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Recent developments in receptor tyrosine kinase inhibitors: A promising mainstay in targeted cancer therapy

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Abstract

During the past two decades, significant advances have been made in the discovery and development of targeted inhibitors aimed at improving the survival rates of cancer patients. Among the multitude of potential therapeutic targets identified thus far, Receptor Tyrosine Kinases (RTKs) are of particular importance. Dysregulation of RTKs has been implicated in numerous human diseases, particularly cancer, where aberrant signaling pathways contribute to disease progression. RTKs have a profound impact on intra and intercellular communication, and they also facilitate post-translational modifications, notably phosphorylation, which intricately regulates a multitude of cellular processes. Prolonged phosphorylation or the disruption of kinase regulation may lead to significant alterations in cell signaling. The emergence of small molecule kinase inhibitors has revolutionized cancer therapy by offering a targeted and strategic approach that surpasses the efficacy of traditional chemotherapeutic drugs. Over the last two decades, a plethora of targeted inhibitors have been identified or engineered and have undergone clinical evaluation to enhance the survival rates of cancer patients. In this review, we have compared the expression of different RTKs, including Met, KDR/VEGFR2, EGFR, BRAF, BCR, and ALK across different cancer types in TCGA samples. Additionally, we have summarized the recent development of

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CRediT authorship contribution statement

Rahul Kumar: Writing – original draft, Software, Methodology, Investigation, Funding acquisition, Data curation. **Harsh Goel:** Visualization, Software, Methodology, Investigation. **Raghu Solanki:** Visualization, Software, Methodology, Investigation. **Laxminarayan Rawat:** Visualization, Software, Methodology, Investigation. **Saba Tabasum:** Visualization, Software, Methodology, Investigation. **Pranay Tanwar:** Visualization, Supervision, Software, Methodology, Investigation. **Soumitro Pal:** Supervision, Methodology, Funding acquisition. **Akash Sabarwal:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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small molecule inhibitors and their potential in treating various malignancies. Lastly, we have discussed the mechanisms of acquired therapeutic resistance with a focus on kinase inhibitors in EGFR mutant and ALK-rearranged non-small cell lung cancer and BCR-ABL positive chronic myeloid leukemia.

Keywords

Cancer; Receptor tyrosine kinases; Tyrosine kinase inhibitors; Targeted therapy; Therapeutic resistance

1. Introduction

Malignant tumors pose a significant health threat, ranking among the leading causes of death worldwide. According to a report released by the International Agency for Research on Cancer (IARC), more than 10 million cancer-related deaths occurred worldwide in 2020, with predictions of further increases in the coming years [1]. In the United States alone, the American Cancer Society projected an annual death toll of over 608,570 [2]. The escalating cancer statistics highlight the urgency for the scientific community to focus on improved anti-cancer therapy and disease management. The emergence of kinase inhibitors, which surpass traditional drugs in treatment, offers a strategic approach to combat cancer.

The kinase family, comprising homologous proteins encoded in almost 2 % of the human genome, plays a crucial role in cellular regulation [3]. Normally tightly regulated in cells, kinases are key players in post-translational modifications, particularly phosphorylation, which governs various cellular processes [4]. Prolonged phosphorylation or kinase dysfunction can significantly alter cell signaling, potentially promoting tumorigenesis [5]. Recent advancements underscore the pivotal role of kinases in cancer progression, from initiation to metastasis. Over the past few years, numerous kinase inhibitors have been discovered, developed, and clinically tested. Gleevec (imatinib mesylate), introduced in 2001, marked the first successful therapeutic Abl tyrosine kinase inhibitor for treating chronic myeloid leukemia (CML) [6]. With over 90 kinase inhibitors approved worldwide in the last two decades, their efficacy in cancer treatment is evident [7]. However, certain limitations associated with these inhibitors may confer a selective advantage to transformed cells, affecting prognosis. Exploring potential inhibitors and inhibition mechanisms not only mitigates adverse effects but also steers toward precision medicine, reshaping cancer management strategies.

This review delves into the kinase superfamily, focusing on receptor tyrosine kinases (RTKs) and their roles under normal and diseased conditions. Additionally, we examine available inhibitory mechanisms targeting RTKs with minimal side effects. We also present a concise compilation of approved drugs targeting receptor tyrosine kinases (RTKs), along with a detailed examination of the various types of RTK inhibitors and their mechanisms of action. This comprehensive approach distinguishes our work from existing reviews by offering a thorough compilation and analysis of the latest RTK-targeted therapies and their clinical applications. Lastly, we complement prior revisions with current insights into managing

chemotherapy-induced resistance in CML and non-small cell lung carcinoma (NSCLC) including future insight.

2. Kinase family and receptor tyrosine kinases

The human genome encodes the kinase superfamily, comprising approximately 555 members. These protein kinases are categorized into two primary classes based on sequence similarity: eukaryotic protein kinase (ePK), encompassing 497 kinases, and atypical protein kinases (aPKs), comprising 58 kinases [8]. Within the ePKs, sequence similarity within the kinase domain further divides them into nine broad groups: TK (tyrosine kinase), TKL (tyrosine kinase-like), STE (serine/threonine kinases), CK1 (casein kinase 1), AGC (protein kinase A/G/C related), CAMK (Ca2+/calmodulin-dependent kinases), CMGC (Cdk, MAPK, GSK, Cdk-like related), RGC (receptor guanylyl cyclase) and others (include CK2 & IκB kinases.) [9,10]. TK, one of the major groups in the ePKs family, comprises 95 kinase members [11], playing a crucial role in cellular communication and interaction with the surroundings.

TKs are further subdivided based on their location into RTKs and non-receptor TKs (nRTKs). RTKs, located in the cell membrane, transmit signals from the extracellular to the intracellular region, while nRTKs, cytosolic proteins, relay intracellular signals within the cell [12,13].

RTK predominantly resides in the cell membrane, catalyzing the transfer of γ phosphate from phosphate-donating molecules such as ATP to specific substrates' hydroxyl (OH) group [14]. Concurrently, they activate downstream signal transduction pathways and regulate various cellular processes, including cell differentiation, proliferation, survival, apoptosis, and angiogenesis [15]. Over 90 distinct RTK-related genes have been identified, encoding 58 different types of RTK proteins, further grouped into 20 subfamilies based on the sequence of the kinase domain [10,16]. Despite variations, RTK proteins share a conserved architecture throughout evolution, featuring a glycosylated extracellular domain (ECD) facilitating ligand binding, followed by a transmembrane domain, an intracellular tyrosine kinase domain, and an intracellular region containing a juxta membrane regulatory region, a tyrosine kinase domain (TKD), and a carboxyl (C-) terminal tail.

Phosphorylation of RTKs can occur via three different processes: *cis*-auto phosphorylation (e.g., Glycogen synthase kinase-3 beta, (GSK-3 beta)), *trans*-auto phosphorylation (e.g., Insulin-like growth factor1 receptor (IGF1R)), and another kinase-mediated process (e.g., MAPK) [17–19]. Following phosphorylation, RTKs serve as docking sites for additional substrates, relaying information to the nucleus and modulating transcription and translation patterns. Using the UALCAN database, we compared the expression levels of several key RTKs frequently overexpressed in various cancers (Fig. 1) [20,21].

3. Activation of receptor tyrosine kinases under normal physiological state

Phosphorylation of RTK is essential for both intra and intercellular communication, tightly regulated under normal physiological conditions. Typically, RTKs exhibit ligand specificity becoming activated upon binding with their specific ligands to the ECD, leading to receptor dimerization (Fig. 2). RTK dimerization occurs through various mechanisms a) ligand-mediated dimerization: In this scenario, the ECD of the receptors does not directly participate in dimerization (e.g. Tropomyosin receptor kinase A (TrkA)) [22] b) Receptor-mediated dimerization: occurs in the absence of interaction between activating ligands (e.g. Epidermal growth factor receptor (EGFR)) [23] c) Ligand homodimerization: Where two receptors bind simultaneously to a ligand and interact through their dimer interface (e.g. Stem cell factor receptor (SCFR)) [24,25] d) Interaction through accessary molecules: In some cases, molecules such as heparin (e.g., FGFR) also participate in the receptor dimerization process [26,27].

Before ligand-induced dimerization, the kinase domain of RTKs undergoes *cis*-auto inhibition through intramolecular interaction, a mechanism that varies across different types of RTKs. Ligand binding disrupts this inhibitory interaction, inducing a conformational change in the cytoplasmic C-terminal [28]. Consequently, the intracellular kinase domain becomes activated, initiating the cis or *trans*-auto-phosphorylation of tyrosine residues. Phosphotyrosines then serve as binding sites, recruiting a diverse array of downstream signaling molecules, and acting as an assembly platform for other signaling proteins. These molecules transmit information to the nucleus, regulating a wide range of transcriptional activities primarily involved in cell growth, proliferation, migration, and angiogenesis [29–31].

4. Role of receptor tyrosine kinases in cancer

Under normal circumstances, the function of kinases is tightly regulated to maintain a balance between their active and inactive states. However, when RTKs undergo oncogenic activation or transforming abilities, they become constitutively active. This aberrant signaling disrupts the equilibrium between cell proliferation and death [32,33]. Dysregulated RTKs alter the normal cellular biology and confer oncogenic properties, leading to RTK-mediated tumorigenesis (Fig. 3). Dysregulation of RTKs can occur through various mechanisms (a) Gain of driver mutation: Examples include the L858R point mutation in EGFR [34] (b) Overexpression or genomic amplification: For instance, human epidermal growth factor receptor 2 (HER2) in lung or breast cancer [35] (c) Chromosomal rearrangement or translocation: Such as the BCR-ABL genes in leukemia cases [36] (d) Duplication of kinase domain: Observed in the ErbB family and other kinase families in various cancers [37] (e) Autocrine activation: Illustrated by the synergistic binding of transforming growth factor alpha (TGFα) ligand with the EGFR in lung cancer [38].

5. Receptor tyrosine kinase inhibitors: types and mechanisms of action

Recent advances in understanding the molecular mechanisms underlying cancer cell signaling have highlighted the significant association of kinases with tumorigenesis. Small molecule kinase inhibitors have emerged as highly effective therapeutic agents, classified into five major types (I–V) based on their mode of action (Fig. 4). (1) Type I inhibitors: These inhibitors compete with ATP, mimicking the heterocyclic purine ring and binding reversibly to the ATP binding pocket of kinases. By preventing the transfer of phosphate groups, they impede kinase activity [39–41]. However, type I inhibitors often exhibit limited selectivity against targeted kinases, potentially inhibiting off-target kinases associated with cardiac function [42,43]. (2) Type II inhibitors: Intrinsically selective, type II inhibitors bind to their target kinase, which possesses gatekeeper residues in their inactive form, [44]. They disrupt the overall orientation of the kinase by binding reversibly to the hydrophobic region of DFG-Asp out kinase confirmation, sterically hindering ATP binding. [45]. (3) Type III inhibitors: These inhibitors bind allosterically at sites other than ATP binding cleft, negatively modulating kinase activity. They exhibit the highest degree of selectivity due to variations in the allosteric binding site, rendering them exclusive against particular kinases [46]. (4) Type IV inhibitors: Also known as substrate-directed kinase inhibitors, these molecules interact reversibly at the substrate binding domain. They are uncompetitive with ATP but competitive with specific substrates, providing specificity towards the kinase [47]. (5) Type V kinase inhibitors: Reversible inhibitors that bind two different regions of the protein kinase domain and are therefore bivalent [48,49].

In addition to these conventional kinase inhibitors, there are alternative inhibitors targeting different regions of RTKs to inhibit the signaling cascade. For example, in the case of FGFR, SSR128129E (SSR) allosterically binds to the extracellular region of the target FGFR, inhibiting its kinase activity [50].

6. Clinical use of approved small molecule inhibitors: focus on receptor tyrosine kinases and other key targets

Given the frequent dysregulation of RTKs in cancer and their association with disease progression and poor prognosis, targeting these receptors has emerged as a promising therapeutic strategy. Recent advancements in the development of inhibitors specifically targeting RTKs have revolutionized cancer treatment (Fig. 5). By November 2023, over 100 small molecules or antibodies against specific RTKs had been approved for clinical use by regulatory bodies such as the FDA and the European Medicines Agency (EMA) (Table 1). Notable examples include Imatinib, Gefitinib, and Cetuximab, which have been approved for the treatment of various cancers. Moreover, numerous other RTK inhibitors are anticipated to receive approval in the coming years, further expanding the therapeutic options against cancer.

7. Acquired resistance mechanisms to receptor tyrosine kinase inhibitors and alternative approaches

Patients often initially respond favorably to RTK inhibitors; however, prolonged treatment may induce resistance, ultimately resulting in treatment failure disease progression. Tumor cells can employ various survival strategies, such as acquiring mutations or activating alternate pathways, to resist the inhibitory signals from RTK inhibitors [51].

Imatinib was the first RTK inhibitor approved by the FDA in 2001 for the treatment of CML [52]. However, over time, point mutations, particularly at T315I in Abl, cause patients to become nonresponsive and resistant to Imatinib therapy [53–55]. T315 acts as a gatekeeper residue and serves as a point of contact between the Abl and target inhibitors. Substitution of Thr at 315 with the bulkier side chain of Ile creates steric hindrance and blocks the hydrophobic pocket to form additional H-bonds, providing stability to the enzyme-inhibitor complex [40]. Apart from the T315I mutation, there are some other non-synonymous substitutions (M244V, G250E, Y253F/H, E255K/V, M351T, and F359V) that together account for around 85 % of all mutations related to the development of resistance [56]. Additionally, circular RNAs (such as circ_0009910, and circ_0080145) are also reported to enhance Imatinib resistance in CML and could be a potential target against resistant cells [57,58].

Patients who are unable to achieve complete cytogenetic responses (CCR) to imatinib treatment at regular doses, dose escalation, or early consideration of different generations of inhibitors should be considered for favorable long-term prognosis or CCR, [56]. Dose escalation of imatinib is one common approach to overcoming suboptimal or relapsed conditions, especially in patients showing low-level resistance [59]. Moreover, second-generation inhibitors (such as nilotinib, dasatinib, and bosutinib) are recommended for effective therapeutic strategies. These inhibitor acts with higher potency against a broad spectrum of mutations, except for T315I [60]. A phase 2 DASCERN randomized study (NCT01593254) supports the early switching to dasatinib, which could be beneficial for CML patients in the chronic phase [61]. To overcome the resistance due to T315I, combined therapy of imatinib or dasatinib along with interferon-alfa is recommended [62,63]. The limitation associated with second-generation inhibitors led to the development of third-generation inhibitors such as omacetaxine or & ponatinib. They were clinically approved for the effective treatment of CML cases having positive Ph or T315I mutant kinases [64]. A phase 2 interventional clinical trial (NCT00375219) concludes omacetaxine has the potential to be a safe and efficient therapy option for CML patients who have the T315I mutation with manageable hematologic and non-hematologic toxicities. Due to substantial safety concerns and the likelihood of arterial occlusive events (AOE), ponatinib is only prescribed to individuals having T315I mutation or who have failed the first two lines of therapy [65]. In 2021, another third-line option became available with the approval of asciminib to address the life-threatening adverse outcome of ponatinib. asciminib demonstrated its effectiveness in managing chronic cases in which other Abl kinase inhibitors failed or were ineffective against the T315I mutation (NCT02081378) [66]. It is an allosteric inhibitor with high specificity and potency against the myristoyl pocket of the fusion (BCR-ABL1) protein

and immobilizes it into an inactive conformation [67]. After assessing the wide range of mutations and their associated risk on prognosis, clinicians chose between the expanded available inhibitors to increase the progression-free survival of the patients.

Similar to what was seen with Abl kinase, EGFR also acquired resistance to specific chemotherapeutic agents during therapy. Detailed analysis of EGFR and its mutation provides insight into the drug-resistant mechanisms and the development of next-generation kinase inhibitors. In 2003, gefitinib was the first approved EGFR inhibitor followed by erlotinib for the treatment of NSCLC. These are used as first-generation inhibitors against activating mutations (R858L or exon 19 del) [68]. Despite showing an initial favorable response with the current regime of primary therapy, most patients eventually become less sensitive to these drugs and develop resistance, possibly by acquiring additional mutations as seen in CML treatment with imatinib [69].

A strikingly similar mechanism was observed in NSCLC, in which a substitution occurred at position 790, involving gatekeeper residues, replacing threonine with a bulkier hydrophobic side chain of methionine. This point mutation at the ATP binding site creates steric hindrance and loss of the binding cleft for the inhibitor, enhancing the binding affinity for ATP [70]. To overcome the limitations associated with gefitinib and erlotinib, second-generation inhibitors (afatinib and dacomitinib) were designed with enhanced potency against $EGFR^{T790M}$ [71].

In 2016, a multicentre, randomized phase III clinical trial (NCT02824458) was initiated in China to evaluate the effectiveness of gefitinib with or without apatinib as a first-line therapy in EGFR mutant NSCLC [72]. This study showed that patients had a superior progression-free survival (PFS) of 13.7 months when they received apatinib along with gefitinib compared to gefitinib alone (PFS-10.2 months) [73].

Despite being approved to overcome the drawbacks of first-generation inhibitors, a major downside was observed with afatinib and dacomitinib. They exhibit significant activity against the kinase domain of the EGFR family, but the therapeutic threshold required for clinical efficacy is unattainable due to dose-limiting associated toxicity [74]. There exists a challenge in terms of selectivity against the effective use of these drugs in a clinical setting, prompting the development of third-generation inhibitors (osimertinib) [75].

Currently, osimertinib is used as a first-line therapy among individuals with advanced NSCLC and works efficiently against activating mutations of EGFR, including EGFR T790M mutation [76–78]. A randomized AURA3 Clinical trial (NCT02151981) conducted with 419 patients having T790M-positive advanced NSCLC showed that osimertinib treatment resulted in a median PFS of 10.1 months for a total of 279 patients, as opposed to 4.4 months for the 140 patients who received platinum therapy plus pemetrexed. [79]. Another ADAURA clinical trial (NCT02511106) assessed the efficacy of osimertinib in an adjuvant setting. The result found a significant 5-year overall survival (OS) (85 %) in EGFR-mutated, stage IB to IIIA NSCLC individuals with completely resected tumors [80]. Thus, osimertinib showed greater efficacy in managing patients with advanced T790M

NSCLC. In contrast, osimertinib administered to NSCLC patients acquired EGFR L858R/L718V mutation confers resistance, but it retains the sensitivity to afatinib [81].

Considering its efficacy, the progression-free survival (PFS) or disease-free survival (DFS) of the NSCLC patients is worse. Due to its molecular heterogeneity, NSCLC cells can find alternate routes to escape the inhibitory action of osimertinib. Apart from acquiring additional mutations, this leads to the generation of new mechanisms of resistance that are independent or off-target of EGFR. These include MET or HER2 gene amplification, phenotypic transformation, activation of MAPK-PI3K pathway, cell cycle alteration, and oncogene fusion (such as FGFR3, NTRK, RET, ALK, BRAF) [78,82,83]. As a result, the compound's ability to provide long-term clinical benefit is limited.

Furthermore, ALK rearrangement is found in 5–17 % of NSCLC patients, making ALK another target after EGFR [84,85]. Many different versions of ALK fusion protein have been discovered so far, but EML4-ALK is one of the most prevalent types within a subset of NSCLC identified in 2007 [86]. Crizotinib is a first-generation ALK/MET/ROS1 tyrosine kinase inhibitor (TKI) approved in 2011 by the US FDA for the treatment of advanced ALK-rearranged NSCLC [87]. Although most patients with ALK-rearranged NSCLC respond to crizotinib, they develop resistance within 1 to 2 years of treatment due to mutations within the ALK tyrosine kinase domain, ALK fusion gene amplification, and alternative pathway-mediated survival signal activation (bypass pathway) activation via amplification or mutation of other receptor tyrosine kinases [88].

The presence of Leucine at the 1196 position regulates the accessibility of crizotinib to the hydrophobic pocket and inhibits the binding of the substrate within the catalytic site. Substitution of leucine with methionine sterically hinders the ability of inhibitors to bind and develop resistance toward a particular drug. Various other variants (G1269A, S1206Y, V1180L, G1202R, and C1156Y) discovered so far confer resistance through various on or off-target mechanisms [89].

Ceritinib and alectinib are two second-generation potent ALK inhibitors that have demonstrated robust clinical activity in patients who developed resistance against crizotinib-resistant ALK-positive NSCLC [90]. In phase I and II clinical studies, ceritinib elicited responses in both crizotinib-naive and crizotinib-refractory patients who harbored an ALK resistance mutation [91]. Based on this impressive clinical activity, ceritinib received US FDA approval in April 2014 for the treatment of crizotinib-refractory, ALK-rearranged NSCLC [92,93]. Ceritinib-resistant was detected in the tumor sample due to Src activation, and MAP2K1 K57N activating mutations [94].

The brain is a common site of relapse in patients treated with crizotinib. Crizotinib targets p-glycoprotein (P-gp), whereas alectinib crosses the blood–brain barrier and is highly effective for CNS lesions with ALK-positive NSCLC patients [93]. Based on these outcomes, alectinib received approval in December 2015 for the treatment of metastatic ALK-positive NSCLC patients who were intolerant to crizotinib [94–96].

Patients treated with alectinib also confer resistance, as they do for crizotinib and ceritinib, due to MET gene amplification and upregulation of neuregulin-1 (NRG1) in ALK-positive

patients [90]. Several new ALK inhibitors are currently under development. Among them, brigatinib is another second-generation ALK inhibitor reported to overcome resistance to other first and second-generation ALK inhibitors in preclinical models and randomized clinical trials [97]. Brigatinib was approved in April 2017 by the FDA with orphan drug designation for the treatment of crizotinib-resistant, ALK-positive NSCLC [98].

In March 2021, based on the study B7461006 (NCT03052608), lorlatinib was approved as a third-generation inhibitor by the US FDA for the management of patients who developed ALK G1202R mutation. It can cross the blood–brain barrier more effectively than previous ALK-directed TKI and has shown promising results in overcoming the resistance that inhibits ALK [99]. Together, the above findings indicate the potential for an effective, personalized regimen involving rotation between first, second, and third-generation ALK inhibitors to maximize the response of ALK-positive NSCLCs.

8. Future directions

Individual drugs are typically employed to treat cancer, and they have had some degree of success; however, cancer cells acquire resistance to the treatments, rendering the treatment ineffective. To address these limitations, a sequential, combined, or mixed therapy approach can be employed. It always remains elusive to choose between these therapies and difficult to assess the cost-benefit ratio of a particular drug. Sequential therapy is based on the mutation profile and existing information about the off-target resistance mechanism of targeted RTK. Whereas combined therapy refers to the concurrent administration of a drug regimen. The efficacy of single agents like monoclonal antibodies (mAbs) is limited. To enhance their efficacy, a combination with other chemotherapeutic agents may be employed to increase the efficacy of the drugs.

The discovery of small molecule kinase inhibitors has revolutionized targeted therapy and will continue to dominate the field of precision oncology. Cancer patients who undergo targeted therapy typically live longer and with a better quality of life. Although only 8–10 % of protein kinases have been studied and targeted for cancer treatment so far. The emergence of acquired resistance remains a significant challenge and compromises their effectiveness after investing millions of dollars and years of trial. Thus, the development of resistance and disease progression is a major clinical problem, and more studies are needed to understand the underlying molecular mechanisms leading to therapeutic resistance.

Interestingly, immunotherapy-based approaches are emerging as an alternative to conventional therapies. The early success of ipilimumab (used to treat certain types of melanomas) as a checkpoint inhibitor that targets CTLA-4, a protein receptor that downregulates the immune system, has sparked future interest in exploring immunotherapy strategies across different cancers. These classes of drugs are used to boost the patient’s immune system (T cells) to kill malignant cells. Another immunotherapy-based approach includes cell-based therapy in which T cells are isolated from the patients followed by genetic engineering, enabling them to recognize cancer cells and infuse them back intravenously. This type of live cell therapy showed encouraging results in blood cancer

treatments; however, for solid tumors, it has not yet achieved the same milestone and is currently under investigation.

Furthermore, the growth of AI (artificial intelligence) with its advancements in tools provides cutting-edge algorithms and accelerates therapeutic opportunities. It may help to reduce the obstacles faced during the discovery, optimization, and development phases along with the associated costs. Additionally, AI profoundly may transform towards precision medicine which involves a deep understanding of the pathogenicity behind the disease to tailor therapy to individual patients.

9. Conclusions

RTKs are transmembrane receptors of great clinical interest due to their role in various diseases including cancer. Small molecule kinase inhibitors have been utilized to inhibit defective signaling through RTKs. However, the development of therapeutic resistance is a major clinical limitation that mainly occurs due to genetic alteration and may be present initially at the time of diagnosis or acquired as a result of therapy. Clinicians must be aware of the mutational status of the targeted receptor and the available treatment algorithms. As previously mentioned, resistance mechanisms exhibit heterogeneity, which accelerates the development of next-generation as well as multi-kinase inhibitors. Over the last two decades, more than a hundred small-molecule kinase inhibitors or monoclonal antibodies (mAbs) have received approvals from various drug regulatory authorities. Despite all this development, it remains a challenge for clinicians to meet patients' needs in the present clinical setting and embark on various other trials. Currently, a greater number of drugs are in the trial phase, aiming to improve therapeutic effectiveness by optimizing personalized therapy and developing strategies to overcome resistance and cytotoxicity.

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Abbreviations:

ALL	Acute lymphocytic leukemia
AML	Acute myeloid leukemia
ADCC	Antibody-dependent cellular cytotoxicity
AGC	protein kinase A/G/C related
ALK	Anaplastic lymphoma kinase
ATC	Anaplastic thyroid cancer
aPK	atypical protein kinase

BTK	Bruton tyrosine kinase
CAMK	Ca2+/calmodulin-dependent kinases
CCR	complete cytogenetic responses
CLL	Chronic lymphocytic leukemia
CK1	casein kinase 1
CMGC	Cdk, MAPK, GSK, Cdk-like related
CSF-1 receptor	Colony stimulating factor 1 receptor
CML	Chronic myelogenous leukaemia
DFS	Disease free survival
ECD	Extracellular domain
EGFR	Epidermal growth factor receptor
EMA	European medicines agency
ERBB2	Erb-b2 receptor tyrosine kinase 2
ePK	eukaryotic protein kinase
FDA	Food and Drug Administration
FGFRs	Fibroblast growth factor receptors
FAK	Focal adhesion kinase
FL	Follicular lymphoma
FLT3	Fms-like tyrosine kinase 3
GISTs	Gastrointestinal stromal tumors
GSK-3 beta	Glycogen synthase kinase-3 beta
HER2	Human epidermal growth factor receptor 2
IARC	International Agency for Research on Cancer
IGF1R	Insulin like growth factor1 receptor
JAK2	Janus Kinase 2
KFDA	Korea food & drug administration
LGG	Low-grade gliomas
LGSOC	Low-grade serous ovarian carcinoma
MCL	Mantle cell lymphoma

MZL	Marginal zone lymphoma
MAPKs	Mitogen-activated protein kinases
mTOR	Mechanistic Target of Rapamycin kinase
MTC	Medullary thyroid carcinoma
MEK	Mitogen-activated protein kinase kinase
mAbs	monoclonal antibodies
NCI	National Cancer Institute
NTRK	Neurotrophic tyrosine receptor kinase
NMPA	National Medical Products Administration
nRTKs	non-receptor TKs
NRG1	Neuregulin-1
NSCLC	non-small cell lung carcinoma
PTCL	Peripheral T-Cell lymphoma
Ph	Philadelphia chromosome
PIK3CA/D/G	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit alpha/delta/gamma
PDGFR	Platelet-derived growth factor receptor
PFS	progression-free survival
RGC	Receptor guanylyl cyclase
RET	Rearranged during transfection
RCC	Renal cell carcinoma
SCFR	Stem cell factor receptor
SEER	Surveillance Epidemiology and End Results
STE	Serine/threonine kinases
SCLC	Small cell lung cancer
SLL	Small lymphocytic lymphoma
TGFα	Transforming growth factor alpha
TRK	Tropomyosin receptor kinase
TK	Tyrosine kinase

TKD	tyrosine kinase domain
TKL	tyrosine kinase-like
VEGFR2	Vascular endothelial growth factor receptor 2

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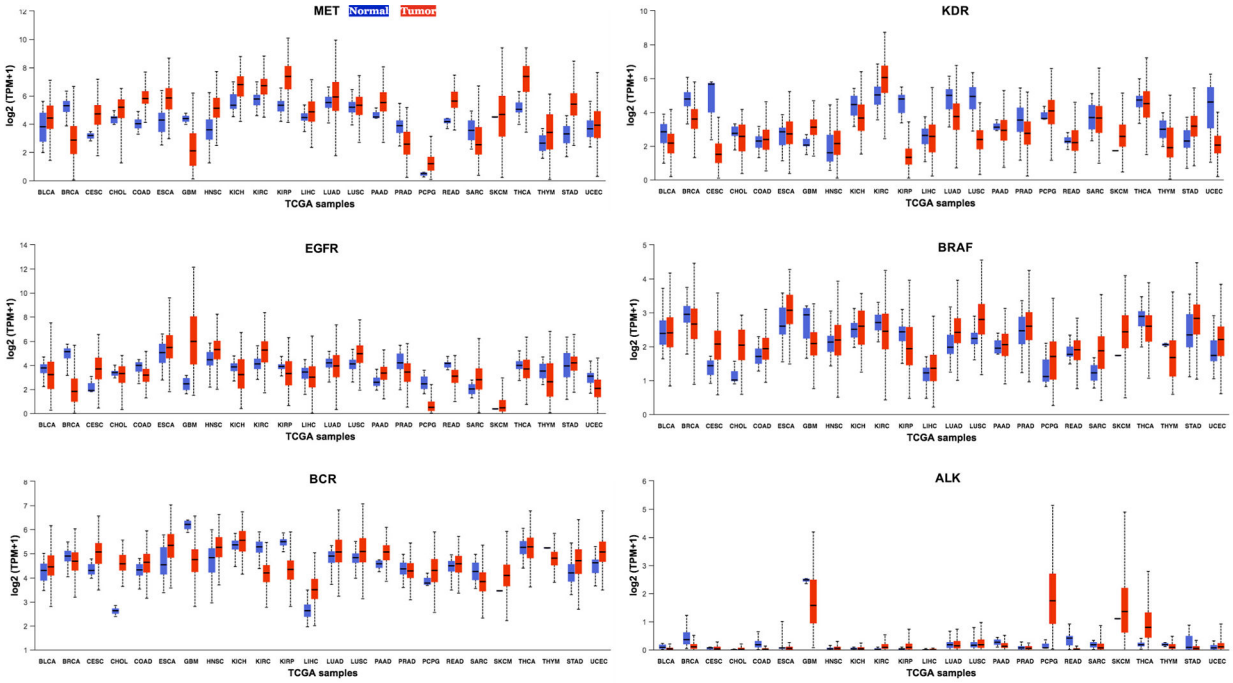

Fig. 1. Differential Expression of Receptor Tyrosine Kinases in Various Cancer Types.

Expression of Met, KDR (VEGFR2), EGFR, BRAF, BCR and ALK across different cancer types in TCGA samples tumor vs normal samples were analysed using UALCAN database. BLCA- Bladder Urothelial Carcinoma, BRCA- Breast invasive carcinoma, CESC- Cervical squamous cell carcinoma and endocervical adenocarcinoma, CHOL- Cholangiocarcinoma, COAD- Colon adenocarcinoma, ESCA- Esophageal carcinoma, GBM- Glioblastoma multiforme, HNSC- Head and Neck squamous cell carcinoma, KICH- Kidney Chromophobe, KIRC- Kidney renal clear cell carcinoma, KIRP- Kidney renal papillary cell carcinoma, LIHC- Liver hepatocellular carcinoma, LUAD- Lung adenocarcinoma, LUSC- Lung squamous cell carcinoma, PAAD- Pancreatic adenocarcinoma, PRAD- Prostate adenocarcinoma, PCPG- Pheochromocytoma and Paraganglioma, READ- Rectum adenocarcinoma, SARC- Sarcoma, SKCM- Skin Cutaneous Melanoma, THCA- Thyroid carcinoma, THYM- Thymoma, STAD- Stomach adenocarcinoma, UCEC- Uterine Corpus Endometrial Carcinoma.

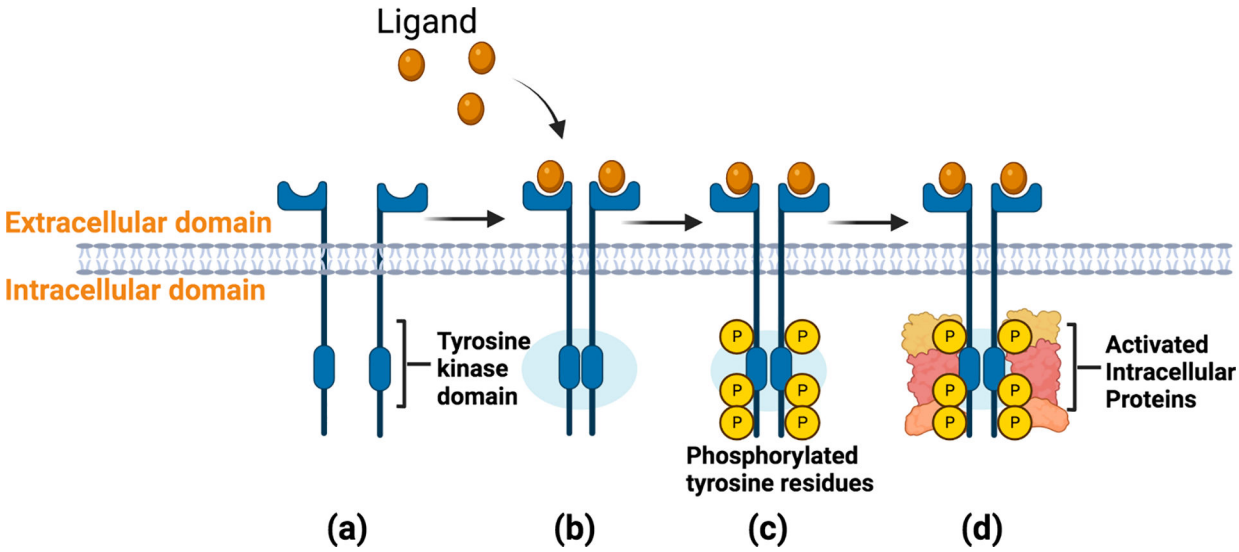

Fig. 2.

Mechanisms of Receptor Tyrosine Kinase Activation. (a) Inactive RTK: In its inactive state, the RTK remains unstimulated, with its kinase activity dormant (b) Kinase activity stimulated through dimerized RTK: Upon ligand binding, RTKs often undergo dimerization, where two RTK molecules come together. This dimerization stimulates the kinase activity of the RTKs, initiating the signaling cascade. (c) RTK is activated via autophosphorylation: Once dimerized, the activated RTKs undergo autophosphorylation. This process involves the transfer of phosphate groups from ATP molecules to specific tyrosine residues within the RTK itself, leading to further activation. (d) Signal relayed by activated signaling proteins into the interior of the cell: The activated RTKs serve as docking sites for various signaling proteins. These proteins, upon binding to the phosphorylated tyrosine residues on the RTK, become activated themselves. They then relay the signal initiated by the RTKs to the interior of the cell, triggering downstream cellular responses. Adapted and reproduced with permission [100]. Springer Nature https://link.springer.com/article/10.1007/s00018-023-04729-4.

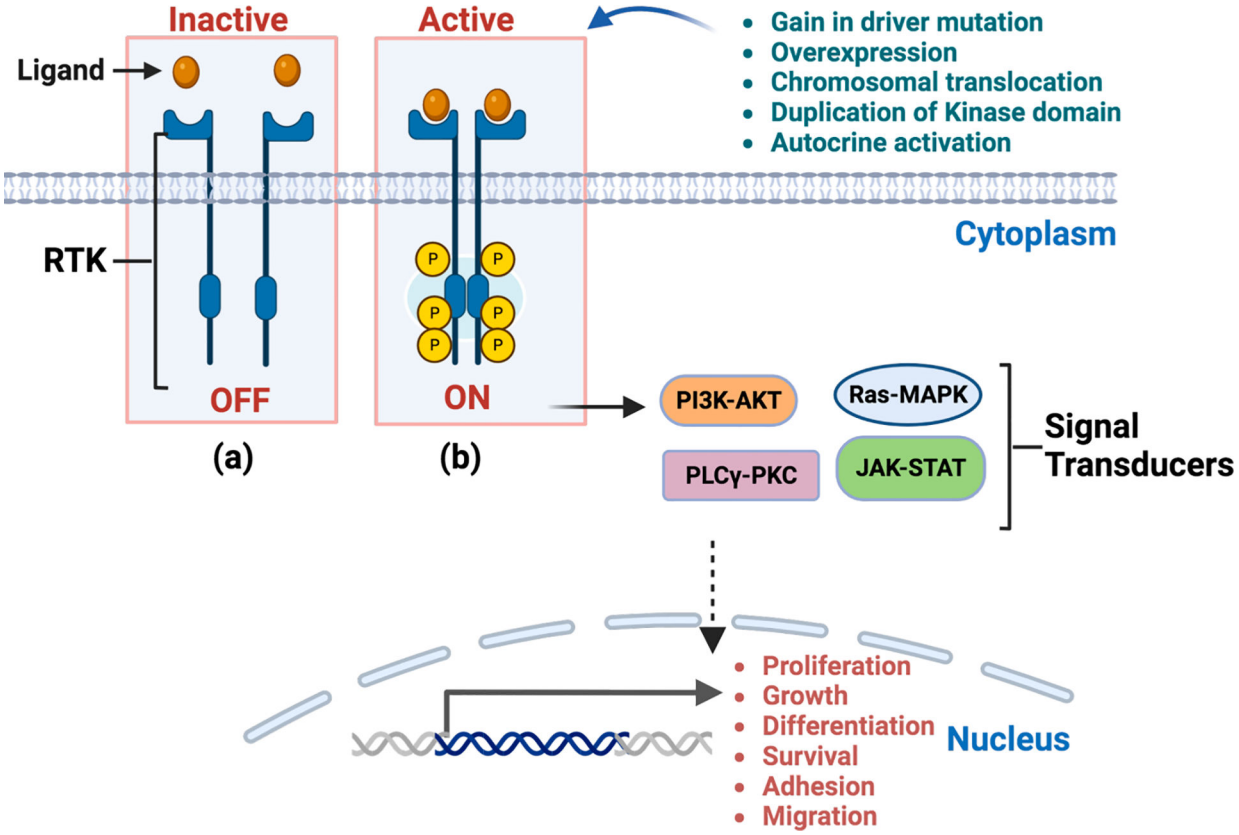

Fig. 3. Schematic Representation of Receptor Tyrosine Kinase Activation and its Impact on Downstream Pathways Involved in Pro-tumorigenic Signaling.

(a) In the absence of stimuli or ligand RTK remains in OFF or inactivated state, (b) RTK activation-Ligand binding induces dimerization of RTKs, this dimerization activates the intracellular kinase domain of the receptors leading to autophosphorylation of tyrosine residues within the cytoplasmic tails of RTKS. Phosphorylated RTKs activate downstream signaling pathways leading to increased transcription of genes involved in cell proliferation, suppression of apoptosis, angiogenesis and migration and invasion.

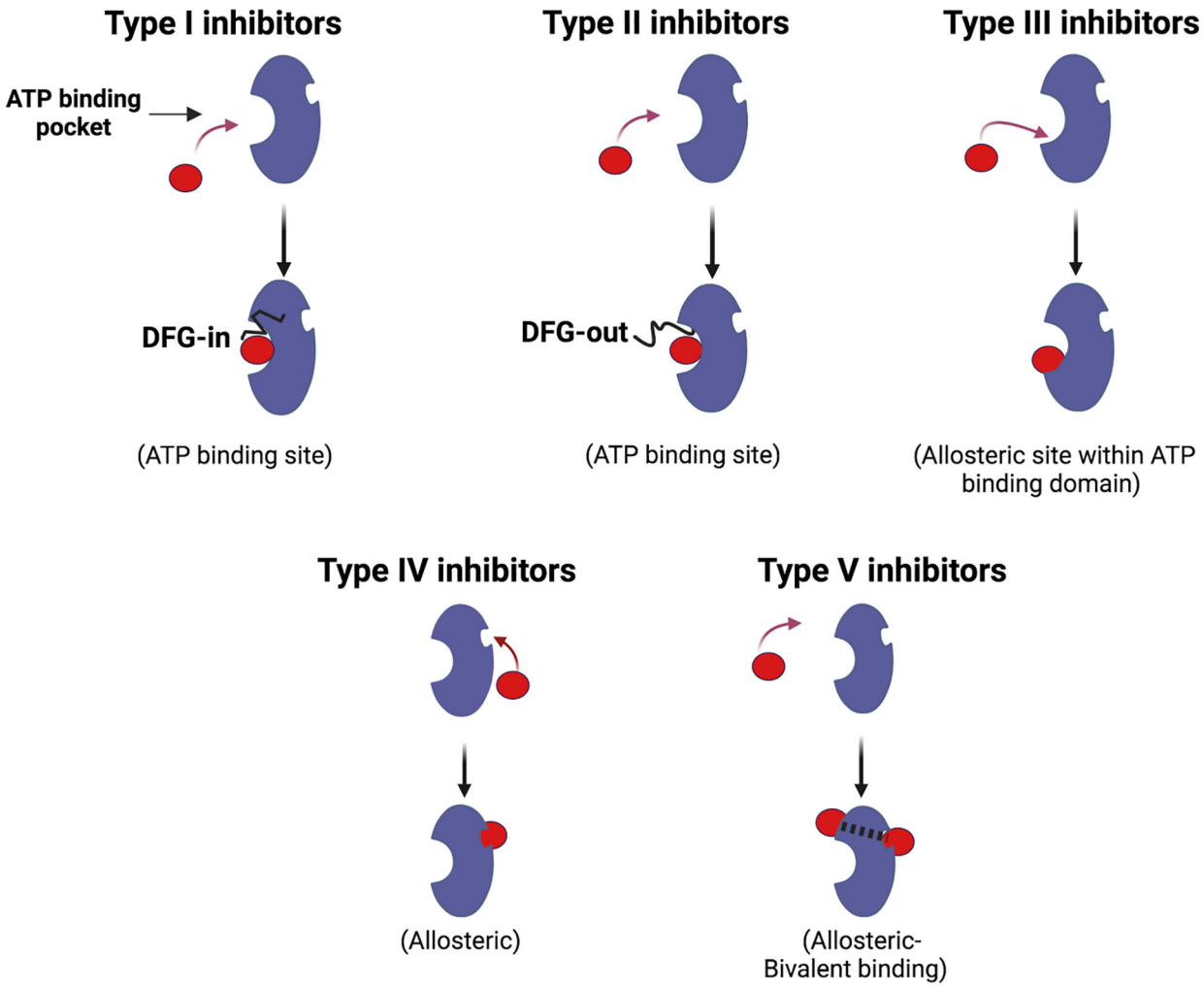

Fig. 4. Different Types of Kinase Inhibitors and Their Mechanisms of Action.

Type I inhibitors engage with the active conformation of the kinase, wherein the aspartate residue within the DFG (Asp-Phe-Gly) motif is oriented towards the ATP binding pocket. Conversely, type II inhibitors stabilize the inactive state of the enzyme, causing the aspartate residue to protrude outward from the binding site. Type III inhibitors act through the allosteric site located within the ATP binding pocket. Type IV inhibitors also target an allosteric site; however, its position may vary outside the ATP binding pocket. Type V inhibitors interact with both the allosteric site and the ATP binding pocket simultaneously.

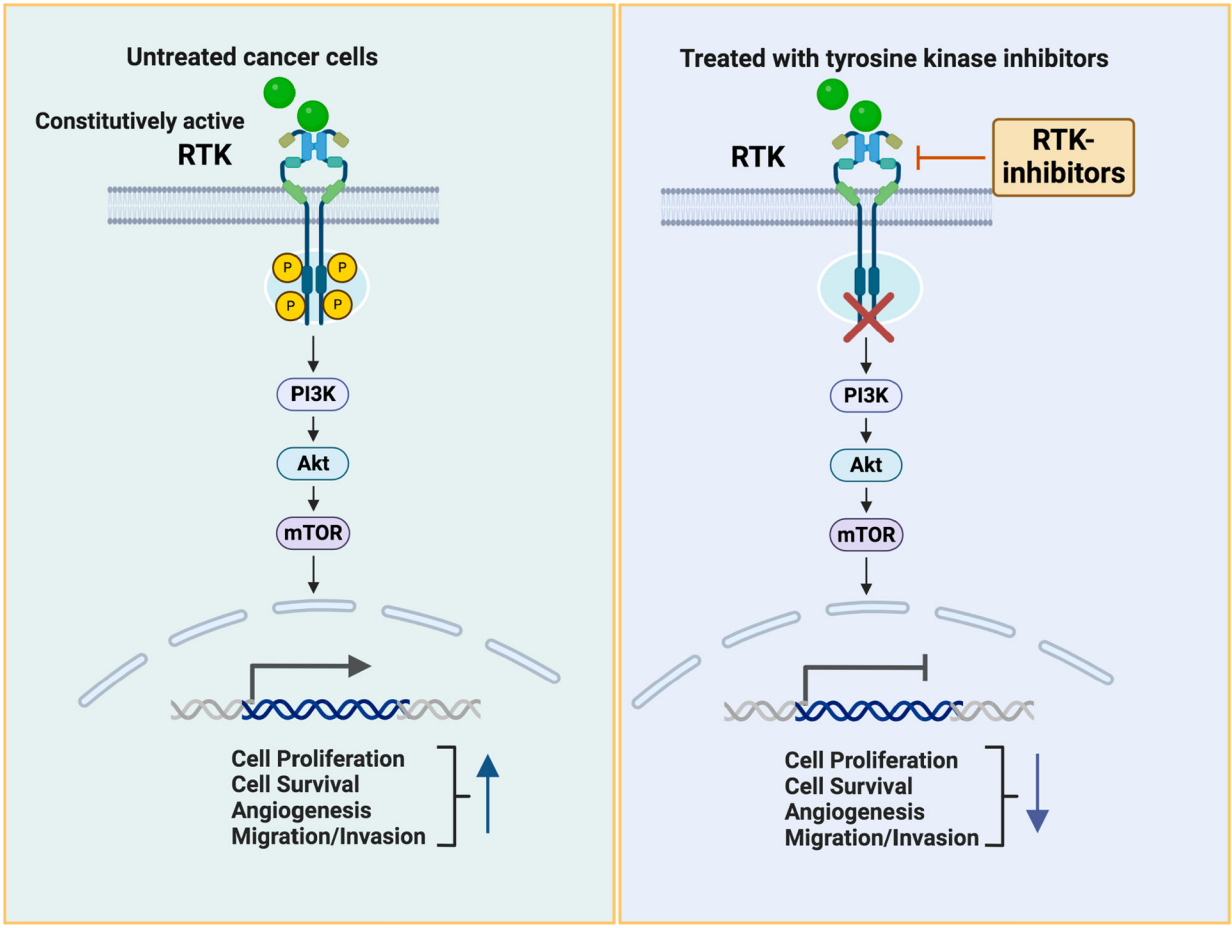

Fig. 5. General Mechanisms of Action of Tyrosine Kinase Inhibitors.

Small molecule inhibitors inhibit the ligand-mediated phosphorylation of RTKs, thereby preventing the activation of downstream protumorigenic signaling pathways. This inhibition leads to downregulation of transcription of genes that are involved in cell proliferation, survival, angiogenesis and migration and invasion.

Table 1

List of clinically approved kinase inhibitors for cancer treatment.

Generic name	Brand name	Company	Target Kinase	Cancer	Approved by (year)
trastuzumab	Herceptin	Genentech	ERBB2	Breast and Stomach	FDA (1998), EMA (2000)
imatinib	Gleevec	Novartis	Abl, c-Kit, PDGFR	CML, GIST	FDA (2001) EMA (2001)
gefitinib	Iressa	AstraZeneca	EGFR	NSCLC	FDA (2003)EMA (2009)
cetuximab	Erbitux	Eli Lilly and Company	EGFR	Head and neck, Colorectal	FDA (2004)EMA (2004)
erlotinib	Tarceva	Roche-OSI	EGFR	NSCLC, Pancreas	FDA (2004)EMA (2005)
sorafenib	Nexavar	Bayer-Onyx	VEGFR2, PDGFR, KIT, FLT3, BRAF	RCC, HCC	FDA (2005)EMA (2006)
sunitinib	Sutent	Pfizer	VEGFR, KIT (CD117), PDGFR, RET, CSF1R, FLT3	RCC, GIST	FDA (2006)EMA (2008)
panitumumab	Vectibix	Amgen	EGFR	Colorectal	FDA (2006)EMA (2007)
dasatinib	Sprycel	Bristol-Myers Squibb	ABL, PDGFR, KIT, SRC	CML, ALL	FDA (2006)EMA (2006)
lapatinib	Tyverb	GlaxoSmithKline	ERBB2	Breast	FDA (2007)EMA (2008)
nilotinib	Tasigna	Novartis	ABL, PDGFR KIT	CML	FDA (2007)EMA (2007)
temsirolimus	Torisel	Pfizer-Wyeth	mTOR	RCC	FDA (2007)EMA (2007)
everolimus	Afinitor	Novartis	mTOR	Benign and cancerous tumors	FDA (2009)EMA (2009)
pazopanib	Votrient	GlaxoSmithKline	VEGFR2 PDGFR c-KIT	RCC	FDA (2009)EMA (2010)
crizotinib	Xalkori	Pfizer	ALK, MET	NSCLC	FDA (2011)EMA (2012)
vandetanib	Caprelsa	AstraZeneca	RET, VEGFR FGFR, EGFR	Thyroid	FDA (2011)EMA (2012)
ruxolitinib	Jakavi	Novartis-Incyte	JAK2	Myelofibrosis	FDA (2011)EMA (2012)
vemurafenib	Zelboraf	Roche-Plexxikon	BRAF	Melanoma	FDA (2011)EMA (2012)
icotinib	Conmana	Betta Pharmaceuticals	EGFR	NSCLC	NMPA (2012)
omacetaxine mepesuccinate	Synribo	Teva Pharmaceuticals	ABL	CML	FDA (2012)
pertuzumab	Perjeta	Genentech	ERBB2	Breast	FDA (2012)EMA (2013)
ponatinib	Iclusig	ARIAD Pharmaceuticals	ABL	CML, ALL	FDA (2012)EMA (2013)
axitinib	Inlyta	Pfizer	VEGFR, PDGFR, KIT RET,CSF1R, FLT3	RCC	FDA (2012)EMA (2012)
bosutinib	Bosulif	Pfizer	ABL	CML	FDA (2012)EMA (2013)
cabozantinib	Cabometyx	Exelixis	VEGFR2, c-Met PDGFR, KIT, FLT3	Medullary thyroid, RCC	FDA (2012)EMA (2014)
ibrutinib	Imbruvica	Janssen Pharmacyclic	BTK	CLL, MCL, Blood cell Cancer	FDA (2013)EMA (2013)

Generic name	Brand name	Company	Target Kinase	Cancer	Approved by (year)
afatinib	Gilotrif	Boehringer Ingelheim	EGFR	NSCLC	FDA (2013)EMA (2013)
dabrafenib	Tafinlar	GlaxoSmithKline	BRAF	NSCLC, Thyroid	FDA (2013)EMA (2013)
regorafenib	Stiverga	Bayer	VEGFR2	Colorectal, GIST	FDA (2012)EMA (2013)
trametinib	Mekinist	GlaxoSmithKline	MEK	Melanoma, NSCLC, ATC with BRAFV600E	FDA (2013)EMA (2014)
idelalisib	Zydelig	Gilead Sciences	PIK3CD	CLL, FL, SLL	FDA (2014)EMA (2014)
nimotuzumab		Biotech Pharm.	EGFR	Head and neck, Glioma	NMPA (2014)CDSCO (2014)
ramucirumab	Cyramza	Eli Lilly and Company	VEGFR2	NSCLC, Colorectal	FDA (2014)EMA (2014)
ceritinib	Zykadia	Novartis	ALK	NSCLC with ALK translocations	FDA (2014)EMA (2015)
rivoceranib		Elevar	VEGFR2	HCC	NMPA (2014)
alectinib	Alecensa	Roche	ALK	NSCLC with ALK translocations	PMDA (2014)FDA (2015)EMA (2017)
necitumumab	Portrazza	Eli Lilly and Company	EGFR	NSCLC	FDA (2015)EMA (2015)
radotinib	–	Daewoong Pharmaceutical	BCR-ABL PDGFR	CML	MFDS (2015)
palbociclib	Ibrance	Pfizer	CDK4/6	Breast	FDA (2015)EMA (2016)
lenvatinib	Lenvima 10	Eisai	VEGFRs	Thyroid, Kidney	FDA (2015)EMA (2015)
cobimetinib	Cotellic	Roche Exelixis	MEK1/2	Melanoma, breast	FDA (2015)EMA (2015)
osimertinib	Tagrisso	AstraZeneca	EGFR	T790M + ve NSCLC	FDA (2015)EMA (2016)
olmutinib		Boehringer Ingelheim	EGFR	T790M + ve NSCLC	MFDS (2016)
olaratumab	Lartruvo	Eli Lilly and Company	PDGFRa	STS	FDA (2016)EMA (2016)
ribociclib	Kisqali	Novartis	CDK4/6	Breast	FDA (2017)EMA (2017)
brigatinib	Alunbrig	ARIAD Pharmaceuticals	ALK T790M EGFR	ALK-rearranged metastatic NSCLC	FDA (2017)EMA (2018)
midostaurin	Rydapt	Novartis	FLT3	AML (FLT3 mutation +)	FDA (2017)EMA (2017)
neratinib	Nerlynx	Wyeth-Pfizer-Puma	EGFR	Breast	FDA (2017)EMA (2018)
abemaciclib	Verzenio	Eli Lilly and Company	CDK4/6	Breast	FDA (2017)EMA (2018)
copanlisib	Aliqopa	Bayer	PI3K	FL	FDA (2017)
tivozanib	Fotivda	AVEO Pharmaceutical	VEGFR	RCC	2017 EMA
acalabrutinib	Calquence	AstraZeneca Acerta Pharma	BTK	MCL, CLL	FDA (2017)EMA (2018)
simotinib		Jiangsu Simcere Pharmaceutical	EGFR	Solid tumours	NMPA (2018)
encorafenib	Braftovi	Novartis-Array-Pfizer	MEK/RAF	Melanoma with BRAF (V600E or V600K)	FDA (2018)EMA (2018)
binimetinib	Mektovi	Array-Novartis-Pfizer	MEK 1/2	BRAF mutant melanoma	FDA (2018)EMA (2018)
duvelisib	Copiktra	Verastem Oncology	PIK3D/G	CLL, SLL	FDA (2018)
dacomitinib	Vizimpro	Pfizer	EGFR (ex19del or L858R)	NSCLC with EGFR mutations	FDA (2018)EMA (2019)

Generic name	Brand name	Company	Target Kinase	Cancer	Approved by (year)
gilteritinib	Xospata	Astellas Pharma	FLT3, RTKs	AML with FLT3 mutation	FDA (2018)EMA (2019)NMPA (2021)
larotrectinib	Vitrakvi	LOXO-Bayer	TRKs	Solid tumors with NTRK fusions	FDA (2018)
catequentinib	-	Advenchen Laboratories	VEGFRs	NSCLC	NMPA (2018)
lorlatinib	Lorbrena	Pfizer	ALK	ALK + ve NSCLC	FDA (2018)EMA (2019)
fruquintinib	Elunate	Hutchison MediPharma	VEGFR	Colorectal	NMPA (2018)
erdafitinib	Balversa	Janssen	FGFRs	Urothelial	FDA (2019)
alpelisib	Piqray	Novartis	PIK3CA	Breast	FDA (2019)
pexidartinib	Turalio	Daiichi Sankyo	CSF1R, c-KIT FLT3	TGCT	FDA (2019)
entrectinib	Rozlytrek	Roche	NTRK1/2/3 ROS1, ALK	ROS1 + ve NSCLC, NTRK fusion solid tumors	FDA (2019)
fedratinib	Inrebic	Celgene	JAK2, FMS-like TK 3	Myelofibrosis	FDA (2019)EMA (2021)
zanubrutinib	Brukinsa	Beigene	BTK	MCL	FDA (2019)EMA (2022)
umbralisib	UKONIQ	TG Therapeutic	PI3KD	MZL	FDA (2019)
tenalisib		Rhizen Pharm.	PI3KD/G	PTCL, Breast	FDA (2019)
flumatinib	–	Jiangsu Hansoh Pharmaceutical	Bcr-ABL PDGFR	Ph + CML	NMPA(2019)
avapritinib	Ayvakit	Blueprint Medicines	mutants KIT PDGFR	GIST	FDA (2020)
tucatinib	Tukysa	Seattle Genetics	ERBB2	Breast	FDA (2020)EMA (2021)
pemigatinib	Pemazyre	Incyte	FGFR	cholangiocarcinoma with FGFR2 fusion	FDA (2020)
capmatinib	Tabrecta	Novartis	c-MET	MET mutation + ve NSCLC	FDA (2020)
selpercatinib	Retevmo	Eli Lilly and Company	RET fusions	NSCLC, MTC, thyroid	FDA (2020)
ripretinib	Qinlock	Deciphera Pharmaceuticals	KIT, PDGFRA	GIST	FDA (2020)
paxalisib	–	Kazia Therapeutics	PI3K	Glioblastoma	FDA (2020)
pralsetinib	Gavreto	Blueprint Medicines	RET	RET fusion + ve NSCLC MTC	FDA (2020)
almonertinib	–	Hansoh Pharma	EGFR	NSCLC (T790M EGFR)	NMPA(2020)
tirabrutinib	Velexbru	Ono Gilead	BTK	CNS lymphoma	PMDA(2020)
pyrotinib	Irene	Jiangsu Hengrui	EGFR, HER2/4	Breast	NMPA(2020)
orelabrutinib	HIBRUKA	InnoCare	BTK	MCL, CLL, SLL	NMPA(2020)
margetuximab	Margenza	Raven Biotech	Her2	Breast	FDA (2020)
infigratinib	Truseltiq	Novartis	FGFR2	cholangiocarcinoma	FDA (2021)
tepotinib	Tepmetko	EMD Serono	MET ex 14 alterations	NSCLC	PMDA(2020)FDA (2021)
trilaciclib	Cosela	G1 Therapeutics	CDK4/6	SCLC	FDA (2021)
surufatinib	Sulanda	Hutchmed	VEGFR1–3	Neuroendocrine tumors	NMPA(2021)

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Generic name	Brand name	Company	Target Kinase	Cancer	Approved by (year)
savolitinib	Orpathys	AZ-Hutchmed	c-MET	NSCLC, RCC, Gastric, Colorectal	NMPA(2021)
lazertinib	LECLAZA	Yuhan-Janssen	EGFR	NSCLC with EGFR mutations	MFDS (2021)
mobocertinib	Exkivity	Janssen	EGFR	NSCLC with EGFR ex 20 mutations	FDA (2021)
furmonertinib	Ivesa	Allist Pharm.	EGFR	NSCLC (EGFR T790M)	NMPA(2021)
amivantamab	Rybrevant	Janssen	EGFR/MET	NSCLC with EGFR ex 20 mutations	FDA (2021)
asciminib	Scemblix	Novartis	Bcr-ABL	Ph + CML	FDA (2021)
defactinib		Pfizer-Verastem	FAK	LGSOC	FDA (2022)
pacritinib	Vonjo	CTI BioPharm	JAK/IRAK	Myelofibrosis	FDA (2022)
futibatinib	Lytgobi	Taiho Pharma	FGFR2	cholangiocarcinoma	FDA (2022)
pirtobrutinib	Jaypirca	Eli Lilly and Company	BTK	MCL	FDA (2023)
dabrafenib	Tafinlar	Novartis	BRAF	LGG with a BRAF V600E mutation	FDA (2023)

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