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EGFR: AN IMPORTANT PERSPECTIVE IN CANCER THERAPY

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ABSTRACT: Cancer is the second leading cause of death in the western world. Despite advances in diagnosis and treatment, overall survival of patients remains poor. Scientific advances in recent years have enhanced our understanding of the biology of cancer. Human protein tyrosine kinases (PTKs) play a central role in human carcinogenesis and have emerged as the promising new targets. Several approaches to inhibit tyrosine kinase have been developed. These agents have shown impressive anticancer effects in preclinical studies and are emerging as promising agents in the clinic. The remarkable success of BCR-ABL tyrosine kinase inhibitor Imatinib (STI571) in the treatment of chronic myeloid leukemia has particularly stimulated intense research in this field. In this review, we focus on the role of tyrosine kinases in cancer and the development of specific small molecule inhibitors for therapy. We also provide a critical analysis of the current data on epidermal growth factor receptor (EGFR) inhibitors and highlight areas for future research. Innovative approaches are needed to fully evaluate the potential of these agents, and a concerted international effort will hopefully help to integrate these inhibitors in cancer therapy in the near future.

KEYWORDS: Tyrosine kinase inhibitors; Cancer; EGFR; EGF.

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1. INTRODUCTION

Cancer is the leading cause of death in the western world. Despite advances in diagnosis and treatment, overall survival of patients still remains poor. Until recently, surgery, chemotherapy, radiotherapy, and endocrine therapy have been the standard treatment options available for patients. This has improved survival in several types of solid tumors, but treatment-related toxicity and emergence of drug resistance have been the major cause of morbidity and mortality. Hence, there is an urgent need to develop newer more effective therapies to improve patient outcomes. Rapid scientific advances in recent years have enhanced our understanding of the biology of cancer. Consequently, several novel targets have been identified. Tyrosine kinases have emerged as a new promising target for cancer therapy. This review will focus on the role of EGFR in cancer and the development of specific EGFR blockers for cancer therapy with emphasis on small molecule inhibitors [1].

Human protein tyrosine kinases (PTKs)

Human genome sequence analysis has identified about 518 human protein kinases (constituting about 1.7% of all the human genes). Within this large protein kinase complement, at least 90 tyrosine kinase genes have been identified [2]. Among these, 58 are receptor tyrosine kinases (RTKs) and 32 are non receptor tyrosine kinases (NRTKs). Based on their extracellular and non catalytic domain sequences, the RTKs and NRTKs have been further grouped into 20 and 10 subfamilies, respectively [3]. (Table 1 & 2). RTKs contain an amino-terminal extracellular Ligand-binding domain, a hydrophobic transmembrane helix, and a cytoplasmic domain, which contains a conserved protein tyrosine kinase core and additional regulatory sequences. Ligand binding to the extracellular domain results in receptor imerisation/oligomerisation, leading to activation of cytoplasmic tyrosine kinase activity and phosphorylation of tyrosine residues. Autophosphorylated tyrosine residues serve as a platform for the recognition and recruitment of a specific set of signal transducing proteins that modulate diverse cell signaling responses. Non receptor tyrosine kinases have a common conserved catalytic domain (similar to RTKs) with a modular N-terminal, which has different adapter protein motifs. Tyrosine kinases play a critical role in the regulation of fundamental cellular processes including cell development, differentiation, proliferation, survival, growth, apoptosis, cell shape, adhesion, migration, cell cycle control, T-cell and B-cell activation, angiogenesis, responses to extracellular stimuli, neurotransmitter signaling, platelet activation, transcription, and glucose uptake [4].

Table 1: Receptor tyrosine kinases and cancer

Receptor TK subfamilies	Cancer Associated	Receptor TK subfamilies	Cancer Associated
EGFR	Breast, ovary, lung, glioblastoma multiforme, , stomach,colon, granulosa cell tumours and others	RYK	Ovarian
VEGFR	Tumour angiogenesis, Kaposi sarcoma, haemangiosarcoma	DDR	Breast, ovarian cancer
PDGFR,	Glioma, glioblastoma, ovary , Chronic myelomonocytic leukaemia (CMML), , malignant histiocytosis, glioma, endometrium GIST, myelodysplasia, Acute myeloid leukaemia (AML)	RET	Thyroid (papillary and medullary), multiple endocrine neoplasia
FGFR	AML, lymphoma, solid tumours, stomach, breast, prostate, Multiple myeloma	ROS	Glioblastoma, astrocytoma
NGFR	Papillary thyroid cancer, Neuroblastoma, Congenital fibrosarcoma, acute myeloid leukaemia	LMR	-
HGFR	Papillary thyroid, rhabdomyosarcoma, liver, kidney, Colon, liver	LTK	non-Hodgkin lymphoma, LTK
EPHR	Melanoma, Stomach, oesophagus, colon, Breast	Insulin-R	Cervix, kidney (clear cell), sarcomas
AXL	AML	MUSK	-
KLG/CCK	--	ROR	-
TIE	Stomach, capillary haemagioblastoma TEK Tumour angiogenesis	RTK 106	-

Table 2: Non-receptor tyrosine kinases and cancer

Non-Receptor TK subfamilies	Cancer Associated	Non- Receptor TK subfamilies	Cancer Associated
ABL	Chronic myeloid leukaemia (CML), AML, ALL, CMML	FAK	Adhesion, invasion and metastasis of tumours
FRK	Breast	ACK	-
JAK	AML, ALL, T-cell childhood ALL, atypical CML Leukaemia, B-cell malignancies	CSK	-
SRC-A, B	AML, CLL, EBV-associated lymphoma, colon, breast, pancreas, neuroblastoma, melanoma	FES	-
SYK	Breast	TEC	-

Tyrosine kinases and human cancer

Tyrosine kinases play a central role in oncogenic transformation of cells. This is achieved in several ways. Gene amplification and/or over expression of PTKs (e.g. EGFR and HER-2 over expression that is commonly seen in several cancers) cause enhanced tyrosine kinase activity with quantitatively and qualitatively altered downstream signaling. Genomic rearrangements like chromosomal translocation can result in fusion proteins with constitutively active kinase activity. Gain of function mutations or deletion in PTKs within the kinase domain or extracellular domain result in constitutively active tyrosine kinase. EGFR family of tyrosine kinases is the most widely investigated. EGFR (HER-1) over expression is associated with a poor prognosis in ovarian, head and neck, esophageal, cervical, bladder, breast, colorectal, gastric, and endometrial cancer [5]. EGFR is activated by binding of its specific ligands, including EGF and TGF-α. On activation of EGFR by its growth factor ligands, EGFR undergoes a transition from an inactive monomeric form to an active homodimers. EGFR may pair with another member of ErbB receptor family, such as HER2 (erbB-2/neu), to create an activated heterodimer. EGFR dimerization stimulates the intrinsic intracellular protein tyrosine kinase activity. As a result, autophosphorylation of several tyrosine (Y) residues in the C-terminal domain (Y992, Y1045, Y1068, Y1148 and Y 1173) of EGFR occurs. This autophosphorylation elicits downstream activation and initiate several signal transduction cascades leading to DNA synthesis, cell proliferation, cell migration, adhesion, apoptosis and angiogenesis (Figure 1). Changes to EGFRs gene (over expression, dysregulation or mutation) can lead to continual or abnormal activation of receptor causing unregulated cell division, which can account for cancer [6].

Figure 1: Potential targets for cancer therapy

1 = Tyrosine kinase domain inhibitors, **2** = Tyrosine kinase receptor blockers (e.g., monoclonal antibodies), **3** = Ligand modulators (e.g., monoclonal antibodies), **4** = RNA interference and antisense technology, **5** = Gene therapy strategy, **6** = Inhibitors of Src tyrosine kinase, **7** = BCR-ABL inhibitors, **8** = Downstream signal transduction pathway inhibitor.

Architecture of the EGFR

EGFR are transmembrane receptor/proteins present on cell membranes. The EGFR is synthesized from a 1210-residue polypeptide precursor. The EGFR is a member of the ErbB family of receptor, a subfamily of four closely related receptor tyrosine kinases: EGFR (HER1/erb-1), HER2 (erbB-2/neu), HER3 (erbB3) and Her-4 (erbB-4). They have extracellular component/domain, a hydrophobic transmembrane component/domain and an intracellular tyrosine kinase component/domain. The EGFR extracellular portion (Ectodomain) consists of four domains that we refer to as the L1, CR1, L2, and CR2 domains (Fig. 2). The structure determinations of ectodomain fragments of the EGFR and ErbB3 show the L1 and L2 domains to consist of so-called β-solenoid or β-helix folds, which resemble the corresponding domains of the IGF-1 receptor. Ligand binds between the L1 and L2 domains of the EGFR. The CR1 and CR2 domains consist of a number of small modules, each appearing to be held together by one or two disulfide bonds. The juxta membrane (JM) region appears to have a number of regulatory functions, i.e., down regulation and Ligand dependent internalization events. The carboxy-terminal (CT) domain of the EGFR contains tyrosine residues where phosphorylation modulates EGFR mediated signal

transduction. There are also several serine threonine residues (and another tyrosine residue) where phosphorylation has been inferred to be important for the receptor down regulation processes and sequences thought to be necessary for endocytosis [7, 8].
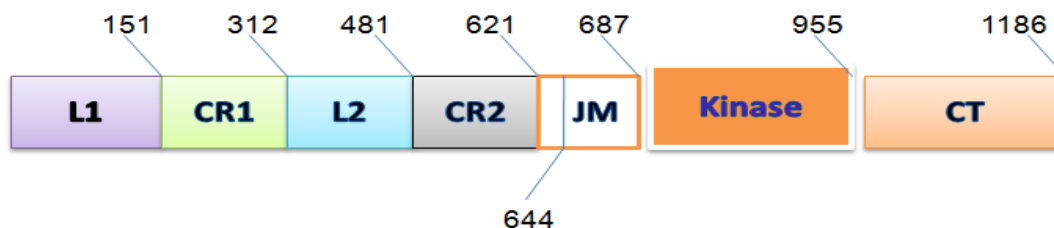

Figure 2: Representation of domains of the EGFR sequence

Signaling pathways activated by the EGFR

In the absence of ligand binding, the EGFR exists on cells as both monomers and dimmers Yet Ligand binding to the EGFR kinase is required to elevate the receptor's tyrosine kinase activity. Given the functional diversity of proteins that complex with, or are phosphorylated by, the EGFR, it is hardly surprising that EGF stimulation of a cell results in the simultaneous activation of multiple pathways [9].

1. Shc, Grb2, and the Ras/MAPK pathway
2. The JAKs and STATs pathways
3. Phospholipid metabolism: PLD, PLC_, and PI3-K
4. The Src family of kinases

Development of Tyrosine Kinase (EGFR) Inhibitors

Several approaches to target PTKs have been developed (Figure 1). Classification of such inhibitors based on their mode of action. Receptor tyrosine kinases are multidomain proteins. The catalytic domain (Mg-ATP complex binding site) has emerged as the most promising target for drug design in recent years. Understanding of the molecular interactions of the various parts of the 'ATP binding site' (adenine region, sugar region, hydrophobic pocket, hydrophobic channel, and the phosphate-binding region) has accelerated drug development. Although ATP-binding site is highly conserved among tyrosine kinases, minor differences in kinase domain architecture have allowed development of highly selective inhibitors. Data on EGFR co-crystallized with its inhibitor OSI-774 (Erlotinib) were published and provide valuable insight into the mechanism of action of compound. Most small molecules bind in the vicinity of the ATP-binding site of their target kinases, using a part of their scaffold to mimic the binding of the adenine moiety of ATP. Such ATP mimics are competitive inhibitors of the substrate-binding sites within the catalytic domain and compete with endogenous ATP for binding. Early potent lead compounds had poor solubility and so to increase solubility, new compounds were generated, but they had reduced affinity to the kinase domain. To overcome these problems, irreversible inhibitors were developed in the hope that covalent attachment of a selective inhibitor to the kinase domain would

completely abolish catalytic activity and would translate into potent drugs. By considering this, CI-1033 (Pfizer) and EKB-569 (Wyeth) inhibitors were developed which bind irreversibly to EGFR and HER- 2, respectively [10]. Small molecules that target more than one tyrosine kinase have also been developed, and they have the potential to block multiple pathways and produce enhanced anticancer effect. PKI-166 inhibits EGFR and HER-2. In the 1980s, first natural tyrosine kinase inhibitors quercetin and genistein were reported. Since then, an overwhelming number of natural and synthetic small molecules inhibitors have been described. Tyrosine kinase inhibitors can be broadly categorised into natural products and related derivatives (Quercetin, genistein, staurosporine, erbastatins, clavilactones); quinazolines, pyridopyrimidines, and related heterocyles (e.g., ZD1839); phenylamino-pyrimidines (e.g., STI 571); tryphostins and analogues (e.g. SU1498, SU0020); indoles and oxindoles (e.g.SU5416, SU5402) [11]. Development of *monoclonal antibodies* against tyrosine kinase receptors particularly against EGFR has been reported. Herceptin (Trastuzumab: monoclonal antibody against HER-2) is licensed for use in HER-2 over expressing breast cancer. Monoclonal antibodies block ligand–receptor interaction and hence ligand-induced signaling. They also increase receptor down regulation and internalization. Immune-mediated responses including complement-mediated lysis and antibody-dependent cellular toxicity induced by monoclonal antibodies have been described. Some evidence suggests that, by cross-linking or binding to receptors, they can modulate signaling activity such that they may trigger apoptosis or growth inhibition in cells. Antisense oligonucleotides are designed to interact with mRNA and block transcription. Such an approach has been developed to target EGFR, VEGFR IGF-1R, and TGF-a r [12]. Recombinant antibody technology has allowed the design, selection, and production of humanised/human antibodies, human–mouse chimeric, or bispecific antibodies [13]. Various approaches and certain developed drugs for inhibition of EGFR has been shown in Table 3.

Table 4: Approaches for targeting EGFR

Approaches for targeting EGFR
1] Small molecule inhibitors:
✓ ZD1839 (Iressa, Gefitinib)
✓ OSI-774 (Tarceva, Erlotinib, CP-358774)
✓ MV833
✓ Soluble Flt-1 and Flk-1
✓ CI-1033 (PD183805) GFB 116
✓ PKI-166 VEGF Trap
✓ CGP-59326A NM3
✓ EKB-569 VEGF 121-diphtheria toxin
✓ GW 572016 conjugate
2] Monoclonal antibodies against receptors:
✓ IMC-C225 (Cetuximab)
✓ ABX-EGF
✓ Y10
✓ MDX-447 (EMD 82633)
✓ h-R3
✓ EMD 72000
3] Gene therapy approaches

In this review, we focus on the current status of small molecule inhibitors of EGFR in cancer therapy.

Small Molecule Inhibitors

In the past few years, a large number of preclinical and clinical studies of tyrosine kinase inhibitors have been reported. The most promising and extensively investigated and used drugs have shown in Table 3.

Targeting EGFR family

Selective small-molecule inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) commonly referred to as EGFR tyrosine kinase inhibitors (EGFR-TKIs) are in the vanguard of the new attack on cancer directed at specific biochemical signal-transduction pathways. Following are the some remarkable success of the EGFR family inhibitors [14].

ZD1839 (Gefitinib)

Gefitinib is an anilinoquinazoline small molecule inhibitor of EGFR tyrosine kinase. Specifically, this agent competes with the binding of ATP to the tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and resulting in inhibition of signal transduction. Gefitinib may also induce cell cycle arrest and inhibit angiogenesis. Gefitinib is a selective tyrosine kinase receptor inhibitor used in the therapy of non-small cell lung cancer [15].

OSI-774 (Erlotinib)

Erlotinib is a quinazoline derivative and highly selective inhibitor of EGFR tyrosine kinase. It is competing with adenosine triphosphate. It is reversibly binds to the intracellular catalytic domain of epidermal growth factor receptor (EGFR) tyrosine kinase, thereby reversibly inhibiting EGFR phosphorylation and blocking the signal transduction events and tumorigenic effects associated with EGFR activation. It is used in the treatment of non-small cell lung cancer [16].

CI-1033 (Canertinib)

Canertinib is a 4-anilinoquinazoline and an irreversible pan-erbB inhibitor. It is highly selective for the EGFR family of tyrosine kinases erbB-1, erbB-2 and erbB-4. Although erbB-3 does not have an active tyrosine kinase domain, signalling through this pathway is also blocked by CI-1033 as it inactivates the catalytically active hetero dimerisation partners by covalently modifying a specific cysteine residue (Cys-773) in the ATP binding site of these receptors. It inhibits the growth of a panel of cell lines (colon cancer, breast carcinoma, and epidermoid carcinoma cell lines) [17].

GW2016 (Lapatinib)

Lapatinib is a synthetic, orally-active quinazoline with potential antineoplastic properties. Lapatinib reversibly blocks phosphorylation of the epidermal growth factor receptor (EGFR), ErbB2, and the Erk-1 and-2 and AKT kinases; it also inhibits cyclin D protein levels in human tumor cell lines and xenografts. It is used in the therapy of advanced breast cancer and other solid tumors [18].

PKI166

It is a reversible pyrrolo-pyrimidine inhibitor of the EGFR tyrosine kinase. PKI-166 treatment inhibits EGFR autophosphorylation, c-*fos* mRNA expression and cell proliferation in cancer cells [19].

AG1478 (Tyrphostin)

It is a quinazoline derivative and competitive inhibitor of the ATP binding site in the kinase domain, is a highly potent and specific reversible tyrosine kinase inhibitor of the EGFR. It has shown significant anti-proliferative effects in glioblastoma, leiomyoma, colorectal carcinoma and naso-pharyngeal carcinoma cells [20].

BIBW 2992 (Afatinib)

Afatinib is an orally bioavailable anilino-quinazoline derivative and inhibitor of the receptor tyrosine kinase (RTK) epidermal growth factor receptor (ErbB; EGFR) family. Additionally, afatinib inhibits the EGFR T790M gatekeeper mutation which is resistant to treatment with first-generation EGFR inhibitors. It is used in the therapy of selected forms of metastatic non-small cell lung cancer [21, 22].

PF299 (Dacomitinib)

Dacomitinib is a highly selective, orally bioavailable small-molecule inhibitor of the HER family of tyrosine kinases with potential anti-neoplastic activity. Dacomitinib specifically and irreversibly binds to and inhibits human Her-1, Her-2, and Her-4, resulting in the proliferation inhibition and apoptosis of tumor cells that over express these receptors. It has been investigated for the treatment of Lung Cancer [23].

HKI-272 (Neratinib)

Neratinib is an orally available, 6,7-disubstituted-4-anilinoquinoline-3-carbonitrile irreversible inhibitor of the HER-2 receptor tyrosine kinase with potential anti-neoplastic activity. It reduces the autophosphorylation in cells, apparently by targeting a cysteine residue in the ATP-binding pocket of the receptor. Neratinib also inhibits proliferation of EGFR-dependent cells [24].

AG 490 (Tyrphostin B42)

It is an inhibitor of EGFR with IC50 of 0.1 μM in cell-free assays, 135-fold more selective for EGFR versus ErbB2, also inhibits JAK2 with no activity to Lck, Lyn, Syk and Src [25].

ZD6474 (Vandetanib)

Vandetanib is an orally bioavailable 4-anilinoquinazoline. Vandetanib selectively inhibits the tyrosine kinase activity of vascular endothelial growth factor receptor 2 (VEGFR2), thereby blocking VEGF-stimulated endothelial cell proliferation and migration and reducing tumor vessel permeability. This agent also blocks the tyrosine kinase activity of EGFR. [26].

CO1686 (Rociletinib)

Rociletinib is Pyrimidine based an orally available small molecule, irreversible inhibitor of EGFR with potential anti-neoplastic activity. Rociletinib binds to and inhibits mutant forms of EGFR, including T790M, thereby leading to cell death of resistant tumor cells [27].

AZD8931 (Sapitinib)

Sapitinib is a quinazoline derivative with erbB receptor tyrosine kinase inhibition activity. It inhibits erbB tyrosine receptor kinases and result in inhibition of cellular proliferation and angiogenesis in tumors expressing erbB [28].

AST-1306 (Allitinib)

It is quinazoline derivative, a novel irreversible inhibitor of EGFR and ErbB2, highly selective for ErbB family than other kinases [29].
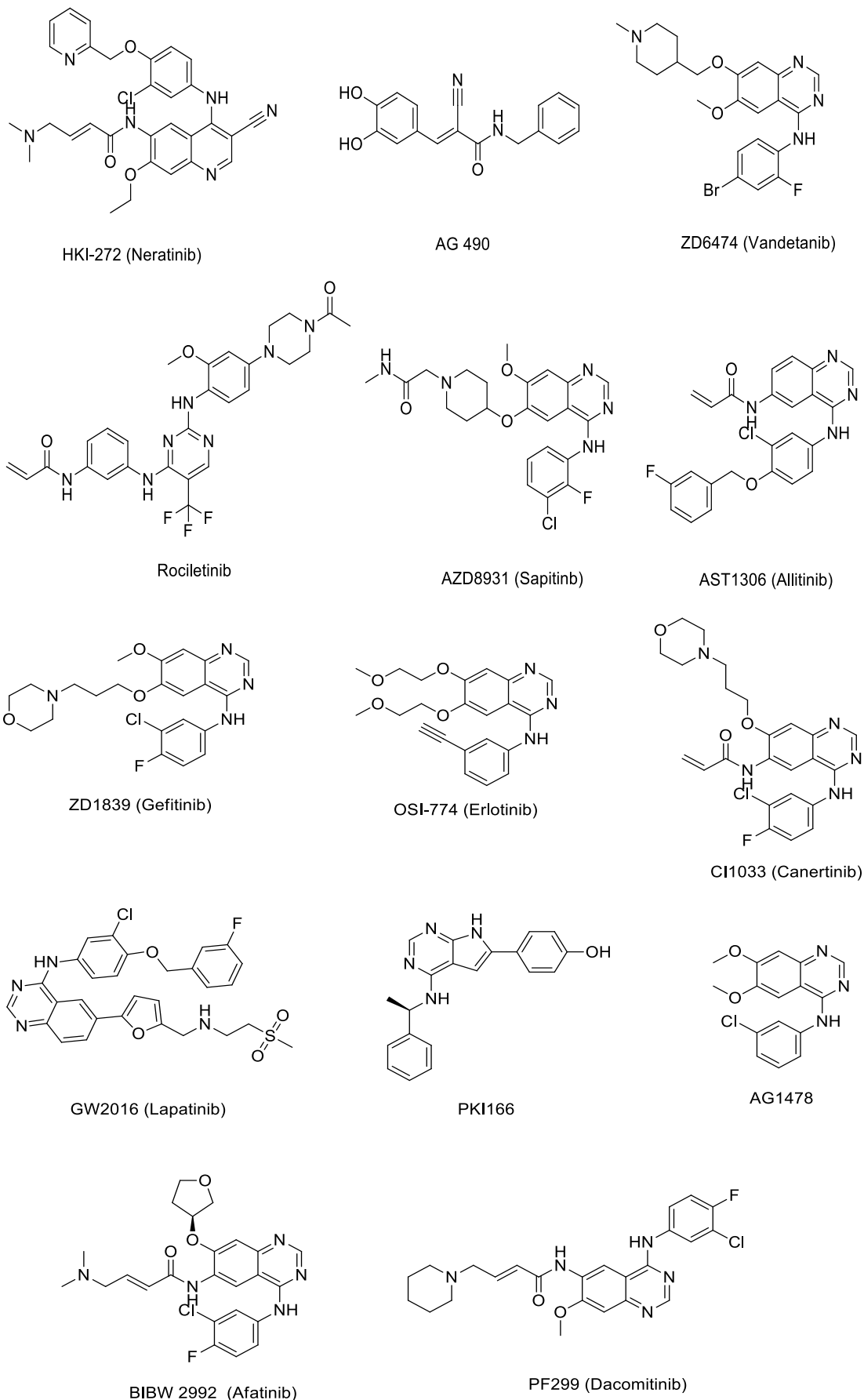
HKI-272 (Neratinib)

AG 490

ZD6474 (Vandetanib)

Rociletinib

AZD8931 (Sapitinib)

AST1306 (Allitinib)

ZD1839 (Gefitinib)

OSI-774 (Erlotinib)

CI1033 (Canertinib)

GW2016 (Lapatinib)

PKI166

AG1478

BIBW 2992 (Afatinib)

PF299 (Dacomitinib)

Figure 3: Chemical structures of small molecules that inhibit growth factor signaling pathways

Other EGFR inhibitors

CP-724714

It is a potent, selective inhibitor of HER2/ErbB2**,** 640-fold selectivity against EGFR, InsR, IRG-1R, PDGFR, and VEGFR2. It was proposed that CP-724714 induced inhibition of hepatic efflux transporters that contributed to an accumulation of drug and bile levels in the liver leading to hepatobiliary cholestasis. CP-724714 has since been discontinued in clinical development [30].
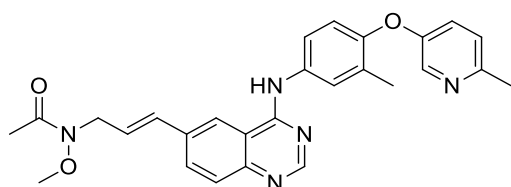
EKB-569 (Pelitinib)

Pelitinib is a 3-cyanoquinoline pan-ErbB tyrosine kinase inhibitor with potential antineoplastic activity. It irreversibly binds covalently to EGFR ErbB-1, -2 and -4, thereby inhibiting receptor phosphorylation and signal transduction and resulting in apoptosis and suppression of proliferation in tumor cells that over express these receptors [31].
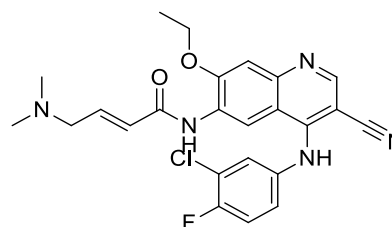
TAK-285

TAK-285 is an orally active irreversible potent dual EGFR/HER2 inhibitor [32].
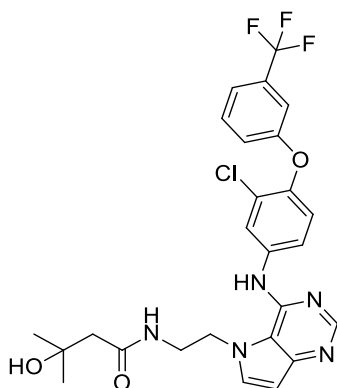
AC-480 (BMS-599626)

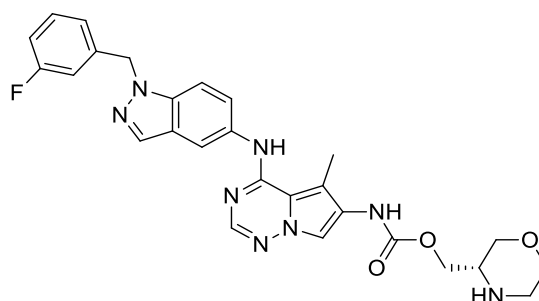AC-480 is an orally bioavailable reversible EGFR, HER2, and HER4 inhibitor [33].

CP-724714 (Sesquisuccinate)

EKB-569 (Pelitinib)

TAK-285

AC-480

Figure 4: Chemical structures of Dual acting small molecules that inhibit growth factor signaling pathways

Side effects caused by small molecule inhibitors

Small molecule inhibitors commonly cause gastrointestinal side effects including diarrhoea, nausea, and vomiting. Whether this represents the effect of EGFR inhibition on the intestinal epithelial cells or reflects the enterohepatic circulation of the drug or its metabolite or the effect of the drug on other kinase targets in the epithelium is unclear. Wide spread use of ZD1839 has shown that it induces pulmonary fibrosis in about 2–4% of patients (0.5% deaths) [34].

Development of resistance to small molecule inhibitors

Preclinical and clinical studies of Imatinib (STI571) in chronic myeloid leukemia provide insights into the development of therapeutic resistance to tyrosine kinase inhibitors. Several lines of evidence indicate that BCR-ABL gene amplification is an important mechanism for resistance to STI571 in CML. Mutations in the ATP-binding pocket such that STI571 no longer has the affinity to bind this site may also account for resistance in some patients. Increased levels of EGFR mRNA and protein but not those of HER2, HER3, and HER4 were observed in PC-9/ ZD cells that are resistant to Gefitinib (ZD1839) in a recently presented study. Increased EGFR/HER2 hetero dimer formation was demonstrated in PC-9/ZD cells. Exposure to ZD1839 increased the formation of these dimers but resulted in only partial inhibition of the auto phosphorylation of EGFR in PC-9/ZD cells. This difference in the inhibition by ZD1839 was most apparent at Tyr1068 of EGFR. Acquired resistance to ZD1839 in breast cancer cells may also result from increased IGF1-R signaling [35].

Critical Issues in Development of Tyrosine Kinase Inhibitors

The clinical trials of tyrosine kinase inhibitors in solid tumors have been largely unsuccessful. There are multiple mechanisms by which solid tumors can achieve *'kinase dependency'* such as translocations which lead to fusion proteins with constitutively activated kinase, mutations within kinase genes leading to constitutive activation, mutations within phosphatases that negatively regulate kinases and constitutively secreted ligand that leads to kinase activation. *Comprehensive kinome sequencing analysis* can be used to identify genetic alterations in a spectrum of tumors. *Microarray-based technology* to assess expression of kinases in tumors is another approach. Phosphorylation status of kinases in tumors can also be evaluated using phospho-specific antibodies, and mass spectroscopy can be used for protein identification [36].

2. CONCLUSION

Elucidation of the various steps initiated in response to EGFR activation has clearly demonstrated that EGFR plays a crucial role in regulating cell functions, and its aberrant expression in cancer cells may influence prognosis and survival. This knowledge has provided a foundation for rational anticancer drug development. The two most widely investigated pharmacologic strategies for inhibiting EGFR function to date are using monoclonal antibodies to block ligand binding to the extracellular portion of EGFR and using low-molecular-weight inhibitory molecules to interfere

with intracellular phosphorylation of intracellular EGFR tyrosine kinase. Both strategies have yielded agents that interrupt cellular proliferation and also facilitate apoptosis, indicating that these agents possess cytotoxic as well as cytostatic properties. Because these EGFR inhibitors have a different site and mechanism of action than traditional cytotoxic treatments, combinations of the EGFR with chemotherapy and radiation produce additive or synergistic anticancer activity with toxicity profiles that often do not overlap with traditional cytotoxic chemotherapy. A concerted international effort by the pharmaceutical industry and academia is urgently needed to achieve these goals and fully realize the potential of tyrosine kinase inhibitors in cancer therapy. The need remains for a therapeutic agent that can have a long term impact on the treatment of cancer and to ensure disease free survival.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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