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TYROSINE KINASE INHIBITORS AS TARGETED ANTICANCER AGENTS: MECHANISMS, AND THERAPEUTIC APPLICATIONS

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ABSTRACT

Uncontrolled cell proliferation and dysregulated signaling pathways are hallmarks of the diverse group of disorders known as cancer. Tyrosine kinase-mediated signal transduction, which controls angiogenesis, metastasis, cell survival, and proliferation, is a key factor in oncogenesis. Despite its effectiveness in quickly proliferating cells, conventional chemotherapy is frequently constrained by systemic toxicity, non-specific targeting, and the emergence of drug resistance. As a result, targeted treatments that specifically block carcinogenic signaling molecules have been developed, providing increased effectiveness and fewer side effects. Tyrosine kinase inhibitors (TKIs), which are particularly made to stop aberrant kinase activity that propels tumor growth, have become a key component of precision oncology. TKIs have shown notable clinical advantages in a number of cancers, such as lung cancer, breast cancer, and chronic myeloid leukemia, by enhancing quality of life and survival rates. Targeting both receptor and non-receptor tyrosine kinases, TKIs have a variety of pharmacological modes of action. Genetic mutations, drug metabolism, and resistance mechanisms all affect how effective they are. There are still issues with them despite their therapeutic potential, such as primary and acquired resistance, high treatment costs, side effects, and inconsistent patient adherence. Future directions for TKI research include combination treatments, next-generation inhibitors, patient selection based on biomarkers, and methods for overcoming resistance. Optimizing patient outcomes, directing treatment selection, and developing precision medicine techniques in oncology all depend on an understanding of the pharmacology and clinical use of TKIs.

KEYWORDS: signal transduction, precision medicine, cancer pharmacology, tailored therapy, tyrosine kinase inhibitors.

INTRODUCTION

With millions of new cases and deaths each year and notable regional and gender-based variations in incidence, cancer continues to be a major global public health burden. Surgery, radiotherapy, and chemotherapy are the mainstays of conventional cancer treatment; chemotherapy is essential for both localized and metastatic disease. However, systemic toxicity, poor tumor selectivity, low solubility and bioavailability, and the emergence of multidrug resistance caused by efflux transporters like P-glycoprotein are some of the significant drawbacks of conventional chemotherapeutic agents. These disadvantages frequently result in decreased patient quality of life, treatment failure, and dose reduction. Nanotechnology-based drug delivery systems (NDDS), which enhance drug solubility, stability, pharmacokinetics, and targeted tumor accumulation while lowering off-target toxicity, have become a promising solution to these problems.

Targeted cancer therapies that specifically block cancer-specific signaling pathways involved in proliferation, angiogenesis, immune evasion, and apoptosis have evolved thanks to parallel developments in molecular biology. Although resistance mechanisms caused by pathway reactivation, compensatory signaling, and epigenetic changes continue to limit long-term efficacy, agents targeting VEGF/VEGFR, EGFR/HER-2, CDKs, BCL-2, and immune checkpoints like PD-1/PD-L1 and CTLA-4 have shown significant clinical benefits. Tyrosine kinases (TKs), especially receptor tyrosine kinases (RTKs), are important therapeutic targets because they regulate cellular proliferation, survival, migration, and angiogenesis, all of which are crucial in the development of cancer. Tumor cells can avoid apoptosis and continue to grow uncontrollably when RTKs like EGFR and HER-2/neu are dysregulated.

This causes constitutive activation of downstream PI3K/Akt and MAPK signaling pathways. Precision oncology saw a breakthrough with the clinical success of EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer. Later generations of TKIs were created to address resistance mutations like T790M. Although survival outcomes have been greatly enhanced by third-generation inhibitors such as osimertinib, resistance is still unavoidable because of secondary mutations, bypass signaling, and clonal evolution under treatment pressure. Tie-1, FGFR-4, and Eph receptors are examples of emerging RTKs involved in tumor angiogenesis that have drawn interest due to their functions in vascular stability and tumor microenvironment modulation. With the help of genome-wide screening tools like CRISPR-Cas9, a growing understanding of resistance biology is propelling the development of next-generation inhibitors and logical combination therapies targeted at long-term cancer control.[1,2,3,4]

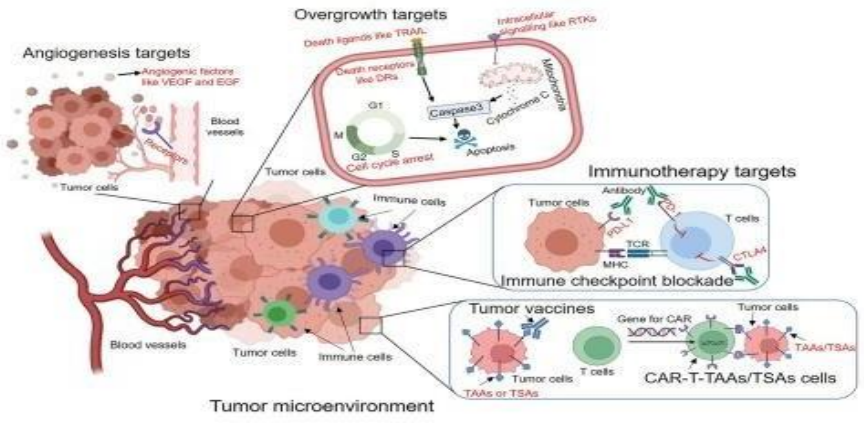


Fig. 1: Overview of major molecular targeted cancer therapies inhibiting tumor angiogenesis, overgrowth, and immune evasion, highlighting key targets (red) including VEGF/EGF signaling, RTKs, TRAIL–death receptor pathways, immune checkpoints (PD-1/PD-L1, CTLA-4), and tumor antigens (TAAs, TSAs).[2]

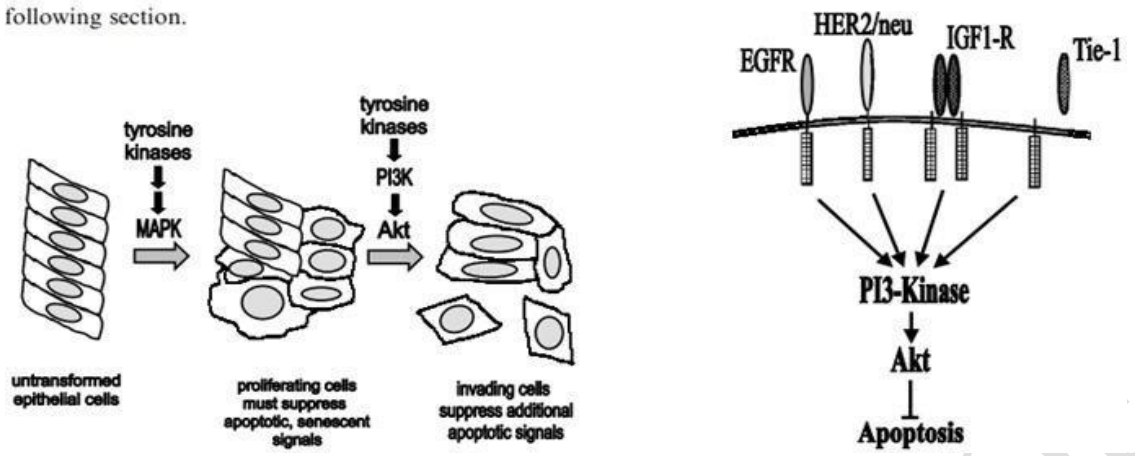


Fig. 2: Tyrosine kinases and receptor tyrosine kinases promote cancer cell survival and invasiveness by suppressing apoptosis during proliferation and loss of cell–cell contact, primarily through convergent activation of the PI3K–Akt signaling pathway, resulting in Akt-mediated phosphorylation of downstream targets and inhibition of apoptotic signaling.[3]

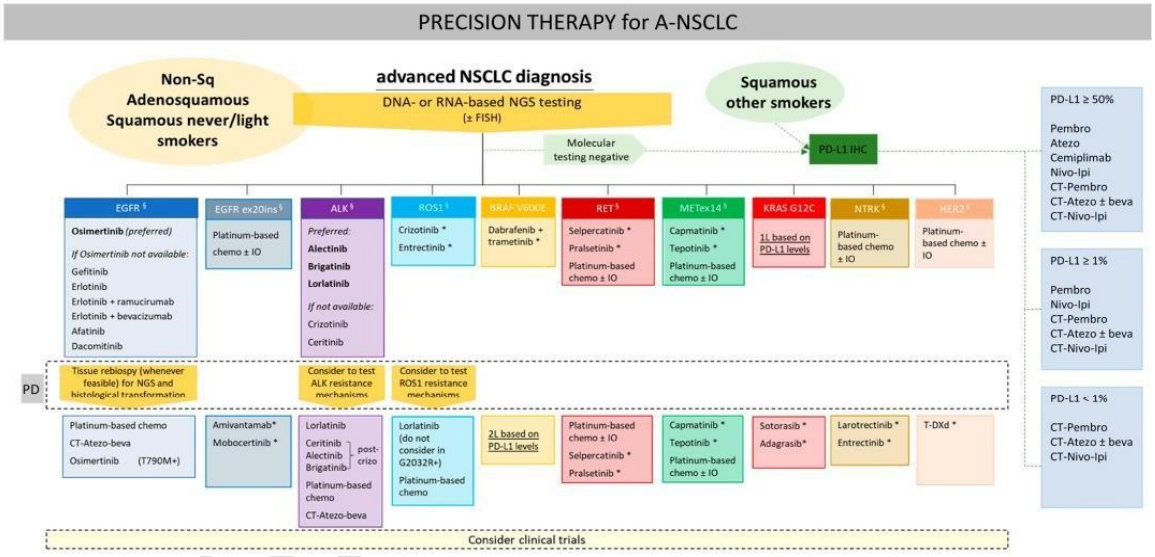


Fig. 3: Current treatment strategies for advanced NSCLC guided by molecular testing, highlighting frontline use of novel-generation TKIs across driver mutations, including tyrosine kinase inhibitors, small-molecule inhibitors, bispecific antibodies, and antibody–drug conjugates, with chemotherapy and immunotherapy options (atezolizumab, pembrolizumab, nivolumab, ipilimumab, bevacizumab) used according to molecular and clinical context.[4]

2. Tyrosine Kinases

Structure and function of Tyrosine Kinases

By transforming extracellular stimuli into well-coordinated intracellular responses, tyrosine kinases are essential for controlling basic cellular functions such as cell proliferation, survival, differentiation, migration, metabolism, and immune signaling. Tyrosine kinase activation creates phosphotyrosine docking sites, which attract adaptor and effector proteins and precisely regulate downstream signaling cascades in space and time. Tyrosine kinase signaling dysregulation brought on by gene amplification, activating mutations, overexpression, or loss of negative regulatory control results in persistent

oncogenic signaling that promotes the development, growth, angiogenesis, metastasis, and resistance to treatment of tumors. Consequently, targeted inhibition of aberrant tyrosine kinases with monoclonal antibodies and small-molecule tyrosine kinase inhibitors has emerged as a key tactic in precision oncology, greatly enhancing clinical outcomes in a variety of cancer types.[5]

Receptor tyrosine kinases (RTKs)

Transmembrane proteins consist of an external ligand-binding domain, a single transmembrane helix, and an intracellular tyrosine kinase domain. In normal cells, RTK activation is carefully regulated and starts with ligand binding, which causes receptor dimerization and relieves cis-autoinhibition of the kinase domain, resulting in stepwise autophosphorylation. Phosphorylated tyrosine residues act as docking sites for adaptor proteins like IRS1, FRS2, and Gab1, activating downstream signaling pathways like MAPK, PI3K/Akt, JAK/STAT, and PKC, which regulate cell survival, proliferation, differentiation, metabolism, and cell cycle progression.RTKs become abnormally activated in cancer cells through a variety of processes, including receptor overexpression, gain-of-function mutations, chromosomal translocations or fusions, and autocrine ligand stimulation. Oncogenic RTKs such as EGFR, VEGFR, FGFR, PDGFR, IGF-1R, and c-Met promote tumor development, angiogenesis, metastasis, and therapy resistance by constitutively activating survival pathways such as PI3K/Akt and MAPK. These dysregulated RTK signaling networks are critical in oncogenesis and serve as significant targets for tyrosine kinase inhibitor-based cancer treatments.[6]

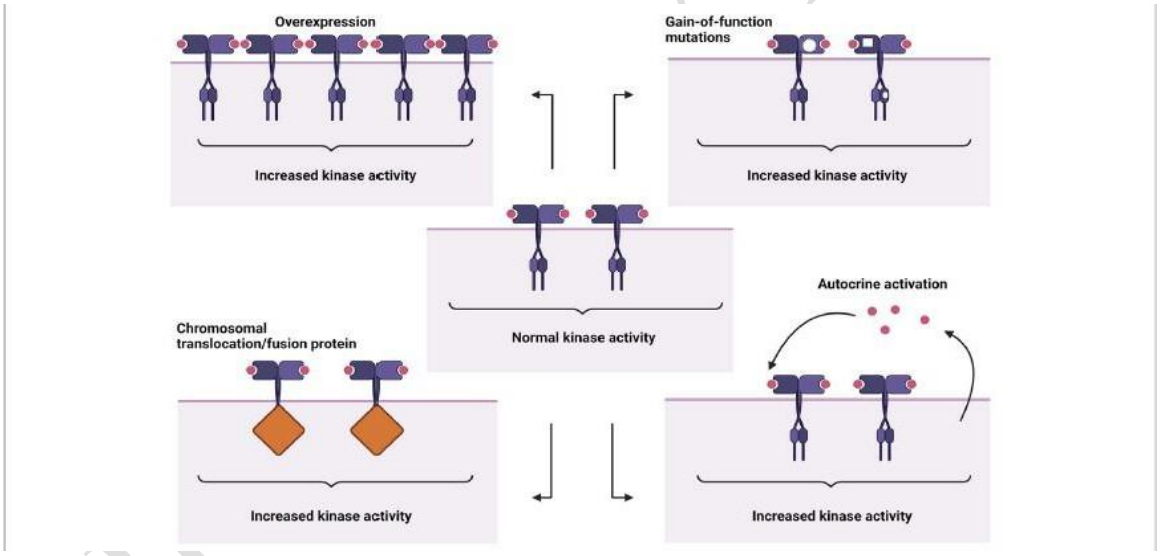


Fig. 4: Mechanisms of aberrant receptor tyrosine kinase (RTK) activation, including receptor overexpression, gain-of-function mutations, autocrine ligand stimulation, and chromosomal translocations resulting in fusion proteins. Illustration created using BioRender.com.[6]

Non-receptor tyrosine kinases

Non-receptor tyrosine kinases (NRTKs) are divided into nine primary subfamilies based on kinase domain sequence homology: Abl, FES, JAK, ACK, SYK, TEC, FAK, Src, and CSK. These cytoplasmic kinases control critical cellular activities as proliferation, survival, migration, immunological signaling, and cytoskeletal dynamics. Aberrant activation of NRTKs occurs through chromosomal translocations, overexpression, activating mutations, or dysregulated upstream signaling, which contributes significantly to hematological malignancies and solid tumors. Abl kinases (ABL1/ABL2) are the most studied NRTKs due to the oncogenic BCR-ABL fusion in CML and ALL, which causes constitutive

kinase activity and is efficiently addressed by TKIs such as imatinib and newer-generation inhibitors. JAK kinases drive cytokine signaling via the JAK-STAT pathway, and mutations like JAK2V617F are highly associated with myeloproliferative diseases. Src family kinases, including FAK, SYK, TEC, ACK, and FES, regulate oncogenic signaling networks implicated in tumor growth, immune evasion, metastasis, and therapy resistance, making them promising therapeutic targets. Recent interest has been focused on natural compounds (e.g., omacetaxine, gambogic acid, triptolide, curcumin) as alternative or supplementary NRTK inhibitors, notably in TKI-resistant cancer.[7]

2.2 Role of Tyrosine Kinases in Normal Cellular Physiology

Receptor tyrosine kinases (RTKs) are membrane-spanning receptors essential for normal cellular physiology, as they detect and transduce extracellular signals such as growth factors, hormones, and cytokines. RTKs share a conserved modular structure comprising an extracellular ligand-binding domain, a single transmembrane α-helix, and an intracellular protein tyrosine kinase domain; ligand binding induces receptor dimerization and trans-autophosphorylation of key tyrosine residues, activating kinase function and creating docking sites for downstream signaling proteins. These phosphorylated sites recruit adaptor and effector proteins containing SH2 or phosphotyrosine-binding domains, leading to activation of major signaling pathways including RAS–MAPK, PI3K–AKT, and PLCγ–PKC that regulate cell proliferation, metabolism, migration, and survival. While RTK signaling is tightly controlled under physiological conditions, its dysregulation—through ligand-dependent autocrine loops, receptor overexpression or amplification, activating mutations, oncogenic fusions, or receptor transactivation—drives persistent oncogenic signaling, exemplified by aberrant MET activation in cancer, which promotes tumor growth, invasion, angiogenesis, and poor clinical outcomes Although RTK signaling is strictly regulated in physiological settings, its dysregulation—caused by ligand-dependent autocrine loops, receptor overexpression or amplification, activating mutations, oncogenic fusions, or receptor transactivation—drives persistent oncogenic signaling, such as aberrant MET activation in cancer, which encourages tumor growth, invasion, angiogenesis, and unfavorable clinical outcomes.[8,9]

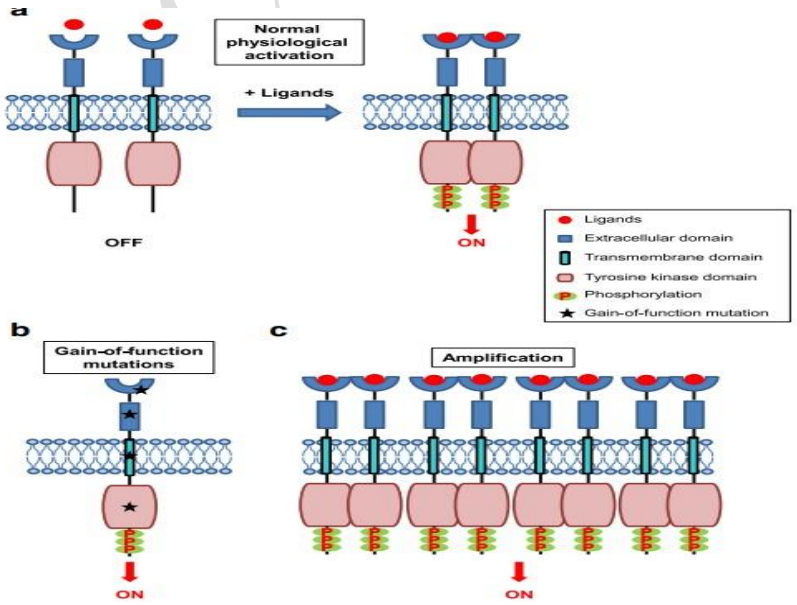
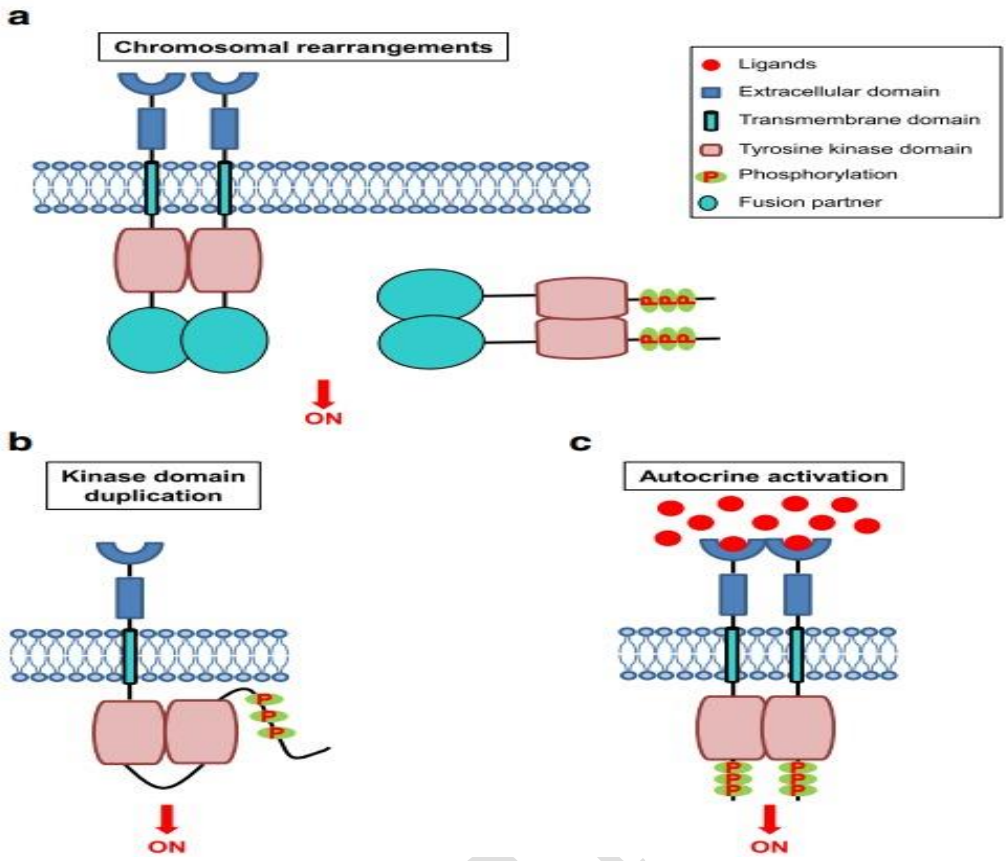


Fig. 5: Mechanisms of physiological and oncogenic RTK activation: In normal physiology, ligand-induced RTK dimerization triggers kinase activation and C-terminal phosphorylation, whereas oncogenic gain-of-function mutations or receptor overexpression due to gene amplification cause constitutive, ligand-independent RTK activation.



Mechanisms of oncogenic RTK activation: Chromosomal rearrangements, kinase domain duplication, or autocrine ligand overproduction lead to constitutive RTK activation through fusion oncoprotein formation, ligand-independent intramolecular dimerization, or persistent ligand-driven dimerization and signalling.2.3. Mechanisms Leading to Met Dysregulation in Tumor Cells.

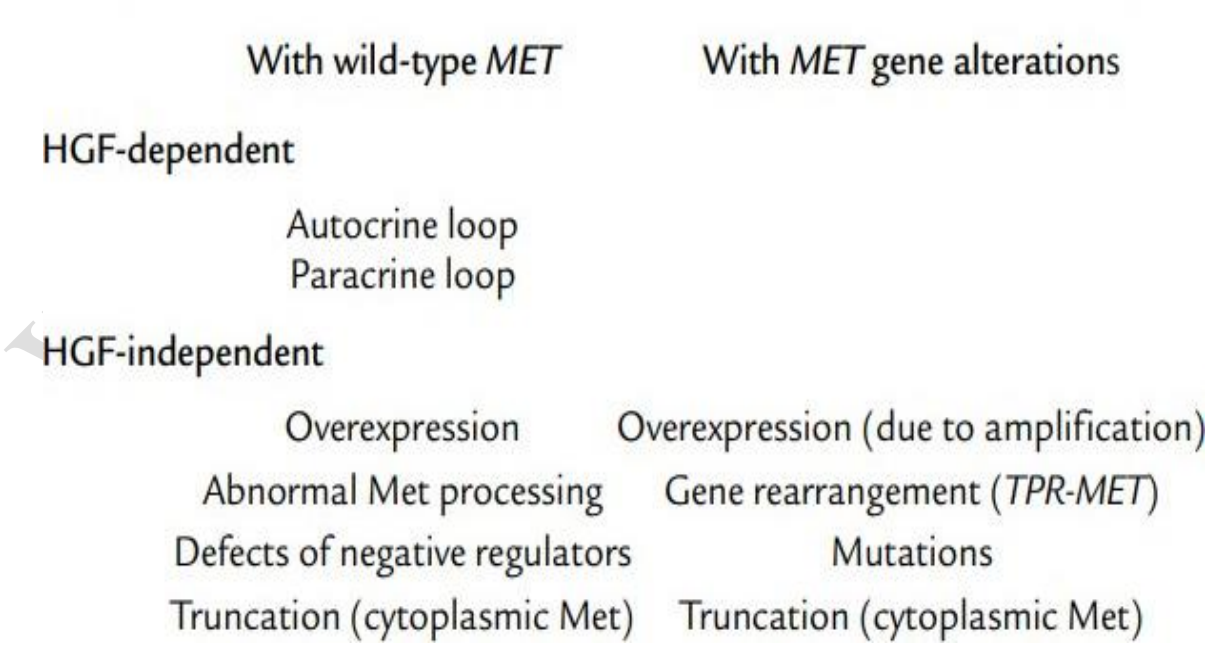


Fig. 6: Mechanisms Leading to Met Dysregulation in Tumor Cells[9]

2. Mechanism of Action of Tyrosine Kinase Inhibitors Allosteric inhibition and ATP-competitive inhibition

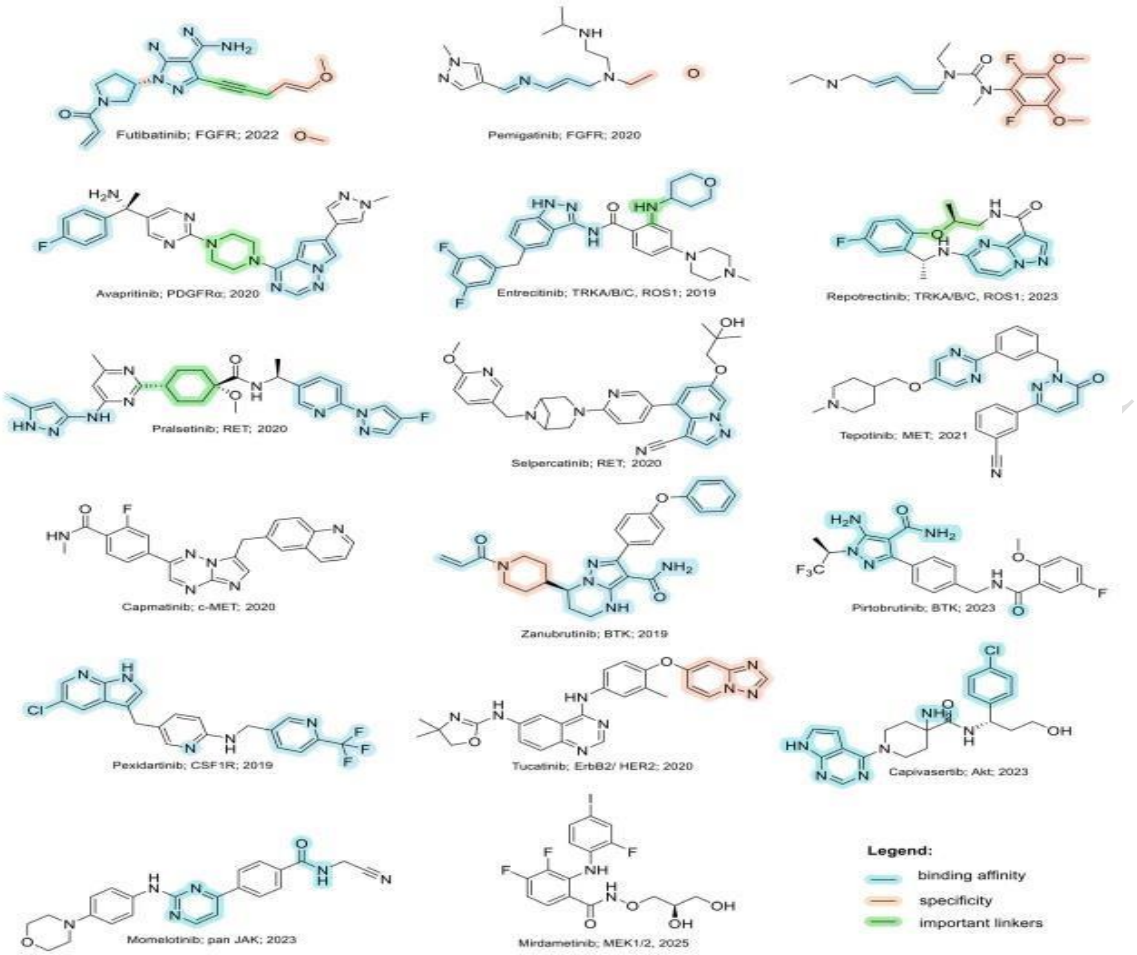


Fig. 7: FDA-approved ATP-competitive kinase inhibitors since 2019: structures, targets, and approval year.[11]

Tyrosine kinase inhibitors provide efficient and targeted cancer treatment by utilizing both ATP-competitive and allosteric mechanisms. As demonstrated by Abl kinase inhibitors like GNF-2 that target the myristoyl pocket and continue to be effective against challenging mutations like T315I, allosteric inhibitors provide enhanced selectivity and activity against resistance mutations by binding regulatory sites outside the ATP-binding pocket. This approach has been effectively applied to other kinases, such as FAK, ITK, IGF-1R, mTOR, PI3K, and important NF-κB pathway regulators, frequently lowering off-target toxicity.The most well-known class of targeted anticancer drugs, ATP-competitive inhibitors, on the other hand, effectively target kinases like EGFR, FGFR, ALK, MET, BTK, and JAK by binding the conserved ATP-binding site and taking advantage of nearby structural features to increase potency and selectivity. ATP-competitive inhibition is still essential to precision oncology despite issues with selectivity and acquired resistance, and allosteric techniques offer supplementary ways to get around resistance.[10,11]

Irreversible inhibition

Unlike reversible ATP-competitive inhibitors, irreversible tyrosine kinase inhibitors (TKIs) create covalent bonds with their kinase targets to achieve sustained target inhibition, which prolongs pathway suppression. In the ErbB receptor family, this method of overcoming resistance—specifically, EGFR mutations—has been thoroughly investigated. Second-generation drugs like afatinib, dacomitinib, and neratinib showed improved efficacy in EGFR-mutant cancers, while early irreversible inhibitors like canertinib and pelitinib were restricted by toxicity. Afatinib emerged as an effective first-line

therapy in non-small cell lung cancer. Third-generation mutant-selective irreversible inhibitors were created with improved clinical potential to address T790M-mediated resistance and lessen wild-type EGFR toxicity.Beyond RTKs, irreversible inhibition has proven to be very effective in non-receptor kinases like Bruton's tyrosine kinase, where ibrutinib has shown impressive results in B-cell cancers. Irreversible TKIs are a useful tactic in contemporary targeted cancer therapy because of improvements in the therapeutic window brought about by advances in mutant-selective design, despite toxicity concerns.[12]

Impact on downstream signaling pathways (MAPK, PI3K/AKT, JAK/STAT) Curcumin's Impact on the MAPK Signaling Pathway

By modifying receptor tyrosine kinase (RTK)-driven signaling pathways, specifically the MAPK, PI3K/Akt/mTOR, and JAK/STAT cascades, which control cell proliferation, survival, differentiation, angiogenesis, and apoptosis, curcumin has wide-ranging anticancer effects. Tumor growth and treatment resistance are driven by constitutive activation of these pathways, which is frequently caused by RTK overexpression, Ras or B-Raf mutations, PIK3CA alterations, or PTEN loss. Curcumin primarily inhibits upstream RTKs to suppress MAPK signaling, which results in decreased ERK1/2 and JNK phosphorylation, downregulation of AP-1, c-Jun, and c-Fos, decreased cyclin expression, and apoptosis induction. Curcumin simultaneously suppresses EGFR, HER-2, IGF-1R, VEGFR, and PDGFR, which reduces Akt and mTOR phosphorylation, inhibits downstream effectors like S6K and 4EBP1, decreases angiogenesis and metabolic reprogramming, and increases apoptotic signaling, partially by activating negative regulators like PTEN and PPARγ. Furthermore, curcumin limits STAT nuclear translocation, VEGF expression, angiogenesis, metastasis, and immune evasion in a variety of solid tumors and hematological malignancies by lowering phosphorylation of JAKs and STAT3/STAT5 and indirectly through RTK inhibition.[13]

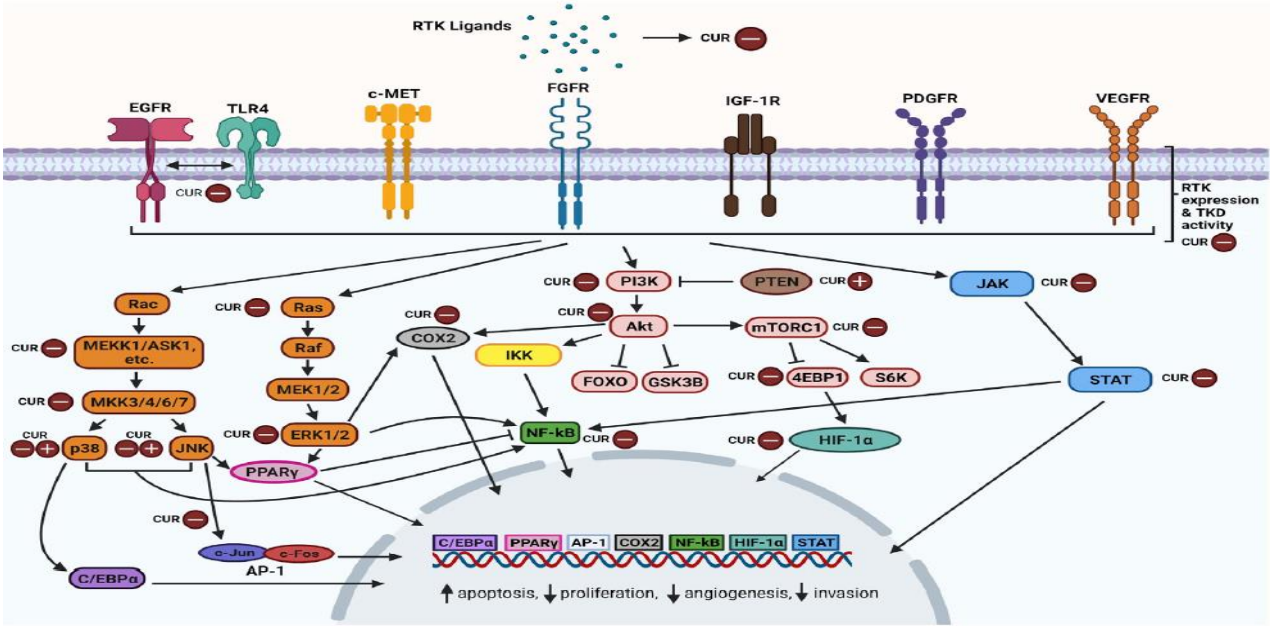


Fig. 8: Overview of curcumin (CUR) inhibition of receptor tyrosine kinases (RTKs) including EGFR, TLR4, c-MET, FGFR, IGF-1R, PDGFR, and VEGFR, and their downstream signaling pathways MAPK (Ras/Raf/MEK/ERK, JNK, AP-1), PI3K/Akt/mTOR (PI3K, Akt, mTORC1, 4EBP1, S6K, PTEN, FOXO, GSK3B, PPARγ, COX-2), JAK/STAT (JAKs, STATs), and NF-κB (IKK, NF-κB, HIF-α), modulating cell proliferation, survival, apoptosis, angiogenesis, and metastasis.[13]

2. CLASSIFICATION OF TYROSINE KINASE INHIBITORS

2.1 Based on Target Specificity

A. EGFR INHIBITORS

The T790M mutation causes rapid resistance to first-generation EGFR TKIs, such as gefitinib and erlotinib, which are reversible ATP-competitive inhibitors used in NSCLC. Although they increased activity against common EGFR mutations, second-generation irreversible inhibitors (afatinib, dacomitinib) were linked to increased toxicity and C797S-mediated resistance. Although resistance still develops, third-generation mutant-selective TKIs like osimertinib successfully targeted T790M mutations with increased survival and safety. In order to combat resistant EGFR variants, fourth-generation allosteric EGFR inhibitors (EAI001, EAI045) that target ATP-independent sites, especially when combined with cetuximab, show promise.[14]

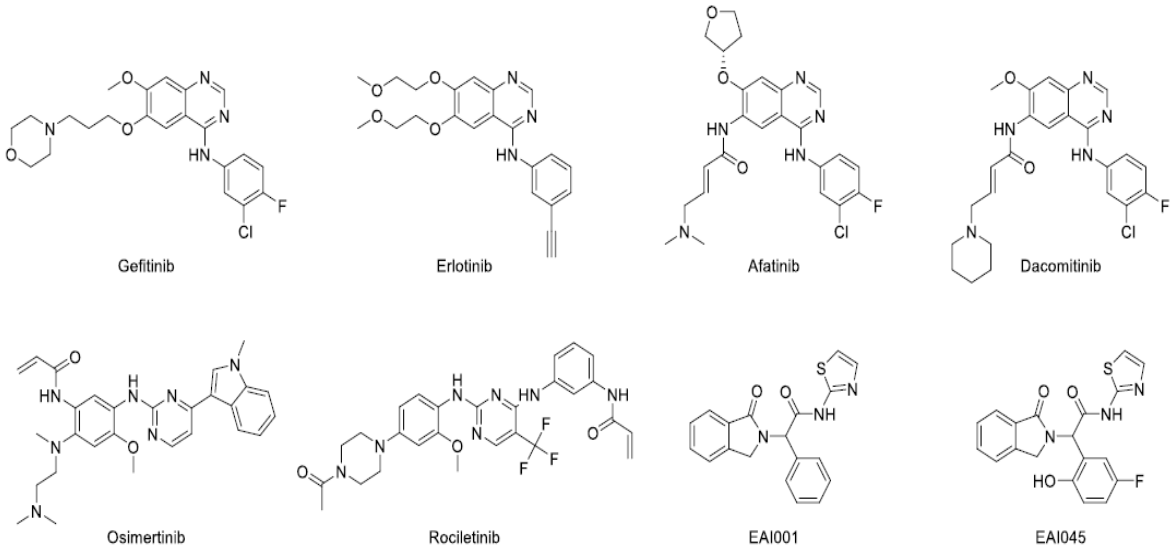


Fig. 9: Chemical structure of EGFR TKI (first to fourth generations).[14]

B. VEGFR INHIBITORS

Dysregulation of protein kinases, especially in receptor tyrosine kinases (RTKs), is crucial to the pathophysiology of cancer. These kinases control vital cellular functions like proliferation, migration, angiogenesis, differentiation, and survival. Vascular endothelial growth factor receptors (VEGFR1-3) are important targets for the development of anticancer drugs because they are essential for tumor angiogenesis and lymphangiogenesis. The FDA has approved about 70 kinase inhibitors to date; the majority of these are multikinase inhibitors, and some of them target VEGFRs in conjunction with PDGFRs, FGFRs, RET, and c-Kit. Sorafenib, sunitinib, pazopanib, vandetanib, axitinib, cabozantinib, regorafenib, apatinib, nintedanib, lenvatinib, anlotinib, and fruquintinib are examples of clinically approved VEGFR tyrosine kinase inhibitors. Their selectivity varies, but they consistently exhibit anti-angiogenic and antitumor effects across a variety of cancers, including lung cancer, thyroid cancer, gastrointestinal stromal tumors, and renal cell carcinoma. When taken as a whole, these substances demonstrate the therapeutic value of VEGFR inhibition as a fundamental component of anti-angiogenic cancer treatment.[15]

BCR-ABL INHIBITORS

Dasatinib: BCR: ABL1 and SRC family kinases are strongly inhibited by dasatinib (DA), a second- generation multitarget tyrosine kinase inhibitor that is taken orally. With the notable exception of the T315I mutation, it is about

300 times more potent than imatinib (IM) and works against the majority of IM-resistant BCR: ABL1 mutations. Unlike other TKIs, DA establishes fewer direct contacts with the kinase domain and preferentially binds to the active (DFG-in) conformation of the ABL1 kinase.In terms of structure, the right-terminal functional group of DA fills a hydrophobic cavity created by T315, V299, and surrounding residues rather than extending deeper into a particular binding pocket. As a result, DA binding does not require fixing of the DFG motif in a specific conformation, allowing the activation loop (A-loop) to stay in an extended, active state. DA projects outward toward the hinge area on the other end, where it forms several van der Waals contacts and two hydrogen bonds.[15]

Furthermore, the DA–ABL1 complex's phosphate-binding loop (P-loop) maintains a significant degree of conformational flexibility, suggesting that binding does not need a rigid P-loop conformation. DA's broad activity and high affinity against a variety of BCR: ABL1 mutants, especially those affecting the P-loop, may be explained by this adaptable binding method. Nuclear magnetic resonance (NMR) research, however, indicates that DA mostly interacts with ABL1 in its active conformation. DA shows decreased inhibitory action against mutations in two crucial regions: the hydrophobic pocket and the hinge region, despite its wide mutation coverage. In particular, the gatekeeper residue T315 is necessary for efficient binding due to the interaction between DA and this residue, which is mediated by hydrogen bonds and van der Waals interactions. Consequently, even the less popular T315.ASignificant resistance to DA is conferred by mutation. On the other hand, ponatinib (PON) and nilotinib (NL) interact more deeply with ABL1's inactive conformation, somewhat compensating for lost interactions. This susceptibility of DA is further demonstrated by clinically significant resistance mutations like V299L and F317L (hinge region).[15]

Dasatinib (DA) is an oral second-generation multitarget tyrosine kinase inhibitor that significantly inhibits BCR: ABL1 and SRC family kinases. It is roughly 300 times more effective than imatinib (IM) and targets most IM-resistant BCR: ABL1 mutations, with the notable exception of the T315I mutation. In contrast to other TKIs, DA preferentially binds to the active (DFG-in) conformation of the ABL1 kinase and makes fewer direct contacts with the kinase domain. Rather than extending farther into a specific binding pocket, the right-terminal functional group of DA fills a hydrophobic cavity formed by T315, V299, and surrounding residues. The activation loop (A-loop) can remain in an extended, active state because DA binding does not necessitate fixing the DFG motif in a particular conformation. DA extends in the direction of the hinge region on the opposite end, where it creates two hydrogen bonds and multiple van der Waals contacts. Moreover, the phosphate-binding loop (P-loop) of the DA–ABL1 complex retains a considerable amount of conformational flexibility, indicating that binding does not require a rigid P-loop conformation. This flexible binding mechanism may account for DA's wide activity and high affinity against a range of BCR: ABL1 mutants, particularly those that impact the P-loop. However, studies using nuclear magnetic resonance (NMR) show that DA primarily interacts with ABL1 in its active conformation. Despite its broad mutation coverage, DA exhibits reduced inhibitory action against mutations in two critical regions: the hinge region and the hydrophobic pocket. Specifically, the interaction between DA and the gatekeeper residue T315, which is mediated by hydrogen bonds and van der Waals interactions, is essential for effective binding. Thus, even the lesser-known T315. A mutation confers a significant resistance to DA. Conversely, nilotinib (NL) and ponatinib (PON) interact more deeply with the inactive conformation of ABL1, partially making up for lost interactions. Clinically significant resistance mutations such as V299L and F317L (hinge region) further illustrate this DA susceptibility.

Bosutinib is another dual ABL1/SRC kinase inhibitor that, like dasatinib, primarily binds to the active conformation of the ABL1 kinase domain. However, in the BOS–ABL1 complex, the DFG motif adopts a flipped conformation, with the D381 and F382 residues positioned against the typical DFG-in state. Aside from this distinction, BOS and DA have comparable binding modalities, mutation selectivity profiles, and general efficacy.One notable structural distinction is that BOS forms numerous van der Waals contacts with the T315 residue, whereas DA primarily relies on hydrogen bonding. But when isoleucine is used in place of T315, these connections are broken, leading to BOS dissociation and resistance. Another clinically significant resistance mutation, V299L, is present in the hydrophobic pocket adjacent to T315. A larger leucine residue causes steric hindrance, which lowers the affinity of BOS binding.[15]

C. ALK INHIBITORS IN LUNG CANCER

Inhibitors of Anaplastic Lymphoma Kinase (ALK) in NSCLC

Patients with ALK-rearranged non-small cell lung cancer (NSCLC) have significantly better outcomes thanks to inhibitors of anaplastic lymphoma kinase (ALK), with crizotinib, alectinib, and ceritinib serving as the cornerstone of current treatment. After phase I–III PROFILE trials showed better overall response rates (57–74%) and progression-free survival (7.7–10.9 months) when compared to chemotherapy, crizotinib, a first-generation oral ALK inhibitor that also targets MET and ROS1, was approved in 2011. Although the majority of patients develop resistance within a year as a result of secondary ALK mutations, gene amplification, or bypass signaling. Second-generation ALK inhibitors were created in order to get around these restrictions.Alectinib, a more potent and highly selective ALK inhibitor, has been adopted as the first-line treatment for ALK-positive NSCLC due to its excellent central nervous system penetration, strong activity against multiple crizotinib-resistant mutations, and high response rates in both treatment-naïve and crizotinib-resistant patients with a favorable safety profile. Ceritinib, another second-generation inhibitor intended to overcome crizotinib resistance, has been approved by regulators for use in patients who progress on or are intolerant to crizotinib because it has demonstrated strong efficacy in both crizotinib-pretreated and treatment-naïve patients, with overall response rates approaching 70% and manageable gastrointestinal and hepatic toxicities. When taken as a whole, these ALK inhibitors demonstrate the therapeutic efficacy of molecularly targeted treatment for ALK-rearranged non-small cell lung cancer (NSCLC) and emphasize the continued need for next-generation drugs to address resistance mechanisms.[16]

D. MULTI-TARGETED TKIS IN LUNG CANCER

Sunitinib, vandetanib, and sorafenib are examples of multitargeted tyrosine kinase inhibitors that have had mixed results in NSCLC. With an 11% response rate and a brief progression-free survival, sunitinib showed modest activity in previously treated non-small cell lung cancer (NSCLC), whereas combination therapy with erlotinib enhanced response but not overall survival, with the exception of a few East Asian patients. In phase III trials, vandetanib, which targets EGFR, VEGFR, and RET, only slightly increased progression-free survival and had no overall survival benefit. Sorafenib, which inhibits VEGFR and RAF kinases, was linked to a higher death rate in squamous cell carcinoma and did not improve outcomes in first-line NSCLC trials. As a result, these medications have not played a significant clinical role in NSCLC.[17]

2.2. Based on Generations

A. First-generation TKIs

In the phase III BR.21 trial, erlotinib—the first EGFR tyrosine kinase inhibitor approved by the FDA for non-small cell lung cancer—showed improved response rate (8.9% vs. <1%), median progression-free survival (2.2 vs. 1.8 months),

and overall survival (6.7 vs. 4.7 months) when compared to placebo. This was the first significant OS benefit of an EGFR TKI in non-small cell lung cancer. The groundbreaking IPASS trial, which found that gefitinib significantly increased progression-free survival when compared to carboplatin–paclitaxel, especially in patients with activating EGFR mutations, established gefitinib's role as first-line therapy in EGFR-mutant NSCLC.Subsequent trials, including First-SIGNAL, OPTIMAL, and EURTAC, further demonstrated the superiority of EGFR TKIs over chemotherapy in EGFR-mutant NSCLC. In the phase III ICOGEN trial, icotinib, an oral first-generation EGFR TKI approved in China, was found to be non-inferior to gefitinib, with a better safety profile and a median PFS of 4.6 months versus 3.4 months, supporting its use as an effective treatment option for patients with advanced non-small cell lung cancer (NSCLC) who have progressed after platinum-based chemotherapy.[18]

B. Second-generation TKIs

Afatinib, neratinib, and dacomitinib are examples of second-generation irreversible EGFR tyrosine kinase inhibitors (TKIs) that were created to covalently bind to the EGFR kinase domain in order to overcome acquired resistance to first-generation TKIs, particularly the EGFR T790M mutation. Afatinib, an irreversible anilino-quinazoline EGFR TKI, showed notable clinical activity in EGFR-mutant NSCLC, with durable responses in early trials and improved progression-free survival (PFS) versus placebo in the LUX-Lung 1 trial; in the first-line setting, LUX-Lung 2 demonstrated an overall response rate (ORR) of 61%, and LUX-Lung 3 confirmed superior PFS and ORR when compared to pemetrexed–cisplatin, which led to its approval as a first-line therapy. Neratinib, an unrecoverablepan-Erb asset, demonstrated encouraging preclinical efficacity against T790M-positive and EGFR- mutant NSCLC. still, poor tolerability, especially severe diarrhea that limited medicine exposure and led to low response rates, hindered its clinical development. In a phase II trial of treatment- naïve EGFR- mutant NSCLC, dacomitinib, which targets EGFR and other members of the ErbB family, achieved an ORR of 53 and a median PFS of 11.5 months. still, as demonstrated in the phase III NCIC CTG BR.26 trial, it did n't ameliorate overall survival in latterly- line settings, and as a result, it is n't advised for cases who progress following previous EGFR TKI remedy.[18]

C. Third-generation TKIs

Third- generation, mutant- picky impediments that specifically target T790M- mutant EGFR while sparing wild- type EGFR have been developed because the EGFR T790M mutation is the most frequent cause of acquired resistance to first- and alternate- generation EGFR TKIs innon-small cell lung cancer. Approved by the FDA in 2015, osimertinib(AZD9291) exhibits roughly200-fold selectivity for T790M- mutant EGFR and showed an ORR of 61 and a median PFS of 9.6 months in T790M-positive cases in the Air phase I trial; pooled phase II data latterly reported an ORR of 66 and a median PFS of 11.0 months, establishing osimertinib as a pivotal treatment for EGFR- mutant NSCLC. Another third-generation inhibitor, rociletinib (CO-1686), showed a median PFS of 13.1 months and an ORR of 59% in patients with T790M, but its development was later limited. In phase I/II trials, olmutinib (HM61713) also demonstrated noteworthy activity in T790M-positive NSCLC, demonstrating the clinical significance of third-generation TKIs in overcoming T790M-mediated resistance.[18]

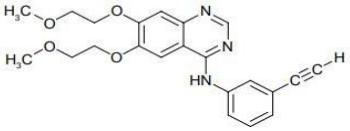
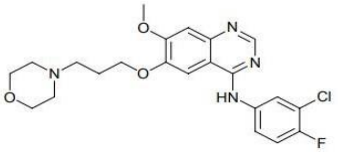
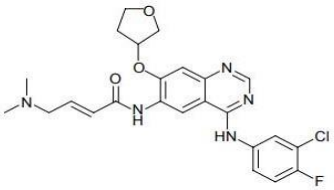
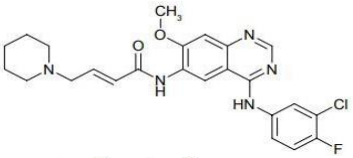
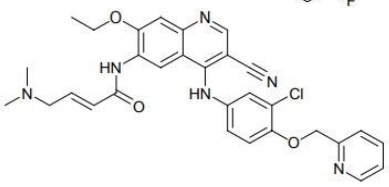
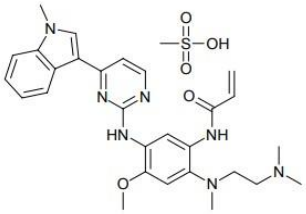
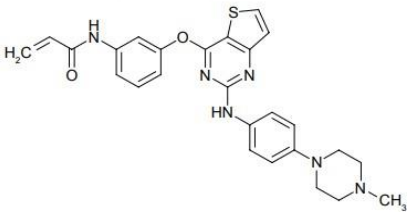
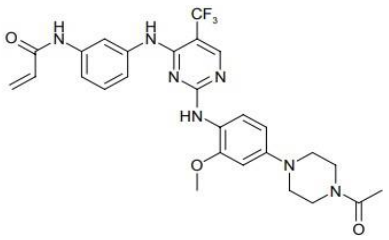
Generic name	Trade name	Formula	Systematic name	Structure
Erlotinib	Tarceva®	$C_{22}H_{23}N_3O_4$	*N*-(3-ethynylphenyl)-6,7-bis (2-methoxyethoxy)quinazolin-4-amine	
Gefitinib	Iressa®	$C_{22}H_{24}ClFN_4O_3$	*N*-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine	
Afatinib	Gilotrif®	$C_{24}H_{25}ClFN_5O_3$	*N*-[4-[(3-chloro-4-fluorophenyl) amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide	
Dacomitinib		$C_{24}H_{25}ClFN_5O_2$	(2*E*)-*N*-{4-[(3-chloro-4-fluorophenyl) amino]-7-methoxy-6-quinazolinyl}-4-(1-piperidinyl)-2-butenamide	
Neratinib		$C_{30}H_{29}ClN_6O_3$	(2*E*)-*N*-[4-[[3-chloro-4-[(pyridin-2-yl) methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide	
Osimertinib	Tagrisso™	$C_{28}H_{33}N_7O_2{\cdot}CH_4O_3S$	*N*-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2yl]amino} phenyl)prop-2-enamide mesylate salt	
Olmutinib		$C_{26}H_{26}N_6O_2S$	*N*-[3-({2-[4-(4-methylpiperazin-1-yl) anilino]thieno[3,2-d]pyrimidin-4-yl} oxy)phenyl]prop-2-enamide	
Rociletinib		$C_{27}H_{28}F_3N_7O_3$	*N*-[3-[[2-[4-(4-acetylpiperazin-1-yl)-2-methoxyanilino]-5-(trifluoromethyl) pyrimidin-4-yl]amino]phenyl]prop-2-enamide	

Fig. 10: The Chemical Structure, Iupac Nomenclature, and Molecular Formula of Pharmacological Profile of Tkis.

2.3 Pharmacodynamics in lung cancer

Tyrosine kinase inhibitor (TKI) resistance, which is caused by pharmacodynamic mechanisms that either change drug targets or activate alternate survival pathways, continues to be a significant problem in cancer treatment. As demonstrated by EGFR-TKI resistance in NSCLC, where the T790M gatekeeper mutation limits first-generation

inhibitors and later the C797S mutation decreases the efficacy of third-generation agents like osimertinib, target-dependent resistance frequently involves amplification or mutations of the kinase. Enhanced DNA damage repair via the BER, NER, and HR/NHEJ pathways is one example of target-independent resistance. This leads to multidrug resistance and the creation of inhibitors like PARP, ATM, ATR, and DNA-PK inhibitors. Through extracellular matrix (ECM) remodeling, the tumor microenvironment also fosters resistance. Collagen I, fibronectin, integrins, and laminins activate pathways such as PI3K/Akt, MAPK, and FAK, while ECM stiffness initiates YAP/TAZ signaling. Through self-renewal, quiescence, effective DNA repair, and activation of the Hedgehog, Notch, Wnt/β-catenin, PI3K/Akt, and NF-κB pathways, cancer stem cells (CSCs) also contribute to TKI resistance. Lastly, resistance is further strengthened by dysregulation of apoptosis, which includes compromised intrinsic and extrinsic pathways, overexpression of BCL-2 and IAPs, and activation of non-apoptotic death mechanisms like autophagy and ferroptosis. This highlights the necessity of combination therapies that target several resistance pathways.[19]

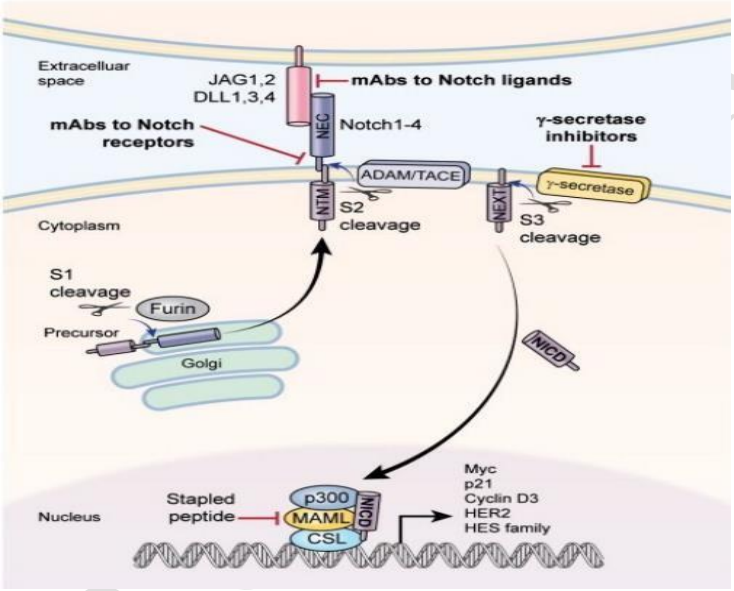


Fig. 11: The structure of Notch pathway. The scheme was adopted from Takabe et al.

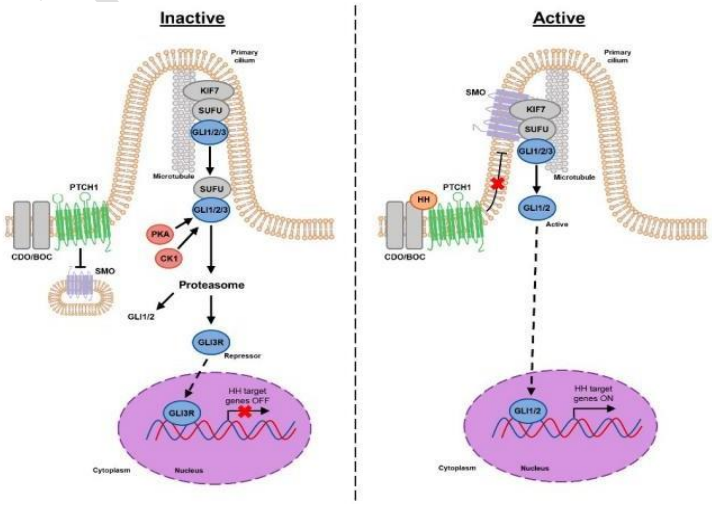


Fig. 12: The structure of Hedgehog pathway. The scheme was adopted from Doheny et al.

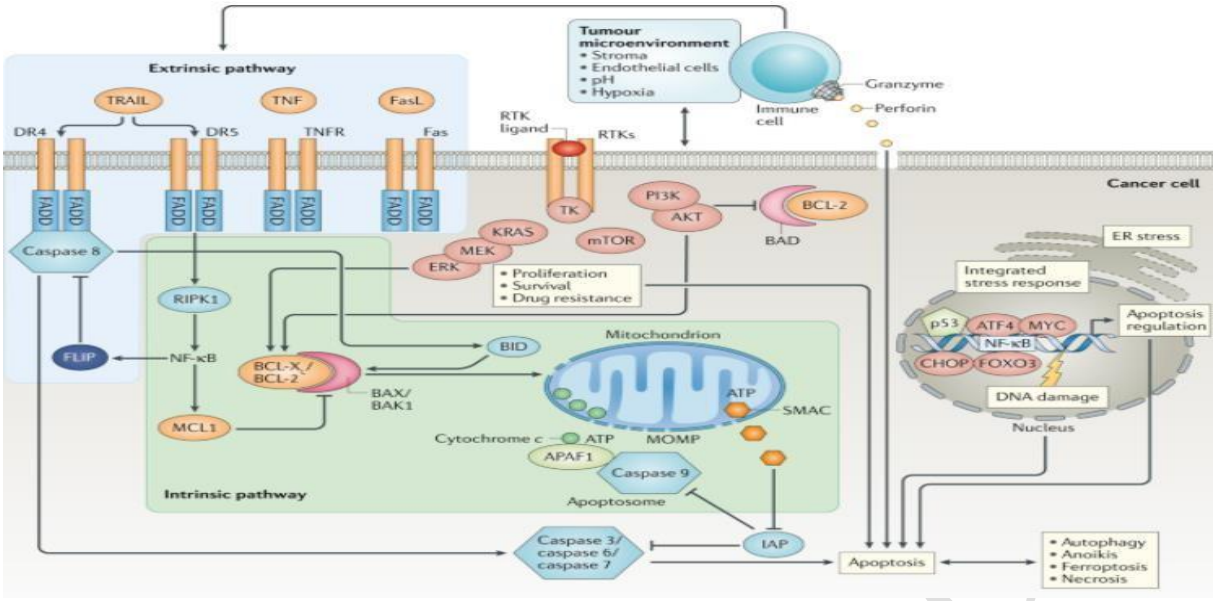


Fig. 13: Extrinsic and intrinsic pathways of apoptosis and their network. The scheme was adopted from Carneiro et. Al.

Pharmacokinetics

2.3.1 Absorption

Most tyrosine kinase inhibitors are taken orally and absorb very quickly, with peak plasma concentrations being reached within 3-6 hours, with the exception of sunitinib, which achieves peak levels later (6-12 hours). Among TKIs, imatinib has nearly full oral bioavailability (>98%) that is stable across formulations and doses and unaffected by meal or antacid usage. Gefitinib and erlotinib have moderate bioavailability (~60%), and food has variable and clinically negligible effects.

However, due to considerable interpatient variability, erlotinib should be administered fasting. Several TKIs, notably lapatinib and nilotinib, exhibit a strong food effect, particularly with high-fat meals, resulting in significant increases in systemic exposure. This impact is considered to be caused by delayed stomach emptying and increased micelle production, rather than increases in solubility alone.

Sorafenib and dasatinib have low or clinically insignificant dietary effects, whereas sunitinib absorption is mainly food independent. Overall, TKIs exhibit significant interpatient heterogeneity in absorption, which is largely understood and poses a key therapeutic problem.[20]

2.3.2. Distribution

TKIs are mostly linked to albumin and α1-acid glycoprotein (AGP), leading to widespread dispersion and lengthy half-lives. Imatinib, gefitinib, erlotinib, sunitinib, dasatinib, and lapatinib all have high tissue penetration, especially in well-perfused organs such the liver, lungs, and gastrointestinal system. TKIs have low central nervous system (CNS) penetration, which is mostly owing to active efflux by transporters such as ABCB1 (P-gp) and ABCG2 at the blood-brain barrier. Although preclinical models imply that inhibiting these transporters may increase CNS exposure, the therapeutic significance of these findings is unclear. The binding to AGP has been found to considerably influence free drug concentrations and may affect treatment efficacy, particularly as AGP levels are typically elevated.[20]

2.3.3. Metabolism

TKI metabolism is largely handled by the cytochrome P450 (CYP) system, with CYP3A4 functioning as the principal metabolic enzyme for nearly all TKIs. Additional enzymes, including CYP3A5, CYP2D6, CYP2C9, CYP2C19, CYP1A1, and CYP1A2, as well as UDP-glucuronosyltransferases (UGTs), participate to variable degrees depending on the medication. Several TKIs (such as imatinib, gefitinib, lapatinib, and nilotinib) block CYP enzymes involved in their own metabolism, potentially altering exposure throughout long-term therapy. Some TKIs, such as imatinib and sunitinib, contain active metabolites, while others' metabolites contribute minimally to clinical success. Despite substantial in vitro characterization, the therapeutic significance of minor metabolic pathways and enzyme polymorphisms is little known, particularly under steady-state circumstances.[20]

2.3.4 Excretion

TKIs are removed largely through the hepatobiliary system, with fecal excretion accounting for the vast bulk of drug clearance. Renal excretion typically contributes just a small portion of overall clearance. A substantial amount of unaltered drug recovered in stools for certain TKIs (e.g., sorafenib and nilotinib) may indicate inadequate absorption and/or restricted metabolic conversion.

Data on the effect of hepatic and renal dysfunction on TKI pharmacokinetics are scarce and, in some circumstances, conflicting. While low to moderate hepatic impairment appears to have no effect on several TKIs, severe hepatic dysfunction has been demonstrated to significantly enhance exposure to medicines like imatinib and lapatinib. Interestingly, renal impairment has also been observed to effect imatinib. pharmacokinetics, despite the fact that it is primarily eliminated through the liver. Given that cancer patients typically have organ failure following treatment, more research into dose optimization under these settings is needed.[20]

2.4 Drug–Drug Interactions

A significant obstacle in cancer treatment is tyrosine kinase inhibitor (TKI) resistance, which is brought on by pharmacodynamic mechanisms that change drug targets or trigger alternative survival pathways. As demonstrated by EGFR-TKI resistance in NSCLC, where the T790M gatekeeper mutation restricts first-generation inhibitors and the C797S mutation lowers the effectiveness of third-generation agents like osimertinib, target-dependent resistance frequently involves kinase mutations or amplification. Enhanced DNA damage repair via the BER, NER, and HR/NHEJ pathways is one example of target-independent resistance. This leads to multidrug resistance and the creation of inhibitors like PARP, ATM, ATR, and DNA-PK inhibitors. Furthermore, polypharmacy from comorbidities and supportive medications makes drug-drug interactions (DDIs) clinically significant in non-small cell lung cancer (NSCLC), where even small pharmacokinetic changes can result in toxicity or treatment failure. In addition to CYP-mediated interactions, transporter-mediated interactions involving P-glycoprotein (P-gp) and BCRP can impact the absorption and tissue distribution of EGFR-TKIs like afatinib and osimertinib, while pH-modifying medications can decrease the absorption of pH-dependent EGFR-TKIs like gefitinib and erlotinib. Despite successful molecular targeting, undetected DDIs may jeopardize results due to the limited therapeutic window and the requirement for extended inhibition. Therefore, to maximize treatment and guarantee safe and effective use in clinical practice, a thorough medication review, avoidance of strong enzyme inducers, careful selection of concurrent medications, counseling for quitting smoking, and preference for EGFR-TKIs with lower interaction potential are crucial.[21]

	Metabolized by CYP										May inhibit	May induce
	3A4	3A5	2D6	1A1	1A2	1B1	2C8	2C9	2C19	2E1		
Erlotinib	+++	+++	+	+	++	+	+	+	–	–	CYP3A4 (m) CYP2C8 (m) CYP1A1 (s)	CYP1A1 CYP1A2
Gefitinib	+++	++	+++	++	+	–	–	–	–	–	CYP2C19 (w) CYP2D6 (w)	–
Afatinib	–	–	–	–	–	–	–	–	–	–	–	–
Osimertinib	+++	+++	–	–	–	–	–	–	–	–	–	CYP3A (w)
Icotinib	+++	++	–	–	+++	–	–	–	–	+++	NR	CYP1A2

Fig. 14: Role of cytochrome P450 enzymes in the metabolism of approved EGFR–TKIs for NSCLC Notes: +++, major metabolic pathway; ++, additional significant metabolic pathway; +, minor metabolic pathway; −, no interaction.

Abbreviations: w, weak; m, moderate; s, strong; NR, not reported; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

Interaction with		Gefitinib	Erlotinib	Afatinib	Osimertinib	Icotinib[b]
Acid-reducing agents		+	+	–	–	NR
CYP3A4	Inducers	+	+	–	+	+
	Inhibitors	+	+	–	–	+
Smoking status		–	+	–	–	+
UDP-glucuronosyltransferase		–	–	–	–	–
Transporter proteins	P-gp	–	–	+	–	NR
	BCRP	–	–	–	–	NR

Fig. 15: Clinically relevant interactions of EGFR–TKIs approved for NSCLC therapy.

Notes

[a] Potentially significant impact on the clinical efficacy of the EGFR-TKI. [b] Limited published data available. +, Indicates a potentially clinically significant interaction; −, indicates no evidence of a clinically significant interaction.

Abbreviations

CYP3A4, cytochrome P450 3A4; NR, not reported; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; UDP, uridine diphosphate.

3. Clinical Applications of Tyrosine Kinase Inhibitors

A. Role of Tyrosine Kinase Inhibitors in the Treatment of Chronic Myeloid Leukaemia

Tyrosine kinase impediments(TKIs), which target the BCR- ABL oncoprotein specifically, have revolutionized the treatment of habitual myeloid leukemia(CML). Previous treatments like interferon- α and stem cell transplantation were supplanted by imatinib, the first BCR- ABL TKI approved for habitual- phase CML, which showed better hematologic, cytogenetic, and molecular responses along with increased tolerability and survival. Imatinib was approved as the first- line treatment in the major IRIS trial, which demonstrated long- term overall survival of nearly 85 and a low threat of developing advanced complaint. Imatinib is generally well permitted, but it can beget side goods like edema, rash, cramping in the muscles, gastrointestinal symptoms, and myelosuppression. Rare but dangerous venom like hepatotoxicity and cardiac dysfunction necessitate long- term monitoring. Despite its effectiveness, some

patients become resistant to or intolerant of imatinib, which led to the creation of second-generation TKIs, most notably dasatinib and nilotinib. With the exception of T315I, these drugs are more potent and active against the majority of imatinib-resistant BCR-ABL mutations. They have also shown strong cytogenetic and molecular response rates in both first-line and second-line settings. They were approved as first-line treatments for newly diagnosed CML-CP after clinical trials like DASISION and ENESTnd demonstrated their superiority over imatinib in producing quicker and deeper responses. However, different toxicity profiles must be taken into account when choosing a medication: nilotinib is linked to metabolic abnormalities, hepatotoxicity, and QT prolongation, while dasatinib is linked to pleural effusion and bleeding risk. To maximize long-term results and preserve treatment adherence, careful patient selection, frequent monitoring, and proactive management of side effects are crucial.[22]

Parameter	Imatinib[13]	Nilotinib[14]	Dasatinib[15]
Recommended starting dose (adults with Ph+ CML-CP)	400 mg daily	300 mg bid for newly diagnosed pts. 400 mg bid for imatinib-resistant or -intolerant pts.	100 mg daily
Mechanism of action	Inhibits *BCR-ABL*, PDGFR, and *c-KIT*	Inhibits *BCR-ABL*, PDGFR, *c-KIT*, *CSF-1R*, and *DDR*	Multikinase inhibitor; inhibits *BCR-ABL*, *Src* family (*Src*, *Lck*, *Yes*, *Fyn*), *c-KIT*, *Epha2*, and PDGFRB
Relative in vitro potency against wild-type or mutant *BCR-ABL*[65]	1	~20	~325
t_{max}	2-4 h	3 h	0.5-6 h
Serum protein binding	95%	98%	96%
Metabolism (principal cytochrome P450 isoenzyme)	CYP3A4	CYP3A4	CYP3A4
Dose adjustment for hepatic impairment at baseline[a]	Mild/moderate: none Severe: reduce dose by 25%	Reduce dose in all cases[b]	Mild/moderate: none Severe: none
Elimination $t_{1/2}$	18 h	17 h	3-5 h
Excretion	Fecal	Fecal	Fecal

CML = chronic myeloid leukemia; CML-CP = chronic myeloid leukemia-chronic phase; Ph = Philadelphia; PDGFR = platelet-derived growth factor receptor; $t_{1/2}$ = half-life; t_{max} = time to maximum concentration.
[a]Mild = mild hepatic impairment (Child-Pugh Class A); moderate = moderate hepatic impairment (Child-Pugh Class B); severe = severe hepatic impairment (Child-Pugh Class C).
[b]See full prescribing information for nilotinib.[14]

Fig. 16: Pharmacology and Pharmacokinetics of Tyrosine Kinase Inhibitors Approved for CML.

B. Acute lymphoblastic leukaemia

Tyrosine Kinase Inhibitors' Function in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukaemia

Tyrosine kinases were identified as crucial therapeutic targets when the BCR-ABL1 fusion gene was found to be the primary oncogenic driver in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). This led to the creation of BCR-ABL tyrosine kinase inhibitors (TKIs), which prevent ATP binding and subsequent proliferative signaling. The first BCR-ABL TKI, imatinib, showed notable antileukemic activity and increased remission rates in both frontline and relapsed Ph+ ALL; however, because resistance developed quickly, responses to monotherapy were frequently transient. Imatinib significantly improved complete remission rates, depth of molecular responses, short-term survival, and transplant eligibility when used in conjunction with induction and consolidation chemotherapy. It was also successful and well tolerated in elderly or unfit patients. Resistance, which is caused by BCR-ABL1 kinase domain mutations (most notably T315I), activation of alternative pathways like SRC kinases, and increased drug efflux, is still a significant problem despite these advancements. As a result, second-generation TKIs were created, such as dasatinib and nilotinib, which demonstrated activity against the majority of imatinib-resistant mutations with the exception of T315I. Dasatinib was especially effective in patients who had received extensive pretreatment. All things considered, TKIs have taken center stage in the treatment of Ph+ ALL; however, in order to achieve long-term disease control, newer drugs and combination strategies are needed.[22]

3.1 Solid Tumors

Overview of Tyrosine Kinase Inhibitors' Function in Solid Tumors

Tumor growth, angiogenesis, and metastatic spread are all significantly influenced by receptor tyrosine kinases such VEGFR, PDGFR, KIT, and FGFR. Tumor vascularization and resistance to traditional treatment are encouraged by dysregulation of these signaling pathways. In certain cancers, targeting angiogenic signaling—specifically, the VEGF–VEGFR axis—has shown notable antitumor activity and improved survival. Sunitinib is an oral multitargeted tyrosine kinase inhibitor that inhibits VEGFR-1/2, PDGFR-α/β, KIT, FLT3, and related kinases to provide strong antiangiogenic and anticancer effects. Preclinical research supported its clinical development by demonstrating dose- dependent inhibition of tumor growth and endothelial death. CYP3A4-mediated metabolism with an active metabolite (SU012662) was identified by pharmacokinetic studies as a factor in prolonged target inhibition. These characteristics made sunitinib a crucial treatment for angiogenesis-driven cancer.[23]

A. Tyrosine Kinase Inhibitors' Function in Renal Cell Carcinoma

Loss of the von Hippel–Lindau (VHL) gene is frequently linked to renal cell carcinoma (RCC), especially clear-cell RCC, a highly vascular cancer that accumulates hypoxia-inducible factor (HIF) and overexpresses VEGF and PDGF. Immunotherapy has modest benefits, while conventional chemotherapy and radiation therapy are generally useless. Targeting angiogenesis mediated by PDGF and VEGF, sunitinib showed significant therapeutic activity in metastatic RCC. In patients who were not responding to cytokine treatment, phase II trials demonstrated extended progression-free survival and substantial partial response rates. Sunitinib outperformed interferon-α in terms of response rate, progression-free survival, and overall survival, according to a key phase III trial. Sunitinib became the accepted first-line treatment for metastatic RCC due to its tolerable toxicity profile.[23]

B. Tyrosine Kinase Inhibitors' Function in Intestinal Stromal Tumors

Tyrosine kinase inhibition is a logical treatment approach for gastrointestinal stromal tumors (GISTs), which are primarily caused by activating mutations in KIT or PDGFRα. Even though imatinib is still the first-line treatment, a sizable percentage of patients experience primary or secondary resistance.

Because sunitinib inhibits KIT, PDGFRs, and VEGFRs, it has become a successful second-line treatment. Clinical trials showed that patients with imatinib-resistant or intolerant GIST had better overall and progression-free survival. Interestingly, the response to treatment differed depending on the mutational status; tumors with KIT exon 9 mutations or wild-type KIT showed higher results. Sunitinib is now the recommended second-line treatment for advanced GIST, according to these data.[23]

C. Tyrosine Kinase Inhibitors' Function in non–small cell lung cancer (NSCLC)

In advanced non–small cell lung cancer (NSCLC), platinum-based doublet chemotherapy remains the standard of care; however, targeted therapies have significantly expanded treatment options.

Antiangiogenic targeting of the VEGF pathway with bevacizumab demonstrated improved survival when combined with chemotherapy, establishing VEGF as a valid therapeutic target. Tyrosine kinase inhibitors (TKIs), particularly the EGFR-TKI erlotinib, have shown clinical activity in advanced and pretreated NSCLC. Preclinical and clinical studies revealed enhanced antitumor effects when EGFR and VEGF pathways were simultaneously inhibited. Phase II trials of erlotinib combined with bevacizumab reported meaningful progression-free and overall survival benefits. Although the

phase III Betar Lung trial did not demonstrate a significant overall survival advantage, maintenance therapy with bevacizumab plus erlotinib improved progression-free survival. Collectively, these findings support the role of TKIs as an important component of systemic therapy in selected NSCLC patients.[24]

4. Adverse Effects

Tyrosine kinase inhibitors (TKIs) interfere with important cellular signaling pathways, which results in a wide range of adverse effects across multiple systems. In solid tumors, gastrointestinal toxicities like diarrhea, nausea, vomiting, mucositis, and anorexia are common, early, dose-dependent, and more frequent; colitis and perforation are uncommon but serious side effects. While pancreatic dysfunction (lipase/amylase elevation or pancreatitis) is uncommon and primarily associated with nilotinib and sorafenib, hepatotoxicity, which is characterized by elevated AST, ALT, and GGT, is typically early and transient and occurs more frequently with nilotinib, bosutinib, and ponatinib. While severe reactions are rare, dermatological reactions (rash, pruritus, dry skin, nail changes) are very common, especially with EGFR and BCR-ABL inhibitors. TKIs can alter bone and mineral homeostasis, cause fluid retention and electrolyte abnormalities (particularly hypophosphatemia), and interfere with glucose metabolism. Hypogonadism, adrenal insufficiency, and hypothyroidism are examples of endocrine effects. Clinically significant and occasionally fatal pulmonary toxicities include drug-induced pneumonitis, interstitial lung disease, and pleural effusion (particularly with dasatinib). There have also been reports of neurological and vascular events, hematological cytopenias, opportunistic infections (particularly with BTK inhibitors), ocular toxicities, renal impairment with proteinuria, and increased bleeding risk. Headache, an unclear long-term risk of secondary cancers, and possible pregnancy-related complications are other issues. To guarantee the safe and efficient use of TKIs, all of these toxicities require close observation, early detection, and customized treatment.[25]

5. Tyrosine Kinase Inhibitor Resistance Mechanisms

5.1. With over 100 mutations affecting over 70 amino acid residues, tyrosine kinase inhibitor (TKI) resistance is most frequently caused by mutations within the kinase domain. These mutations result in either increased ATP affinity or decreased drug binding through steric hindrance. The EGFR T790M gatekeeper mutation, which improves ATP binding, decreases TKI efficacy, and increases EGFR kinase activity, thereby promoting tumor survival, is primarily responsible for the frequent development of gefitinib resistance in NSCLC within 10–16 months. The BCR-ABL T315I mutation, which breaks a crucial hydrogen bond and confers resistance to both first- and second-generation TKIs, is primarily responsible for imatinib resistance in chronic myeloid leukemia.Other resistance mechanisms include activating FLT3 mutations in acute myeloid leukemia and secondary mutations in KIT and PDGFRA in gastrointestinal stromal tumors, all of which limit inhibitor binding while maintaining kinase function. Oncogenic signaling is further sustained by genetic alterations like EML4–ALK fusions and rare EGFR secondary mutations, as well as changes in downstream signaling components like PIK3CA. In general, therapy-induced genomic instability and selective pressure on pre-existing resistant clones lead to acquired TKI resistance, highlighting the complexity of resistance mechanisms.[26]

5.2 Molecular Underpinnings of Tyrosine Kinase-Targeted Therapy Resistance

Tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) have shown clinical success, but resistance often arises through various molecular mechanisms that allow tumor cell survival. Genetic changes are the most frequent cause, especially kinase domain mutations that decrease drug binding by changing the ATP-binding pocket or raising ATP

affinity. Examples of these mutations include EGFR T790M in NSCLC and BCR-ABL T315I in CML, as well as comparable mutations in KIT/PDGFRA, FLT3, ERBB2, and BRAF after targeted therapy. While genomic deletions affecting tumor suppressors or regulatory microRNAs increase oncogenic and anti-apoptotic signaling, gene amplification of targets like EGFR, BCR-ABL, and FLT3, or alternative oncogenes like MET, further reduces drug efficacy by restoring downstream signaling. Epigenetic modifications, such as promoter hypermethylation of tumor suppressor genes and hypoxia-induced factors like HIF-1α that activate alternative growth pathways, also contribute to resistance. Furthermore, cancer cells evade inhibition by activating compensatory signaling networks that include non-target kinases like AXL and SRC, RTK crosstalk (like EGFR–MET and EGFR–IGF-1R), and overexpression of anti-apoptotic proteins. Drug sequestration by plasma proteins, elevated efflux via ABC transporters, or decreased expression of influx transporters all contribute to altered drug bioavailability. The multifactorial nature of therapeutic resistance is highlighted by the fact that resistance to mAbs is primarily caused by non-genetic mechanisms, such as downstream pathway mutations, alternative RTK overexpression, receptor variants, increased ligand production, and steric masking of target receptors.[27]

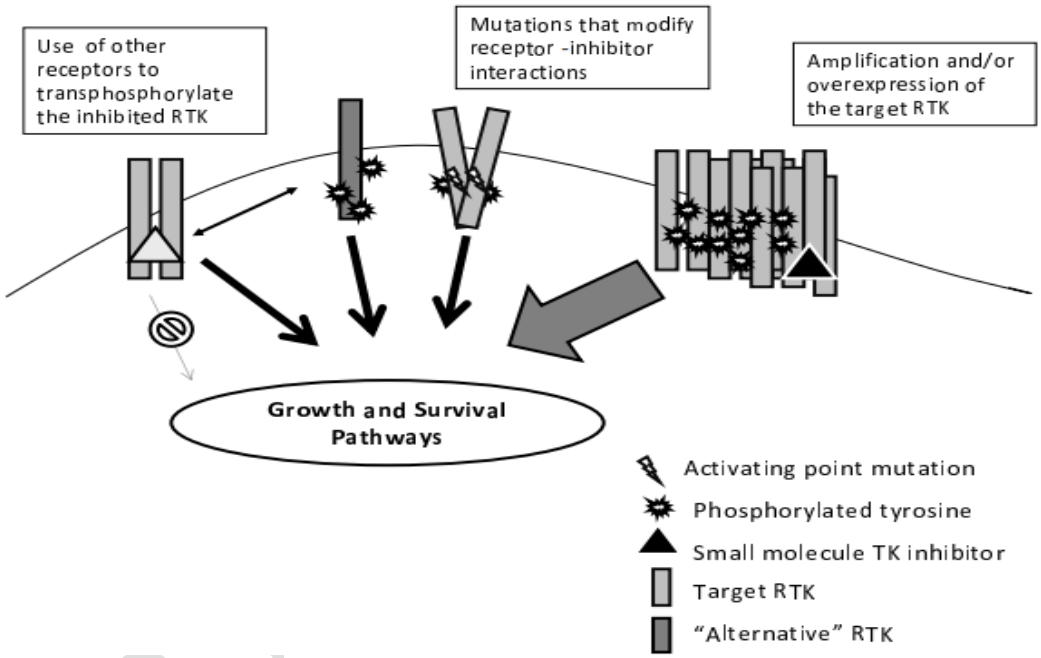


Fig. 17: Schematic summary of the main molecular mechanisms of acquired resistance to.[28]

5.3 Techniques for Overcoming EGFR-TKI Resistance

The development of newer-generation inhibitors and the use of combination therapies are the current approaches to overcome EGFR-TKI resistance, which is still a significant problem in advanced non-small cell lung cancer. Second-generation pan-ErbB inhibitors, like afatinib and dacomitinib, were developed as a result of resistance to first-generation EGFR-TKIs; however, their use was restricted due to toxicity and ineffectiveness against the T790M mutation. While more recent fourth-generation drugs seek to address combined T790M and C797S mutations, third-generation EGFR-TKIs, especially osimertinib, selectively target mutant EGFR and have demonstrated notable efficacy in T790M-positive NSCLC. In certain contexts, combination strategies that target parallel receptors like MET and VEGF, alternative signaling axes like JAK-STAT and Src, or downstream pathways like PI3K/Akt/mTOR and MAPK have shown enhanced antitumor activity. Ongoing efforts to address EGFR-TKI resistance are further highlighted by additional experimental approaches, such as drug repurposing and autophagy inhibition.[28]

6. Recent Advances and Emerging TKIs: selection, cautious

By enabling precision-based treatment of actionable oncogenic drivers, next-generation tyrosine kinase inhibitors (TKIs) have revolutionized the management of non-small cell lung cancer (NSCLC). Third-generation EGFR-TKIs, like osimertinib, have been established as first-line therapy because of their strong CNS penetration, improved survival outcomes, and effectiveness against T790M resistance. Though resistance is still unavoidable due to secondary mutations, bypass signaling, and tumor heterogeneity, parallel developments in TKIs targeting ALK, ROS1, RET, MET, BRAF, and NTRK alterations have further improved outcomes in oncogene-driven NSCLC, requiring repeat molecular profiling and the creation of fourth-generation TKIs and novel targets.For TKI-refractory disease, antibody-drug conjugates have shown promise, especially trastuzumab-deruxtecan in HER2-altered NSCLC.

Simultaneously, immune checkpoint inhibitors (ICIs), either by themselves or in conjunction with chemotherapy, have improved outcomes in non-small cell lung cancer (NSCLC) without driver mutations. However, their benefit is limited in EGFR- or ALK-mutant disease, and close sequencing with TKIs has been linked to serious toxicities like interstitial lung disease and hepatotoxicity. Therefore, to maximize efficacy, postpone resistance, and enhance long-term survival in NSCLC, biomarker-guided treatment sequencing, and logical combination strategies continue to be crucial.[29,30]

7. Challenges and Limitations of TKIs

Patients and healthcare systems around the world are severely impacted financially by rising cancer medication costs, especially for targeted therapies and next-generation TKIs. Access is still unequal, particularly in low- and middle-income countries, even though nations like those in Europe and Japan control costs through health technology assessments and cost-effectiveness measures. The difficulty of striking a balance between innovation, affordability, and equitable access is highlighted by the financial toxicity caused by high costs, long-term treatment, and cumulative toxicities, which can result in psychological distress, a lower quality of life, poor adherence, and treatment discontinuation. The cost of medications, complicated regimens, side effects, low health literacy, mental health problems, and the constraints of the healthcare system all contribute to the ongoing, multifactorial problem of patient adherence. Higher overall healthcare costs, more hospital admissions, and worse clinical outcomes are all consequences of non-adherence. Long-term treatment success requires a multidisciplinary approach that includes patient education, simplified therapies, financial support, and better healthcare communication, even though digital health tools offer promising solutions for monitoring and improving adherence.[31,32]

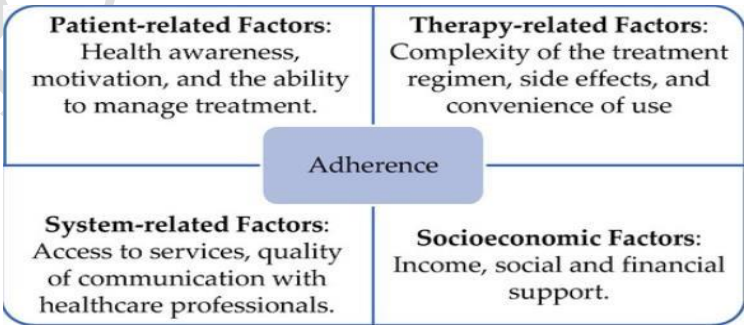


Fig. 18: Key factors influencing adherence.

9. Future Perspectives

Role of artificial intelligence in drug discovery tyrosine kinase inhibitors: Tyrosine kinase inhibitor (TKI) discovery and development are increasingly incorporating artificial intelligence (AI) to address the intricacy, high cost, and

protracted timelines of drug development and discovery (DDD). The complex molecular and cellular mechanisms underlying tumor pathophysiology necessitate the analysis of large and varied biological datasets in cancer drug research. Large-scale genomic, proteomic, and chemical data can be processed quickly and accurately thanks to AI technologies like machine learning, deep learning, neural networks, and network-based approaches. This makes lead optimization, target identification, and validation more effective. The success rate of finding new kinase targets and expediting the early stages of TKI discovery in oncology has greatly increased due to the expanding use of AI-driven applications, online platforms, and specialized databases. Simultaneously, AI is becoming more and more involved in precision oncology within the context of genomics-driven cancer medicine, where targeted therapeutic decisions are guided by genomic insights. Because cancer is essentially a genetic disease with dysregulated oncogenes and tumor suppressor genes, oncology has become a leading area of precision medicine. Large-scale cancer genome projects have improved patient stratification for targeted therapies like TKIs, molecular diagnostics, and biomarker discovery when combined with sophisticated computational tools. Although there are still issues with ethics, data interpretation, and trial viability—particularly in rare and pediatric cancers—these developments have also made it possible to create creative clinical trial designs that are specific to particular genetic changes. Overall, by enhancing mechanistic comprehension, streamlining treatment selection, and assisting in the creation of next-generation targeted therapies, AI-supported genomics continues to bolster precision oncology.[33,34]

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