

REVIEW

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Exploring receptor tyrosine kinases-inhibitors in Cancer treatments



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Abstract

Background: Receptor tyrosine kinases (RTKs) are signaling enzymes responsible for the transfer of Adenosine triphosphate (ATP) γ -phosphate to the tyrosine residues substrates. RTKs demonstrate essential roles in cellular growth, metabolism, differentiation, and motility. Anomalous expression of RTK customarily leads to cell growth dysfunction, which is connected to tumor takeover, angiogenesis, and metastasis. Understanding the structure, mechanisms of adaptive and acquired resistance, optimizing inhibition of RTKs, and eradicating cum minimizing the havocs of quiescence cancer cells is paramount.

MainText: Tyrosine kinase inhibitors (TKIs) vie with RTKs ATP-binding site for ATP and hitherto reduce tyrosine kinase phosphorylation, thus hampering the growth of cancer cells. TKIs can either be monoclonal antibodies that compete for the receptor's extracellular domain or small molecules that inhibit the tyrosine kinase domain and prevent conformational changes that activate RTKs. Progression of cancer is related to aberrant activation of RTKs due to due to mutation, excessive expression, or autocrine stimulation.

Conclusions: Understanding the modes of inhibition and structures of RTKs is germane to the design of novel and potent TKIs. This review shed light on the structures of tyrosine kinases, receptor tyrosine kinases, tyrosine kinase inhibitors, minimizing imatinib associated toxicities, optimization of tyrosine kinase inhibition in curtailing quiescence in cancer cells and the prospects of receptor tyrosine kinase based treatments.

Keywords: Signaling, Tumor invasion, Receptor tyrosine kinases, Tyrosine kinase inhibitors, Inhibition

Background

Approximately 2000 kinases are known and 518 kinase genes are found in human with 90 being tyrosine kinases, fifty-eighty (58) of which are Receptor Tyrosine Kinases (RTKs), thirty-two (32) are Non-Receptor Tyrosine Kinases (NRTKs) [1]. Protein Tyrosine kinases are responsible for catalyzing phosphorylation reactions of the tyrosine molecules using ATP as their donor; they are important mediators of signaling cascades [2]. They play key roles in differentiation, metabolism, growth [3, 4], response to stimuli, and adhesion [5]. Tyrosine kinases are involved in a handful of neoplastic growth. Protein tyrosine kinase is of two types, cell surface receptor protein

kinases (RTKs) and Non-receptor protein kinases (NRTKs) [6]. Receptor tyrosine kinases belong to the family of cell surface receptors that transduce a response upon binding to a ligand. They are transmembrane proteins that pass through the biological membrane and have an extracellular domain (ectodomains) where ligands can bind [7]. Examples of these are, Vascular Endothelial Growth Factor Receptor (VEGFR), Epidermal Growth Factor Receptor (EGFR), Platelet-Derived Growth Factor Receptor (PDGFR), and Fibroblast Growth Receptor (FGR) while Non-receptor tyrosine kinases are located within the cytosol, they are activated upon binding to an already activated receptor tyrosine kinase receptor and are accountable for the activation of receptor by phosphorylation without the presence of a ligand [8]. Examples include v-SRC (Rous sarcoma virus), Bcr-Abl (Abelson protooncogene- break-point cluster region) fusion [9]. Due to the importance of tyrosine kinases in the modulation of the signaling pathways, Sir Cohen suggested that protein kinases may be the

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main drug targets of the twenty-first century [10]. The basis of signal transduction by tyrosine residues was supported by reports that revealed that EGFR [11], the insulin receptor (INSR) [12] and the platelet-derived growth factor receptor (PDGFR) [12] are protein tyrosine kinases that are auto-phosphorylated by individual ligand. RTKs possess identical structures that are made up of an extracellular ligand-binding domain, a single transmembrane helix, and an intracellular region that contains a juxtamembrane regulatory region, a tyrosine kinase domain (TKD) and a carboxyl (C-) terminal tail [13]. Dysregulation of RTK is linked with the incidence of many diseases in which cancer is chief [14]. Multiple RTKs are involved in neoplastic development and metastasis, they are recognized as plausible targets for developing anti-neoplastic drugs. Inhibition of RTKs remains a systemic strategy for tumor treatments [15]. A vast majority of cancer patients experience relieve upon the use of TKIs, however, acquired and adaptive resistance continue to exist. Strategies to curb resistance to target therapy is of utmost priority. Also, Quiescent cancer cells complicate diagnosis, target therapeutic drugs (TKIs) interventions, chemotherapy and are generally difficult to tackle. The current treatment regimen that involves the use of tyrosine kinase Inhibitors for rapidly dividing cells do not kill quiescent cells that continue to exist and furnishes the relapse of cancer, possible ways forward are discussed herein.

Structure of the receptor tyrosine kinases

Receptor tyrosine kinases possess identical structure (Fig. 1). RTKs structure is composed of a ligand-binding extracellular domain accompanied by a single transmembrane domain, juxtamembrane region, cytosolic tyrosine kinase domain (TKD), and a flexible C-terminal tail [16]. The extracellular domain of RTKs differs between subfamilies, they are distinct in their binding patterns and modules that predict ligand identification and assemblage. Ligands bind to different receptors with great specificity as a result of the diversity across the families. The extracellular domain dimerizes when a ligand binds [17]. A characteristic prototype of RTK activation is composed of monomeric receptor polypeptides that are turned into a potent signaling homodimeric complex due to ligand binding, leading to a conformational transformation that stimulates the intracellular tyrosine kinase domain [17]. Several ligand recognition and RTK-complex formation are expressed by different RTKs, the VEGF system for example is composed of ligand identification by seven extracellular immunoglobulin-like domains, which aid VEGFR dimerization, this differs from the epidermal growth factor-related RTK family (ErbB) where only one epidermal growth factor (EGF) molecule binds a single EGFR polypeptide and activate EGFR dimerization resulting in the formation of an EGFR-EGF tetramer complex [18]. RTKs are unique and are different as a result of the

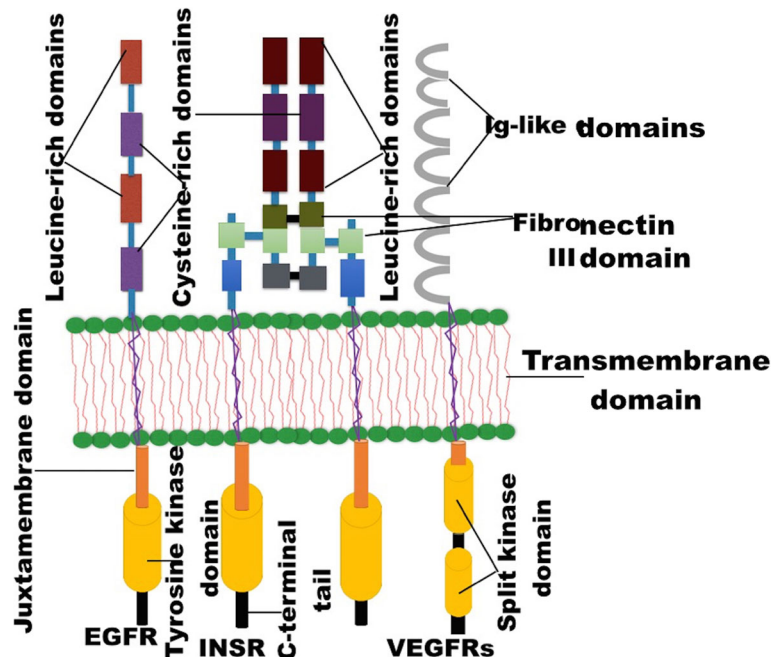


Fig. 1 Structure of RTKs subfamilies. The ligand-binding extracellular domains differ across RTKs subfamilies from immunoglobulin-like (Ig-like) fold type (VEGFRs), fibronectin type III (FnIII) domains (INSR) and Leucine-rich repeat and cysteine-rich domains (EGFR). The Juxtamembrane connect the transmembrane domain to the tyrosine kinase domain (TKD), the TKD contains the catalytic site of the RTKs. The C-terminal domain contains the tyrosine residues, where phosphorylation takes place, it also provide the docking sites for the cytoplasmic signaling molecules to bind

various extracellular domains ranging from immunoglobulin-like (Ig-like) fold type, fibronectin Type III (FnIII) domains, and many more [Fig. 1] [19]. Monoclonal antibody-based drugs such as cetuximab target these domains [20].

Activation and signal transduction of RTK

Auto-inhibition

Basal enzymatic activities are believed to be ongoing in the resting state, that is when ligands are not binding to the RTK. The resting state is hypothesized to oscillate between dynamic states even when devoid of ligand binding. In the resting state of RTK, for example, c-Src, a soluble tyrosine kinase still phosphorylate the tyrosine kinase domain (TKD) and hence prompt signaling [18]. This is prevented by the juxtamembrane domain and the C-terminal tail that interact with the TKD in a way that wades off activation, notwithstanding, residual kinase activity possibly still take place [21].

Activation of RTK

RTK ligand binding-induced dimerization causes trans-autophosphorylation of auto-inhibitory elements, leading to structural transformation within the TKD. The TKD is composed of an N-lobe and a C-lobe with an ATP-binding domain sequestered in between them. The phosphorylated tyrosine side chains act as binding sites for proteins containing phosphotyrosine-recognition domains, such as the Src homology 2 (SH2) domain or the phosphotyrosine-binding (PTB) domain [22]. Tyrosine phosphorylation also helps remove the juxtamembrane auto-inhibition of the TKD [23]. Mutation of the juxtamembrane domain, resulting in constitutive active c-KIT and PDGFR overexpression in certain cancer has been reported [24]. The multi-domain architectures of the RTKs and the various modes of ligand binding account for the enormous mechanisms of receptor activation. However, a central theme in RTK activation is the phosphorylation of the cytoplasmic domain tyrosine residues, this is the foundation of communication in the signaling cascades [25] (Fig. 1).

Receptor tyrosine kinases

Receptor tyrosine kinases (RTK) are family of transmembrane cell surface receptors that relate extracellular signals into the cell. This plays an important function in cell growth and development [26, 27].

Epidermal growth receptors (EGFR)

The Epidermal Growth Receptors (EGFR), represent one of the most significant receptor tyrosine kinases that play crucial functions in cancer cell proliferation. EGFR is a transmembrane glycoprotein of the ERBB receptor tyrosine kinase superfamily. It mediates a phosphorylation downflows through a series of tyrosine kinases, PI3K–PTEN–AKT, MAPK, ERK, and JAK/ STAT pathways,

thereby drives angiogenesis, invasion, survival, and metastasis. The mutations of EGFR are found in several solid tumors and NSCLC [28, 29]. EGFR inhibitor can either be small-molecule tyrosine kinase inhibitors (TKIs) or monoclonal antibodies [30, 31].

Tumors with EGFR expression and mutation are responsive to a particular TKIs, for example, gefitinib and erlotinib, first-generation EGFR TKIs, second-generation EGFR TKI, afatinib, and the third-generation EGFR TKI, osimertinib [32–35]. EGFRs are composed of four members, receptor tyrosine kinases that share akin structure and roles; ErbB1 (EGFR or HER1), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4). Reduction in the survival figures of breast cancer is believed to be as a result of HER-2, this account for about 10–20% of the disease [36].

Irregularities of EGFR members activate the downflow pro-oncogenic signaling, including the RAS-RAF-MEK-ERK MAPK and AKT-PI3K-mTOR pathways. These consequently activate several biologic expression that is altruistic to the proliferation of cancer cells [37].

Vascular endothelial growth factor (VEGFR)

The VEGFR is composed of VEGFR1, VEGFR2, and VEGFR3 family members. The VEGFR family of tyrosine kinase bears 7 immunoglobulin-like domains. Both the VEGF and VEGFR are responsible for vasculogenesis and angiogenesis [38]. The VEGF is composed of at least 7 members, including the viral genome–derived VEGF-E. VEGF-A and its receptors VEGFR-1 and VEGFR-2 mediate physiological and pathological conditions, while, VEGF-C/D and their receptor VEGFR-3 carry out angiogenesis at the formation and development of an embryo, though their main function is in lymphangiogenesis [38]. Anti-VEGF-VEGFR drugs (antibody and kinase inhibitors), bevacizumab, sunitinib, etc., are equipped for the management of solid cancers. The binding of VEGF-A to VEGFR-1 (Flt-1) and VEGFR-2 (KDR/ Flk-1) lead to their activation. The affinity of VEGF-A is more towards VEGFR-1 when compared with VEGFR-2 but with weaker tyrosine kinase activity in VEGFR-1. The associated proangiogenic function of VEGFR is solely through the ligand-activated action of VEGFR-2 [39]. Contrary to other RTKs that act through the Ras (Rapidly Accelerating Sarcoma) pathway or PI3K (phosphatidylinositol 3-kinase) pathway, VEGF-VEGFR acts through PLC γ -PKC-MAPK pathway [40]. VEGFR-3 operated similar tyrosine kinase activities like the other VEGFRs. The PKC and Ras pathways have been implicated to be stimulated for lymphangiogenesis in VEGFR-3 [40]. VEGF play crucial roles in neoplastic growth and vascularization of endothelial cells [41].

Platelet-derived growth factor

Platelet-derived growth factor (PDGF) signaling is composed of four ligands, PDGFA-D, and two receptors,

PDGFR α and PDGFR β [42]. Colonial stimulating factor-1 receptor (CSF1R), the stem cell growth factor receptor (SCGFR), FLK2/FLK3 are also members of the PDGFR. PDGFR bears 5 immunoglobulin-like domains in the extracellular domain [43]. To a large extent, PDGFR is found in the fibroblasts, smooth muscle cells, they are also present in the kidney, testis and, brain [44]. According to Dong et al. (2004) PDGFR α signaling is needed for the recruitment of VEGF-producing stromal fibroblasts for tumor angiogenesis and growth [45]. According to Gotzmann et al. (2006) PDGF contribute significantly to TGF- β mediated tumor progression of hepatocytes [46]. DGF-PDGFR stimulate at least two pathways: the PI3K-AKT and MAPK pathways [47]. Targeted therapies, imatinib, nilotinib, and sunitinib are capable of disrupting PDGFR signaling [48].

Insulin receptor

Insulin, produced from the pancreas beta cell, mediate metabolic profile by adapting substrate metabolism, protein synthesis, and energy storage [49]. Insulin is known to activate cell growth [49]. The action of insulin on various cells is through the insulin receptor [50]. The insulin receptor is a tyrosine kinase receptor, it is a transmembrane receptor that is predominantly activated by insulin, insulin-related growth factors, IGF-1 and IGF-2, and some insulin analogs [50]. Ligand binding to the insulin receptor causes autophosphorylation at the tyrosine residues. The autophosphorylation of the insulin receptor follows the PI3K/AKT pathway [51]. The RAS/RAF/MEK/ERK pathway is also activated by the binding of insulin to the insulin receptor [50]. Papa et al. (1990) reported that over 80% of breast cancer incidence had significantly high expression of the insulin receptor [52]. Suffice it to say that high expression of the insulin receptor is not specific to only breast cancer, insulin expression has also been implicated in other cancers as well [52, 53].

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors are known to be efficacious in cancer management targeting drivers of tumorigenesis [54]. There are various classifications of tyrosine kinase inhibitors based on their mode of action. Ab initio small-molecule tyrosine kinase inhibitors were grouped into type I, II, and III [55]. According to Dar and Sakot, (2011) type I inhibitors bind to the active conformation of a kinase in the ATP pocket (DFG-IN), type II binds at an inactive (DFG-OUT) conformation of a kinase, while the type III, allosteric ligands, bind to a site different from the active site (Non-ATP competitive inhibitor) [55]. Zuccotto et al. (2009) however, introduced a new classification of inhibitor, type II1/2 inhibitors bind to the protein kinases with the DFG-Asp in and C-helix out conformation [56]. Furthermore, Gavrin and Saiah,

2003 separated allosteric effectors into two classes (III and IV) where the type III inhibitors bind within the cleft between the small and large lobes adjacent to the ATP binding pocket and type IV inhibitors bind outside of the cleft and the phospho-acceptor region [57].

Bivalent molecules that stretch through two regions of the protein kinase domain were tagged by Lamba and Gosh, 2012 as type V inhibitors [58]. The classification in this review, employed the aforementioned parameters in an addendum to subdivisions and yardsticks, tagging them as types I, II, allosteric, substrate directed, and covalent inhibitors.

Type I kinase inhibitors

Type I kinase inhibitors are ATP-competitors that simulate the purine ring of the adenine moiety of ATP. They act within the phosphorylated active orthosteric site of the kinases. The binding of type I inhibitors are targeted at altering the active conformation of the kinase thereby hindering the transfer of phosphate group [59]. Type I inhibitors are made up of the heterocyclic ring which takes up the purine binding site, serving as a platform for side chain that takes up the adjoining hydrophobic region [60]. There are ten (10) FDA-approved tyrosine kinase inhibitors are the moment; bosutinib, crizotinib, dasatinib, erlotinib, gefitinib, lapatinib, pazopanib, ruxolitinib, sunitinib, and vemurafenib. They are EGFR-TKIs, they compete with adenosine triphosphate (ATP) at the ATP-binding site in the intracellular domain of EGFR [61]. Gefitinib and erlotinib, the earliest small-molecule kinase inhibitors have the approval of the FDA, they are used for the NSCLC [41]. Erlotinib is also approved as a first-line treatment of pancreatic cancer [62]. Resistance to imatinib prompted the use of dasatinib, a type I inhibitor of Abl as first-line therapy for recently diagnosed Ph + CML [63, 64]. Crizotinib, a type I inhibitor of anaplastic lymphoma kinase (ALK) is approved for the first-line treatment of ALK and NSCLC [65]. Notwithstanding, the success of type I kinase inhibitors, come the associated cardiotoxicity and cardiac failures due to off-target binding [66]. In this regard, there should be routine observation during the treatment with type I kinase inhibitors, in addition to an all-inclusive assessment of medical history and predisposing factor to identify patients that are predisposed to cardiovascular issues [67].

Type II kinase inhibitors

Type II inhibitors target the DFG-Asp out conformation, the inactive enzyme form [68]. They form reversible interactions with the target kinases by hydrogen bond formation within the lipophilic pocket of the protein in the 'hinge region' and also form extra interactions in the open DFG-out conformation. It is believed that the high degree of specificity with type II kinase inhibitors when

compared with type I kinase inhibitors are as a result of lipophilic interactions in type II kinase inhibitors. This perhaps explains the observed decrease in toxicity in type II when compared with type I [69]. Examples of type II kinase inhibitors are imatinib, sorafenib, axitinib, nilotinib, ponatinib, and Sunitinib. Imatinib, the first TKI drug approved for cancer treatments has paved ways during the year for more than 20 different kinds of TKIs with better efficacy. Today, imatinib remains the first-line treatment for chronic myeloid leukemia (CML). Though, imatinib lacks the potency to achieve complete hematologic response in diseased patients [70]. Adaptive and acquired resistance, as well as toxicity to imatinib, is well documented [71]. Imatinib has been linked with mild to moderate toxicity;

Imatinib toxicity and possible way forward

Cardiac toxicity Various reports have failed to prove the use of imatinib leads to cardiotoxicity [70]. It is believed that several patients that developed cardiotoxicity, and/or myocardial infarction are elderly, over sixty-five years of age, and are predisposed to cardiac diseases or have pre-existing cardiac-related issues [72]. Cardiac toxicity is not a risk factor in the prolonged administration of imatinib [71]. In light of this, patients predisposed to cardiac dysfunctions or with the cardiac problem should be monitored closely, if there are indications of cardiac dysfunctions, a different treatment option should be considered.

Pregnancy According to Pye et al. (2008) there is a high percentage of normal delivery in patients exposed to imatinib, however, there remains a risk of serious fetal malformation [73]. There are also reports of harmful effects of imatinib on pregnancy when both or one of the partners are exposed to imatinib [71]. Pregnant mice exposed to imatinib experienced teratogenic features ranging from abnormal spleen, head, and eye development and many more. There have been reports of male infertility, characterized by a low sperm count oligospermia [74]. Given all these, a female of childbearing age should keep away from imatinib when contemplating pregnancy, and their male counterpart should consider the possibilities of sperm freezing and storage.

Skin toxicity Skin toxicity is commonly observed with imatinib in advanced gastrointestinal stromal tumors (GIST) and chronic myeloid leukemia (CML). This can be treated with the application of steroid cream without a need for cessation of treatment or reduction in dosage. However, with the obvious failure of steroids, there should be a cessation of treatment followed by gradual reintroduction of imatinib [75].

Gynecomastia Imatinib decreases testosterone production by inhibition of c-kit and PDGF-R [76]. Decreased in the release of testosterone over a while can result in gynecomastia [76]. Clinical cases supporting the development of gynecomastia with the use of imatinib [77, 78]. Tavil et al. (2013) reported the development of gynecomastia in a 14-year-old boy exposure to imatinib for a period of one and half year [78]. Male patients scheduled to receive imatinib treatment may be observed for serum testosterone levels and other reproductive hormone profiles before the commencement of treatment and examination of their breasts during routine medical check-ups.

Immune function As a result of imatinib and other tyrosine kinases off-target inhibition of c-kit, PDGF-R and other tyrosine kinases that contribute to normal physiological functions, imatinib tend to have an impact on the immune responses. These tend to have negative effects on patients' immune responses. Hypogammaglobulinemia is confirmed to be associated with prolonged use of imatinib in chronic lymphocytic leukemia (CLL), CML and gastrointestinal stromal tumor (GIST) patients [79]. Co-administration of imatinib and immunotherapy will go a long way to ameliorate the effect of TKI on the immune response [80].

Hepatotoxicity The development of hepatic failure and other hepatotoxic features are established with the use of imatinib [81]. Haq et al. (2018) showed the development of severe hepatotoxicity in a patient placed on adjuvant treatment with imatinib following resection of a primary gastrointestinal stromal cell tumor of jejunum [82]. Treatment with steroids and cessation of imatinib administration reverse the imatinib-induced hepatotoxicity [82].

Secondary malignancies There has been no serious report as to the veracity of the suspicion of formation of secondary malignancy with the use of imatinib especially [83]. Notwithstanding, patients on imatinib should be adequate for the development of a secondary clonal event.

Generally, the use of nanoparticle should be exploited in the exposure to imatinib, as reported by Sheeba et al. (2015) nanoencapsulation of imatinib produced desired results in cancer cells, with virtually zero cardiotoxicity [84].

Other type II kinase inhibitors and their toxicity

Sorafenib is an FDA approved type II kinase inhibitor of different kinases; B-Raf, CDK8 protein-serine/threonine kinases and the VEGFR1/2/3 receptor protein-tyrosine kinases [64]. This drug is used for the treatment of hepatocellular, renal cell, and differentiated thyroid carcinomas [85, 86]. Patients should endeavor to call their

health-care team between visits to swiftly address issues of toxicity if noticed with sorafenib treatment [87].

Nilotinib is also an FDA-approved type II inhibitor of the Abl non-receptor protein-tyrosine kinase that is endorsed for the treatment of Ph + CML. It was developed as a second-line medication for imatinib-resistant CML owing to point mutations in BCR–Abl [88]. Some patients receiving nilotinib have been reported to die suddenly, while some developed cardiac side effects [89]. Therefore, before nilotinib treatment patients should be monitored for hypokalemia or hypomagnesemia and the deficiencies corrected. There should be an avoidance of attendant drugs that lengthen the QT interval and strong CYP3A4 inhibitors [90].

Axitinib is a type II tyrosine kinase inhibitor of the VEGFR1/2/3, and PDGFR β , and c-kit tyrosine kinases, it is endorsed for second-line treatment of Renal cell carcinoma (RCC), advanced thyroid cancer, and advanced non-small cell lung cancer [91–93]. Some toxic effects observed in patients administered axitinib hypertension, thrombotic events, hemorrhage, and GI perforation [94]. Most adverse effects of axitinib are reversible, management is possible through dose adjustments or interference to obtain optimal dosing [94].

Type III or allosteric inhibitors

Type III kinase inhibitors (allosteric inhibitors) bind at a site adjoining the ATP-binding pocket and mediates kinase activity [95]. Type III kinase inhibitors operate as a steady-state non-competitive or uncompetitive inhibitor, ATP does not hinder their interaction with the target kinase. They exhibit the highest form of specificity by binding to specific kinases, inducing a conformational shift in the target enzyme, thereby blocking kinase functions [96].

Allosteric inhibitors that are at different preclinical stages operate through MAPK kinase 1 and 2 (MEK1/2) and Akt signaling inhibition. MEK inhibitors reported to possess therapeutic effects in NSCLC include; CI-1040 (PD184352), PD0325901, selumetinib, refametinib, pimasertib, trametinib, RO4987655, TAK-733, WX-554, MEK Sterol Regulatory Element Binding Protein, and cobimetinib [96]. The existence of a high level of homology in the ATP-binding pocket of AKT, protein kinase A, and protein kinase C constituted hinderance to the initial development of AKT inhibitors [97]. However, a novel allosteric agent acting elsewhere of the ATP-binding domain prevent downstream AKT signaling cascades [98]. MK-2206 inhibition of the pleckstrin homology domain of AKT hinders AKT translocation to the cell membrane [97]. MK-2206 is an allosteric AKT1/2/3 inhibitor with proof of preclinical effectiveness [97].

Type IV kinase inhibitors or substrate-directed inhibitors

These types of inhibitors target regions outside the ATP-binding domain, they are not ATP-competitive but substrate-competitive. An example of these is ON012380 (under clinical trial), that target regions outside the ATP-binding and it is not affected by mutations that characterized CML-resistant imatinib [99]. ON012380 induces apoptosis to recognized imatinib-resistant mutants at no toxicity [99].

Type V tyrosine kinase inhibitors or covalent inhibitors

These type of inhibitors form covalent bonds with non-catalytic cysteine residues within the ATP binding pocket [100]. Covalent targeting-kinase inhibitors demonstrate foremost binding affinity and selectivity [101]. Three of the numerous irreversible covalent tyrosine kinase inhibitors have the approval of FDA [100] and they include; Afatinib which possess therapeutic effects in metastatic non-small cell lung cancer (NSCLC) patients [102]. Another example is the Bruton's tyrosine kinase (BTK) inhibitor Ibrutinib, for B-cell malignancies. Lastly, Osimertinib is used for the treatment of patients with EGFR T790M mutation [103]. Osimertinib has demonstrated great potency in patients with advanced non-small cell lung cancer (NSCLC) and sensitizing EGFR mutation [104].

Exploring the inhibition of RTKs in therapeutics

The interaction between the receptor and ligand accounts for the phosphorylation of kinases and other signaling cascades. TKIs can either inhibit the receptor-ligand interaction for example trastuzumab in breast cancer or inhibit the kinase domain of RTKs. Inhibitors of the tyrosine kinase domain hinder the activation of the RTKs by competitively inhibit the ATP binding site. The tyrosine kinase domain Inhibitors can either be natural or synthetic compound(s) [105, 106].

Inhibition of vascular endothelial growth factor

Vascular Endothelial Growth Factor is known to mediate angiogenesis, a consequential factor in neoplastic advancement, multiplication, and development. Inhibition of the growth factor, therefore, serves a great purpose in the treatment of cancer [107, 108]. Angiogenesis, a highly regulated means of blood vessels development for neoplastic cells, which aids the survival of cancer cells [109]. Inhibition of the angiogenic growth factor includes obstruction of the VEGF from its receptors by the development of monoclonal antibodies [[110, 111] and or development of small molecules that can inhibit the phosphorylation of tyrosine kinase domain [112].

Inhibition of epidermal growth factor (EGF)

EGF is essential for tumor metastasis, progression, angiogenesis, and growth. Thus, it is an auspicious target in cancer treatment; its overexpression is implicated in cancer development [113]. Inhibition of EGF through the development of small molecular inhibitors e.g. erlotinib and gefitinib have demonstrated a great deal in the treatment of cancer [113–117]. Development of Monoclonal antibodies e.g. Cetuximab, which inhibits the extracellular receptor domain of the RTKs have also played a tremendous role in cancer treatment [115].

Inhibition of insulin growth factor

The Insulin growth factor (IGF) receptor contributes greatly to tumorigenesis. Activation of this growth factor needs to be inhibited in curbing the menace of cancer. Inhibition of IGF has been achieved through small-molecule inhibitors of the ATP binding domain or prevention of substrate from binding to the insulin growth factor receptor and hitherto forestalling the activation of tyrosine kinases that are germane to carcinogenesis [116].

Inhibition of fibroblast growth factor

Fibroblast Growth Factor (FGF) display essential roles in proliferation, migration, and apoptosis. Alterations of FGF have been reported in cancer [116]. FGF is implicated in tumorigenesis and promotion of cancer growth, therefore, inhibition of this growth factor has demonstrated halting of cancer progression. Small-molecules kinase inhibitors can interrupt RTK signaling. They have been reported to possess broad specificity across FGF receptors, VEGF and other RTKs for example AZD4547 [117]. According to Sun et al. (2007) inhibition of FGFR have been also been achieved with the use of monoclonal antibodies [117].

Tyrosine kinase receptors/tyrosine kinase inhibitors and quiescent Cancer cells

Cancer is a mixture of both rapidly dividing cells and slowly dividing cells. The rapidly dividing cells are responsive to tyrosine kinase inhibitors, by obstructing the signaling pathways of cancer cell proliferation. Some of the cancer cells divide slowly while some do not divide at all [118]. It has been clinically proven that some of the slow dividing cells may remain quiescent for a while, and in this stage, they are irresponsive to the treatment of any kind. However, they may eventually reenter the cell cycle and continue to replicate and inadvertently lead to disease relapse [119]. The proliferating speed of cancer cells is a function of the time spent in the G1 phase. Oncogenic factors can speed up the G1 phase movement, so also the tumor microenvironment contributes a whole lot to the transit through the G1 phase, sometimes imbalance in the microenvironment can

make a tumor cell to stop proliferation altogether [120]. Quiescent cancer cells complicate diagnosis, target therapeutic drugs (TKIs) interventions, chemotherapy and are generally difficult to tackle. The current treatment regimen that involves the use of tyrosine Kinase Inhibitors for rapidly dividing cells do not kill quiescent cells that contribute to cancer relapse [121].

Targeting of quiescent cells by HDAC inhibitors in combination with Imatinib

Chronic myelogenous leukemia (CML) is due to the modification of a hematopoietic stem cell by the BCR-ABL gene. Imatinib causes respite in CML patients, however, leukemia stem cells (LSCs) are not removed and turn out to be a probable source of relapse. According to Zhang et al. (2010) treatment of CML with Histone Deacetylase Inhibitors (HDACis) together with imatinib successfully cause apoptosis in quiescent CML progenitors that are resistant to removal by imatinib alone. HDACis treatment provides a functional master plan to aim LSCs in CML patients exposed tyrosine kinase inhibitors [122].

DYRK1B inhibition and quiescent Cancer cells

Quiescent cells are unresponsive to environmental stress elements, chemotherapeutic and target therapy drugs. It is very germane to hinder cell cycle exit and re-entry of quiescent cells, to maximize the efficacy of cytotoxic drugs and tyrosine kinase inhibitors. The protein kinase dual-specificity tyrosine phosphorylation-regulated kinase 1B (DYRK1B) sustains quiescence by preventing G0/G1-S phase transition. Decrease and perhaps the inhibition of DYRK1B promotes cell cycle re-entry and favors apoptosis of quiescent cancer cells that expresses DYRK1B. Also, DYRK1B inhibition makes cancer cells to be responsive chemotherapeutic drugs that target proliferating cells [123].

Transforming growth factor β (TGF- β)-induced quiescence

Squamous cell carcinomas (SCCs) are heterogeneous and are upheld by basal tumor propagating cancer cells (TPCs) situated down the tumor-stroma interface [124]. They expressed a large amount of $\alpha 6\beta 4$ and $\beta 1$ integrins [125] and SRY (sex-determining region Y)-box 2 (Sox2) [126] and are differentiated into suprabasal SCC cells that lack growth potentials. According to Brown and Schober, (2018) TGF- β is a crucial regulator of TPC quiescence in SCCs [127]. Targeting TGF- β signaling with orthodox chemotherapy is probably a feasible therapeutic alternative of curbing quiescence associated resistance in SCCs [127].

Mirk kinase inhibition and quiescent cancer cells

A vast number of metastatic cells, composed of spheroids within ascites fluid are quiescent. These cells

demonstrate little or no proliferating potential, with a good number of them in the G0/G1 phase [128]. Thus ovarian cancer cells containing spheroids are composed of extremely malignant cells that are secured from quite a good number of drugs that target proliferating cells because of their reversible dormant nature. The *Mirk/dyrk1B* gene is usually overexpressed in ovarian cancers [129]. *Mirk* promotes the survival of cancer cells by attenuating toxic ROS levels and potentiate the upregulation of a good number of antioxidant genes, perhaps by exploiting its transcriptional activator roles. *Mirk* expression is usually very high in quiescent cancer [129]. Deng et al. (2014) reported that *Mirk* kinase inhibitor EHT5372 and RAD001 attenuate spheroid volume, aid apoptosis, and decreased cell numbers in ovarian cancer cell lines [129]. Consequently, *Mirk/dyrk1B* kinase is a probable target in pancreatic and ovarian cancers.

Autophagy inhibition and quiescent leukemic stem

Chronic myeloid leukemia (CML) is as a result of correlative chromosomal translocation within a haematopoietic stem cell (HSC) resulting in the formation of the fusion oncoprotein BCR-ABL. Albeit the success recorded with BCR-ABL-targeting tyrosine kinase inhibitors (TKIs) [130], a large number of failure is still associated with TKI therapeutic interventions probably as a result of BCR-ABL kinase mutation, constitutive oncogene activation, advancement to the blast or accelerated phase [131]. TKIs produce no therapeutic response on leukemic stem cells (LSCs) [132], this has led to the persistence of the disease and treatment-free remission (TFR) has become elusive [132].

Autophagy is extremely conserved evolutionary catabolic process employed for the recycling of cytoplasmic material. This process allows cellular homeostasis and aids the survival of cells after stress factors [133]. Autophagy has a principal cytoprotective function in cancer therapy [134]. Baquero et al. (2019) showed that the combination of Lys05 or PIK-III with TKIs, carefully target LSCs. This is a pointer to the elimination of cancer stem cells in CML patients [135].

Equating antibodies and small-molecule therapies in cancer treatment

Antibodies and small molecules alike are favorable in targeted cancer therapies [136]. The advent of target therapy has significantly improved the outlook of cancer treatment [136]. The focal approach of target therapy at the moment is therapeutic monoclonal antibodies (mAbs), and small-molecule inhibitors (Fig. 2). Tyrosine kinases are a good target of small molecule inhibitors, the clinical effective response of these inhibitors in different cancer types have been well documented [137, 138]. The effective response of mAbs in different cancer types have also been well

documented [139]. Trastuzumab (Herceptin) targets the ectodomain domain of the ErbB family member (ERBB2) and is the first to be clinically approved [140], it has demonstrated good anti-tumor potential [141]. Pertuzumab is reported to have an effective response in various types of cancer [136]. The ERBB2-targeted therapeutics, trastuzumab, and Pertuzumab employ signal blockade involving inhibition of ligand interactions, receptor downregulation and interference with receptor dimerization to bring about their therapeutic responses [141].

The overexpression of EGFR in different forms of cancers is well documented [142]. Hence, the mAbs (cetuximab, panitumumab) target against EGFR has been approved [143 (Fig. 2)]. Small-molecule compounds meanwhile, penetrate the plasma membranes and interact with the cytoplasmic receptor tyrosine kinase domain and intracellular downstream signal molecules (Fig. 2). Comparison between these classes of target therapies is depicted in Table 1.

Future prospects in the treatment of cancer with tyrosine kinase inhibitors (TKis)

Though only a fragment of the kinome is targeted currently, the advancement of tyrosine kinase inhibitors over the past decades have been tremendously progressive and encouraging. A vast majority of cancer patients experience relieve upon the use of TKIs, however, acquired and adaptive resistance continue to exist and hence constitute a serious barrier in targeted cancer treatment [144].

Mutation of T790 M

Mutation of T790 M is as a result of EGFR gene 20 exon 790th codon missense [145]. About half of the population of people with NSCLC that are resistant to gefitinib or erlotinib were equally positive for T790 M mutation [146]. It is believed that the steric hindrance posed by methionine which affects hydrogen bonds formation between TKIs and tyrosine kinases is largely responsible for the inability of TKIs to bind to tyrosine kinases [147, 148]; some reports also depicts that acquired TKI resistance from T790 M mutation and EGFR-sensitive mutations reduce affinity for TKI due to increase in intracellular ATP affinity [149].

One of the strategies to curb the resistance associated with T790 M mutation and EGFR-sensitive mutations is the application of broad-spectrum receptor tyrosine kinase inhibitors; as reported by Graves-Deal et al. (2019) [150] multi-RTK inhibitors crizotinib, cabozantinib and, BMS- 777607 assisted in overcoming acquired cetuximab resistance in CC- CR cells.

The application of osimertinib in conjunction with oxidative phosphorylation (OxPhos) inhibitors is under preclinical investigation. Martin et al. (2016) showed that

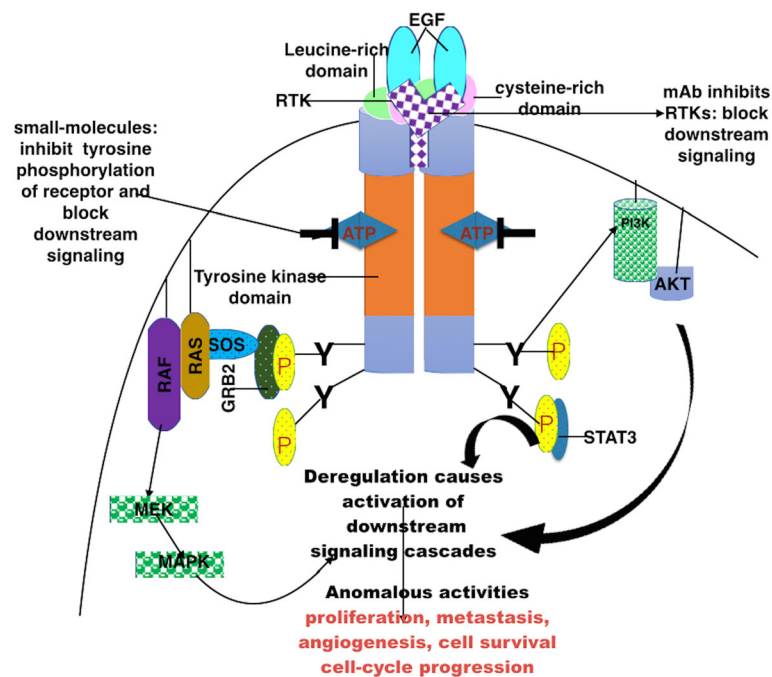


Fig. 2 Mechanisms of RTKs (EGFR) signal transduction, small molecule inhibition and monoclonal antibody inhibition in target therapy. This depicts EGFR and RTK signaling. The extracellular domain is Leucine-rich binding domain and cysteine-rich domains, the kinase domain is the ATP catalytic domain and the C-terminal domain is composed of tyrosine residues (Y). The Ras–Raf–MEK–MAPK pathway is activated through stimulation by growth factor receptor. The phosphatidylinositol 3-kinase (PI3K)–AKT and signal transducer and activator of transcription (STAT) proteins (STAT1, STAT3, and STAT5) are also activated. The synergistic effects of these pathways bring about proliferation, cell motility, adhesion, and angiogenesis. Deregulation of the pathway causes activation of the downstream oncogenic signaling cascades. Small-molecule tyrosine kinase inhibitors block downstream signaling by competitively competing for the ATP at the catalytic site of the kinase domain while monoclonal antibodies (mAbs) with an outstanding degree of specificity block signaling by binding to the leucine-rich and cysteine-rich ectodomain (cetuximab in EGFR)

osimertinib resistance was vanquished with the inhibition of oxidative phosphorylation in a preclinical model of EGFR-driven lung adenocarcinoma [151]. EGFR irreversible inhibitors have rescued patients with unsuccessful EGFR-TKI therapy by acting on the ATP binding site of EGFR, forming a covalent bond with the receptor kinase region, and hitherto inhibiting several of the EGFR receptor family [152]. Besides, Yeon et al. (2019) suggested a twofold inhibition of the extracellular domain (ECD) and tyrosine kinase domain of EGFR [153].

MET crosstalk-related resistance

The hepatocyte growth factor (HGF)–mesenchymal-epithelial transition factor (MET) pathway plays a pivotal role in neoplasm. MET confers resistance on EGFR-targeting drugs by a crosstalk reaction with epithelial growth factor receptor (EGFR) proteins and inadvertently substituting their activity. About 20% of NSCLC associated TKI-resistance are linked to c-MET gene amplification [154]. With the involvement of c-Met in EGFR-TKI resistance, a combination of c-Met inhibitor and EGFR-TKI is likely to upturn the resistance [155]. At the moment, the use of tivantinib (ARQ 197) and

erlotinib for advanced or metastatic non-small cell lung cancer are encouraged [155].

Protein kinase Akt's covalent-allosteric inhibition

The pivotal roles of kinases as regard protein phosphorylation in signal transduction make them interesting and important targets in drug discovery [156]. Dysregulation of the PI3K/Akt signaling is linked to a variety of tumors [157]. Also, activation of mutated Akt together with its overexpression is reported promoters in some metastatic breast cancers that are connected to resistance in TKI-therapy [158]. Inhibition of Akt by small-molecule remains a target intervention for cancer treatment. Competitive ATP inhibition in the kinase domain is well documented [159]. Even so, due to the highly conserved ATP-binding pocket of Akt and its AGC (cAMP-dependent protein kinase 1 (PKA), cGMP-dependent protein kinase (PKG) and protein kinase C (PKC)) isoforms, selectivity by inhibitors remains a very big concern [160]. Allosteric inhibitors are effective at binding at the remote sites of the protein and hence, favor the inactive conformation and at the same time attenuating the problem of selectivity [161]. Asciminib (ABL001), the first allosteric BCR, discovered by Schoepfer et al. (2018) is now in the

Table 1 Comparison of Small-molecule Inhibitors and Monoclonal Antibodies

	Small-molecule inhibitors	Monoclonal Antibodies (mAbs)
Drug properties and Development	<ul style="list-style-type: none"> • Short time required for Development • Less monetary cost in development • More convenient to administer • Small molecules (around 500Da), orally administered • Easy passage through the blood brain barrier • Short drug half life • Enter the cytoplasm and act on molecules • More potent with solid tumors • Target intracellular tyrosine kinase domain 	<ul style="list-style-type: none"> • Longer time required for Development • Huge monetary cost in development • Less convenient • Large proteins (around 15KDa), intravenously administered • Incapable of passage through the blood brain barrier • Longer drug half life • Act only on cell surface molecules • More potent with circulating cancer cells • Target extracellular ligand-binding domain
Specificity	<ul style="list-style-type: none"> • Less specific, associated with off target phenomenon • Possess the potential to inhibit different signaling pathways • There is no connection between the therapeutic effects of small-molecule inhibitors and the activation of the immune response against tumor cells 	<ul style="list-style-type: none"> • Bind antigens expressed on the tumor-cell surface with high specificity • Specific for extracellular ligand-binding domains • mAbs exert not only direct inhibitory effects on tumor growth but also possess the ability to activate indirect accessory anti-tumors activities such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)
Adverse effects	<ul style="list-style-type: none"> • The adverse effects associated with small-molecule inhibitors are mild 	<ul style="list-style-type: none"> • The observed adverse effects of mAb therapies are mild

clinic [162]- On the other hand, Uhlenbrock et al. (2109) depict structural and chemical insights into the covalent-allosteric inhibition of the protein kinase, Akt [163].

Integrins in resistance to TKIs

Integrins are cell surface receptors, that play significant parts in the association with the extracellular matrix (ECM). The signaling of integrin regulates cell proliferation, differentiation, adhesion, apoptosis and many more [164]. Integrin lacks enzymatic activities and hence their binding to a ligand causes recruitment of cytoplasmic

kinases, for example, the focal adhesion Kinases (FAKs). The recruitment of the FAKs causes autophosphorylation and reveal a docking site for Scr, a proto-oncogene tyrosine kinase [165]. The NF- κ B (nuclear factor- κ B), MAPK (mitogen-activated protein kinase) and PI3K (phosphoinositide-3-kinases) pathways are activated by the FAK/Scr complex and hitherto collaborate with a few of the RTKs (epidermal growth factor receptor (EGFR), c-Met, platelet-derived growth factor receptor (PDGFR), insulin-like growth factor receptor (IGFR) and vascular endothelial growth factor receptor (VEGFR)) to

advance the neoplastic processes and at the same time promoting resistance to target therapy.

According to Cruz da Silva et al. (2019) [166] one of the strategies to combat the resistance associated with integrin/RTK cooperation is by developing treatments that interfere with integrin/RTK complex formation. Camorani et al. (2017) [167] report on Aptamers's disruption of the EGFR-integrin $\alpha\beta 3$ complex and hitherto inhibiting the growth of triple-negative breast cancers gives credence to Cruz da Silva et al. (2019) proposed strategy [166]. Meanwhile, sensitivity was reported by Laurenzana et al. (2019) [168] to be restored to vemurafenib acquired resistance in melanoma cells by targeting EGFR/uPAR with the aid of an integrin antagonist. All these are pointers to the prospect of understanding the mechanisms of integrin/RTK in attenuating the resistance associated with target therapy.

Resistance to BRAF-targeted therapy

With the breakthrough of target therapy in cancer treatment came the pain associated with intrinsic and acquired resistance. The short-lived anti-cancer effects noticed in BRAFV600E-mutant metastatic melanoma treated with BRAF inhibitors are good examples [169, 170]. According to Talebi et al. (2018) [171] the lipogenic pathway, mediated by Sterol Regulatory Element Binding Protein (SREBP-1) is culpable in oncogenic BRAF constitutive activation and instrumental to therapy resistance. SREBP-1 inhibitors together with BRAF inhibitors should be adopted to defeat resistance to BRAFV600E-targeted therapy [171].

Resistance to Lapatinib in ERBB2

The expression of about 25% human epidermal growth factor receptor 2 (Her2, ERBB2) in human breast cancer is correlated with dismal prognosis [172]. Though a lot of ERBB2-target therapies and ERBB2/EGFR kinase inhibitor (lapatinib) gave good results in cancer patients. The cases of acquired resistant with the use of lapatinib call for concern [173]. According to Yallowitz et al. (2018) the adaptation of lapatinib-resistant cells is as a result of the heat shock factor 1 (HSF1 [174]. HSF 1 activity is increased in lapatinib-resistant tumor cells [174]. HSF 1 controls a wide range of events that protect cancer cells from proteotoxic stress. TP53 gene (mutp53) mutation contribute about 72% of ERBB2-positive breast cancer and with poor prognosis [175, 176]. Yallowitz et al. (2018) reported that mutp53 support MAPK and PI3K signaling, thereby triggering HSF1 activation and also communicate with HSF1 directly to facilitate its binding to DNA response elements, as a result activating HSPs (heat shock proteins) transcription [174]. HSPs in turn, bolster up tumor development by stabilizing the oncogenic ERBB2, EGFR, mutp53 and HSF1 [177]. Lapatinib

resistance can, therefore, be prevented by a combinatorial therapy of lapatinib and HSF1 inhibitors [178].

Adaptive resistance to ERK

The success of therapeutic drugs targeting oncogenic signaling is often time short-lived due to adaptive and acquired resistance, resulting in signaling reactivation in the face of the therapeutic drugs. Dysregulation of the ERK (extracellular signal-regulated kinase) signaling promotes a sizeable chunk of neoplasm in human. Negative feedback is generally responsible for the evolution of tumor adaptive resistance [178]. The non-receptor protein tyrosine phosphatase SHP2 (PTPN11) controls downstream RTKs signaling. According to Ahmed et al. (2019) treatment with an allosteric small-molecule inhibitor of SHP2, SHP099 interfere with the SHP2/GRB2 combination and repressed SHP2 phosphorylation in addition to the action of RAS and ERK in HER2- or EGFR-increased cancerous tumors [179].

Conclusion

RTKs play significant tasks in neoplastic growth and development. The design of novel and more potent TKIs is imperative and achievable with a deeper and in-depth comprehension of the conformation and modes of inhibitions of RTKs. Various treatment regimens that can attenuate toxicity, eradicate relapse due to quiescence cancer cells and enhance a cancer-free state should be exploited.

Abbreviations

ABL-BCR: Abelson protooncogene- breakpoint cluster region; ATP: Adenosine triphosphate; EGF: Epidermal Growth Factor; EGFR: Epidermal Growth Factor Receptor; FGR: Fibroblast Growth Receptor; Gbr2: Growth factor receptor-bound protein-2; GPCRs: G protein-coupled receptors; HSP: Heat shock proteins; INSR: insulin receptor; Jak: Janus kinase; MEK: mitogen-activated protein/extracellular signal-regulated kinase; Met: (A gene that makes a protein called MET, which is involved in sending signals within cells and in cell growth and survival); NRTKs: Non-Receptor Tyrosine Kinases; PDGFR: Platelet Derived Growth Factor Receptor; PI3K: phosphatidylinositol 3-kinase; PKC: protein kinase C; PLCy: phospholipase C γ 1; RAF: Rapidly Accelerated Fibrosarcoma; RAS: Rapidly Accelerating Sarcoma; RAS: Rat accelerating Sarcoma; RTKs: Receptor tyrosine kinases; SH2: Src homology 2; SoS: Son of Sevenless; STAT: signal transducer of activation; TKIs: Tyrosine kinase inhibitors; VEGFR: Vascular Endothelial Growth Factor Receptor; v-SRC: Rous sarcoma virus; MAPK: Mitogen-Activated Protein Kinase; ERK: Extracellular signal-regulated kinase; AKT: Protein kinase B; MTOR: mammalian target of rapamycin; HER2: epidermal growth factor receptor 2; ERBB2: Erb-B2 receptor tyrosine kinase 2; mAbs: monoclonal antibodies; IGF: the Insulin growth factor; GIST: gastrointestinal stromal tumors; HDACis: Histone Deacetylase Inhibitors; CML: Chronic myelogenous leukemia; DYRK1B: dual specificity tyrosine phosphorylation-regulated kinase 1B; SCCs: squamous cell carcinomas; β (TGF: Transforming Growth Factor; TPCs: tumor propagating cancer cells; SRY: sex determining region Y; Mirk: Minibrain-related kinase; DYRK1B: dual specificity tyrosine phosphorylation-regulated kinase 1B; HSC: haemato-poietic stem cell; TFR: treatment-free remission; MET: mesenchymal-epithelial transition factor; FAKs: focal adhesion Kinases; BRAF: a human gene that encodes a protein called B-Raf; SREBP-1: Sterol Regulatory Element Binding Protein; HSF1: heat shock factor 1; PTPN11: tyrosine phosphatase SHP2; c-kit: proto-oncogene receptor tyrosine kinase; CLL: chronic lymphocytic leukemia; QT interval: Q wave to the end of the T wave; QTc: length of the corrected QT; RCC: Renal cell carcinoma; BTK: Bruton's tyrosine kinase; PKA: cAMP-dependent protein kinase 1; PKG: GMP-dependent protein kinase; PKC: protein kinase C (AGC)

Authors' contributions

All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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