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Personalized approaches to lung cancer treatment: A review of targeted therapies, pharmacogenomics, and combination strategies

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ABSTRACT

Globally, lung cancer—more specifically, non-small cell lung cancer (NSCLC)—contributes significantly to the death toll from cancer. Recent advances in molecular research have identified key genetic mutations that drive tumor growth, including those in the EGFR, KRAS, ALK, and MET genes, accounting for around 80 % of lung cancers that are categorized as non-small cell lung cancer (NSCLC). The advent of targeted therapies such as Tyrosine kinase inhibitors (TKIs) and monoclonal antibodies, have revolutionized cancer treatment by specifically inhibiting oncogenic pathway. However, despite this advancements, treatment outcomes remain suboptimal due to intrinsic heterogeneity of cancers and the development of resistance mechanisms. The cancer treatment landscape is constantly changing to address these challenges and improve patient outcomes. Customization of cancer therapies through pharmacogenomics is hindered by tumor adapatability and resistance, limited prognostic biomarkers and suboptimal monotherapies, necessitating innovative research in adoptive therapies biomarker development and combination therapies. Ongoing trails aims to enhance treatment endurance via the advancement of combination regimens incorporating multiple targeted therapies or synergistic combination immunotherapy with chemotherapy. Ongoing research is focused on optimizing CRISPR-Cas9 delivery system, improving specificity and minimizing half target effect. Emphasizes the crucial role of molecular mutations, the advantages and disadvantages of targeted medicines, and the prospects for enhancing the effectiveness of lung cancer treatment results are all highlighted in this Review.

1. Introduction

Cancer is the leading cause of death in the united states, exhibiting an alarming rate of 1.8 million new onset and 606,520 fatality occur annually. The most prevalent forms include lung cancer, breast cancer, and prostate cancer (Cancer Statistics). Lung cancer is the vital medical condition distinguished by dysregulated multiplication of malignant cells within the lungs poses considerable threat including serious impact and potential mortality (https://wwwwhoint/news-room/fact-sheets/detail/lung-cancer). According to statistics in India on lung cancer, there are roughly 72,510 new cases diagnosed with the disease each year, making up 5.8 % of all cancer cases, and 66,279 fatalities from the disease, or 7.8 % of all cancer-related deaths (Sung et al., 2021). In areas where smoking rates are high, cigarette smoking accounts for 80 %–90 % of instances (l et al., 2013). Two distinct forms of lung cancer are small cell lung cancer (SCLC) and Non-small cell lung cancer (NSCLC). Subtypes of non-small cell lung cancer (NSCLC) like Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma accounts for 80 %–85 % of cases of lung cancer (American Cancer Society, n.d.). Adenocarcinoma the most dominant type of cancer in the United States, and it is directly connected to a history of smoking. Adenocarcinoma remains to be the leading contributer of lung cancer deaths in the United States, despite decrease in overall incidence and mortality. It accounts for around 40 % of all lung malignancies and has its origins in mucosal glands. This subtype, which is also the most prevalent in non-smokers, typically appears near the periphery of the lung and frequently occurs in regions with persistent inflammation or scar tissue (Li et al., 2018a). Lung adenocarcinoma, commonly identified around the age of 71, is the most dominant strain of non-small cell lung cancer, emerging from mucin producing cells and frequently arising in the lung terminal (Byun et al., 2018; https://wwwcancercentercom/cancer-types/lung-cancer/types/adenocarcinoma-of-the-lung#what-is-adenocarcinoma-of-the-lung). Adenocarcinoma of is divided into four types: Minimally invasive adenocarcinoma, Adenocarcinoma In Situ, invasive, and its variants. Timely discovery improves outcomes. Advanced stages spread to various areas, with lymph node invasion starting in bronchial lymph

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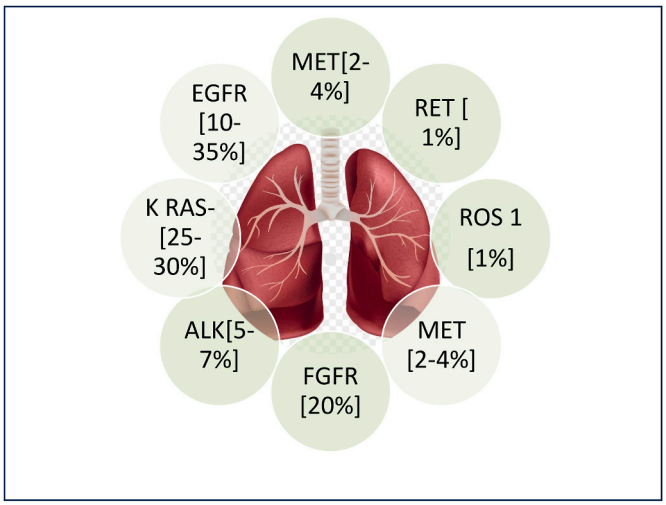

Fig. 1. The most frequent altered genes in NSCLC.

node and potentially reaching to cross lung metastasis. Certain alteration in the EGFR gene or ALK fusion oncogenes, which can be targeted by specific tyrosine kinase inhibitors (Yang et al., 2018; Oh et al., 2018). NSCLC treatment advances now include targeted therapies targeting molecular factors like K-Ras, EGFR, and ALK, with cytochrome P450 family playing a key role in drug metabolism during chemotherapy (Gross et al., 2015; Gazdar, 2009). Targeted therapies for tumor development and progression are based on understanding cellular networks and crucial nodes. Molecular studies revealed oncogenic mutations triggering oncoproteins, leading to tumors. Therapeutic agents targeting deregulated tumor promoting protein, like cetuximab, have shown effectiveness in treating specific oncogenes. This strategy is approved for the patients with EGFR-positive NSCLC (Gross et al., 2015; Pirker et al., 2009) hyperactivating mutations in the K-Ras gene are frequent in 25–35 % of NSCLC patients, particularly in the patients with adenocarcinoma.Thesealterations lead to an abnormal kinase fusion protein, resulting in continuous kinase activation[(Mortaza Haghgoo et al.), (BRAF in non-small cell lung cancer (NSCLC))]. MET gene is crucial for tumor growth, survival, migration, invasion, and angiogenesis. Research is exploring the MET signaling pathway as a potential target to overcome resistance in NSCLC (Schmidt et al., 1997, 1999) (see Fig. 1).

1.1. Targeted pathways in non small cell lung cancer

1.1.1. Epidermal growth factor receptor

G protein-coupled receptors (GPCRs) are vital membrane proteins that transduce a wide range of environmental signals, including light, ions, hormones, and neurotransmitters, into intracellular messages. These receptors are responsible for various physiological processes, such as learning, memory, and vision (Crilly et al., 2021). GPCRs are divided into five major families according to shared characteristics in their seven transmembrane (TM) domains: Adhesion Family [24 receptors], Frizzled/Taste Family [24 receptors], Glutamate Family [15 receptors], Secretin Family [15 receptors], and Rhodopsin Family [701 receptors] (Fredriksson et al., 2003). Even with all the research that has been done, most of the roughly 800 GPCRs are referred to as orphan receptors because there is not a complete understanding of their physiological function (Howard et al., 2001).

Structurally, GPCRs consist of an extracellular N-terminal region, three extracellular loops (exoloops), three intracellular loops (cytoloops), a C-terminal region, and seven TM segments forming the core. The C-terminal cysteine residues undergo palmitoylation, creating a fourth intracellular loop. Each transmembrane domain contains 20–27 amino acids, though the C-terminal (12–359), N-terminal (7–595), and loop (5–230) segments vary, reflecting their distinct functional roles. There is a weak relationship between the length of the N-terminal and the ligand size (Ji et al., 1998), indicating that larger ligands, such as polypeptides and glycoprotein hormones, are accommodated by longer N-terminal segments. The calcium receptor is an exception because its N-terminal segment is very long, approximately 600 amino acids (Cattaneo et al., 2014). The heptahelical structure defines GPCRs as transmembrane receptors.

GPCRs lack inherent enzymatic activity; instead, their action is mediated by heterotrimeric G protein binding, which comprises Gα, Gβ, and Gγ subunits. Ligand binding to the GPCR results in activation of the G protein and subsequent dissociation into GTP-bound Gα and Gβγ subunits. These subunits control the function of several intracellular enzymes including phospholipase C, adenylate cyclase, and kinases resulting in the formation of second messengers that have a diverse impact on cellular processes (Gusach et al., 2020). High-resolution imaging technologies have greatly enhanced the knowledge on GPCR structures and their interaction with multiple ligands and signaling partners (Kö and se, 2017).

GPCRs and receptor-tyrosine kinases (RTKs) are major targets for drug discovery. In cancer cells, oncogenic signaling by EGFR through GPCR is a major factor in migration, invasion, and proliferation. A number of GPCR ligands trigger EGFR signaling in cancer cells by activating specific GPCR complexes (Liu et al., 2018). Tyrosine kinase inhibitors (TKIs) have been found to be highly effective in patients with EGFR mutations, particularly in lung cancer (https://wwwcancercentercom/cancer-types/lung-cancer/types/adenocarcinoma-of--the-lung#what-is-adenocarcinoma-of-the-lung). The human genome has more than 90 protein tyrosine kinase genes, of which 58 code for transmembrane RTKs that belong to 20 subfamilies, such as the EGFR family (Blume-Jensen et al., 2001). The family comprises four members: ErbB4/Her4, EGFR/ErbB1/Her1, ErbB2/Her2, and ErbB3/Her3. ErbB2 is an orphan receptor, whereas ErbB3 has aberrant kinase activity. Ligand-induced heterodimerization is essential to activate all ErbB receptors (Mitsudomi et al., 2010; Citri and Yosef, 2006; Arteaga et al., 2014).

Binding of EGF to EGFR results in receptor dimerization and activation, followed by increased kinase activity. *Trans*-autophosphorylation of EGFR follows, which sets off several downstream signaling pathways responsible for cell survival, migration, and proliferation. Activation results in the formation of complexes of signaling proteins like Grb2, Shc, and PI3K, leading to the activation of Ras, which activates the ERK pathway and transcription factors. Moreover, PI3K-AKT pathway and PLC-γ1 are responsible for cell migration and survival, and participate in EGFR activation (Wang, 2016). Activation of GPCRs causes conformational changes that release the α, β, and γ subunits. These subunits bind to targets, producing inositol trisphosphate (IP3), phospholipase C, and diacylglycerol (DAG), which activate protein kinase C (PKC) and raise intracellular calcium levels. GPCRs also stimulate the MAPK pathway, leading to EGFR transactivation, autophosphorylation, and dimerization, thereby controlling cellular functions including growth, differentiation, and survival. Hence, GPCRs control EGFR signaling through several mechanisms, both direct and indirect, to regulate a wide range of physiological functions (Fischer et al., 2003).

EGFR mutations are often found in the catalytic tyrosine kinase domain in the form of a leucine-to-arginine point mutation at codon 858 (L858R) in exon 21 or an in-frame exon 19 deletion (E19del). These mutations result in constitutive EGFR activation. The L858R mutation extends ligand-dependent activation by stabilizing the receptor's activation loop, whereas the E19del mutation reduces the size of the ATP-binding cleft, increasing ligand-dependent activation. First-generation TKIs act on these mutations by inhibiting EGFR from autophosphorylation in response to EGF (Rosell et al., 2009a; Yun et al., 2007; Shigematsu et al., 2005a; Barker et al., 2001; Moyer et al., 1997) (see Fig. 2).

1.1.2. Kirsten rat associated sarcoma pathway

GTPases function as molecular switch oscillating between active GTP-bound states and inactive GDP-bound and, K-Ras controls numerous cellular process such as cell division, cell growth and survival. Guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) control this cycle (Kim et al., 2021a). The structurally conserved N-terminal domain of Ras proteins is essential for interacting with regulatory proteins and binding guanine nucleotides. There are four isoforms of the Ras gene family: K-Ras4A, K-Ras4B, H-Ras, and N-Ras. Of them, KRAS mutations are especially important since they make up around 70 % of all Ras mutations seen in malignancies (Toulany, 2022). Mutations predominately cluster at codons 12, 13, and 61, where single nucleotide changes leading to significant functional alterations are caused by single nucleotide substitutions (Mo et al., 2018). lung adenocarcinomas detected in approximately 30 % of lung adenocarcinomas patients and are especially observed in advanced non-small cell lung cancer (NSCLC). There is a significant amount of genomic heterogeneity among KRAS-mutant tumors since over 80 % of these mutations are located at codon 12, where glycine is substituted by different amino acids (Veluswamy et al., 2021). In normal circumstances, the binding of guanosine triphosphate (GTP) activates Ras proteins, while the hydrolysis of GTP to guanosine diphosphate (GDP) deactivates them. GEFs, which promotes encourage the GDP and GTP exchange while GAPs enhance GTP hydrolysis, controlling this activation-deactivation cycle. Cancer associated KRAS mutations exhibits reduced GAP binding and enhance interaction with GEFS, leading to constitutive activation of downstream signaling cascades even in the absence of growth factor (Downward, 2003; Aran and Omerovic, 2019). Receptor tyrosine kinases (RTKs) including the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptor (PDGFR) actives the RAS signalling pathway by inducing receptor oligomerization activating kinase activity and exposing catalytic domains. Growth factor receptor-bound protein 2 (Grb2), an adaptor proteins binds to phosphorylated receptors through its Src homology 2 [SH2] domain, recognizing phosphothyrosine sites created by the receptor phosporization. following Grb2 recruiment Son of Sevenless homolog 1 (SOS-1) and other GEFs catalyses RAS, GDP and GTP exchange (Kim et al., 2021b).Activating the protein and triggering.Raf/Mek/Erk cascade, modulating gene expression, cell proliferation and differentiation by modifying gene expression through Erk-mediated transcription, is one of the downstream effectors that Ras interacts with once it is active. Furthermore, by blocking apoptosis and bolstering anabolic activities, Ras activation activates the phosphatidylinositol 3-kinase (PI3K)/Pdk1/Akt pathway, which in turn promotes cell survival and proliferation. Additionally, Ras triggers Ral-GEFs, which in turn trigger RalA and RalB proteins implicated in cell motility and vesicle trafficking (Avruch et al., 2001; Lemmon and Schlessinger, 2010) (see Fig. 3).

1.1.3. Anaplastic lymphoma kinase pathway

Anaplastic Lymphoma Kinase (ALK), a receptor tyrosine kinase found primarily in the nervous system, is oncogenic in cancer cells via three predominant mechanisms: gene fusions, gene amplifications, and activating point mutations (Peng et al., 2022). The PI3K-AKT signaling pathway plays a significant role in cell growth, survival, and metabolism regulation. It comprises three AKT isoforms—Akt1, Akt2, and Akt3—mapped on chromosomes 14q32, 19q13, and 1q44, respectively (Murthy et al., 2000). Akt activation has the ability to modulate forkhead transcription factors, suppress p53-induced apoptosis, and inhibit pro-apoptotic proteins like BAD and BAX (Tan, 2020). Receptor tyrosine kinases (RTKs), which are stimulated by ligands such as insulin or growth hormones, activate the PI3K-AKT pathway. Activation of this pathway recruits and activates phosphoinositide 3-kinase (PI3K), which phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to form phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 brings Akt to the membrane, where it becomes completely activated through phosphorylation at serine 473 by mTORC2 and threonine 308 by 3-phosphoinositide-dependent protein kinase-1 (PDK1) (Tan, 2020). Akt controls cell growth, survival, and metabolism by affecting downstream effectors, such as glycolytic enzymes, mTORC1, and apoptotic regulators. PTEN and other phosphatases are essential regulators of this pathway (Glaviano et al., 2023; Iksen and Pongrakhananon, 2021). Dysregulation of this pathway is associated with several disorders, including cancer.

The catalytic subunit p110α of PI3K is encoded by the PI3KCA gene, which is often mutated in many cancers, including non-small cell lung cancer (NSCLC). PI3KCA mutations in exons 9 and 20 result in the constitutive activation of PI3K. About 7 % of lung adenocarcinoma (LUAD) and 35 % of lung squamous cell carcinoma (LUSQ) exhibit PI3KCA mutations (ManningBD, 2007; Lau et al., 2021; Scheffler et al., 2015). Oncogenic mutations of the p85 subunit, including E542K, E545K, and E545Q, block the inhibitory binding between the p85 N-terminal Src homology 2 (SH2) domain and the p110 catalytic subunits, leading to further activation of the pathway (Huang et al., 2007; Miled et al., 2007). Loss of PTEN destabilizes the PI3K/AKT pathway, leading to high PIP3 levels and hyperactivation of AKT, which drives tumor growth and disrupts the balance of the tumor microenvironment.

Mutations in the PI3KCA gene, which codes for the p110α catalytic subunit of phosphoinositide 3-kinase (PI3K), are a key factor in NSCLC development and progression. Oncogenic mutations in the helical and kinase domains of PI3KCA hyperactivate PI3K, resulting in overproduction of PIP3, which activates AKT, a central protein in cancer development. Mutant PI3KCA drives cell proliferation, encourages angiogenesis, and suppresses apoptosis, leading to unlimited tumor growth and drug resistance to standard therapies (Yamamoto et al., 2008; Pérez-Ramí et al., 2015; Carriere et al., 2011; Chen et al., 2015) (see Fig. 4).

1.1.4. Fibroblast growth factor receptors pathway

Fibroblast growth factor receptors are key orchestors of cellular proliferation and differentiation including development,wound healing, and noplastic transformation by promoting mitosis in epithelial and mesenchymal cells.their signalling pathways are vital for lung morphogenesis and are implicated in the onset and progression of respiratory disorders (Yang et al., 2021). Classical FGFs like FGF1 and FGF2 are critical for cell proliferation and angiogenesis, interacting with various FGFRs. These receptors are categorized into four main types: FGFR1, FGFR2, FThe first Fibroblast growth factor was isolated from pituatry tissue in 1973,subsequent research has lead to the discovery of atleast 22 distinct FGFs IN humans,forming a complex family of signalling molecules that interact with FGFRs to regulate cellular proliferation,differentiation (Ornitz and Itoh, 2001; Katoh and Katoh, 2006). FGFR4 and GFR3, each with isoform diversity that impact the outcome and specificity of this signaling. Other FGFs, such as FGF3, FGF7, and FGF10, participate in organ development and epithelial proliferation. metabolic processes including glucose and lipid metabolism and phosphate homeostasis are regulated by Specialized FGFs like FGF21 and FGF23 (Fu et al., 2004; Kharitonenkov et al., 2005; Razzaque and Lanske, 2007; Tomlinson et al., 2002).The binding of FGFs to FRs transmembrane recptors,iniates a signalling cascades. Heparan sulfate glycosaminoglycans (HSGAGs)acts as co receptors,modulate the FGFs-FGFRs transmembrane interaction,increasing binding affinity and efficacy and facilitates FGFR dimerization. Activated FGFRs will further triggers the downstream signaling pathways, consisting of the RAS/-RAF/MEK/ERK pathway, also denoted as the MAPK (Mitogen-Activated Protein Kinase) pathway. This cellular pathway is vital for cell division and is often dysregulated in cancer (Raman et al., 2003; Casci et al., 1999; Zhao and Zhang, 2001; Fürthauer et al., 2002). PI3K/AKT pathway, which is important in cancers and other diseases with abnormal cell survival regulation is also stimulated by FGF activation,. PI3K, a serine/threonine kinase, yields phosphatidylinositol (3,4,5)-trisphosphate (PIP3), which further activates AKT, a serine/threonine kinase engaged in survival,metabolism, growth, and, limiting apoptotis

cascade (Lamothe et al., 2004). PLCγ pathway, causing PLCγ to hydrolyze PIP2, producing inositol trisphosphate (IP3) and diacylglycerol (DAG), causing intracellular calcium release and protein kinase C activation, influencing cell migration and adhesion is also regulted by this signalling cascade (Dailey et al., 2005; Liao et al., 2013; Ding et al., 2008). FGFR1 gene amplification (22 % of cases)by fluourscensce in situ hybridisation (FISH).and chromosmal rearrangements drive oncogenic signalling in squamous cell lung cancer,fostering tumorigenesis (Turner and GroseFibroblast, 2010; Jackson and Medeiros, 2010) (see Fig. 5).

1.1.5. *Mesenchymal epithelial transition factor pathway*

MET oncogene, encodes the tyrosine kinase receptor which is also known as hepatocyte growth factor receptor (HGFR). Its 140 kDa transmembrane β-chain and 50 kDa extracellular α-chain, connected by disulfide bridges, regulate various physiological functions like cell migration, survival,growth, and differentiation (im et al., 2009; Sattler et al., 2007; Stella and Comoglio, 1999). This pathway is initiated when HGF (hepatocyte growth factor) interact with the MET receptor, causing dimerization and subsequent autophosphorylation, this activation enables tyrosine kinase activity (Hammond et al., 2001; Peruzzi and Bottaro, 2006).

MET receptor undergo subsequent autophosphorylation within the docking site, recruiting key adaptor proteins like CRK, PI3K, GRB2, SHC, PLCγ, SHIP-2, SRC and STAT3. MET will also interacts with GRB2-associated binding protein 1, generating additional binding sites for downstream adaptors. GAB1 can bind directly or indirectly [83 84]. MET signaling involves phosphorylation of Janus kinase 1 (JNK) and binding to Chicken tumor virus regulator of kinase (CRK) and Signal transducer and activator of transcription (STAT3). STAT3 directly affects cell proliferation,tubulogenesis and invasion, while focal adhesion kinase (FAK) promotes cell migration. Negative regulation is mediated by PLCγ, PTPs and increased intracellular calcium levels can also contribute to negative regulation. MET pathways are more common in Non-small cell lung cancer, (Organ et al., 2011; Zhang et al., 2018a; Spitaleri et al., 2023). MET signaling plays crucial role in NSCLC patients via various mechanisms, acting as both a primary and secondary driver after resistance to EGFR TKIs (Salgia, 2017; Yu et al., 2020a). Activation of MET pathway in NSCLC leads to poor prognosis and resistance to EGFR inhibitors. MET amplification activates the ERBB3/PI3K/AKT signaling, promoting tumor growth and metastasis. This complicating treatment strategies. Dual inhibition of MET and EGFR represents a promising therapeutic approach. METMAb, a monoclonal antibody targeting MET, demonstrated improved progression-free survival in a Phase II studies. Further ongoing research is needed to address new mutations and emerging resistance mechanisms (Belalcazar et al., 2012; Drilon et al., 2017) (see Fig. 6).

1.1.6. *V ROS oncogene homolog 1 pathway*

Rearranged during Transinfection regulates cell differentiation, proliferation, growth, and survival. Rearrangement, especially through gene fusions, can cause abnormal kinase activity and deregulation of critical pathways, but the specific ligand triggering ROS1 activation remains unknown (Charest et al., 2006; Jun et al., 2012). ROS1 rearrangements are present in 0.9–2.6 % of NSCLCs, and their interaction with other oncogenes or tumor suppressor pathways can lead to more aggressive cancer forms[(Gendarme et al., 2022), (Gainor et al., 2013)]. SLC34A2 and CD74 fusion partners promote oncogenesis,by creating hybrid proteins particularly in NSCLC, and influence tumor growth and cellular signaling via different processes (Rikova et al., 2007; Takeuchi et al., 2012). The ROS1-FIG4 fusion distrupts normal cellular function, driving oncogenesis through enchanced kinase activity, distrupted FIG4 phosphatase function and activation of downstream signalling pathways (Govindan et al., 2012). The KDELR2-ROS1 fusion protein represents a unique oncogenic entity,blending KDELR2-ROS1 fusion protein,potentially altering its subcellular localization and protein-protein interactions (Zhu et al., 2016) (see Fig. 7).

1.1.7. *Rearranged during Transinfection pathway*

Since its discovery in 1985 the RET receptor tyrosine kinase recognized as a vital regulator in the developmental processes like kidney and enteric nervous system development, neuron differentiation, and cell differentiation, proliferation, and migration (Regua et al., 2022a; Schuchardt et al., 1994; Chi et al., 2009; Enomoto et al., 2001). The RET gene, has 21 exons and 5 introns located on chromosome 10. Its structure includes an extracellular domain, transmembrane domain, juxtamembrane region,intracellular kinase domain, and C-terminal tail. The transmembrane domain embeds the protein into the cell membrane,the extracellular domain binds ligands and the intracellular kinase domain regulates tyrosine phosphorylation. The juxtamembrane region regulates kinase activity and receptor dimerization (Bhattarai et al., 2022; RET). RET signaling cascade initiates upon GDNF family ligands interaction with to GFRα co-receptors, promoting receptor dimerization and activation, followed by autophosphorylation which then triggers PI3K/AKT, RAS/RAF/MEK/ERK, JAK2/STAT3, and PLCγ downstream signaling cascades. Cadherins stabilize cell-cell junctions, nuclear translocation and STAT3 phosphorylation. RET's active conformation is stabilised by RET-Y905, Src kinase binding is promoted by Y981 following by Grb2 binds to RET, this enhances cell proliferation and differentiation (Li et al., 2019; Perrinjaquet et al., 2010a, 2010b; Ibanez, 2013; Schuringa et al., 2001; Regua et al., 2022b). Key marker and therapeutic target in non-small cell lung cancers is KIF5B-RET fusion protein, that results in genetic rearrangement of the KIF5B gene with the RET gene, leading to uncontrolled cascade, promoting cancer cell survival and proliferation (Takahashi et al., 2020; Romei et al., 2016; Kohno et al., 2012) (see Fig. 8).

1.1.8. *B RAF murine sarcoma viral oncogene homolog B 1 pathway*

RAF family proteins, play a vital role in regulating MAPK pathway, disregulated in up to 30 % of human cancers, with BRAF mutations found in 2 % of NSCLCs (Sforza et al., 2022; Tissot et al., 2016). EGFR triggered MAPK signalling which governs cell growth however mutations in BRAF or RAS disrupts this regulatory mechanisms,resulting in unchecked cell proliferation and tumor development (Abdayem and Planchard, 2022; Yan et al., 2022). BRAF mutations are divided into three types based on the location of the mutation and its functional effect,the V600E mutation in BRAF constitutes a class1 oncogenic event characterised by persistent MAPK signalling,resulting in robust BRAF kinase activity and heightened sensitivity to BRAF and MEK inhibitors. Class II mutants signal as RAS-independent dimers and are found in the activation section or P-loop. Examples of these mutants include K601, L597, G464, and G469. Class III mutations, which are located in the DFG motif, P-loop, or catalytic loop, show reduced BRAF kinase activity but can activate the Raf-1 proto-oncogene CRAF to improve MAPK pathway signaling (Yarchoan et al., 2015; Caparica et al., 2016; Yao et al., 2015, 2017) (see Fig. 9).

2. Targeted drug therapies for NSCLC

2.1. *EGFR targeting drugs*

An important element in the spread of non-small-cell lung cancer (NSCLC) is the epidermal growth factor receptor (EGFR). Small molecular tyrosine kinase inhibitors, which block EGFR, have become a promising therapeutic approach (Heist and Christiani, 2009). For patients with EGFR-positive non-small cell lung cancer (NSCLC), the first-line therapies include cetuximab, a monoclonal antibody, and gefitinib, an EGFR tyrosine kinase inhibitor (Sim et al., 2018; Sebastian et al., 2014) For patients with advanced NSCLC harboring activating EGFR mutations,erlotinib provides a targeted and improved progression -free survival and reduced toxicity compared to chemotherapy (Reck et al., 2011). EGFR mutation -positive advanced NSCLC,Osmimertinib, athird generation EGFR TKI,offers enchanced effectiveness in advanced NSCLC with EGFR mutations. (Soria et al., 2018). Novel EGFR-targeted

treatments including nazartinib (EGF816) and HM61713 (olmutinib) are being investigated. Approved in South Korea, HM61713, exclusively targets mutations in the EGFR gene, including T790 M. Phase I/II clinical studies have demonstrated encouraging outcomes (Zhang et al., 2018b; Wang et al., 2016a). Preclinical research has shown that nazartinib, an irreversible, mutant-selective EGFR TKI, may effectively target T790 M and EGFR-activating mutations (Tan et al., 2020). Nazaretinib demonstrated a suggested phase 2 dosage of 150 mg once day in a phase 1 dose-escalation trial, with rash, diarrhea, and exhaustion being the most frequent side effects (Jia et al., 2016).Amivantamab, a bispecific EGFR-MET antibody, in combination with lazertinib (a third-generation EGFR TKI), has shown promising efficacy in EGFR-mutated NSCLC. In the Phase 3 MARIPOSA trial, the combination resulted in superior progression-free survival compared to osimertinib monotherapy, offering a potential new first-line treatment (Cho et al., 2022). Sugemalimab, a PD-L1 monoclonal antibody, with chemotherapy showed notable survival advantages in the Phase 3 trial and has been approved in metastatic NSCLC without EGFR/ALK mutations (Sakamoto and Jimeno, 2023). Sunvozertinib, a new oral EGFR exon 20 insertion inhibitor, has been promising in the Phase 3 clinical trial and offers a potent therapeutic option for patients whose tumors are resistant to the common EGFR TKIs (Wang et al., 2022)

2.2. K RAS targeting drugs

Janssen's Tipifarnib, an effective Ras farnesyltransferase inhibitor, is also a promising therapeutic agent for the treatment of neoplasms of different forms (Norman, 2002). Kidney-related adverse effects were linked to treatment in initial clinical trials, but no major issues arose (Martinez de la Cruz et al., 2021). The ability to block specific KRAS mutations directly has been achieved in recent times. Earlier, KRAS had been targeted indirectly.

Specific and irreversible inhibitor of KRAS G12C is a small molecule inhibitor, sotorasib (Hong et al., 2020). In preclinical models of KRAS G12C-mutant lung cancer xenograft models, sotorasib, a multikinase inhibitor, was found to be effective in significantly inhibiting tumor progression and causing regression, as evidenced by Hallin et al. (2020) (Hallin et al., 2020). The efficacy of sotorasib has been confirmed in clinical trials; Phase 1 and 2 trials had anticancer activity in patients with previously treated NSCLC and advanced solid tumors with a KRAS p.G12C mutation (Riely et al., 2021; Skoulidis et al., 2021). A Phase 3 trial (CodeBreaK 200 trial) showed that sotorasib led to robust progression-free survival (PFS) compared with docetaxel in patients with advanced NSCLC with KRAS G12C mutations, with a hazard ratio (HR) of 0.66 (95 % CI, 0.51–0.86; $p = 0.0017$) and median PFS of 5.6 months vs. 4.5 months with docetaxel. The safety profile was good with reduced rates of Grade 3 or more adverse events when compared to chemotherapy (de Langen et al., 2023).

Likewise, adagrasib (MRTX849) is a selective, potent, and irreversible covalent inhibitor of KRAS G12C, permanently and covalently binding to maintain KRAS in an inactive form. The Phase 1/2 KRYSTAL-1 study proved the clinical activity and tolerability of adagrasib's adverse-event profile (Jä et al., 2022; Ou et al., 2022). Adagrasib was superior to docetaxel in terms of efficacy and response durability, with a median PFS of 6.5 months vs 4.5 months for docetaxel-treated patients, in the Phase 3 KRYSTAL-12 trial. In addition, adagrasib had improved central nervous system (CNS) penetration and was thus especially useful in patients with brain metastases (Luo et al., 2023).

Both sotorasib and adagrasib have shown high clinical efficacy and tolerability in treating KRAS G12C-mutant NSCLC, especially in advanced or metastatic disease and as second-line treatment after initial treatment. The favorable safety profiles, along with better progression-free survival, make both of these drugs useful additions to the arsenal in treating KRAS-mutant lung cancer.

2.3. AKT targeting drugs

Treatment options for non-small cell lung cancer (NSCLC) have significantly improved as a result of the introduction of targeted medicines. The FDA expedited approval of crizotinib, the first ALK-directed tyrosine kinase inhibitor (TKI), in 2011 (Lin et al., 2017) due to its strong clinical efficacy in advanced ALK-rearranged NSCLC. Subsequent phase III studies showed crizotinib's advantage over chemotherapy.

Promising results have also been observed with second-generation ALK inhibitors, such as ceritinib, alectinib, and brigatinib (Kim et al., 2016; Gettinger et al., 2016). In addition, a number of AKT inhibitors, which fall under the ATP-competitive and allosteric inhibitor groups, are presently undergoing clinical development (Bhutani et al., 2013). In preclinical models and phase I clinical trials, the ATP-competitive inhibitor ipatasertib (GDC-0068) has shown good AKT signaling inhibition and anticancer responses (Shariati et al., 2019).

Preclinical research has demonstrated the possibility of further AKT inhibitors, including capivasertib (AZD5363), ARQ092, and afuresertib (GSK2110183) (Addie et al., 2013; Davies et al., 2012; Lapierre et al., 2016; Zhang et al., 2014; He et al., 2018; Wang et al., 2016b; Liang et al., 2017). When coupled with other medications, the ATR kinase inhibitor uprosertib (GSK2141795) has been shown to improve treatment results in NSCLC models and clinical studies (Fukushima and Pommier, 2018; Pommier et al., 2016). Clinical studies involving humans and mice models have demonstrated the anti-tumor effectiveness of ceralasertib (AZD6738) (Lee et al., 2017; Cross et al., 2020).

Another AKT inhibitor, GDC-0077, is being studied in human clinical trials after exhibiting strong anti-tumor effect in preclinical animal models (Gillespie et al., 2020; Parker et al., 2021).

Recently, capivasertib (Truqap) gained FDA approval in November 2023 as a combination with fulvestrant for the treatment of hormone receptor-positive, HER2-negative metastatic or locally advanced breast cancer with PIK3CA, AKT1, or PTEN alterations. This was an approval based on the Phase 3 CAPItello-291 trial that showed the combination resulted in statistically significant improvement of progression-free survival (PFS) to 7.3 months compared with 3.1 months on fulvestrant alone. The safety profile was tolerable well, with controllable adverse events, such as diarrhea, rash, and hyperglycemia (Dilawari et al., 2024).

Likewise, inavolisib (Itovebi) was approved during October 2024 for intravenous use together with palbociclib and fulvestrant in patients with endocrine-resistant, PIK3CA-mutated, hormone receptor-positive, HER2-negative metastatic or locally advanced breast cancer. The INAVO120 Phase 3 trial proved inavolisib to have impressive improvement in PFS over that of placebo without a significantly undesirable toxicity profile (Blair, 2025).

2.4. RET targeting drugs–

One to two percent of patients with non-small-cell lung cancer (NSCLC) have RET rearrangements, which constitutively activate downstream pathways related to cell growth, survival, proliferation, and differentiation. RET-rearranged NSCLC patients have undergone testing with several multi-kinase inhibitors, such as cabozantinib, vandetanib, and lenvatinib, with differing degrees of success. FDA approval for the therapy of metastatic RET fusion-positive NSCLC was due to the recent evidence of higher success rates and favorable tolerability by two selective RET inhibitors, selpercatinib and pralsetinib (Cascetta et al., 2021a; Drilon et al., 2020a; Gainor et al., 2021).

To ascertain the efficacy of selpercatinib or pralsetinib as first-line treatment for RET-positive non-small cell lung cancer patients, Phase III clinical trials are currently ongoing. Cabozantinib is an oral multikinase inhibitor of VEGFR2, MET, ROS1, AXL, KIT, and TIE2 but is less effective against RET ($IC50 = 5.2$ nM). Clinical trials showed efficacy in NSCLC with RET rearrangements and manageable side effects and response rates (Ju et al., 2012; Drilon et al., 2016).

The LIBRETTO-001 trial showed remarkable findings for selpercatinib, a new-generation RET kinase inhibitor, with a 64 % overall response rate (ORR) and median duration of response (DOR) of 17.5 months in both treated and untreated patients (Cascetta et al., 2021b; Gautschi et al., 2017; Drilon et al., 2018). In May, the FDA approved selpercatinib with accelerated approval.

By contrast, pralsetinib (BLU-667) is a strongly selective and potent RET inhibitor explicitly engineered to defeat the shortcomings of previous treatments. Both in vivo and in vitro studies proved to be effective on resistance mutations as well as on oncogenic forms of RET in vitro and in vivo. At first-in-human trials, clinical responses were maintained in patients bearing RET-altered NSCLC and medullary thyroid carcinoma (MTC) without measurable off-target toxicities (Subbiah et al., 2018).

The Phase I/II ARROW trial assessed pralsetinib in RET fusion-positive NSCLC, with an overall response rate (ORR) of 61 % in treatment-naïve patients and 70 % in patients who had received prior treatment, with a median duration of response (DOR) of 22.3 months. The safety profile was tolerable, with the most frequent adverse events being hypertension, elevated liver enzymes, and neutropenia. Pralsetinib's activity in advanced RET fusion-positive NSCLC validates its position as a highly effective and tolerable treatment, especially for patients with no history of systemic therapy (Griesinger et al., 2022).

2.5. FGFR targeting drugs

Given its growth-promoting properties and the increased frequency of FGF/FGFR-related abnormalities in squamous NSCLC compared to adenocarcinoma, targeting the FGF/FGFR signaling pathway presents a viable treatment approach for squamous non-small cell lung cancer (NSCLC) (Salgia, 2014). This strategy is being investigated in clinical trials with a range of multitargeted tyrosine kinase inhibitors.

Nintedanib (BIBF1120), a strong oral tyrosine kinase inhibitor targets several proangiogenic and pro-fibrotic pathways, such as Src, FGFR, Flt-3 kinases,PDGFR, and VEGFR (Roth et al., 2015). When its combined with docetaxel, nintedanib has shown promising effect as a second-line treatment for advanced non-small cell lung cancer (NSCLC), especially in patients with lung adenocarcinoma, despite of this it did not increase overall survival rate in malignant pleural mesothelioma (Scagliotti et al., 2019; Reck et al., 2014)

Certain NSCLC patients have demonstrated promise for treatment with lorlatinib and ponatinib, two more tyrosine kinase inhibitors. Lorlatinib is most widely utilized for ALK-positive mutations, whereas ponatinib targets only lung cancer with FGFR1 amplification or mutations (Tan et al., 2019; LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet], 2012). The CROWN study's long-term data provides evidence for lorlatinib's sustained advantage over crizotinib (Solomon et al., 2023). FGF ligand traps, such as FP-1039 (GSK3052230), have the ability to neutralize various FGFs that bind to FGFR1, exhibiting a satisfactory safety profile and having the potential to be used with conventional chemotherapy (Tolcher et al., 2016). Selective FGFR inhibitors have demonstrated considerable effectiveness in FGFR-altered malignancies and strong suppression of FGFR activity, such as INCB054828 (pemigatinib) and futibatinib (Liu et al., 2015; Subbiah et al., 2022a; Rodó et al., 2024; Javle et al., 2023). Novel anticancer treatments are being explored in conjunction with monoclonal antibodies that target programmed cell death protein 1 (PD-1) such as budigalimab (ABBV-181) (Italiano et al., 2022).

2.6. BRAF targeting drugs

The BRAF pathway offers viable therapeutic target for NSCLC Sorafenib,a multikinase inhibitor with activity aginst BRAF, CRAF, VEGFR2, PDGFR-β, and c-Kit,demonstrates anticancer efficacy contingent upon EGFR mutations.Nonethless preclinical research reveals sorfenibs potential as a targeted BRAF inhibitor,providing a rationale for its repurposing in BRAF driven NSCLC (Wilhelm et al., 2004; Blumenschein, 2008). BRAF V600E mutations are the particular target of dabrafenib and vemurafenib, two advanced-generation BRAF inhibitors. In pretreated NSCLC patients with BRAF V600E mutations, vemurafenib showed a 42 % objective response rate (ORR) and a 7.3-month progression-free survival (PFS) (Hyman et al., 2015; Gautschi et al., 2015). Dabrafenib also demonstrated considerable clinical efficacy in NSCLC with BRAF V600E mutations, particularly when coupled with trametinib, another MEK inhibitor (Planchard et al., 2016). Novel RAF inhibitors, such as BGB-283, have showed excellent outcomes in treating BRAF V600-mutant solid tumors, including NSCLC, with acceptable safety profiles (Planchard et al., 2017, 2021). When used in conjunction with binimetinib (an MEK inhibitor) and encorafenib (a BRAF inhibitor), individuals with metastatic NSCLC who also carry the BRAF V600E mutation have shown promise.

binimetinib and encorafenib precisely aimed the BRAF V600E mutation and block the related MAPK signaling cascade, which increases apoptosis and reduces the proliferation of tumor cells as studied in preclinical research, (Baik et al., 2024; Wagle et al., 2012). The combination has improved progression-free survival and overall response rates in patients with BRAF V600E-mutant metastatic NSCLC, according to clinical studies, including the Phase 3 COLUMBUS study (Falchook et al., 2016; Larkin et al., 2014).

2.7. MET targeting drugs

Robust clinical research focused on investigating MET – targeting therapeutics non-small cell lung cancer (NSCLC). The MET signaling pathway plays a pivotal role in cancer growth and metastasis, and Three primary classes of MET inhibitors: HGF monoclonal antibodies and decoys, small molecule inhibitors and MET monoclonal antibodies. HGF monoclonal antibodies, including ABT-700 and ficlatuzumab (AV-299), have demonstrated promising results in the treatment of squamous cell carcinoma of the head and neck and non-small cell lung cancer (Sacco et al., 2015; Patnaik et al., 2014; Smith and Doe, 2020). MET monoclonal antibodies, such Onartuzumab (MetMAb) and Glesatinib (MGCD265), have proven capacity to decrease tumor development and metastasis in preclinical trials (Kinoshita and Ikeda, 2015; Kim and Kim, 2017).

Furthermore, MET is also targeted by crizotinib, which is mainly recognized as an ALK inhibitor and has demonstrated potential advantages in MET-positive malignancies (Shaw and Kim, 2013). Abnormal MET signaling is disrupted by small molecule inhibitors such as Crizotinib, Cabozantinib, Tivantinib, MAK683, and Foretinib (Kim and Cho, 2018; Shaw et al., 2013; Abou-Alfa et al., 2018; Jä et al., 2014; Tarrant et al., 2017; McDermott et al., 2013).

Vebreltinib (Bozitinib) is a MET tyrosine kinase inhibitor (TKI) with selective activity against MET exon 14 skipping mutation-positive NSCLC. In Phase III trials, it had an objective response rate (ORR) of ~50 % in treatment-naïve patients and 40 % in previously treated patients, with median progression-free survival (PFS) of 8.5 months. Its safety profile was tolerable, with edema, nausea, and mild hepatic enzyme elevations as common adverse events, making it a promising choice for MET-driven lung cancer (Yang et al., 2024). A numerous of active clinical studies are investigating at MET-targeting therapeutics in non-small cell lung cancer (NSCLC). For instance ongoing trials, which include NCT04563042, NCT04127823, NCT03750702, NCT03697367, and NCT04265603, provide potential treatments for patients with tumors driven by MET (McDermott et al., 2013; Yang et al., 2024; ClinicalTrials.gov, 2024a; ClinicalTrials.gov, 2024b; ClinicalTrials.gov, 2024c; ClinicalTrials.gov, 2024d; ClinicalTrials.gov, 2024e). These studies underscore the continuous attempts to utilize MET-targeting medicines in cancer treatment, bringing fresh hope for better cancer treatment outcomes.

POTENTIAL STRATEGIES TO OVERCOME RESISTANCE-

POTENTIAL STRATEGIES TO OVERCOME RESISTANCE-		
	MECHANISM	STRATEGIES
On-Target Resistance	1. Secondary mutations in the target kinase prevent drug binding and reduce drug efficacy. 2. Common mutations include EGFR T790 M (confers resistance to first-generation TKIs) and C797S (causes resistance to third-generation TKIs like osimertinib).	* Next-generation TKIs: Osimertinib is effective against T790 M mutations. * Novel allosteric inhibitors: Designed to bind outside the ATP pocket and overcome mutations like C797S. * Combination therapies: Dual EGFR inhibitors may help prevent resistance.
Bypass Signaling Activation	1. Cancer cells activate alternative signaling pathways, reducing dependence on the original target. 2. Key bypass pathways include MET, HER2, AXL, and IGF-1R, which drive tumor progression independent of EGFR inhibition.	* Combination therapies targeting alternative pathways: • MET inhibitors (e.g., tepotinib, capmatinib) combined with TKIs. • HER2 inhibitors (e.g., trastuzumab, neratinib) in HER2-mutant lung cancers. • AXL inhibitors (e.g., bemcentinib) to reduce epithelial-to-mesenchymal transition (EMT). *Dual-targeted therapy: Combining TKIs with monoclonal antibodies (e.g., amivantamab).
Phenotypic Transformation	1. Histological changes allow cancer cells to evade targeted therapies. 2. NSCLC to SCLC transformation occurs in a subset of EGFR-mutant lung cancers. 3. Epithelial-to-mesenchymal transition (EMT) leads to a more invasive, drug-resistant phenotype.	*Chemotherapy: Platinum-based regimens (etoposide/carboplatin) are used when NSCLC transforms into SCLC. *Differentiation therapy: Targets transcription factors to restore epithelial characteristics. *Immunotherapy: Immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) help recognize transformed cancer cells.
Drug Efflux and Pharmacokinetic Mechanisms	Increased expression of ABC transporters (e.g., P-gp, BCRP, MRP1) actively pumps out drugs from cancer cells, reducing intracellular drug concentration	*Efflux pump inhibitors: Agents targeting ABC transporters can restore drug sensitivity. *Dose modifications: Higher or altered dosing schedules can overcome drug clearance issues. * Nanoparticle-based drug delivery: Encapsulating TKIs in nanoparticles enhances intracellular retention.
Tumor Microenvironment (TME) Influence	The tumor microenvironment (TME) promotes drug resistance through: • Stromal interactions: Cancer-associated fibroblasts (CAFs) secrete growth factors. • Immune evasion: Tumors express PD-L1 to suppress immune response. • Hypoxia-induced resistance: Hypoxic regions in tumors alter drug metabolism	* Immunotherapy: • PD-1/PD-L1 inhibitors (e.g., pembrolizumab, atezolizumab) restore T-cell function. * Anti-angiogenic agents: • VEGF inhibitors (e.g., bevacizumab, ramucirumab) reduce hypoxia and enhance drug delivery. *Targeting stromal interactions: • Hedgehog pathway inhibitors (e.g., vismodegib) disrupt fibroblast-mediated resistance

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3. Highlighting the pharmacogenomices of NSCLC

Pharmacogenomics plays a pivotal role in non-small cell lung cancer (NSCLC) treatment. By detecting genetic variants affecting medication response, healthcare practitioners can boosts therapy efficacy, predict and prevent adverse responses, and enhance patient outcomes. Shorter treatment duration, fewer prescriptions needed, less adverse drug responses, enhancing drug trials success, more rigorous drug approval processes, and enabling early disease identification are all possible outcomes of pharmacogenomics [(T Aneesh et al., 2009). (Lu, 1998)].

3.1. Genomics of EGFR

Several genetic mutations, such as EGFR, ROS1, BRAF, ALK, KRAS, and MET exon 14 skipping mutation, influence treatment response for NSCLC (Domvri et al., 2013). EGFR mutations are significant biomarkers that influence prognosis and help in predicting the success of targeted therapy. Exon 20 mutations (5–10 % of EGFR mutations), L858R mutations (40–45 % of EGFR mutations), exon 19 deletions (45 % of EGFR mutations), and the T790 M mutation (50–60 % of cases of resistance) are a few of the frequent EGFR alterations (O'Leary et al., 2020; Shigematsu et al., 2005b; Rosell et al., 2009b). Exon 19 deletions combined with L858R mutations can be managed successfully with EGFR tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib. Exon 20 mutations, however, confer marked resistance to TKIs of the first and second generations. Third-generation TKIs such as osimertinib are needed to treat the T790 M mutation (Mok et al., 2017). Additional variants that affect sensitivity or resistance to particular EGFR inhibitors include T854A, D761Y, and L747S.

The C797S mutation, which occurs in the ATP-binding site of EGFR and prevents osimertinib and other third-generation inhibitors from binding, is one of the molecular resistance mechanisms to EGFR inhibitors. Following initial treatment efficacy, this mutation is a significant cause of osimertinib resistance. MET amplification, which initiates the activation of other signaling pathways that bypass EGFR, is another significant mechanism. MET amplification stimulates the MET receptor to become activated, which triggers downstream survival pathways that are independent of EGFR signaling. Additionally, by permitting the survival and expansion of tumor cells despite EGFR inhibition, bypass signaling through additional receptor tyrosine kinases (RTKs) or downstream signaling molecules such as the PI3K-AKT and MAPK cascades could serve to promote resistance. These mechanisms emphasize both the complexity of EGFR blockade and the necessity for more esoteric, custom treatment approaches.

EGFR inhibitors are available as therapeutic options and have evolved through the first, second, and third generations (osimertinib, afatinib, erlotinib, and gefitinib). Pharmacogenomics can be incorporated into the treatment of non-small cell lung cancer by healthcare providers to save money, enhance treatment outcomes, and enhance patient care. Identification of these genetic alterations in NSCLC, guiding individualized treatment regimens, and optimizing patient outcomes all rely on pharmacogenomic testing (Yu et al., 2015, 2020b; Li et al., 2018b).

3.2. Genomics of ALK

A subgroup of NSCLC patients (3–5 %) has ALK gene rearrangements, i.e., the EML4-ALK fusion. This distinct subgroup mainly involves younger, lighter, or non-smoking patients, and those with adenocarcinoma histology. EML4-ALK fusion is the consequence of a genetic rearrangement between the EML4 and ALK genes that triggers aberrant, unregulated cell proliferation and activation of signaling pathways. Pharmacogenomic analysis is important to identify ALK rearrangements to direct targeted therapy with ALK inhibitors in ALK-rearranged NSCLC patients (Shaw et al., 2014b; Lei et al., 2022).

While crizotinib, a first-generation ALK inhibitor, has proven effective, resistance often develops within a year, primarily resulting from secondary mutations in the ALK gene, including the L1196 M gatekeeper mutation (Katayama et al., 2014; Gainor et al., 2016). To counter this resistance, the next generations of ALK inhibitors, such as lorlatinib, ceritinib, alectinib, and brigatinib, have been introduced. These new inhibitors target tumors with resistance mutations, including the particularly challenging-to-treat G1202R mutation (Dagogo-Jack et al., 2018). Other common ALK mutations that are associated with resistance are G1269A, C1156Y, S1206Y/C, and F1174L (Blumenschein, 2008). Also, bypass mechanisms like EGFR activation or MET amplification permit tumor growth even when ALK is inhibited (Solomon et al., 2018).

The development of ALK inhibitors exemplifies the power of pharmacogenomics-driven treatment strategies in NSCLC.

3.3. Genomics of K RAS

Non-small cell lung cancer (NSCLC) is more frequently driven by KRAS oncogene mutation-caused oncogenesis, 90 % of which take place at codon 12. They mostly include replacement mutations of glycine with cysteine (G12C, 40 %), valine (G12V, 21 %), or aspartic acid (G12D, 17 %) (Cascetta et al., 2022). They interfere with GAP-catalyzed hydrolysis to activate KRAS irreversibly with resultant unabated cell growth. Mutational frequencies at codons 13 (2–6 %) and 61 (1 %) are appreciably low. Treatment options for KRAS-mutant NSCLC are combination therapies, indirect inhibitors of KRAS such as SHP2 and MEK inhibitors, and direct KRAS inhibitors such as sotorasib and adagrasib (G12C) and Mirati Therapeutics (G13C) (Prior et al., 2020).

Resistance to KRAS inhibitors can, however, occur, especially through the development of secondary mutations in KRAS or activation of bypass pathways. For instance, mutations like G12V or G12D may lead to decreased drug sensitivity, whereas activation of alternative pathways (e.g., the PI3K-AKT or MAPK pathways) may lead to resistance. Combination therapies are being investigated to counteract these issues. Combining MEK inhibitors with KRAS inhibitors, SH2-domain containing protein tyrosine phosphatase (SHP2) inhibitors, or immunotherapy is an ongoing area of investigation to avoid or delay resistance. Also, the development of next-generation KRAS inhibitors that can target more than one KRAS mutation, including G12D, is an area of focus. In addition, biomarker-driven strategies can aid in personalizing more effective regimens and identifying those patients likely to benefit from particular combination regimens.

Discovery of customized therapies dependent upon KRAS mutation profiles holds valuable promise for enhancing outcomes in patients (Janne et al., 2019).

3.4. Genomics of PDL 1

By modulating immunological responses, Programmed Death-Ligand 1 (PD-L1) plays a crucial role in tumor immunoescape. PD-L1 is induced on the surface of activated T-, B-, and natural killer (NK) cells. It is also up-regulated in a range of tumor types, such as non-small cell lung cancer (NSCLC), with positive rates from 13 % to 70 % and expression rates from 19.6 % to 65.3 % (Mu et al., 2011; Chen et al., 2013).

Oncogenic drivers like EGFR, EML4-ALK, ROS1, KRAS, TP53, MET, and PIK3CA also impact PD-L1 expression in NSCLC (Jiang et al., 2017). PD-L1 expression is also affected by some genetic alterations, for example, rs2227981, rs2297135, and rs1575893 polymorphisms of the PD-L1 gene (CD274), HLA-A, HLA-B, and HLA-C gene variants, tumor mutational burden (TMB), microsatellite instability (MSI), STK11, KEAP1, and TP53 mutations (Moksud et al., 2023). PD-L1 gene expression levels (TPS, CPS), TMB-high (>10 mutations/Mb), MSI-high, and STK11/KEAP1 co-mutations are some of the biomarkers predicting response to PD-L1 inhibitors.

Combination treatments are being investigated, including PD-L1 inhibitor and CTLA-4 inhibitor, VEGF inhibitor, or targeted therapies to alter the tumor microenvironment and augment the immune response. Clinical trials such as KEYNOTE-024, CHECKMATE 026, BFAST, POPLAR, and OAK have established knowledge of the pharmacogenomic interactions with PD-L1 inhibitors like pembrolizumab, nivolumab, and atezolizumab, and continue to guide treatment approaches to NSCLC (Cho et al., 2021).

3.5. Genomics of BRAF

BRAF mutations are found in about 2–4 % of cases of non-small cell lung cancer (NSCLC). Of these mutations, 97 % take place at codon 600, predominantly as the result of a T1799A transversion leading to substitution of valine (V) with glutamic acid (E) at position 600 (V600E) (El-Telbany et al., 2012). V600K (8–20 %), V600R (1 %), V600 M (0.3 %), and V600D (0.1 %) are less frequent alternatives at codon 600, but non-V600 mutations such as K601E and D594 N are infrequent. G469A (39 %), D594G (11 %), G596R, G466R, and T599dup are some of the infrequent mutations. FDA-approved targeted therapies for BRAF V600E-positive metastatic NSCLC are dabrafenib in combination with trametinib; vemurafenib has shown an overall response rate of 42 % in patients with BRAF V600E-positive NSCLC (Cheng et al., 2016).

Resistance to BRAF inhibitors usually occurs by mechanisms such as secondary mutations in BRAF (e.g., the BRAF D594G mutation), activation of bypass signaling pathways (e.g., MEK or ERK activation), and upregulation of alternative receptor tyrosine kinases (such as EGFR or MET). Combination therapies for overcoming these resistances, where both BRAF and MEK are targeted (e.g., dabrafenib and trametinib), are frequently utilized, as they block downstream signaling. In addition, next-generation BRAF inhibitors and targeted therapies against bypass signaling pathways, including EGFR inhibitors or MEK inhibitors, can reverse resistance and enhance clinical outcomes (El-Telbany et al., 2012).

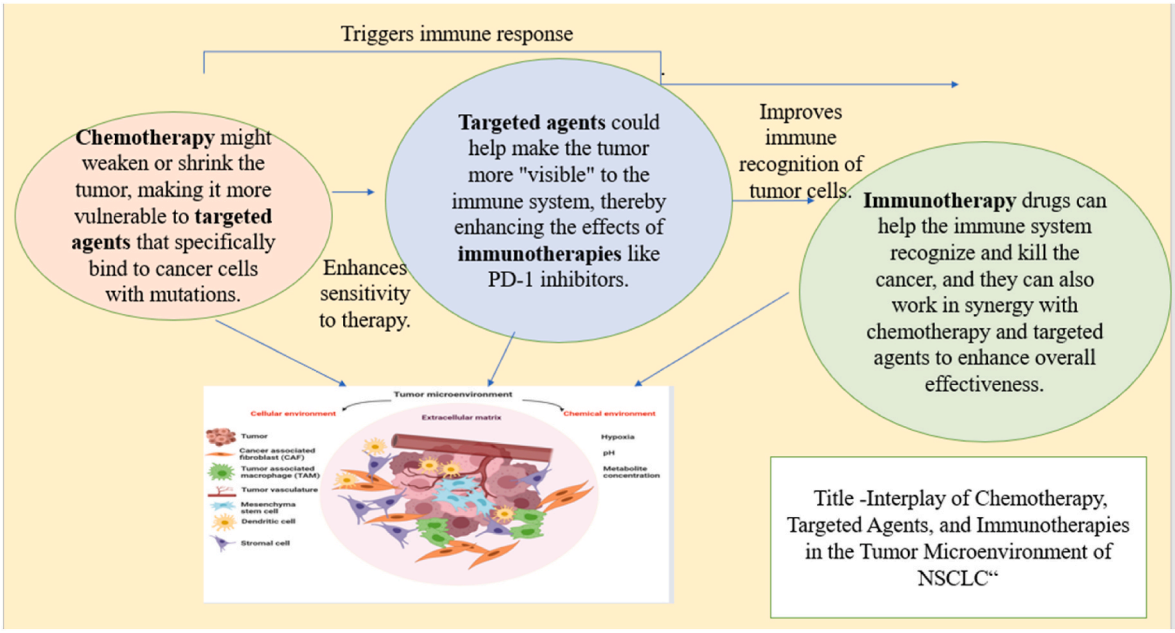
3.6. Genomics of RET

Approximately 1–2 % of lung tumors harbor RET mutations or rearrangements. In non-small cell lung cancer (NSCLC), RET fusions with partner genes like KIF5B, CCDC6, TRIM33, CUX1, NCOA4, and KIAA1468 are frequently observed (Loh et al., 2019). Tyrosine kinase inhibitors (TKIs) like sunitinib, vandetanib, cabozantinib, and sorafenib inhibit tumorigenic transformation and activated RET signaling, whereas the FDA-approved selpercatinib is targeted against RET-positive non-small cell lung cancer (Drilon et al., 2020b). Activation of RET mutations (M918T) and secondary RET mutations (G810R, G810S, and G810C) under the treatment of selpercatinib therapy are one of the mutations that have been identified, (Subbiah et al., 2022b). Additionally, TKI-resistant mutations in the Gly-rich loop (L730, E732, and V738), gatekeeper residue (V804), and hinge strand (Y806, A807, and G810) also exist, and a secondary RET mutation (S904F) has been identified to confer resistance to vandetanib (Nakaoku et al., 2018).

Resistance can be overcome by next-generation RET inhibitors or combination with MEK or EGFR inhibitors. In addition, approaches such as RET inhibitor and immune checkpoint inhibitor combination or selective targeting of resistance mutations (e.g., the G810 mutations) would be able to improve therapeutic efficacy in resistant cases (Drilon et al., 2020b).

4. Combination therapies

Combination drugs are addressing resistance to targeted therapies in non-small cell lung cancer (NSCLC) treatment, as shown by recent advances in this area (Kobayashi et al., 2023). combination therapy generates synergistic effects in the patients who are resistant to monotherapy to induce vigorous anti – tumor responses. New immune combination therapies are immunotherapy plus chemotherapy (IO + Chemo), immunotherapy plus immunotherapy (IO + IO), immunotherapy plus immunotherapy plus chemotherapy (IO + IO + Chemo), and immunotherapy plus anti-angiogenic therapy plus chemotherapy (IO + Anti-angio + Chemo) (). Many combinations have been approved and represent first-line therapy for advanced non-small cell lung cancer (Socinski et al., 2019; Gandhi et al., 2018). These combinations consist of Pembrolizumab + Carboplatin + Paclitaxel/Nab-paclitaxel (KEYNOTE-189), Atezolizumab + Carboplatin + Paclitaxel (IMpower150), Nivolumab + Ipilimumab + Chemotherapy (CHECKMATE 9LA), and Durvalumab + Chemotherapy (PACIFIC). Clinical trials pitting chemotherapy versus combination regimens, including Trem-



elimumab/Durvalumab/Chemotherapy (Hellmann et al., 2019; Johnson et al., 2022) and Nivolumab + Ipilimumab compared with chemotherapy among stage IV NSCLC patients (CHECKMATE-227), have showed better overall survival. Although there are additional treatment-related side events, the IO + Anti-angio + Chemo combination has also proved to be superior in terms of improving short-term survival (Pang et al., 2023). Pembrolizumab + Ramucirumab + Carboplatin + Paclitaxel (KEYNOTE-598) and Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel (IMpower150) are just a couple of examples (Reck et al., 2020b; Socinski et al., 2020).

Nevertheless, while promising outcomes, these combination therapies have certain limitations. One of the most important limitations is the increased toxicity of combining several treatment modalities. Side effects such as immune-related adverse events, hematologic toxicities, and gastrointestinal toxicity can complicate treatment regimens and necessitate further management (Birnboim-Perach and Benhar, 2024). In addition, the absence of reliable biomarkers to determine patient response is an important challenge. Although some biomarkers, including PD-L1 expression, are applied to inform the choice of immunotherapy, they do not invariably predict the effectiveness of combination therapy, and thereby there is potential for both undertreatment and overtreatment (Mé et al., 2023).At a mechanistic level, combination therapies seek to improve therapeutic impact by synergism. For instance, kinase inhibitors (TKIs) may cause immunogenic cell death (ICD), which activates the immune system and promotes anti-tumor immunity upon combination with checkpoint inhibitors. Besides, chemotherapy induces release of tumor antigens recognized by the immune system, whereas immunotherapy is enhancing immune activation. This combination of chemotherapy and immunotherapy can lead to more sustained anti-tumor responses than monotherapy, particularly in patients who are resistant to single-agent therapies. In spite of these advances, a better understanding of the mechanistic synergy and additional studies on biomarkers and toxicity management is essential for enhancing the efficacy and safety of combination regimens in NSCLC (Butterfield and Najjar, 2024).

Interaction between combination therapy, immunotherapy and targeted therapy-

5. Challenges and solutions

Pharmacogenomics presents a number of issues for lung cancer, a significant cause of cancer-related mortality globally. These challenges include resistance to targeted medicines and interpatient heterogeneity in gene expressions (Ruwali et al., 2021). The intricacy of signaling networks, our incomplete knowledge of gene-drug interactions, and ethical and regulatory issues such genetic data privacy pose significant clinical hurdles. The standardization of genetic testing, the interpretation of next-generation sequencing (NGS) data, the constraints on tumor collection and biopsies, the comprehension of pharmacokinetic and pharmacodynamic variability, and the creation of individualized treatment plans are among the technical difficulties (Bao et al., 2020). Another major obstacle to NSCLC pharmacogenetics is the lack of pharmacogenetics biomarkers (Satam et al., 2023a). For screening, patient stratification, prognosis, diagnosis, risk assessment, staging, and forecasting the impact of therapy, biomarkers such as ALK rearrangements, EGFR mutations, and KRAS mutations are crucial (Gromova et al., 2020).

To address these issues, researchers launched NGS-based testing,

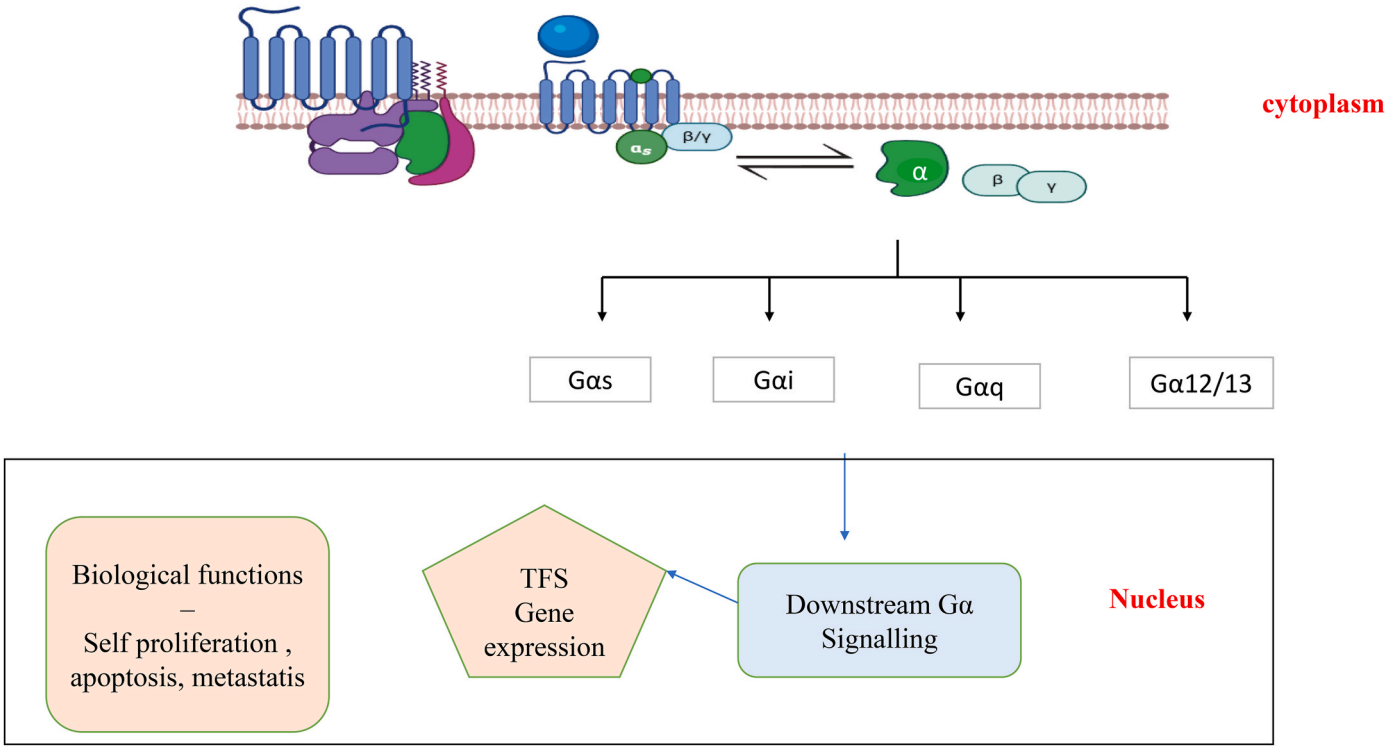


Fig. 2. EGFR pathway in non small cell lung cancer.

developing precision medicine clinical trials, integrating pharmacogenomics into clinical decision-making, enhancing bioinformatics and data analysis capabilities, and encouraging collaborative research and data sharing (Morash et al., 2018). In the future, pharmacogenomics will be integrated into clinical decision-making, pharmacogenomic testing guidelines will be developed, genetic testing will be expanded to diverse populations, and pharmacogenomic-based treatment algorithms will be established (Thandra et al., 2021). Bioluminescence resonance energy transfer, CRISPR-based biosensors, bulk and single-cell NGS, circulating cell-free DNA, and discovery techniques are examples of technological advances (Kabbani et al., 2023). Translational directions include addressing health inequities, guaranteeing access to pharmacogenomics testing, and applying pharmacogenomics results to clinical practice (Kumaran et al., 2023). Personalized medicine may be achieved by combining multi-omics data, creating biomarkers to predict therapy response, and investigating combination medicines customized for each patient (Graw et al., 2021). Current guidelines favor multigene NGS over sequential single-gene testing (Satam et al., 2023b). Due to the drawbacks of molecular analysis of tumor tissue biospecimens, liquid biopsy is a desirable substitute that offers benefits including non-invasiveness and improved tumor heterogeneity representation (Magaki et al., 2019). Although there are several drawbacks, such as a lack of standardized methods and high prices, liquid biopsy enables the early diagnosis of non-small cell lung cancer (NSCLC), identifies mutations for targeted therapy, and finds minimum residual disease (Bertoli et al., 2023).

6. Epigenomics

Epigenetic modifications, such as microRNA expression, DNA methylation, and histone adjustment, have a central role in the initiation and development of lung cancer. DNA methylation alterations silence critical tumor suppressor genes, whereas histone adjustment and microRNA disruption further aggravate cellular dysfunctions leading to cancer development (Balgkouranidou et al., 2013).

Hypermethylation of gene promoters, especially in the WNT signaling pathway, is responsible for lung cancer pathogenesis. Of note, tumor suppressor genes like CDKN2A are commonly hypermethylated, resulting in loss of function and uncontrolled cell growth. Likewise, histone-modifying enzymes like EZH2 play a role in oncogenesis by silencing major tumor suppressor genes in non-small cell lung cancer (NSCLC).

Exosomes and microRNAs have been of great promise as stable biomarkers for the diagnosis of lung cancer and assessment of therapeutic response. Marcus et al. have proven their stability as diagnostic markers, which is also pointing towards their clinical usefulness. Epigenetic changes affect numerous facets of the tumor microenvironment, such as immune evasion, metastasis, angiogenesis, apoptosis, and sensitivity to targeted treatments like chemotherapy and immunotherapy (Son et al., 2011).

Besides that, epigenetic science offers tremendous promise in the way of personalized treatment, early diagnosis markers, new drug targets, and insight into heterogeneity and lung cancer subtypes. Key priorities for future studies are probing the epigenetic changes within variants of lung cancers, explaining how non-coding RNAs can regulate epigenetics, forming combination regimens that couple epigenetic approaches with conventional cancer therapies, embedding biomarkers within clinical treatment and practice, and investigating genetic mutational relationships to epigenetic mechanisms within the lung cancers (Ramazi et al., 2023).

7. Emerging technology in pharmacogenomics

Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 helps to investigate the viability and safety of altering immune checkpoint genes editing may improve T cell treatment. Here, we report findings from a groundbreaking phase I clinical trial employing CRISPR-Cas9 PD-1-edited T cells, in humans and enrolling patients with advanced non-small-cell lung cancer (ClinicalTrials.gov NCT02793856) (Lu et al., 2020). Advancements in CRISPR-Cas systems have sped up the study of genomes. The application of CRISPR-Cas to cancer research has generated a lot of interest, leading to the creation of complementary

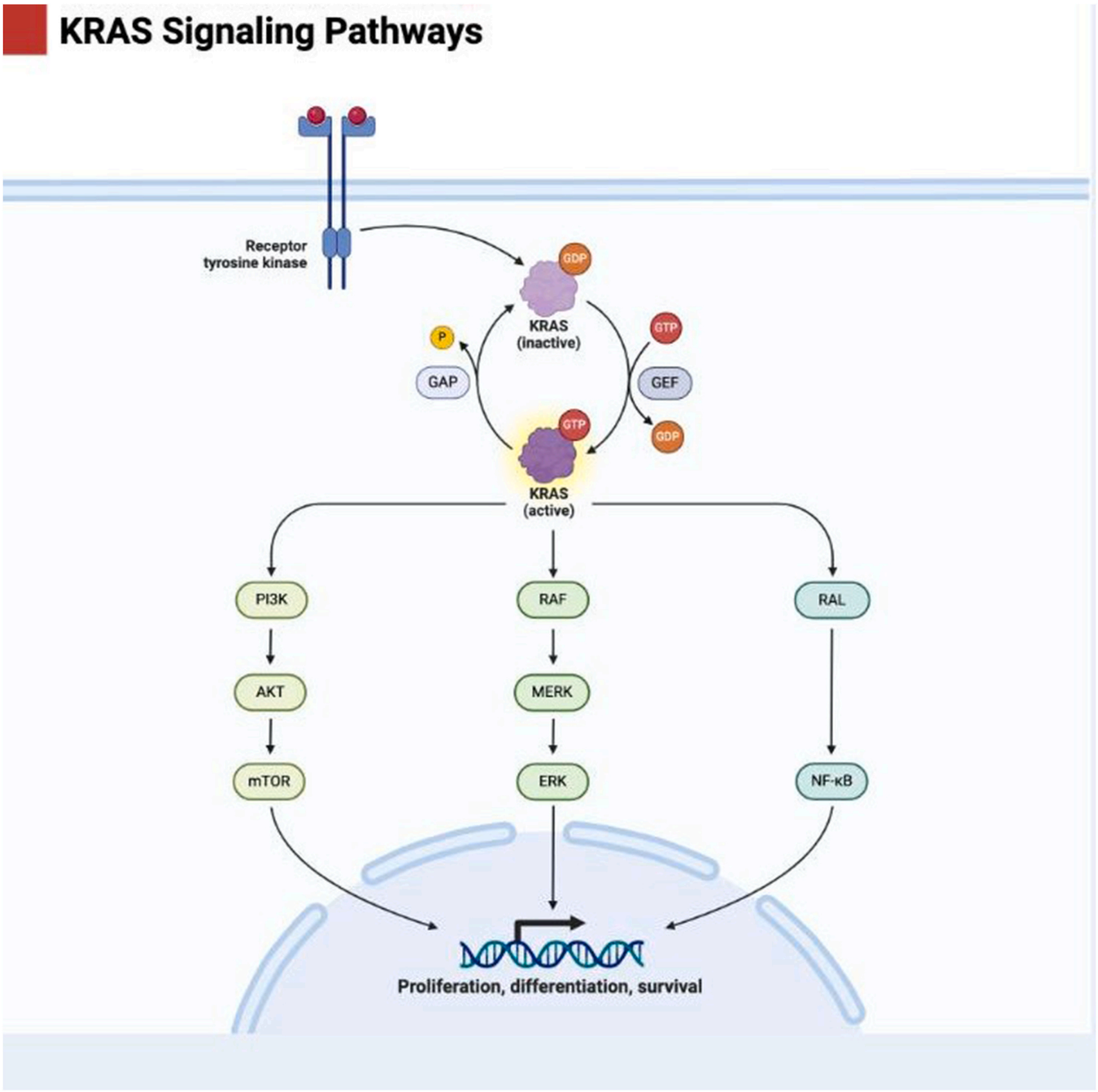


Fig. 3. K- RAS pathway in non small cell lung cancer.

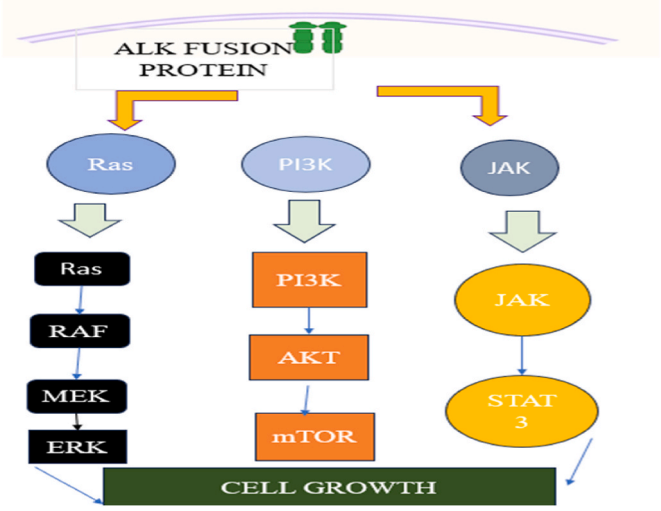


Fig. 4. ALK pathway in non small cell lung cancer.

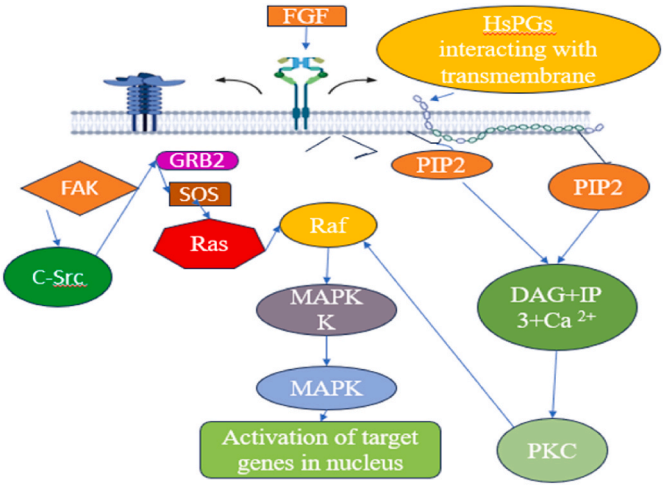


Fig. 5. FGFR pathway in non small cell lung cancer.

techniques for the validation of pharmacological targets and the identification of novel therapeutic targets by screening the whole genomes of cancer cells. Revealing modifications to tumor suppressor genes (TSGs) and oncogenes causing resistance to targeted treatments by activating alternative signaling pathways, CRISPR-based screens have elucidated number of novel cancer drivers (Sreedurgalakshmi et al., 2021). CRISPR, gene-editing technique has revolutionized research and enhabling prise investigation of medication resistance. In this study, we address drug resistance gene mutations, explain how the CRISPR/Cas9 system may correct multidrug resistance in NSCLC, and describe the mechanisms of drug resistance in non-small cell lung cancer (NSCLC). Using the CRISPR/Cas9 system in NSCLC patients' treatment is essential to improving their prognosis and overall quality of life (Huang et al., 2022).

8. Rationale for the study

Lung cancer, particularly non-small cell lung cancer (NSCLC), is a leading cause of cancer-related mortality worldwide, with treatment challenges driven by tumor heterogeneity, acquired resistance, and limited therapeutic efficacy. Despite advancements in targeted therapies such as tyrosine kinase inhibitors (TKIs) and monoclonal antibodies, the development of drug resistance continues to hinder long-term patient survival.

A key breakthrough in cancer therapy is the use of pharmacogenomics, which enables personalized treatment by identifying specific genetic mutations such as EGFR, KRAS, ALK, MET, and BRAF. However, pharmacogenomic-driven therapies are still limited by factors such as tumor adaptability, lack of predictive biomarkers, and suboptimal monotherapies. The integration of combination therapies—involving multiple targeted agents, immunotherapy, and chemotherapy—has emerged as a promising strategy to enhance treatment efficacy and overcome resistance mechanisms.

This study aims to:

1. Analyze the evolving landscape of NSCLC treatment, focusing on the role of targeted therapies and pharmacogenomics.
2. Identify mechanisms of drug resistance and explore strategies to enhance treatment durability.
3. Examine the potential of novel approaches, including CRISPR-Cas9 gene editing, in optimizing precision medicine for NSCLC.

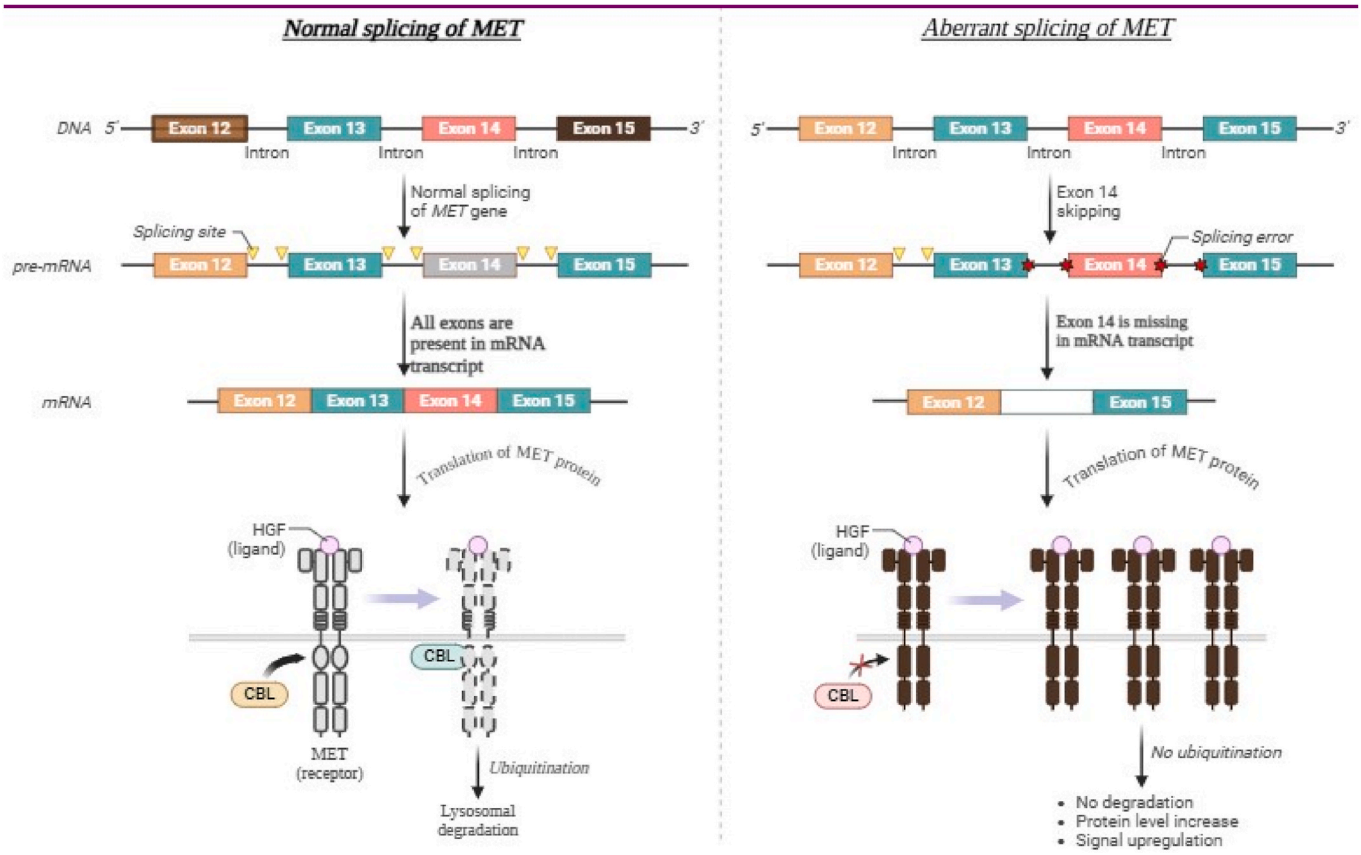


Fig. 6. MET pathway in non small cell lung cancer.

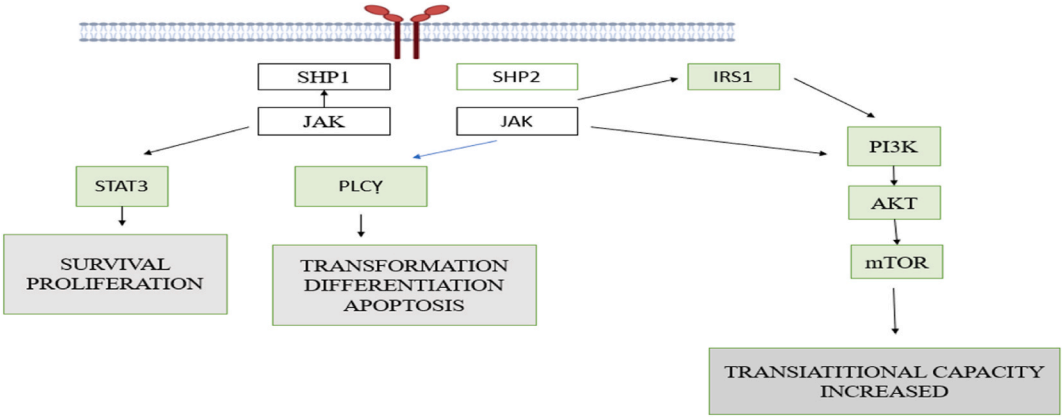


Fig. 7. ROS pathway in non small cell lung cancer.

By addressing these critical challenges, this study provides a comprehensive overview of current treatment strategies, emerging research, and future directions aimed at improving survival outcomes and quality of life for NSCLC patients.

9. Conclusion

Even with remarkable achivement in the management of lung cancer, especially non-small cell lung cancer (NSCLC), problems persevere in achieving prolonged remission and enhancing overall survival. The concentration of targeted medicines, such TKIs and monoclonal antibodies, on certain genetic alterations like EGFR, KRAS, and ALK has significantly improved patient care. However, tumor complexity and acquired resistance mechanisms generally hinders the efficiency of these tretment startegies, resulting to disease progression. Although pharmacogenomics is becoming a more important tool for treating patients individually, its wider applicability is limited by the absence of accessible testing and complete biomarkers. multimodal therapies that combine integrated startegy, such as immunotherapy, chemotherapy, and percision medicines are growing in fame to counteract resistance and enhancing results. Furthermore, CRISPR-Cas9 technology enables precise correction of genetic abnormalities driving oncogenesis. These

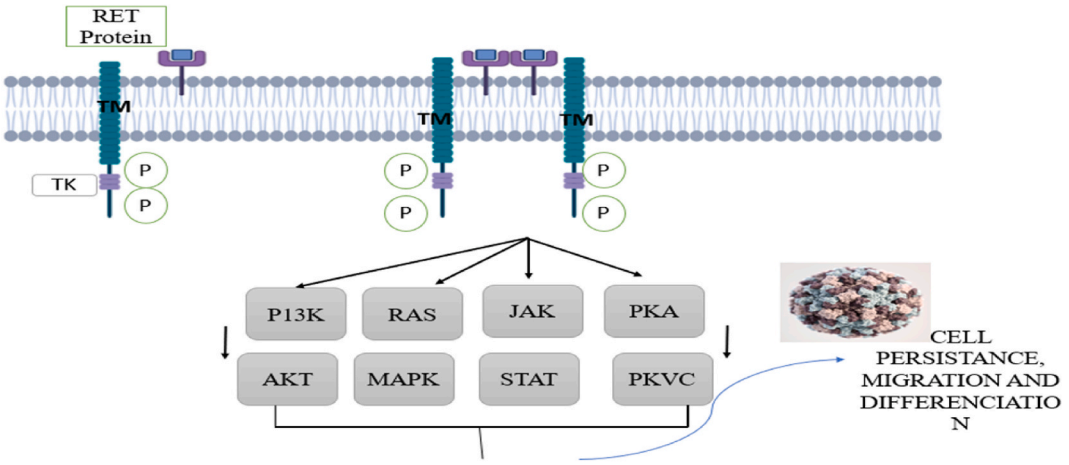


Fig. 8. RET pathway in non small cell lung cancer.

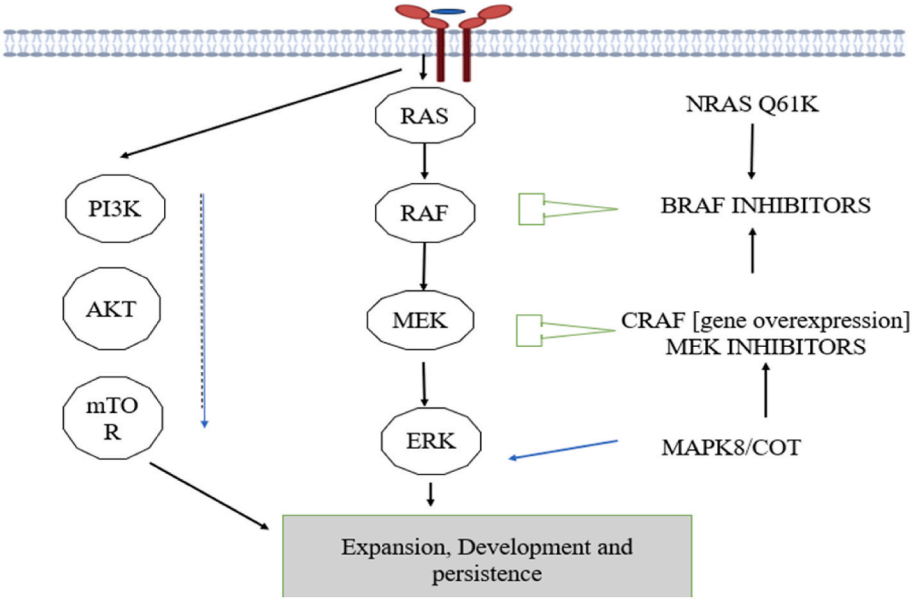


Fig. 9. BRAF pathway in non small cell lung cancer.

developments highlight.

CRediT authorship contribution statement

Namini M: Writing – original draft. **Bhagya G:** Writing – review & editing. **Manjari Sharma:** Writing – review & editing.

Declaration

Figures are created using Biorender Tool.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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