamous NSCLC that was spread to distant body parts and where tumors do not have alterations in EGFR or ALK. This combination is also used as a first-line option.

Significant improvement in efficacy is observed for this combination of drugs compared to only the combination of pemetrexed and carboplatin. According to the findings of the KEYNOTE-189 trial, for individuals who had not been treated for the disease in the past, the average PFS and OS values were 9 and 22 months respectively with this combination. On the

other hand, average values for PFS and OS were 4.9 and 10.7 months respectively are obtained with the combination of chemotherapy drugs alone. Moreover, in NSCLC, combination of pemetrexed and carboplatin can mediate immunologic effects and when pembrolizumab is added to therapy, there is production of synergistic antitumor outcome.

Several adverse events related to this treatment that occur frequently include infusion related reactions, neutropenia, anemia, thrombocytopenia, rash, fatigue, nausea and many more.

### 6.4.1 Mechanism of Action

PD-L1 and PD-L2 on tumor cells interact with T cells PD-1 receptors to promote tumor development. Pembrolizumab interacts with the PD1 and prevents interaction with the ligands. As a result, immune response against the tumour by the T-cells is triggered due to the binding (Raedler, 2015). This will lead to destruction of tumour cells.

Pemetrexed is capable of blocking of enzymes TS, DHFR and GARFT. Major inhibition of TS is observed as no conversion of dUMP to dTMP to DNA occurs. Cellular dTMP levels drop while dUTP levels rise after TS blockade, leading to DNA strand breaks and death (Rossi et al., 2018). Moreover, synthesizing purines from the other two pathways are also inhibited (Velez et al., 2012).

Carboplatin is first up taken by the tumour cells and undergoes aquation by acquiring two molecules of water and losing two chloride ions. Inside the cell, it is able to bind to the N7 positions found in the guanosine and adenosine of the DNA as it is the nucleophilic site. This results in DNA lesions. This includes formation of monoadducts when only a molecule of water is lost from carboplatin. Moreover, DNA adducts will further react to give rise to crosslinks. Greater amount of intrastrand crosslinks is produced of which 1,2-d(GpG) crosslinks are predominant. Interstrand crosslinks are also formed. All these crosslinks lead to deformation of the DNA double helix (Rabik & Dolan, 2007). RNA polymerases stop at the

cross-linked sites during transcription. At this point, the transcription-coupled repair mechanism is called into action. In the event that the repair machinery is ineffective, the cell will initiate apoptosis (Johnstone et al., 2014).

*Table 3: List of Combination Drugs with the Type of Lung Cancer Treated and their Mechanism of Action*

| **Combination of drugs** | **Type of lung cancer treated** | **Mechanism of action** | **References** |
|---|---|---|---|
| Dabrafenib with Trametinib | NSCLC that has metastasized | Inhibits BRAF activation and MEK activation in the MAPK pathway. Blocks ERK phosphorylation and ultimately cell death occurs. | (Khunger et al., 2018) |
| Ramucirumab with Erlotinib | NSCLC that has metastasized | Ramucirumab's Fab binds selectively with VEGFR-2's extracellular domain. Inhibits ligands interaction. Erlotinib competes with ATP and blocks its binding site. No activation of MAPK pathway, Jak2/STAT3 pathway and PI3K/Akt pathway. | (Cobo et al., 2017) (Schettino et al., 2008) |
| Atezolizumab with carboplatin and etoposide | SCLC that has spread extensively | Atezolizumab inhibits PDL-1 binding to PD-1. Elevates T cell activity against tumour cells. Carboplatin causes crosslinking of DNA and cause breaks in double strands. Etoposide blocks topoisomerase II and form irreversible double strand breaks. | (Rabik & Dolan, 2007) (Reck et al., 2020) (van den |

| | | | |
|---|---|---|---|
| | | | Borg et al., 2019) |
| Pembrolizumab with pemetrexed and carboplatin | Non-squamous NSCLC that has metastasized | Inhibition of PD1 by pembrolizumab and thymidylate synthase by pemetrexed. Carboplatin causes crosslinking of DNA. Breaks in double strands and cell death occur. | (Raedler, 2015) (Rossi et al., 2018) (Rabik & Dolan, 2007) |

# Chapter 7

# Conclusion

Lung cancer remains a prominent disease that can compromise patients' wellbeing and QoL. Ongoing research allows for determining greater in-depth knowledge about genetic aberrations associated with NSCLC. Challenges in developing drugs that provide targeted therapy for the KRAS, MET, RET and EGFR exon 20 alterations have finally been alleviated. The newly available drugs for these mutations have been approved by FDA and they show notable efficacy compared to general treatment options that have been in use before. Moreover, new medications have emerged for both the existing generation and the next generation of drug classes in use. They are associated with elevated survival rates, higher specificity for the targets, better tolerability and can overcome resistance to the existing drugs. However, limitations do remain as aggressive adverse effects and eventual resistance development are also observed with the novel drugs. To this date, anticancer medication research is hampered by the fact that the targets for drug development are mostly restricted to tyrosine kinases. Additionally, targeting genomic alterations of SCLC still remains to be a challenge. Progressive use of drug combinations is also found to be associated with better patient outcomes.

# References

Ali, R., Arshad, J., Palacio, S., & Mudad, R. (2019). Brigatinib for ALK-positive metastatic non-small-cell lung cancer: design, development and place in therapy. *Drug Design, Development and Therapy*, *13*, 569–580. https://doi.org/10.2147/DDDT.S147499

American Cancer Society. (2022, August 15). *Tests for Lung Cancer*. https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/how-diagnosed.html

American Cancer Society. (2023, January 12). *Lung Cancer Risk Factors*. https://www.cancer.org/cancer/lung-cancer/causes-risks-prevention/risk-factors.html

American Cancer Society. (2023, January 12). *What Is Lung Cancer?* https://www.cancer.org/cancer/lung-cancer/about/what-is.html

Araki, T., Yashima, H., Shimizu, K., Aomori, T., Hashita, T., Kaira, K., Nakamura, T., & Yamamoto, K. (2012). Review of the treatment of non-small cell lung cancer with gefitinib. *Clinical Medicine Insights. Oncology*, *6*, 407–421. https://doi.org/10.4137/CMO.S7340

Araujo, J. M., Gomez, A. C., Pinto, J. A., Rolfo, C., & Raez, L. E. (2021). Profile of entrectinib in the treatment of ROS1-positive non-small cell lung cancer: Evidence to date. *Hematology/Oncology and Stem Cell Therapy*, *14*(3), 192–198. https://doi.org/10.1016/J.HEMONC.2020.11.005

Ayati, A., Moghimi, S., Salarinejad, S., Safavi, M., Pouramiri, B., & Foroumadi, A. (2020). A review on progression of epidermal growth factor receptor (EGFR) inhibitors as an efficient approach in cancer targeted therapy. *Bioorganic Chemistry*, *99*, 103811. https://doi.org/10.1016/J.BIOORG.2020.103811

Basit, S., Ashraf, Z., Lee, K., & Latif, M. (2017). First macrocyclic 3rd-generation ALK inhibitor for treatment of ALK/ROS1 cancer: Clinical and designing strategy update of lorlatinib. *European Journal of Medicinal Chemistry*, *134*, 348–356. https://doi.org/10.1016/J.EJMECH.2017.04.032

Bauer, T. M., Felip, E., Solomon, B. J., Thurm, H., Peltz, G., Chioda, M. D., & Shaw, A. T. (2019). Clinical Management of Adverse Events Associated with Lorlatinib. *The Oncologist*, *24*(8), 1103–1110. https://doi.org/10.1634/THEONCOLOGIST.2018-0380

Bergonzini, C., Leonetti, A., Tiseo, M., Giovannetti, E., & Peters, G. J. (2020). Is there a role for dacomitinib, a second-generation irreversible inhibitor of the epidermal-growth factor receptor tyrosine kinase, in advanced non-small cell lung cancer? *Expert Opinion on Pharmacotherapy*, *21*(11), 1287–1298. https://doi.org/10.1080/14656566.2020.1746269

Blair, H. A. (2021). Sotorasib: First Approval. *Drugs*, *81*(13), 1573–1579. https://doi.org/10.1007/S40265-021-01574-2

Blaquier, J. B., Cardona, A. F., & Recondo, G. (2021). Resistance to KRASG12C Inhibitors in Non-Small Cell Lung Cancer. In *Frontiers in Oncology* (Vol. 11). Frontiers Media S.A. https://doi.org/10.3389/fonc.2021.787585

Boussageon, M., Swalduz, A., & Pérol, M. (2021). The safety and efficacy of erlotinib and ramucirumab combination in EGFR-mutant non-small-cell lung cancer. *Expert Review of Anticancer Therapy*, *21*(10), 1071–1080. https://doi.org/10.1080/14737140.2021.1958679

Brazel, D., & Nagasaka, M. (2021). Spotlight on Amivantamab (JNJ-61186372) for EGFR Exon 20 Insertions Positive Non-Small Cell Lung Cancer. *Lung Cancer: Targets and Therapy*, *12*, 133–138. https://doi.org/10.2147/LCTT.S337861

Brazel, D., Zhang, S., & Nagasaka, M. (2022). Spotlight on Tepotinib and Capmatinib for Non-Small Cell Lung Cancer with MET Exon 14 Skipping Mutation. *Lung Cancer: Targets and Therapy*, *13*, 33–45. https://doi.org/10.1158/1078-0432.CCR-21-1566

Brenner, A. K., & Gunnes, M. W. (2021). Therapeutic Targeting of the Anaplastic Lymphoma Kinase (ALK) in Neuroblastoma—A Comprehensive Update. *Pharmaceutics 2021, Vol. 13, Page 1427*, *13*(9), 1427. https://doi.org/10.3390/PHARMACEUTICS13091427

Brinkmeyer, J. K., & Moore, D. C. (2016). Necitumumab for the treatment of squamous cell non-small cell lung cancer. *Journal of Oncology Pharmacy Practice*, *24*(1), 37–41. https://doi.org/10.1177/1078155216682365

Brzezniak, C., Carter, C. A., & Giaccone, G. (2013). Dacomitinib, a new therapy for the treatment of non-small cell lung cancer. *Expert Opinion on Pharmacotherapy*, *14*(2), 247–253. https://doi.org/10.1517/14656566.2013.758714

Camidge, D. R., Kim, H. R., Ahn, M. J., Yang, J. C. H., Han, J. Y., Hochmair, M. J., Lee, K. H., Delmonte, A., Garcia Campelo, M. R., Kim, D. W., Griesinger, F., Felip, E., Califano, R., Spira, A. I., Gettinger, S. N., Tiseo, M., Lin, H. M., Liu, Y., Vranceanu, F., … Popat, S. (2021). Brigatinib Versus Crizotinib in ALK Inhibitor–Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial. *Journal of Thoracic Oncology*, *16*(12), 2091–2108. https://doi.org/10.1016/j.jtho.2021.07.035

Campello, M. R. G., Zhou, C., Ramalingam, S. S., Lin, H. M., Kim, T. M., Riely, G. J., Mekhail, T., Nguyen, D., Goodman, E., Mehta, M., Popat, S., & Jänne, P. A. (2022). Mobocertinib (TAK-788) in EGFR Exon 20 Insertion+ Metastatic NSCLC: Patient-Reported Outcomes from EXCLAIM Extension Cohort. *Journal of Clinical Medicine*, *12*(1), 112. https://doi.org/10.3390/JCM12010112

Carbone, D. P., Reck, M., Paz-Ares, L., Creelan, B., Horn, L., Steins, M., Felip, E., van den Heuvel, M. M., Ciuleanu, T.-E., Badin, F., Ready, N., Hiltermann, T. J. N., Nair, S., Juergens, R., Peters, S., Minenza, E., Wrangle, J. M., Rodriguez-Abreu, D., Borghaei, H., … Socinski, M. A. (2017). First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *376*(25), 2415–2426. https://doi.org/10.1056/NEJMoa1613493

Cascetta, P., Sforza, V., Manzo, A., Carillio, G., Palumbo, G., Esposito, G., Montanino, A., Costanzo, R., Sandomenico, C., de Cecio, R., Piccirillo, M. C., la Manna, C., Totaro, G., Muto, P., Picone, C., Bianco, R., Normanno, N., & Morabito, A. (2021). RET Inhibitors in Non-Small-Cell Lung Cancer. *Cancers*, *13*(17), 4415. https://doi.org/10.3390/cancers13174415

Chalmers, A., Cannon, L., & Akerley, W. (2019). Adverse Event Management in Patients with BRAF V600E-Mutant Non-Small Cell Lung Cancer Treated with Dabrafenib plus Trametinib. *The Oncologist*, *24*(7), 963–972. https://doi.org/10.1634/THEONCOLOGIST.2018-0296

Chawla, N., Bui, N. Q., & Seetharam, M. (2021). Evolving role of entrectinib in treatment of NTRK-positive tumors. *Future Oncology*, *17*(22), 2835–2846. https://doi.org/10.2217/FON-2020-0936

Cho, B. C., Simi, A., Sabari, J., Vijayaraghavan, S., Moores, S., & Spira, A. (2022). Amivantamab, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) bispecific antibody, designed to enable multiple mechanisms of action and broad clinical applications. *Clinical Lung Cancer*. https://doi.org/10.1016/j.cllc.2022.11.004

Choudhury, N. J., & Drilon, A. (2020). Decade in review: a new era for RET-rearranged lung cancers. *Translational Lung Cancer Research*, *9*(6), 2571–2580. https://doi.org/10.21037/TLCR-20-346

Chu, C., Choi, J., Eaby-Sandy, B., Langer, C. J., & Lacouture, M. E. (2018). Osimertinib: A Novel Dermatologic Adverse Event Profile in Patients with Lung Cancer. *The Oncologist*, *23*(8), 891–899. https://doi.org/10.1634/THEONCOLOGIST.2017-0582

Cobo, M., Gutiérrez, V., Villatoro, R., Trigo, J. M., Ramos, I., López, O., Ruiz, M., Godoy, A., López, I., & Arroyo, M. (2017). Spotlight on ramucirumab in the treatment of nonsmall cell lung cancer: design, development, and clinical activity. *Lung Cancer: Targets and Therapy*, *8*, 57–66. https://doi.org/10.2147/LCTT.S118996

Cooper, M. R., Chim, H., Chan, H., & Durand, C. (2014). Ceritinib: A New Tyrosine Kinase Inhibitor for Non-Small-Cell Lung Cancer. *Annals of Pharmacotherapy*, *49*(1), 107–112. https://doi.org/10.1177/1060028014553619

Cooper, W. A., Lam, D. C. L., O'Toole, S. A., & Minna, J. D. (2013). Molecular biology of lung cancer. *Journal of Thoracic Disease*, *5*(Suppl. 5). https://doi.org/10.3978/J.ISSN.2072-1439.2013.08.03

Corral de la Fuente, E., Olmedo Garcia, M. E., Gomez Rueda, A., Lage, Y., & Garrido, P. (2022). Targeting KRAS in Non-Small Cell Lung Cancer. *Frontiers in Oncology*, *11*. https://doi.org/10.3389/FONC.2021.792635

Corral, J., Mok, T. S., Nakagawa, K., Rosell, R., Lee, K. H., Migliorino, M. R., Pluzanski, A., Linke, R., Devgan, G., Tan, W., Quinn, S., Wang, T., & Wu, Y. L. (2019). Effects of dose modifications on the safety and efficacy of dacomitinib for mutation-positive non-small-cell lung cancer. *Future Oncology*, *15*(24), 2795–2805. https://doi.org/10.2217/FON-2019-0299

D'Angelo, A., Sobhani, N., Chapman, R., Bagby, S., Bortoletti, C., Traversini, M., Ferrari, K., Voltolini, L., Darlow, J., & Roviello, G. (2020). Focus on ROS1-Positive Non-Small Cell Lung Cancer (NSCLC): Crizotinib, Resistance Mechanisms and the Newer Generation of Targeted Therapies. *Cancers*, *12*(11), 3293. https://doi.org/10.3390/CANCERS12113293

de Groot, P. M., Wu, C. C., Carter, B. W., & Munden, R. F. (2018). The epidemiology of lung cancer. *Translational Lung Cancer Research*, *7*(3), 220–233. https://doi.org/10.21037/TLCR.2018.05.06

Dhillon, S. (2020). Capmatinib: First Approval. *Drugs*, *80*(11), 1125–1131. https://doi.org/10.1007/S40265-020-01347-3

Dong, Y., Xu, J., Sun, B., Wang, J., & Wang, Z. (2022). MET-Targeted Therapies and Clinical Outcomes: A Systematic Literature Review. *Molecular Diagnosis and Therapy*, *26*(2), 203–227. https://doi.org/10.1007/S40291-021-00568-w

Doumat, G., Daher, D., Zerdan, M. B., Nasra, N., Bahmad, H. F., Recine, M., & Poppiti, R. (2023). Drug Repurposing in Non-Small Cell Lung Carcinoma: Old Solutions for New Problems. *Current Oncology*, *30*(1), 704–719. https://doi.org/10.3390/CURRONCOL30010055

Drilon, A., Jenkins, C., Iyer, S., Schoenfeld, A., Keddy, C., & Davare, M. A. (2020). ROS1-dependent cancers — biology, diagnostics and therapeutics. *Nature Reviews Clinical Oncology*, *18*(1), 35–55. https://doi.org/10.1038/s41571-020-0408-9

Dziadziuszko, R., Peters, S., Ruf, T., Cardona, A., Guerini, E., Kurtsikidze, N., Smoljanovic, V., & Planchard, D. (2022). Clinical experience and management of adverse events in patients with advanced ALK-positive non-small-cell lung cancer receiving alectinib. *ESMO Open*, *7*(6), 100612. https://doi.org/10.1016/j.esmoop.2022.100612

Frampton, J. E. (2020). Atezolizumab: A Review in Extensive-Stage SCLC. *Drugs*, *80*(15), 1587–1594. https://doi.org/10.1007/S40265-020-01398-6

Frampton, J. E. (2021). Entrectinib: A Review in NTRK+ Solid Tumours and ROS1+ NSCLC. *Drugs*, *81*(6), 697–708. https://doi.org/10.1007/S40265-021-01503-3

Fujino, T., Suda, K., & Mitsudomi, T. (2021). Lung Cancer with MET exon 14 Skipping Mutation: Genetic Feature, Current Treatments, and Future Challenges. *Lung Cancer: Targets and Therapy*, *Volume 12*, 35–50. https://doi.org/10.2147/LCTT.S269307

Gonzalvez, F., Vincent, S., Baker, T. E., Gould, A. E., Li, S., Wardwell, S. D., Nadworny, S., Ning, Y., Zhang, S., Huang, W. S., Hu, Y., Li, F., Greenfield, M. T., Zech, S. G., Das, B., Narasimhan, N. I., Clackson, T., Dalgarno, D., Shakespeare, W. C., … Rivera, V. M. (2021). Mobocertinib (Tak-788): A Targeted Inhibitor of EGFR Exon 20 Insertion Mutants in Non–Small Cell Lung Cancer. *Cancer Discovery*, *11*(7), 1672–1687. https://doi.org/10.1158/2159-8290.CD-20-1683

Griesinger, F., Curigliano, G., Thomas, M., Subbiah, V., Baik, C. S., Tan, D. S. W., Lee, D. H., Misch, D., Garralda, E., Kim, D. W., van der Wekken, A. J., Gainor, J. F., Paz-Ares, L., Liu, S. v., Kalemkerian, G. P., Houvras, Y., Bowles, D. W., Mansfield, A. S., Lin, J. J., … Mazières, J. (2022). Safety and efficacy of pralsetinib in RET fusion–positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial. *Annals of Oncology*, *33*(11), 1168–1178. https://doi.org/10.1016/j.annonc.2022.08.002

Guo, L., Zhang, H., & Chen, B. (2017). Nivolumab as Programmed Death-1 (PD-1) Inhibitor for Targeted Immunotherapy in Tumor. *Journal of Cancer*, *8*(3), 410–416. https://doi.org/10.7150/JCA.17144

Gupta, N., Pierrillas, P. B., Hanley, M. J., Zhang, S., & Diderichsen, P. M. (2022). Population pharmacokinetics of mobocertinib in healthy volunteers and patients with non–small cell

lung cancer. *CPT: Pharmacometrics & Systems Pharmacology*, *11*(6), 731–744. https://doi.org/10.1002/PSP4.12785

Haibe, Y., Kreidieh, M., Hajj, H. E., Khalifeh, I., Mukherji, D., Temraz, S., & Shamseddine, A. (2020). Resistance Mechanisms to Anti-angiogenic Therapies in Cancer. *Frontiers in Oncology*, *10*, 221. https://doi.org/10.3389/FONC.2020.00221

Halliday, P. R., Blakely, C. M., & Bivona, T. G. (2019). Emerging Targeted Therapies for the Treatment of Non-small Cell Lung Cancer. *Current Oncology Reports*, *21*(3), 1–12. https://doi.org/10.1007/S11912-019-0770-X

Herdeis, L., Gerlach, D., McConnell, D. B., & Kessler, D. (2021). Stopping the beating heart of cancer: KRAS reviewed. *Current Opinion in Structural Biology*, *71*, 136–147. https://doi.org/10.1016/J.SBI.2021.06.013

Herden, M., & Waller, C. F. (2018). Alectinib. *Recent Results in Cancer Research*, *211*, 247–256. https://doi.org/10.1007/978-3-319-91442-8_17

Hirsh, V. (2017). New developments in the treatment of advanced squamous cell lung cancer: focus on afatinib. *OncoTargets and Therapy*, *10*, 2513–2526. https://doi.org/10.2147/OTT.S104177

Hoang, T., Myung, S. K., Pham, T. T., & Park, B. (2020). Efficacy of Crizotinib, Ceritinib, and Alectinib in ALK-Positive Non-Small Cell Lung Cancer Treatment: A Meta-Analysis of Clinical Trials. *Cancers*, *12*(3), 526. https://doi.org/10.3390/CANCERS12030526

Hong, D. S., Fakih, M. G., Strickler, J. H., Desai, J., Durm, G. A., Shapiro, G. I., Falchook, G. S., Price, T. J., Sacher, A., Denlinger, C. S., Bang, Y.-J., Dy, G. K., Krauss, J. C., Kuboki, Y., Kuo, J. C., Coveler, A. L., Park, K., Kim, T. W., Barlesi, F., … Li, B. T.

(2020). KRASG12C Inhibition with Sotorasib in Advanced Solid Tumors. *New England Journal of Medicine*, *383*(13), 1207–1217. https://doi.org/10.1056/NEJMOA1917239

Horn, L., Mansfield, A. S., Szczęsna, A., Havel, L., Krzakowski, M., Hochmair, M. J., Huemer, F., Losonczy, G., Johnson, M. L., Nishio, M., Reck, M., Mok, T., Lam, S., Shames, D. S., Liu, J., Ding, B., Lopez-Chavez, A., Kabbinavar, F., Lin, W., … Liu, S. v. (2018). First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *New England Journal of Medicine*, *379*(23), 2220–2229. https://doi.org/10.1056/NEJMOA1809064

Huang, C. Y., Ju, D. T., Chang, C. F., Reddy, P. M., & Velmurugan, B. K. (2017). A review on the effects of current chemotherapy drugs and natural agents in treating non-small cell lung cancer. *BioMedicine*, *7*(4), 12–23. https://doi.org/10.1051/bmdcn/2017070423

Jänne, P. A., Riely, G. J., Gadgeel, S. M., Heist, R. S., Ou, S.-H. I., Pacheco, J. M., Johnson, M. L., Sabari, J. K., Leventakos, K., Yau, E., Bazhenova, L., Negrao, M. v., Pennell, N. A., Zhang, J., Anderes, K., Der-Torossian, H., Kheoh, T., Velastegui, K., Yan, X., … Spira, A. I. (2022). Adagrasib in Non-Small-Cell Lung Cancer Harboring a KRASG12C Mutation. *The New England Journal of Medicine*, *387*(2), 120–131. https://doi.org/10.1056/NEJMOA2204619

Jiménez-López, J., Bravo-Caparrós, I., Cabeza, L., Nieto, F. R., Ortiz, R., Perazzoli, G., Fernández-Segura, E., Cañizares, F. J., Baeyens, J. M., Melguizo, C., & Prados, J. (2021). Paclitaxel antitumor effect improvement in lung cancer and prevention of the painful neuropathy using large pegylated cationic liposomes. *Biomedicine & Pharmacotherapy*, *133*, 111059. https://doi.org/10.1016/J.BIOPHA.2020.111059

Johnstone, T. C., Park, G. Y., & Lippard, S. J. (2014). Understanding and Improving Platinum Anticancer Drugs – Phenanthriplatin. *Anticancer Research*, *34*(1), 471. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937549/

Kalemkerian, G. P. (2016). Small Cell Lung Cancer. *Seminars in Respiratory and Critical Care Medicine*, *37*(5), 783–796. https://doi.org/10.1055/S-0036-1592116

Karachaliou, N., Fernandez-Bruno, M., Bracht, J. W. P., & Rosell, R. (2019). EGFR first- and second-generation TKIs—there is still place for them in EGFR-mutant NSCLC patients. *Translational Cancer Research*, *8*(Suppl 1), S23–S47. https://doi.org/10.21037/TCR.2018.10.06

Khunger, A., Khunger, M., & Velcheti, V. (2018). Dabrafenib in combination with trametinib in the treatment of patients with BRAF V600-positive advanced or metastatic non-small cell lung cancer: clinical evidence and experience. *Therapeutic Advances in Respiratory Disease*, *12*. https://doi.org/10.1177/1753466618767611

Kobayashi, Y., Fujino, T., Nishino, M., Koga, T., Chiba, M., Sesumi, Y., Ohara, S., Shimoji, M., Tomizawa, K., Takemoto, T., & Mitsudomi, T. (2018). EGFR T790M and C797S Mutations as Mechanisms of Acquired Resistance to Dacomitinib. *Journal of Thoracic Oncology*, *13*(5), 727–731. https://doi.org/10.1016/j.jtho.2018.01.009

Kozuki, T. (2016). Skin problems and EGFR-tyrosine kinase inhibitor. *Japanese Journal of Clinical Oncology*, *46*(4), 291–298. https://doi.org/10.1093/JJCO/HYV207

Kurkjian, C., & Kim, E. S. (2011). Risks and benefits with bevacizumab: evidence and clinical implications. *Therapeutic Advances in Drug Safety*, *3*(2), 59–69. https://doi.org/10.1177/2042098611430109

Lai, X. X., Xu, R. A., Li, Y. P., & Yang, H. (2016). Risk of adverse events with bevacizumab addition to therapy in advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials. *OncoTargets and Therapy*, *9*, 2421–2428. https://doi.org/10.2147/OTT.S96156

Langevin, S. M., Kratzke, R. A., & Kelsey, K. T. (2014). Epigenetics of lung cancer. *Translational Research: The Journal of Laboratory and Clinical Medicine*, *165*(1), 74–90. https://doi.org/10.1016/J.TRSL.2014.03.001

Le, X., Nilsson, M., Goldman, J., Reck, M., Nakagawa, K., Kato, T., Ares, L. P., Frimodt-Moller, B., Wolff, K., Visseren-Grul, C., Heymach, J. v., & Garon, E. B. (2021). Dual EGFR-VEGF Pathway Inhibition: A Promising Strategy for Patients With EGFR-Mutant NSCLC. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*, *16*(2), 205–215. https://doi.org/10.1016/J.JTHO.2020.10.006

Lee, A. (2022). Sotorasib: A Review in KRAS G12C Mutation-Positive Non-small Cell Lung Cancer. *Targeted Oncology*, *17*(6), 727–733. https://doi.org/10.1007/S11523-022-00922-W

Lemjabbar-Alaoui, H., Hassan, O. U. I., Yang, Y. W., & Buchanan, P. (2015). Lung cancer: Biology and treatment options. *Biochimica et Biophysica Acta*, *1856*(2), 189–210. https://doi.org/10.1016/J.BBCAN.2015.08.002

Liang, J., Lu, T., Chen, Z., Zhan, C., & Wang, Q. (2019). Mechanisms of resistance to pemetrexed in non-small cell lung cancer. *Translational Lung Cancer Research*, *8*(6), 1107–1118. https://doi.org/10.21037/TLCR.2019.10.14

Liang, S., Wang, Q., Qi, X., Liu, Y., Li, G., Lu, S., Mou, L., & Chen, X. (2021). Deciphering the Mechanism of Gilteritinib Overcoming Lorlatinib Resistance to the Double Mutant

I1171N/F1174I in Anaplastic Lymphoma Kinase. *Frontiers in Cell and Developmental Biology*, *9*, 3689. https://doi.org/10.3389/FCELL.2021.808864

Lin, J. J., Liu, S., McCoach, C. E., Zhu, V. W., Tan, A. C., Yoda, S., Peterson, J., Do, A., Prutisto-Chang, K., Dagogo-Jack, I., Sequist, L., Wirth, L. J., Lennerz, J. K., Hata, A. N., Mino-Kenudson, M., Nardi, V., Ou, S. H. I., Tan, D. S. W., & Gainor, J. F. (2020). Mechanisms of resistance to selective RET tyrosine kinase inhibitors in RET fusion-positive non-small-cell lung cancer. *Annals of Oncology*, *31*(12), 1725–1733. https://doi.org/10.1016/j.annonc.2020.09.015

Liu, J., Kang, R., & Tang, D. (2021). The KRAS-G12C inhibitor: activity and resistance. *Cancer Gene Therapy*, *29*(7), 875–878. https://doi.org/10.1038/s41417-021-00383-9

Ma, H., Liu, Y., Ding, K., Liu, Y., Zhao, W., Zhu, Y., Chang, X., Chen, Y., Xiao, Z., Yu, Y., Zhou, R., & Zhang, H. (2021). Comparative efficacy and safety of first-line treatments for advanced non-small cell lung cancer with ALK-rearranged: a meta-analysis of clinical trials. *BMC Cancer*, *21*(1), 1–11. https://doi.org/10.1186/S12885-021-08977-0

Malhotra, J., Malvezzi, M., Negri, E., Vecchia, L. C., & Boffetta, P. (2016). Risk factors for lung cancer worldwide. *European Respiratory Journal*, *48*(3), 889–902. https://doi.org/10.1183/13993003.00359-2016

Mann, J. E. (2023). Adagrasib (Krazati™). *Oncology Times*, *45*(2), 8,15-15. https://doi.org/10.1097/01.COT.0000918296.75852.31

Markham, A. (2017). Brigatinib: First Global Approval. *Drugs*, *77*(10), 1131–1135. https://doi.org/10.1007/S40265-017-0776-3

Markham, A. (2020). Lurbinectedin: First Approval. *Drugs*, *80*(13), 1345–1353. https://doi.org/10.1007/S40265-020-01374-0

Markham, A. (2020). Pralsetinib: First Approval. *Drugs*, *80*(17), 1865–1870. https://doi.org/10.1007/S40265-020-01427-4

Mathieu, L. N., Larkins, E., Akinboro, O., Roy, P., Amatya, A. K., Fiero, M. H., Mishra-Kalyani, P. S., Helms, W. S., Myers, C. E., Skinner, A. M., Aungst, S., Jin, R., Zhao, H., Xia, H., Zirkelbach, J. F., Bi, Y., Li, Y., Liu, J., Grimstein, M., … Singh, H. (2022). FDA Approval Summary: Capmatinib and Tepotinib for the Treatment of Metastatic NSCLC Harboring MET Exon 14 Skipping Mutations or Alterations. *Clinical Cancer Research*, *28*(2), 249–254. https://doi.org/10.1158/1078-0432.CCR-21-1566/673934

Mayekar, M. K., & Bivona, T. G. (2017). Current Landscape of Targeted Therapy in Lung Cancer. *Clinical Pharmacology & Therapeutics*, *102*(5), 757–764. https://doi.org/10.1002/CPT.810

Minchom, A., Viteri, S., Bazhenova, L., Gadgeel, S. M., Ou, S. H. I., Trigo, J., Bauml, J. M., Backenroth, D., Bhattacharya, A., Li, T., Mahadevia, P., & Girard, N. (2022). Amivantamab compared with real-world therapies in patients with advanced non-small cell lung cancer harboring EGFR exon 20 insertion mutations who progressed after platinum-based chemotherapy. *Lung Cancer*, *168*, 74–82. https://doi.org/10.1016/j.lungcan.2022.03.005

Mizuta, H., Okada, K., Araki, M., Adachi, J., Takemoto, A., Kutkowska, J., Maruyama, K., Yanagitani, N., Oh-hara, T., Watanabe, K., Tamai, K., Friboulet, L., Katayama, K., Ma, B., Sasakura, Y., Sagae, Y., Kukimoto-Niino, M., Shirouzu, M., Takagi, S., … Katayama, R. (2021). Gilteritinib overcomes lorlatinib resistance in ALK-rearranged cancer. *Nature Communications*, *12*(1), 1–16. https://doi.org/10.1038/s41467-021-21396-w

Montanino, A., Manzo, A., Carillio, G., Palumbo, G., Esposito, G., Sforza, V., Costanzo, R., Sandomenico, C., Botti, G., Piccirillo, M. C., Cascetta, P., Pascarella, G., la Manna, C., Normanno, N., & Morabito, A. (2021). Angiogenesis Inhibitors in Small Cell Lung Cancer. *Frontiers in Oncology*, *11*, 1872. https://doi.org/10.3389/FONC.2021.655316

Morgensztern, D., & Herbst, R. S. (2016). Nivolumab and Pembrolizumab for Non-Small Cell Lung Cancer. *Clinical Cancer Research*, *22*(15), 3713–3717. https://doi.org/10.1158/1078-0432.CCR-15-2998

Morgillo, F., della Corte, C. M., Fasano, M., & Ciardiello, F. (2016). Mechanisms of resistance to EGFR-targeted drugs: lung cancer. *ESMO Open*, *1*(3), e000060. https://doi.org/10.1136/ESMOOPEN-2016-000060

Nagasaka, M., Balmanoukian, A. S., Madison, R., Zhang, S. S., Klempner, S. J., & Ou, S. H. I. (2022). Amivantamab (JNJ-61186372) induces clinical, biochemical, molecular, and radiographic response in a treatment-refractory NSCLC patient harboring amplified triple EGFR mutations (L858R/ T790M/G796S) in cis. *Lung Cancer*, *164*, 52–55. https://doi.org/10.1016/J.LUNGCAN.2021.12.022

National Cancer Institute. (2020). *Non-Small Cell Lung Cancer Treatment (PDQ®): Health Professional Version*. https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq

National Cancer Institute. (2021, June 25). *FDA Approval of KRAS Inhibitor Sotorasib for Lung Cancer Hailed as Milestone*. https://www.cancer.gov/news-events/cancer-currents-blog/2021/fda-sotorasib-lung-cancer-kras

National Center for Biotechnology Information. (2023). *PubChem*. https://pubchem.ncbi.nlm.nih.gov/

Nogueira, T. C. M., & de Souza, M. V. N. (2021). New FDA oncology small molecule drugs approvals in 2020: Mechanism of action and clinical applications. *Bioorganic & Medicinal Chemistry*, *46*, 116340. https://doi.org/10.1016/J.BMC.2021.116340

Nuñez, G. S., Robles, C. M. G., Giraudon, C., Martínez-Leal, J. F., Compe, E., Coin, F., Aviles, P., Galmarini, C. M., & Egly, J. M. (2016). Lurbinectedin Specifically Triggers the Degradation of Phosphorylated RNA Polymerase II and the Formation of DNA Breaks in Cancer Cells. *Molecular Cancer Therapeutics*, *15*(10), 2399–2412. https://doi.org/10.1158/1535-7163.MCT-16-0172

O'Bryant, C. L., Wenger, S. D., Kim, M., & Thompson, L. A. (2013). Crizotinib: A New Treatment Option for ALK-Positive Non-Small Cell Lung Cancer. *Annals of Pharmacotherapy*, *47*(2), 189–197. https://doi.org/10.1345/APH.1R002

Parikh, K., Banna, G., Liu, S. v., Friedlaender, A., Desai, A., Subbiah, V., & Addeo, A. (2022). Drugging KRAS: current perspectives and state-of-art review. *Journal of Hematology & Oncology*, *15*(1), 1–22. https://doi.org/10.1186/S13045-022-01375-4

Parums, D. V. (2022). Editorial: Recent Approval of Sotorasib as the First Targeted Therapy for KRAS G12C-Mutated Advanced Non-Small Cell Lung Cancer (NSCLC). *Medical Science Monitor*, *28*. https://doi.org/10.12659/MSM.938746

Patel, H. M., Pawara, R., & Surana, S. J. (2019). Introduction. *Third Generation EGFR Inhibitors*, 1–24. https://doi.org/10.1016/B978-0-08-102661-8.00001-9

Patel, S., Petty, W. J., & Sands, J. M. (2021). An overview of lurbinectedin as a new second-line treatment option for small cell lung cancer. *Therapeutic Advances in Medical Oncology*, *13*. https://doi.org/10.1177/17588359211020529

Peng, L., Lu, D., Xia, Y., Hong, S., Selvaggi, G., Stebbing, J., Sun, Y., & Liang, F. (2021). Efficacy and Safety of First-Line Treatment Strategies for Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer: A Bayesian Network Meta-Analysis. *Frontiers in Oncology*, *11*, 4641. https://doi.org/10.3389/FONC.2021.754768

Petrini, I., & Giaccone, G. (2022). Amivantamab in the Treatment of Metastatic NSCLC: Patient Selection and Special Considerations. *OncoTargets and Therapy*, *15*, 1197–1210. https://doi.org/10.2147/OTT.S329095

Planchard, D. (2014). Bevacizumab in non-small-cell lung cancer: a review. *Expert Review of Anticancer Therapy*, *11*(8), 1163–1179. https://doi.org/10.1586/ERA.11.80

Poon, C. C., & Kelly, J. J. (2017). Development of crizotinib, a rationally designed tyrosine kinase inhibitor for non-small cell lung cancer. *International Journal of Cancer*, *140*(9), 1945–1954. https://doi.org/10.1002/IJC.30533

Puccini, A., Marín-Ramos, N. I., Bergamo, F., Schirripa, M., Lonardi, S., Lenz, H. J., Loupakis, F., & Battaglin, F. (2019). Safety and Tolerability of c-MET Inhibitors in Cancer. *Drug Safety*, *42*(2), 211–233. https://doi.org/10.1007/S40264-018-0780-X

Rabik, C. A., & Dolan, M. E. (2007). Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treatment Reviews*, *33*(1), 9–23. https://doi.org/10.1016/J.CTRV.2006.09.006

Raedler, L. A. (2015). Keytruda (Pembrolizumab): First PD-1 Inhibitor Approved for Previously Treated Unresectable or Metastatic Melanoma. *American Health & Drug Benefits*, *8*(Spec Feature), 96–100. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4665064/

Reck, M., Shankar, G., Lee, A., Coleman, S., McCleland, M., Papadimitrakopoulou, V. A., Socinski, M. A., & Sandler, A. (2020). Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of patients with metastatic non-squamous non-small cell lung cancer, including patients with EGFR mutations. *Expert Review of Respiratory Medicine*, *14*(2), 125–136. https://doi.org/10.1080/17476348.2020.1701439

Reckamp, K., Lin, H. M., Huang, J., Proskorovsky, I., Reichmann, W., Krotneva, S., Kerstein, D., Huang, H., & Lee, J. (2018). Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer. *Current Medical Research and Opinion*, *35*(4), 569–576. https://doi.org/10.1080/03007995.2018.1520696

Reuther, S., Bassani, N., Murphy, M. F., Dempke, W., Reuther, S., Bassani, N., Murphy, M. F., & Dempke, W. (2022). C-MET Inhibitors as New Members of the NSCLC Treatment Armamentarium—A Pooled Analysis. *Advances in Lung Cancer*, *11*(1), 1–13. https://doi.org/10.4236/ALC.2022.111001

Rocco, D., Battiloro, C., Della Gravara, L., & Gridelli, C. (2019). Safety and Tolerability of Anaplastic Lymphoma Kinase Inhibitors in Non-Small-Cell Lung Cancer. *Drug Safety*, *42*(2), 199–209. https://doi.org/10.1007/S40264-018-0771-Y

Rossi, G., Alama, A., Genova, C., Rijavec, E., Tagliamento, M., Biello, F., Coco, S., Dal Bello, M. G., Boccardo, S., & Grossi, F. (2018). The evolving role of pemetrexed disodium for the treatment of non-small cell lung cancer. *Expert Opinion on Pharmacotherapy*, *19*(17), 1969–1976. https://doi.org/10.1080/14656566.2018.1536746

Ruiz-Ceja, K. A., & Chirino, Y. I. (2017). Current FDA-approved treatments for non-small cell lung cancer and potential biomarkers for its detection. *Biomedicine & Pharmacotherapy*, *90*, 24–37. https://doi.org/10.1016/J.BIOPHA.2017.03.018

Sabbula, B. R., Gasalberti, D. P., & Anjum, F. (2022). Squamous Cell Lung Cancer. *JCR: Journal of Clinical Rheumatology*, *26*(5), e137–e137. https://doi.org/10.1097/rhu.0000000000001010

Sahu, A., Prabhash, K., Noronha, V., Joshi, A., & Desai, S. (2013). Crizotinib: A comprehensive review. *South Asian Journal of Cancer*, *2*(2), 91. https://doi.org/10.4103/2278-330X.110506

Sartore-Bianchi, A., Pizzutilo, E. G., Marrapese, G., Tosi, F., Cerea, G., & Siena, S. (2020). Entrectinib for the treatment of metastatic NSCLC: safety and efficacy. *Expert Review of Anticancer Therapy*, *20*(5), 333–341. https://doi.org/10.1080/14737140.2020.1747439

Sato, M., Shames, D. S., Gazdar, A. F., & Minna, J. D. (2007). A Translational View of the Molecular Pathogenesis of Lung Cancer. *Journal of Thoracic Oncology*, *2*(4), 327–343. https://doi.org/10.1097/01.JTO.0000263718.69320.4C

Schadt, O., & Blaukat, A. (2017). Tepotinib. *Comprehensive Medicinal Chemistry III*, 178–203. https://doi.org/10.1016/B978-0-12-409547-2.12468-0

Schettino, C., Bareschino, M. A., Ricci, V., & Ciardiello, F. (2008). Erlotinib: An EGF receptor tyrosine kinase inhibitor in non-small-cell lung cancer treatment. *Expert Review of Respiratory Medicine*, *2*(2), 167–178. https://doi.org/10.1586/17476348.2.2.167

Schmid, S., Li, J. J. N., & Leighl, N. B. (2020). Mechanisms of osimertinib resistance and emerging treatment options. *Lung Cancer*, *147*, 123–129. https://doi.org/10.1016/j.lungcan.2020.07.014

Sforza, V., Palumbo, G., Cascetta, P., Carillio, G., Manzo, A., Montanino, A., Sandomenico, C., Costanzo, R., Esposito, G., Laudato, F., Damiano, S., Forte, C. A., Frosini, G., Farese, S., Piccirillo, M. C., Pascarella, G., Normanno, N., & Morabito, A. (2022). BRAF Inhibitors in Non-Small Cell Lung Cancer. *Cancers*, *14*(19). https://doi.org/10.3390/CANCERS14194863

Shah, R., & Lester, J. F. (2020). Tyrosine Kinase Inhibitors for the Treatment of EGFR Mutation-Positive Non–Small-Cell Lung Cancer: A Clash of the Generations. *Clinical Lung Cancer*, *21*(3), e216–e228. https://doi.org/10.1016/J.CLLC.2019.12.003

Shah, R. R., & Shah, D. R. (2019). Safety and Tolerability of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors in Oncology. *Drug Safety 2019 42:2*, *42*(2), 181–198. https://doi.org/10.1007/S40264-018-0772-X

Shaw, A. T., Kim, D.-W., Mehra, R., Tan, D. S. W., Felip, E., Chow, L. Q. M., Camidge, D. R., Vansteenkiste, J., Sharma, S., de Pas, T., Riely, G. J., Solomon, B. J., Wolf, J., Thomas, M., Schuler, M., Liu, G., Santoro, A., Lau, Y. Y., Goldwasser, M., … Engelman, J. A. (2014). Ceritinib in ALK -Rearranged Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *370*(13), 1189–1197. https://doi.org/10.1056/NEJMOA1311107

Shen, L., Qiang, T., Li, Z., Ding, D., Yu, Y., & Lu, S. (2020). First-line crizotinib versus platinum-pemetrexed chemotherapy in patients with advanced ROS1-rearranged non-small-cell lung cancer. *Cancer Medicine*, *9*(10), 3310–3318. https://doi.org/10.1002/CAM4.2972

Shirley, M. (2018). Dacomitinib: First Global Approval. *Drugs*, *78*(18), 1947–1953. https://doi.org/10.1007/S40265-018-1028-X

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *CA: A Cancer Journal for Clinicians*, *72*(1), 7–33. https://doi.org/10.3322/caac.21708

Singh, M., & Jadhav, H. R. (2018). Targeting non-small cell lung cancer with small-molecule EGFR tyrosine kinase inhibitors. *Drug Discovery Today*, *23*(3), 745–753. https://doi.org/10.1016/J.DRUDIS.2017.10.004

Singh, S., Jaigirdar, A. A., Mulkey, F., Cheng, J., Hamed, S. S., Li, Y., Liu, J., Zhao, H., Goheer, A., Helms, W. S., Wang, X., Agarwal, R., Pragani, R., Korsah, K., Tang, S., Leighton, J., Rahman, A., Beaver, J. A., Pazdur, R., … Singh, H. (2021). FDA approval summary: Lurbinectedin for the treatment of metastatic small cell lung cancer. *Clinical Cancer Research*, *27*(9), 2378–2382. https://doi.org/10.1158/1078-0432.CCR-20-3901

Singh, V. J., Sharma, B., & Chawla, P. A. (2021). Recent developments in mitogen activated protein kinase inhibitors as potential anticancer agents. *Bioorganic Chemistry*, *114*. https://doi.org/10.1016/J.BIOORG.2021.105161

Smyth, E. C., Tarazona, N., & Chau, I. (2014). Ramucirumab: targeting angiogenesis in the treatment of gastric cancer. *Immunotherapy*, *6*(11), 1177–1186. https://doi.org/10.2217/IMT.14.85

Solomon, B. J., Mok, T., Kim, D.-W., Wu, Y.-L., Nakagawa, K., Mekhail, T., Felip, E., Cappuzzo, F., Paolini, J., Usari, T., Iyer, S., Reisman, A., Wilner, K. D., Tursi, J., & Blackhall, F. (2014). First-Line Crizotinib versus Chemotherapy in ALK -Positive Lung Cancer. *New England Journal of Medicine*, *371*(23), 2167–2177. https://doi.org/10.1056/NEJMOA1408440

Spencer, S. A., Riley, A. C., Matthew, A., & Di Pasqua, A. J. (2019). Brigatinib: Novel ALK Inhibitor for Non–Small-Cell Lung Cancer. *Annals of Pharmacotherapy*, *53*(6), 621–626. https://doi.org/10.1177/1060028018824578

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/CAAC.21660

Syed, Y. Y. (2019). Lorlatinib: First Global Approval. *Drugs*, *79*(1), 93–98. https://doi.org/10.1007/S40265-018-1041-0

Tanaka, K., Nosaki, K., Otsubo, K., Azuma, K., Sakata, S., Ouchi, H., Morinaga, R., Wataya, H., Fujii, A., Nakagaki, N., Tsuruta, N., Takeshita, M., Iwama, E., Harada, T., Nakanishi, Y., Okamoto, I., Tanaka, K., Nosaki, K., Otsubo, K., … Okamoto, I. (2017). Acquisition of the T790M resistance mutation during afatinib treatment in EGFR tyrosine kinase inhibitor-naive patients with non–small cell lung cancer harboring EGFR mutations. *Oncotarget*, *8*(40), 68123–68130. https://doi.org/10.18632/ONCOTARGET.19243

Thandra, K. C., Barsouk, A., Saginala, K., Aluru, J. S., & Barsouk, A. (2021). Epidemiology of lung cancer. *Contemporary Oncology (Poznan, Poland)*, *25*(1), 45–52. https://doi.org/10.5114/WO.2021.103829

Thomas, P., Vincent, B., George, C., Joshua, J., Pavithran, K., & Vijayan, M. (2019). A comparative study on erlotinib and gefitinib therapy in non-small cell lung carcinoma patients. *Indian Journal of Medical Research*, *150*(1), 67–72. https://doi.org/10.4103/IJMR.IJMR_1896_17

Tian, H., Yang, Z., & He, J. (2022). Adagrasib: A landmark in the KRASG12C-mutated NSCLC. *MedComm*, *3*(4), e190. https://doi.org/10.1002/MCO2.190

Toublanc, A. C., Guecamburu, M., Veillon, R., Rosellini, P., Girodet, P. O., & Zysman, M. (2022). Second-line lurbinectedin as a new treatment option for small-cell lung cancer:

Preliminary results in real-clinical practice. *Thoracic Cancer*, *13*(15), 2248–2252. https://doi.org/10.1111/1759-7714.14464

Tsoukalas, N., Aravantinou-Fatorou, E., Baxevanos, P., Tolia, M., Tsapakidis, K., Galanopoulos, M., Liontos, M., & Kyrgias, G. (2018). Advanced small cell lung cancer (SCLC): new challenges and new expectations. *Annals of Translational Medicine*, *6*(8), 145–145. https://doi.org/10.21037/ATM.2018.03.31

U. S. Food & Drug Administration. (2019). *Drug Trials Snapshots: ROZLYTREK | FDA*. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-rozlytrek

U.S. Food & Drug Administration. (2018). *Drug Trials Snapshot: VIZIMPRO | FDA*. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshot-vizimpro

U.S. Food & Drug Administration. (2018). *Drug Trials Snapshots: LORBRENA | FDA*. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-lorbrena

U.S. Food & Drug Administration. (2020). *Drug Trial Snapshot: GAVRETO | FDA*. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trial-snapshot-gavreto

U.S. Food & Drug Administration. (2020). *Drug Trials Snapshots: RETEVMO | FDA*. https://www.fda.gov/drugs/development-approval-process-drugs/drug-trials-snapshots-retevmo

U.S. Food & Drug Administration. (2020). *Drug Trials Snapshots: ZEPZELCA | FDA*. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-zepzelca

U.S. Food & Drug Administration. (2022). *Drug Trials Snapshot: TEPMETKO | FDA*. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshot-tepmetko

van den Borg, R., Leonetti, A., Tiseo, M., Giovannetti, E., & Peters, G. J. (2019). Novel targeted strategies to overcome resistance in small-cell lung cancer: focus on PARP

inhibitors and rovalpituzumab tesirine. *Expert Review of Anticancer Therapy*, *19*(6), 461–471. https://doi.org/10.1080/14737140.2019.1624530

van Meerbeeck, J. P., Fennell, D. A., & de Ruysscher, D. K. M. (2011). Small-cell lung cancer. *The Lancet*, *378*(9804), 1741–1755. https://doi.org/10.1016/S0140-6736(11)60165-7

Vansteenkiste, J. F., van de Kerkhove, C., Wauters, E., & van Mol, P. (2019). Capmatinib for the treatment of non-small cell lung cancer. *Expert Review of Anticancer Therapy*, *19*(8), 659–671. https://doi.org/10.1080/14737140.2019.1643239

Velez, M., Arango, B. A., Perez, C. A., & Santos, E. S. (2012). Safety and efficacy of pemetrexed in maintenance therapy of non-small cell lung cancer. *Clinical Medicine Insights: Oncology*, *6*, 117–124. https://doi.org/10.4137/CMO.S6248

Vyse, S., & Huang, P. H. (2022). Amivantamab for the treatment of EGFR exon 20 insertion mutant non-small cell lung cancer. *Expert Review of Anticancer Therapy*, *22*(1), 3–16. https://doi.org/10.1080/14737140.2022.2016397

Wang, J., Lam, D., Yang, J., & Hu, L. (2022). Discovery of mobocertinib, a new irreversible tyrosine kinase inhibitor indicated for the treatment of non-small-cell lung cancer harboring EGFR exon 20 insertion mutations. *Medicinal Chemistry Research*, *31*(10), 1647–1662. https://doi.org/10.1007/S00044-022-02952-5

Wang, X., Huang, A., Lu, Y., Gao, S., Hu, W., & Cheng, H. (2022). Drug-induced liver injury associated with dacomitinib: A case report. *Frontiers in Oncology*, *12*, 4785. https://doi.org/10.3389/FONC.2022.979462

Wang, Y., Zou, S., Zhao, Z., Liu, P., Ke, C., & Xu, S. (2020). New insights into small-cell lung cancer development and therapy. *Cell Biology International*, *44*(8), 1564–1576. https://doi.org/10.1002/CBIN.11359

Wolf, J., Seto, T., Han, J.-Y., Reguart, N., Garon, E. B., Groen, H. J. M., Tan, D. S. W., Hida, T., de Jonge, M., Orlov, S. v., Smit, E. F., Souquet, P.-J., Vansteenkiste, J., Hochmair, M., Felip, E., Nishio, M., Thomas, M., Ohashi, K., Toyozawa, R., … Heist, R. S. (2020). Capmatinib in MET Exon 14–Mutated or MET-Amplified Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *383*(10), 944–957. https://doi.org/10.1056/NEJMOA2002787

Wu, Q., Qian, W., Sun, X., & Jiang, S. (2022). Small-molecule inhibitors, immune checkpoint inhibitors, and more: FDA-approved novel therapeutic drugs for solid tumors from 1991 to 2021. *Journal of Hematology & Oncology 2022 15:1*, *15*(1), 1–63. https://doi.org/10.1186/S13045-022-01362-9

Xu, J., Wang, J., Zhang, S., Xu, J., Wang, J., & Zhang, S. (2017). Mechanisms of resistance to irreversible epidermal growth factor receptor tyrosine kinase inhibitors and therapeutic strategies in non-small cell lung cancer. *Oncotarget*, *8*(52), 90557–90578. https://doi.org/10.18632/ONCOTARGET.21164

Yang, J., & Gong, W. (2019). Lorlatinib for the treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer. *Expert Review of Clinical Pharmacology*, *12*(3), 173–178. https://doi.org/10.1080/17512433.2019.1570846

Ye, Z., Huang, Y., Ke, J., Zhu, X., Leng, S., & Luo, H. (2021). Breakthrough in targeted therapy for non-small cell lung cancer. *Biomedicine & Pharmacotherapy*, *133*, 111079. https://doi.org/10.1016/J.BIOPHA.2020.111079

Yu, Y., Zhu, F., Zhang, W., & Lu, S. (2022). Comparison of Efficacy and Safety of Brigatinib in First-Line Treatments for Patients with Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Systematic Review and Indirect Treatment Comparison. *Journal of Clinical Medicine*, *11*(11), 2963. https://doi.org/10.3390/JCM11112963

Zago, G., Muller, M., van den Heuvel, M., & Baas, P. (2016). New targeted treatments for non-small-cell lung cancer - role of nivolumab. *Biologics: Targets and Therapy*, *10*, 103–117. https://doi.org/10.2147/BTT.S87878

Zappa, C., & Mousa, S. A. (2016). Non-small cell lung cancer: current treatment and future advances. *Translational Lung Cancer Research*, *5*(3), 288–300. https://doi.org/10.21037/TLCR.2016.06.07

Zhang, H. (2016). Osimertinib making a breakthrough in lung cancer targeted therapy. *OncoTargets and Therapy*, *9*, 5489–5493. https://doi.org/10.2147/OTT.S114722

Zhang, S. S., & Nagasaka, M. (2021). Spotlight on Sotorasib (AMG 510) for KRASG12C Positive Non-Small Cell Lung Cancer. *Lung Cancer: Targets and Therapy*, *12*, 115–122. https://doi.org/10.2147/LCTT.S334623

Zhang, S. S., & Zhu, V. W. (2021). Spotlight on Mobocertinib (TAK-788) in NSCLC with EGFR Exon 20 Insertion Mutations. *Lung Cancer: Targets and Therapy*, *12*, 61–65. https://doi.org/10.2147/LCTT.S307321