ISSN : 2347 - 2243

# Indo - American Journal of Life Sciences and Biotechnology

www.iajlb.com
Email : editor@iajlb.com or iajlb.editor@gamil.com

ISSN 2347-2243
www.iajlb.com
Indo-Am. J. of LifeSc & Bt.,2023 Vol.20 Issue.1, Feb 2023
Indo-American Journal of Life Sciences and Biotechnology

# Economic Evaluation of FDA-Approved Small Molecule Protein Kinase Inhibitors in Oncology and Non-Oncology Indications in the United States

K Ravindranadh[1], L. Ramachandra Reddy[2], G.Pitchaiah[3], K.Naga Hari Krishna[4]

1.Associate Professor , Department of pharmacology , QIS College of pharmacy , Ongole , A.P

2. Assistant Professor , Department of Pharmacognosy , QIS College of pharmacy , Ongole , A.P

3. Professor , Department of Pharmacology , QIS College of pharmacy , Ongole , A.P

4. Assistant Professor , Department of Pharmacology , QIS College of pharmacy , Ongole , A.P

## A B S T R A C T

Protein kinases are the focus of several drug discovery initiatives across the globe because genetic changes such as mutations, overexpression, translocations, and dysregulation of these enzymes contribute to the pathophysiology of numerous diseases. Of the 80 small molecule protein kinase inhibitors that the FDA has authorized, 77 are oral bioavailable medications. According to the information, 69 of these medications are authorized to treat neoplasms, including solid tumors like lung and breast cancer as well as non-solid tumors like leukemia. The remaining 11 medications also target non-neoplastic conditions such ulcerative colitis, rheumatoid arthritis, and psoriasis. The FDA label was used to calculate the dose and quantity of pills needed daily, and the cost of the medications was retrieved from www.pharmacychecker.com. Any government or private insurance coverage, which would pay the whole cost or, more likely, a portion of the advertised price, is not included in this technique. Treatment of neoplastic illnesses averaged $17,900 a month, with futibatinib (used to treat cholangiocarcinomas with FGFR2 fusions) costing $44,000 and binimetinib (melanoma) costing at least $5100. With a high of $17,000 for belumosudil (graft vs. host disease) and a minimum of $200 for netarsudil eye drops (glaucoma), the average monthly cost for treating non-neoplastic disorders was $6800. The incidence of the targeted condition is negatively correlated with the cost of the medications. Since there are less than 200,000 possible patients in the US, several of these medications are or were categorized as orphan pharmaceuticals.

- Corresponding Author
  Ravindranadh
  ravindranadh@gmail.com

## 1. The importance of therapeutic protein kinase inhibitors

The pathophysiology of autoimmune and inflammatory diseases, as well as a number of neoplasms, is significantly influenced by the dysregulation of protein kinase activity, which is caused by genetic changes such as mutations, translocations, and overexpression. As a result, one of the most common pharmacological targets in the twenty-first century is protein kinases [1]. These enzymes may be the focus of 25–33% of commercial and academic drug development initiatives globally. The search for oral therapeutic protein kinase inhibitors was spurred by the 2001 success of imatinib in treating Philadelphia chromosome-positive chronic myeloid-enous leukemia [2–4]. The molecular flaw that causes this leukemia, activated chimeric BCR-Abl protein-tyrosine kinase, was inhibited by imatinib, leading to this extraordinary accomplishment.

Indo-American Journal of Life Sciences and Biotechnology

Worldwide, there are now around 250 oral protein kinase blockers undergoing clinical studies [5]. A comprehensive list of these medications, which is updated often, is available online. About two dozen distinct protein kinases are the target of 80 FDA-approved medications now on the market in the United States (see supplementary information). However, these targets only make up a tiny portion of the 518-member protein kinase superfamily. Worldwide, many of medications that target and untarget protein kinases are undergoing clinical studies [3–5]. Three medications were approved by the FDA while this article was being prepared: (i)

HER2-positive breast cancer is treated with capivasertib, a HER2 antagonist; colorectal cancer is treated with fruquintinib, a VEGFR inhibitor; and ROS1-positive lung cancer is treated with repotrectinib, a ROS1 blocker. Because these medications are new, their costs are not yet accessible, hence these three novel agents are not included in any price estimates in this article. According to Manning et al., there are 40 atypical and 478 normal members of the human protein kinase family [6], including phosphatidylinositol 3-kinase (PI 3-kinase) [4,7]. The following reaction is mediated by protein kinases.

Protein–O:H → protein–O:PO2– + MgATP1– + MgADP + H+

These enzymes are classified as protein-serine/threonine kinases (385 members), protein-tyrosine kinases (90), and protein-tyrosine kinase–like enzymes (43), depending on the type of protein–OH moiety. Both intracellular nonreceptor (32) and transmembrane receptor (58) proteins are members of the protein-tyrosine kinase family. Furthermore, a small subset of intracellular proteins, like MEK1/2, belong to the protein kinase family and catalyze the phosphorylation of both tyrosine and threonine residues in the activation section of their target protein kinases. MEK1/2 and associated catalysts are categorized as dual specificity (DS) protein kinases because of their special characteristic (tyrosine and threonine rather than tyrosine or serine/threonine). The estimate that one in every 40 human genes (518 protein kinase genes out of an estimated 20,000 human protein-encoding genes) corresponds to a protein kinase is another indicator of the significance of the protein kinase family. Thus, these kinases make up around 2.5 percent of the human genome. The discovery by Manning et al. that 244 protein kinases link to cancer amplicons and other disease loci [6] is further proof of the significance of protein kinases as therapeutic targets. Furthermore, it is anticipated that the number of protein kinase targets will rise significantly as more studies on the pathophysiology of other disorders are conducted. As of November 2023, the U.S. FDA has authorized 80 small molecule therapeutic protein kinase antagonists, almost all of which are effective when taken orally. The exceptions are the injectable medications temsir-olimus and trilaciclib, as well as the ocular drop netarsudil. In 2011, the oral bioavailable JAK1/2 protein kinase inhibitor rufolitinib received approval for the treatment of myelofibrosis and polycythemia vera. In 2021, this medication was authorized as a cream to treat atopic dermatitis and is also topically active. Of the 80 authorized medications, 41 target dual specificity protein kinases (MEK1/2), 23 target non-receptor protein tyrosine kinases, 12 target protein-serine/threonine protein kinases, and 41 block receptor protein tyrosine kinases (Table 1). According to the information, 69 of these medications are authorized for the treatment of neoplasms (58 for solid tumors including lung, breast, and colon cancers, six for nonsolid tumors like leukemia, and five for both kinds of tumors). Compared to alternative medicine formulations, protein kinase blockers, which are oral tablets, provide several benefits. For instance, solid versions of oral medications are more stable in storage than liquids and suspensions [8]. More importantly, the patient prefers oral administration over other medicine distribution methods. Because the patient may self-administer at home, their quality of life is higher than with intravenous treatment. This lessens the need of taking time off work to go to a clinic for treatment, which entails costs and revenue loss. The majority of patients prefer the ease of oral medications, even though the majority of cancer treatments are administered intravenously.

Multikinase antagonists make up almost two dozen of the FDA-approved medications. Other FDA-approved medications are probably multikinase inhibitors as the specificity of many small molecule protein kinase blockers has not been fully investigated. There may be benefits and drawbacks to blocking many protein kinases simultaneously. As an example, the therapeutic efficacy of

Indo-American Journal of Life Sciences and Biotechnology

**Table 1**
Principal FDA-approved protein kinase inhibitor drug targets [a].

| Kinase family | Class of Kinase | US FDA approved |
|---|---|---|
| EGFR/ErbB | RY | 10 |
| JAK | NRY | 9 |
| VEGFR | RY | 9 |
| BCR-Abl | NRY | 6 |
| ALK | RY | 5 |
| FGFR | RY | 5 |
| CDK4/6 | S/T | 4 |
| MEK1/2 | Y/T | 4 |
| BTK | NRY | 4 |
| B-RAF | S/T | 3 |
| FKBP | S/T | 3 |
| Flt3 | RY | 3 |
| MET | RY | 3 |
| RET | RY | 2 |
| ROCK | S/T | 2 |
| TRKA | RY | 2 |
| CSF1R | RY | 1 |
| Kit | RY | 1 |
| PDGFR | RY | 1 |
| ROS1 | RY | 1 |
| SYK | RY | 1 |
| TYK2 | NRY | 1 |
| Total | | 80 |

S/T, or protein-serine/threonine kinase; RY, or receptor protein-tyrosine kinase; NYR, or nonreceptor protein-tyrosine kinase; Y/T, Dual Specificity Protein Kinase: Target kinase activation regions are first phosphorylated tyrosine, then threonine.

Blocking two or more targets may be connected to multikinase antagonists. Axl is the receptor for GAS6 (growth arrest-specific protein 6); sunitinib and cabozantinib, for instance, show strong off-target action against the Axl receptor protein-tyrosine kinase, which may increase their clinical efficacy [9]. On the other hand, undesirable side effects might result from inhibiting off-target kinases. The question of whether a magic shotgun is better than Paul Ehrlich's magic bullet therefore arises [10]. Non-neoplastic disorders are treated with eleven of the FDA-approved protein kinase inhibitors. For example, (i) abrocitinib and ruxolitinib are prescribed for the management of atopic dermatitis, (ii) deucravacitinib is used for the treatment of psoriasis, (iii)

tofacitinib is used for the treatment of psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis, (iv) baricitinib is employed for the treatment of rheumatoid arthritis, (v) upadacitinib is prescribed for the treatment of psoriatic arthritis, rheumatoid arthritis, and atopic dermatitis, (vi) sirolimus and belumosudil are prescribed for the management of graft vs. host disease, (vii) nintedanib is used for the treatment of idiopathic pulmonary fibrosis, (viii) fostamatinib is prescribed for the management of chronic immune thrombocytopenia, (ix) netarsudil is employed for the treatment of glaucoma, (x) tofacitinib is prescribed for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis, and ritlecitinib is used for the treatment of alopecia areata (www.brimr.org/ PKI/PKIs.htm). Additionally, sirolimus, ruxolitinib, and ibrutinib are authorized treatments for both cancerous and non-cancerous conditions. Twenty-one of the 80 protein kinase blockers that have received FDA approval are used to treat several diseases. The best example is imatinib, which is authorized to treat eight different conditions. The FDA has authorized imatinib as a first-line therapy for patients with Philadelphia chromosome-positive Chronic myelogenous leukemia, acute lymphoblastic leukemia, gastrointestinal stromal tumors with a KIT mutation, myelodysplastic/myeloproliferative diseases with PDGFR gene rearrangements, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, chronic eosinophilic leukemia, and aggressive systemic mastocytosis without the KIT D816V mutation are among the conditions that can be treated with it as a second-line therapy [11–13]. Additionally, chordomas, desmoid tumors, severe KIT-mutant melanomas, and chronic myelogenous leukemia are treated with imatinib off-label.

after transplanting allogeneic stem cells. Therefore, imatinib is a broad-spectrum inhibitor. The blocking of several kinase targets is associated with this wide range of illnesses. It inhibits the stem cell factor receptor Kit, PDGFRα/β, the nonreceptor protein-tyrosine kinase Abl (and the BCR-Abl chimera, which causes chronic myelogenous leukemia), and the epithelial dis-coidin domain-containing receptors 1 (DDR1) and 2 (DDR2). Collagen-activated DDR1/2 are involved in cell migration, proliferation, differentiation, and extracellular matrix remodeling.

## 2. Tertiary structures of protein kinases and a classification of drug-kinase complexes

### 2.1. The K/E/D/D signature motif and the bilobed protein kinase domain

As a model for all protein kinases, we start by looking at the general structure of the active EGFR protein kinase domain. Knighton et al. first reported protein kinase A (PKA) to have a large carboxyterminal lobe with several conserved α-helices and β-strands (Fig. 1 A) and a tiny amino-terminal lobe [14,15]. A five-stranded antiparallel β-sheet (β1–β5) and an αC-helix with a glutamate that forms a salt bridge with a lysine in the β3-sheet in the active state dominate the amino-terminal lobe [16]. The β1- and β2-strands are connected by a conserved glycine-rich (GxGxxG) ATP-phosphate-binding loop found in the N-lobe. The β- and γ-phosphates of ATP are positioned for catalysis with the aid of the G-rich loop. The adenine component of ATP is docked with the β1- and β2-strands (not visible). Protein kinases' amino-terminal lobe has a conserved glutamate close to the middle of the αC-helix. For the active state to form, a salt-bridge between the αC-glutamate and the β3-lysine must exist; this corresponds to the "αCin" conformation. In contrast, the dormant form of EGFR's β3-lysine and αC-glutamate do not make contact in the "αCout" conformation (Fig. 1 E). The expression of complete kinase activity requires the αCin conformation, although it is not sufficient.

Protein kinase domains have a carboxyterminal lobe that is mostly α-helical and contains six conserved segments (αD-αI) (Fig. 1 A). The majority of the catalytic residues linked to the phosphoryl transfer from ATP to its substrates are found in the four short conserved β-strands (β6–β9) found in the C-terminal lobe. The β6-stand, the catalytic loop, the β7- and β8-strands, and the activation segment—which includes the β9-strand—follow the αE-helix. Protein/peptide substrate binding is made possible by the activation segment's open structure that extends away from the catalytic loop when it is in the active state. An extra αEF-helix is located close to the end of the activation segment in both the dormant and active protein kinase domains (Fig. 1 A). The catalytic core of protein kinases is made up of 12 subdomains (I–VIa, VIb–XI) with conserved amino acid residue signatures, according to Hanks et al. [17]. The catalytic properties of protein kinases are exemplified by the following four amino acids, which form a K/E/D/D (Lys/Glu/Asp/Asp) signature. As previously mentioned, the αC-glutamate (the E of K/E/D/D) and an invariant β3-strand lysine (the K of K/E/D/D) produce salt bridges. Aspartate, the initial D in the K/E/D/D catalytic loop, functions as a base to remove a proton from the substrate's protein–OH group, allowing the hydroxyl group to attack the γ-phosphorous atom of ATP nucleophilically. The first residue in the activation segment is the second aspartate in the K/E/D/D signature. Almost all protein kinases have an activation sequence that starts with DFG (Asp-Phe-Gly) and finishes with APE (Ala-Pro-Glu). DFG marks the start of the EGFR activation segment, whereas ALE (Ala-Leu-Glu) marks its conclusion. The active conformation is represented by the DFG-Din structure. After the DFG-D contacts Mg2+, the α-, β-, and γ-phosphates of ATP are coordinated (not shown). The activation segment comes after the β7- and β8-strands, which are preceded by the main structure of the catalytic HRD loop. The activation segment's binding loop is where the big lobe often binds the peptide/protein substrates. There is a phosphorylatable tyrosine in the EGFR activation region. While activation of most protein kinases requires phosphorylation of one or more residues

Indo-American Journal of Life Sciences and Biotechnology

in the activation section [18], EGFR activation does not need this phosphorylation [19,20]. While catalytically active protein kinase's tertiary structure

Indo-American Journal of Life Sciences and Biotechnology

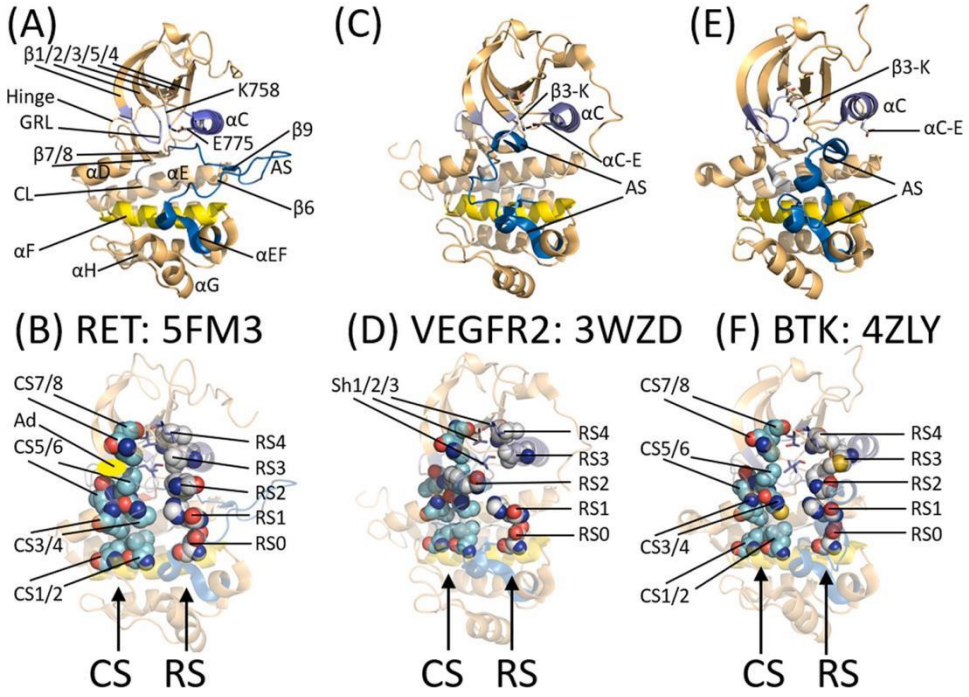


**Fig. 1.** (A) Overview of active RET and (B) its C-spine and R-spine residues. (C) The AS-closed structure of dormant VEGFR2 and (D) its C-spine, R-spine, and shell residues. (E) Overview of the $\alpha C_{out}$ structure of BTK and (F) its C-spine and R-spine residues. AS, activation segment; CL, catalytic loop. CS, catalytic spine; GRL, glycine-rich loop; RS, regulatory spine. This figure was prepared using the PyMOL Molecular Graphics System Version 1.5.0.4 Schro¨dinger, LLC.

domains are similar, Huse and Kuriyan noted that the crystal structures of dormant enzymes reveal distinct inactive conformations [21]. One of the most common inactive enzyme forms is the DFG-$D_{out}$ conformation. When this aspartate is directed outward, the DFG-F is directed into the active site (not shown). Another commonly occurring inactive confor- mation is the αC-helix out state (Fig. 1E) [22]. Also note that the acti- vation segment in the αC-out conformation is in an inactive closed state. To summarize, the three main regulatory elements within the kinase domain include the N-terminal lobe αC-helix (αC-in, active; αC-out, inactive), the C-terminal lobe DFG-D (DFG-$D_{in}$, active; DFG-$D_{out}$, inac- tive), and the C-terminal lobe activation segment (AS-open, active; AS-closed, inactive).

Taylor and Kornev [23] and Kornev et al. [24] analyzed the struc- tures of active and dormant conformations of some two dozen protein kinases and determined functionally important residues by a local spatial pattern (LSP) alignment algorithm. This analysis revealed a skeleton of four nonconsecutive hydrophobic residues that constitute a regulatory or R-spine and eight hydrophobic residues that constitute a catalytic or C-spine. Each spine consists of residues derived from both the small and large lobes. The regulatory spine contains residues from the activation segment and the αC-helix, whose conformations are important in defining active and dormant states. The catalytic spine governs catalysis by directing ATP binding. The two spines dictate the positioning of the protein substrate (R-spine) and ATP (C-spine) so that catalysis results. The proper alignment of the spines is necessary for the assembly of an active kinase.

The protein kinase regulatory spine consists of a residue from the beginning of the β4-strand, from the C-terminal portion of the αC-helix, the phenylalanine of the activation segment DFG, along with the histi- dine of HRD of the catalytic loop. The spinal component from the αC- helix is four residues C-terminal to the conserved αC-glutamate.

Indo-American Journal of Life Sciences and Biotechnology

The backbone of the catalytic loop histidine is anchored to the αF-helix by a hydrogen bond to a conserved aspartate residue within the αF-helix. Going from the aspartate within the αF-helix up to the top residue within the β4-strand, Meharena et al. labeled the residues RS0, RS1, RS2, RS3, and RS4 (Fig. 1B) [22].

The regulatory spine of active protein kinase domains is nearly linear (Fig. 1B) while that of the dormant enzymes possess various distortions. In the inactive DFG-$D_{out}$ form, the DFG-F residue (RS2) is displaced into the active site and separated from RS3/4; this form of the spine is broken (Fig. 1D). In the αC-helix out conformation, RS3 is displaced away from the active site along with the αC-helix (Fig. 1 F). The catalytic spine of protein kinases consists of residues from the small amino-terminal and large carboxyterminal lobes that are completed by the adenine of ATP (Fig. 1B) [22,24]. This spine mediates catalysis by facilitating ATP binding thereby accounting for the term catalytic. The two residues of the small lobe of protein kinase domains that bind to the adenine component of ATP include the alanine from the conserved Ala-Xxx-Lys of the β3-strand (CS8) and a hydrophobic valine residue at the begin- ning of the β2-strand (CS7). Furthermore, a hydrophobic residue from the middle of the β7-strand (CS6) binds to the adenine base in the active enzyme. This residue is flanked by two hydrophobic residues (CS4 and CS5) that bind to a residue near the beginning of the αD-helix (CS3). CS3

HRD, the residues that constitute the spines were not identified by sequence analyses per se. Rather, they were identified by their three- dimensional location based upon a comparison of the X-ray crystallo- graphic structures of some two dozen protein kinases in their active and dormant states [23,24]. Many spine residues interact hydrophobically with their target protein kinase inhibitors [25].

### 2.1. *Classification of protein kinase inhibitors*

We classified protein kinase antagonists based upon the structure of the drug-enzyme complexes including reversible (Groups I, I½, II, III, IV, and V) and targeted covalent irreversible inhibitors (VI) [26,27]. The major classes include the Type I and Type II inhibitors. The Type I in- hibitors bind at the adenine binding site of an active enzyme. Type II inhibitors bind to an inactive DFG-$D_{out}$ enzyme conformation. Type I½ inhibitors bind to an inactive DFG-$D_{in}$ enzyme conformation (e.g., αC-out). Type III and IV inhibitors are allosteric in nature. The Type III inhibitors bind near the adenine binding site while the Type IV in- hibitors bind far from the adenine-binding pocket. Type V inhibitors are bivalent antagonists that span two kinase domain regions (this is a theoretical construct since there are no known such blockers). Type VI antagonists are irreversible targeted covalent inhibitors (TCIs) [27] (Table 2).

## 3. An overview of FDA-approved protein kinase inhibitor targets

### 3.1. *The epidermal growth factor receptor family*

The human EGF receptor (HER) protein-tyrosine kinases are among the most studied signal transduction families in biochemistry [28]. Stanley Cohen pioneered EGF and EGFR research by describing epidermal growth factor (EGF), its receptor (EGFR), and many of its biochemical and physiological actions [29]. He found that EGFR had protein-tyrosine kinase activity and not protein-serine/threonine kinase activity, which was a novel and unexpected discovery at the time (see Ref. [30] for a historical review). Cohen et al. demonstrated that a sol- ubilized 170-kDa polypeptide had both EGF binding capacity as well as protein kinase activity [31]. EGFR was also the first receptor that pro- vided evidence for a relationship between mutation, overexpression, and cancer [32]. The EGFR family is among the most investigated re- ceptor protein-tyrosine kinase families because of its central role in signal transduction and in oncogenesis.

The human EGF receptor (HER) family consists of four members that belong to the ErbB lineage of proteins (ErbB1–4) [33–36]. The *ERBB* gene symbol is taken from the avian viral erythroblastosis (*Erb*) onco- gene with which these

Indo-American Journal of Life Sciences and Biotechnology

receptors are allied. Human gene symbols are generally designated in uppercase italics (*EGFR*). The four members of the human epidermal growth factor receptor gene family include: (i) *EGFR/ERBB1/HER1,* (ii) *ERBB2/HER2/NEU*, (iii) *ERBB3/HER3,* and (iv)

Meharena et al. identified three residues in murine PKA that stabilize the R-spine that they labeled Sh1, Sh2, and Sh3, where Sh refers to shell [22]. The Sh2 residue corresponds to the gatekeeper residue. The name gatekeeper signifies the role of that this residue plays in controlling access to the back cleft. The back cleft is sometimes called the back pocket or hydrophobic pocket II (HPII).

Note that both the R-spine and C-spine are anchored to the αF-helix, which is a very hydrophobic component of the enzyme that is entirely within the protein and not exposed to the solvent. The αF-helix supports the spines, which in turn anchor the protein kinase catalytic machinery. In contrast to the protein kinase amino acid signatures such as DFG or

| | |
|---|---|
| I | Binds in and around the ATP-binding pocket of an active enzyme I½ A/BBinds in and around the ATP-binding pocket of an inactive DFG-$D_{in}$ enzyme |
| I½ A | Extends into the back cleft |
| I½ B | Does not extend into the back cleft |
| II A/B | Bind in and around the ATP-binding site of an inactive DFG-$D_{out}$ enzyme |
| II A | Extends into the back cleft |
| II B | Does not extend into the back cleft |
| III | Allosteric inhibitor bound next to the ATP-binding site |
| IV | Allosteric inhibitor bound away from the ATP-binding site |
| V | Bivalent inhibitor spanning two kinase domain regions |
| VI | Covalent inhibitor |

HER4/ERBB4. Despite the significant overlap, the ErbB nomenclature is linked to the biological sciences, whereas the HER nomenclature is more often used in clinical reporting. Schechter et al. discovered that the Neu oncogene, which is connected to the rat Erbb2 gene of the EGFR family, is present in rat neuro/glioblastomas [37]. NEU is occasionally used in human gene nomenclature, and this discovery supported the idea that the ErbB family of receptors may play a part in the emergence of cancer. Epithelial, mesenchymal, and neuronal cells, as well as their undifferentiated ancestors, all express this family of receptors. Ulrich et al. stated that the receptor has a single hydrophobic transmembrane segment that divides the intracellular protein kinase domain from the extracellular ligand-binding domain, based on the primary amino acid sequence of EGFR as identified by cDNA analysis [38]. Almost all receptor protein kinases are covered by this well-established theory. EGF, amphiregulin, epigen, betacellulin, transforming growth factor-α, epiregulin, heparin-binding EGF-like factor, and neuregulins1/2/3/4 are among the nine activating ligands that attach to the ErbB family of proteins. A description of the specificity of interactions between ligands and ErbB receptors may be found in Ref. [36]. None of these ligands are bound by ErbB2/HER2, and ErbB3 is not a protein kinase. Therefore, it is paradoxical that out of all the potential homo and heterodimer combinations, the ErbB2-ErbB3 dimer is the most active.

The development of several lung malignancies is significantly influenced by EGFR/ErbB1 [9]. According to Herbst et al., 10–40% of lung cancer samples had EGFR kinase-domain mutations [39]. About 10% of Caucasian individuals have EGFR kinase-domain mutations, while 30–40% of Asian patients do. In the small protein kinase lobe, the most frequent mutations were (i) the deletion of five exon-19 residues (746ELREA750), and (ii) the big lobe's exon-21 substitution of an arginine for leucine (L858R). More than

90% of the activating EGFR mutations identified in NSCLC are caused by these two mutations. Nonetheless, over 200 EGFR mutations in NSCLC have been discovered [40]. A description of ErbB family blockers used to treat lung cancer follows. The pathophysiology of breast tumors also involves the ErbB family [33, 34]. Three categories—which are not mutually exclusive—are used to classify breast tumors for therapeutic purposes: (i) hormone receptor-positive, (ii) triple-negative, and (iii) overexpression of ERBB2/HER2/NEU. Breast tumors that lack (i) estrogen receptors, (ii) progesterone receptors, and (iii) HER2 overexpression are referred to as triple-negative breast cancers. According to Wittliff, 20–30% of breast tumors have overexpressed ErbB2, but 10–20% of triple-negative breast cancers lack hormone receptors and do not overexpress ErbB2/HER2 [41]. Before the development of ErbB2 targeted medicines, ErbB2 overexpression was associated with a poor prognosis; however, it is now one of the breast cancer classes that responds better to therapy [36]. Additionally, Wittliff discovered that around 79% of all breast tumors had estrogen, progesterone, or both receptors [41]. Moreover, he discovered that around 56% of breast tumors have both the progesterone and estrogen receptors, while 14% have only the estrogen receptor, 9% have just the progesterone receptor, and 21% have neither receptor.

### *3.2. The Janus kinase (JAK) family*

Tyrosine kinase 2 (TYK2) and JAK1/2/3 are members of the Janus kinase (JAK) family of nonreceptor protein-tyrosine kinases [42,43]. Each of these gene-products has a JAK homology pseudokinase (JH2) domain that interacts with the neighboring protein kinase domain (JH1) and controls its movement. A single polypeptide chain has two protein kinase domains, which is why this enzyme family was named after the two-faced Roman god Janus, who can see both forward and backward. Jokingly, JAK was thought of as Just Another Kinase [44]. Expression of JAK1, JAK2, and TYK2 is seen in almost every kind of

JAK3 is restricted to myeloid, lymphoid, and hematopoietic cells [45]. Interferons, interleukins, and hormones (erythropoietin and thrombopoietin) are among the several cytokines that control the activity of the Janus kinase family [43]. The activation of the Janus kinases linked to ligand binding to different cytokine receptors subsequently mediates the phosphorylation of the receptors. The Janus kinases increase STAT phosphorylation and activation by binding to cytokine receptor phosphotyrosines via the SH2 domain of signal transducers and activators of transcription (STAT). After that, the resultant STAT dimers go into the nucleus and control the expression of hundreds of target proteins. Both JAK1/2 and JAK1/3 signaling are involved in the pathophysiology of myeloproliferative neoplasms and inflammatory diseases, respectively. A mutation that activates JAK2 V617F is seen in about 50% of myelofibrosis cases, 50% of essential thrombocythemia cases, and 95% of individuals with polycythemia vera [46]. Myeloproliferative neoplasms (MPN), acute myelogenous leukemia (AML), and B and T cell acute lymphoblastic leukemia (B-ALL, T-ALL) are among the several hematological conditions linked to mutations in the JAK family gain-of-function. The use of JAK family blockers to treat both cancerous and non-cancerous conditions is explained later.

### *3.3. VEGFR receptors and ligands*

Angiogenesis, lymphangiogenesis, and vasculogenesis are all significantly influenced by the VEGF family and its receptors [47–49]. VEGFR3 is located in lymphatic endothelial cells in adults, while VEGFR1 and VEGFR2 are mostly found in vascular endothelial cells. VEGF (also known as VEGF-A), VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) are the five members of the human VEGF family. A signal sequence found in each of these proteins is broken down during production. Additionally, many isoforms of VEGF, VEGF-B, and PlGF are produced by alternative splicing of their respective pre-mRNAs. Vascular endothelial cells were shown to have VEGF binding sites that corresponded to VEGFR1 (Flt1) and VEGFR2 (Flk1/KDR). VEGFR1 is bound by VEGF, VEGF-B, and PlGF, while VEGFR2 is bound by VEGF and VEGF-C [50,51]. The specificity of action of VEGF, VEGF-B, and PlGF is explained by the presence of these receptors on vascular endothelial cells. VEGF-C and VEGF-D are bound by VEGFR3 (Flt4). These receptors are all type V (five) protein-tyrosine kinases, which are made up of an intracellular protein-tyrosine kinase domain with a kinase insert of 70–100 amino acid residues, a carboxyterminal tail, a single trans-membrane segment, a juxtamembrane segment, and an extracellular component with seven immunoglobulin-like domains (refer to [52] for a description of types I–XX receptor protein-tyrosine kinases). All three VEGF receptors have extracellular immunoglobulin-like domains and a kinase insert, and they are related to the platelet-derived growth factor receptors-α/ß, fibroblast growth factor receptors (1–4), the stem cell factor receptor (Kit), the Flt ligand receptor (Flt3), and the colony stimulating factor-1 receptor (CSF1R) [52].

Because angiogenesis plays a significant part in the pathophysiology of renal cell carcinomas and other neoplasms,

investigators have directed their attention into the biology of VEGFs and VEGFR1/2/3 as well as the creation of inhibitors of the complex and multidimensional angiogenic pathways [49]. The ERK1/2, FAK, PI3-kinase/AKT, and p38 MAP kinase pathways all signal as a result of VEGF's stimulation of the phosphorylation of preformed VEGFR2 dimer activation segment tyrosine residues, which is followed by the phosphorylation of additional protein-tyrosines that attract phospho-tyrosine binding proteins [50,51]. The primary route involved in vasculogenesis and angiogenesis, VEGFR2, is modulated by VEGFR1. The primary function of VEGFR3 and its ligands, VEGF-C and VEGF-D, is lymphangiogenesis. The following is a list of medications that interact with these growth factors and receptors.

### *3.4. Anaplastic lymphoma kinase (ALK)*

The NPM-ALK fusion protein, which is expressed in most anaplastic large-cell lymphomas, was first identified as anaplastic lymphoma kinase in 1994 [53]. The ligands of ALK, which belongs to the insulin receptor protein-tyrosine kinase superfamily, are AUG-α and AUG-β (for augmenter) [54]. The pathophysiology of several diseases, such as anaplastic large-cell lymphoma, diffuse large B-cell lymphoma, and inflammatory myofibroblastic tumors, has been linked to approximately twenty distinct ALK-fusion proteins that are produced by different chromosomal rearrangements [55,56]. The development of around 5% of non-small cell lung tumors is fundamentally influenced by the EML4-ALK fusion protein. The ALK protein kinase domain, which is essential to the carcinogenic process, is activated when the amino-terminal region of the ALK fusion proteins forms dimers. The JAK/STAT cell survival pathway and the Ras/RAF/MEK/ERK1/2 cell proliferation module are involved in downstream signaling from the ALK fusion protein. The development of ALK inhibitors has attracted a lot of attention due to the presence of oncogenic ALK, especially in non-small cell lung cancer. The first medication authorized by the FDA to treat ALK-positive non-small cell lung cancer was crizotinib [57]. The development of second-generation medications to treat NSCLC and other conditions was prompted by the onset of crizotinib drug resistance, which had a median incidence at around 10 months. ALK mutations in the fusion protein account for around 28% of instances of crizotinib resistance; the other cases are caused by activation of other signaling pathways or by unknown mechanisms. [56]. Humans have been shown to have about a dozen distinct mutations in ALK fusion proteins that give resistance to crizotinib. Later on, further ALK inhibitors are discussed.

### *3.5. The Philadelphia chromosome, BCR-Abl, and chronic myelogenous leukemia (CML)*

About 95% of patients of chronic myelogenous leukemia have the Philadelphia chromosome [58]. A reciprocal translocation t (9;22)(q34;q11.2) that produces a truncated chromosome 22 (the Philadelphia chromosome) and a prolonged chromosome 9 is what Janet Rowley found to be the source of the Philadelphia chromosome [59]. The BCR-Abl oncogene is created as a result of this translocation, where Abl is the human homolog of the murine Abelson leukemia virus, which was first found on chromosome 9, and BCR stands for breakpoint cluster region, which was first found on chromosome 22 [60,61]. Because of the formation of the fusion protein, the BCR-Abl kinase is more active and plays a major role in the disease's development. As will be explained later, imatinib and second and third generation inhibitors have been developed that bind to either the ATP-binding site or an allosteric site of BCR-Abl.

Two transcripts, 1a and 1b, are produced by alternative splicing of Abl-1 pre-mRNA [58]. The latter protein has a myristoyl group that is covalently linked to a glycine residue just after the beginning amino-terminal methionine. It is also 19 residues longer than Abl-1a. The N-terminal and C-terminal lobes of catalytically active Abl-1b must be able to move (breathe) in order to mediate the phos-phorylation of its substrates, but the control of Abl-1a is still a mystery. The myristoyl group is essential for the regulation of Abl-1b activity. The SH3 domain, the SH2 domain, and the SH2-kinase linker firmly bind to the protein kinase domain, limiting its mobility and preventing its catalytic activity in order to maintain the Abl-1b kinase in an inactive state. Hantschel et al. found that an enzyme with much more catalytic activity than wildtype Abl-1b was biosynthesised as a result of the ABL1b glycine-to-alanine mutation at position 2 (G2A) [62]. The N-myristoyltransferase-catalyzed myristoylation is inhibited when glycine is converted to any other residue. Abl-1a's first four residues are MLEI, which will not increase N-myristoyl-transferase activity, whereas Abl-1b's are MGQQ.

Furthermore, the G2A mutant protein was extensively phosphorylated in contrast to the wildtype enzyme. These results showed that Abl-1b phosphotransferase activity is adversely regulated by the myristoyl group. The big lobe αI-helix bends as a result of

Indo-American Journal of Life Sciences and Biotechnology

myristate's interaction with Abl-1b. Consequently, the SH3-SH2 complex may firmly bind with the SH1 kinase domain, preventing both its catalytic activity and mobility. The enzyme is active when the backside of Abl-1b cannot attach securely to the protein kinase domain due to the absence of the αI-helix-induced bend. Asciminib interacts with the myristate binding pocket, a type IV allosteric-inhibitor-binding site [58]. Furthermore, the T315I (Abl-1a nomenclature) gatekeeper mutant is susceptible to asciminib. The medication, which is currently the greatest example of a type IV antagonist licensed by the FDA, binds to an allosteric site that is far from the ATP-binding site (28 Å). The types of protein kinase reversible (Groups I, I½, II, III, IV, and V) and targeted covalent irreversible inhibitors (VI) are described in Refs. [63–70]. The FDA has authorized asciminib as a first-line therapy for Philadelphia chromosome-positive CML with the T315I gatekeeper mutation and as a third-line treatment for Philadelphia chromosome-positive CML.

3.6. The growth factors for fibroblasts and their receptors With 22 growth factors, four protein-kinase receptors, and a fifth receptor that lacks intracellular enzyme function, the FGF family is one of the biggest, if not the largest, signaling constellations [71]. The number of possible FGF1–23 and FGFR1–4 interaction combinations is in the hundreds. Deciphering certain signaling pathways becomes more challenging due to this diversity. Despite being referred to as FGF1–23, factors 15 and 19 really represent the same molecule, which is referred to in this publication as FGF(15/19); as a result, there are 22 FGFs in total. Transmembrane fibroblast growth factor receptors (FGFRs) are contacted by 18 of the 22 growth factors, which are glycoproteins produced from the cell of origin. In contrast, voltage-gated sodium channels rely on the intracellular factors (FGF11/12/13/14) as cofactors. The size of the FGFs varies, ranging from 155 residues for FGF1 to 288 residues for FGF2. Seven subfamilies comprise the FGFs [72,73]. FGF1 and FGF2 make up the first subfamily (FGF1). These factors are easily exported from cells by passing through the plasma membrane, despite the fact that they do not have a conventional signal peptide. Their corresponding FGFRs are bound by FGF1/2, which then activates them. These factors have the peculiar ability to go from the cytosol into the nucleus and back into the cell via the plasma membrane. The members of the second subfamily (FGF4) include FGF4, FGF5, and FGF6. There are four members of the third subfamily (FGF7): FGF3, FGF7, FGF10, and FGF22. These factors are released from cells and have a signal peptide. While FGF7 interacts with FGFR2/4, FGF3/10/22 interacts with FGFR1/2. The members of the fourth subfamily (FGF8) include FGF8, FGF17, and FGF18. The traditional signal peptide route secretes these factors, and FGF8/17 interacts with FGFR1/2/3/4 and FGF8 interacts with FGFR2/3/4. FGF9, FGF16, and FGF20 make up the fifth sub-family (FGF9). These are homodimers of ligands. The members of the sixth subfamily, FGF(15/19), are FGF(15/19), FGF21, and FGF23. These growth factors interact with FGFR1/2/3/4 and are released from cells via the traditional signal peptide pathway. Because of their strong affinity for extracellular heparan sulphate glycosaminoglycan chains of heparan sulphate proteoglycans, all of the earlier FGFs operate in an autocrine or paracrine manner in close proximity to the cell that produced them. The first five subfamilies of FGFs are classified as paracrine, whereas the sixth subfamily is classified as endocrine. FGF(15/19) is an endocrine factor that is transported by the circulation to its target cells and receptors, unlike the subfamilies 1–5. Its low affinity for heparan sulfate enables it to diffuse from its site of origin into the circulation and reach its targets [72,73]. FGF11, FGF12, FGF13, and FGF14 make up the seventh subfamily of FGF. These elements exist in the cytosol and nucleus and are not secreted. This subfamily interacts with voltage-gated sodium's cytosolic carboxyterminal tail.

channels in electrically excitable cells such as mature neurons and car- diomyocytes. A summary of antagonists that interact with the FGFRs is given later.

3.7. Protein serine/threonine kinases that are cyclin-dependent Every cell in every tissue and organ has its replication strictly regulated both throughout development and throughout an individual's lifetime [74, 75]. Cells in a healthy adult reproduce when necessary. Every chromosome also has to be precisely duplicated. The S-phase (DNA synthesis), G2 (Gap 2 or premitotic growth), M (mitotic) phase, and G1 (Gap 1 and presynthetic growth) comprise the cell cycle. Before starting mitosis in G2, cells conduct surveillance to ensure the integrity of freshly created DNA while they are getting ready for DNA synthesis in G1. The S-phase involves the replication of chromosomal DNA, whereas the M-phase involves the division of other cellular components among two daughter cells. Cells leave the cycle and reach G0, a nondividing quiescent stage, when they stop proliferating. Senescence, on the other hand, is an irreversible condition of G1 cell cycle arrest, meaning that cells have stopped proliferating and are unable to divide. To pass through the cell division cycle, cyclins and their corresponding cyclin-dependent protein kinases (CDKs) are necessary [74, 75]. Humans have 13 cyclin groups (A, B, C, D, E, F, G, H, J, K, L, T, and Y) and 20 CDKs (1–20). There are two steps involved in activating cyclins. Protein kinase activation begins with interactions between CDKs and cyclins. CDK-cyclin enzyme activity is fully expressed once the CDK-cyclin complex is formed. This is achieved by the CDK activation segment un-dergoes phosphorylation at a conserved threonine residue, which is catalyzed by CDK7. Throughout the cell cycle, the amounts of CDKs remain rather consistent. Proteins called cyclins, whose levels fluctuate during the cell cycle, influence the actions of the CDKs that govern transit through the cell cycle. Their names come from the way that cyclin levels fluctuate up and down during cell division and proliferation. The process that controls CDKs includes the manufacture of their matching cyclins, which raises protein kinase activity, and proteolysis, which lowers enzyme activity. The peak levels of cyclin A2 and cyclin E1 during the G2-phase and G1-

phase, respectively, were only around 1/8th of those of their partner enzyme (CDK2), according to research by Arooz et al. using human HeLa cells [76]. This finding suggests that there are too many CDKs and that their regulatory components are not fully stimulating them. About 13 sets of proteins with molecular weights ranging from 35 to 90 kDa make up the vast family known as human cyclins [74, 75]. Cyclins are produced at different phases of the cell cycle and are subsequently broken down by a complexly controlled process that includes interactions with proteasomes and ubiquitin ligases (E3s). There are three main categories within the cyclin family. A, B, D, E, F, G, and J comprise group I, also known as the cyclin B group; Y is represented by group II; and cyclins C, H, K, L, and T, which are important partners with the transcriptional CDKs, comprise group III, also known as the cyclin C group. The cyclin box is a 100 amino acid residue domain found in these proteins that is made up of five α-helices. While the other cyclins only have one cyclin box, the A, B, D, E, F, and J cyclins have two. Cells contain a number of checkpoints that prevent them from moving onto the next phase too soon or in the wrong way before they have properly completed their current phase, ensuring proper progression through the cell cycle [77]. The first checkpoint occurs at G1-S, when S-phase CDK-cyclin complexes and G1-S are activated. It is also referred to as the start, restriction point, or R-point. Mitogens and growth factors are not necessary for the cell cycle to be completed once it has passed the first checkpoint [74, 75]. The several versions of the G1-S enzymes, which are expressed differently in different cells and tissues, include CDK4, CDK6, and the D-type cyclins (D1/2/3). The S-phase transition requires the CDK2-cyclin E complex. A second checkpoint is formed by G2-M as the M-phase CDK1-cyclin A/B.

When the complex is activated, the cell enters metaphase during mitosis. The third checkpoint is the metaphase-to-anaphase transition, which results in sister-chromatid segregation, mitotic completion, and cytokinesis when a single cell divides into two daughter cells. When the anaphase-promoting complex is stimulated by the M-phase cyclin-CDK complexes, the sister chromatid-holding proteins are broken down by proteolysis, leading to progression.

Following mitogenic stimulation, one or more cyclin D members – depending upon the cell type – are expressed and promote the activation of CDK4/6, which are crucial regulators of the G1-S transition [74,75]. The CDK4/6-cyclin D complexes catalyze the phosphorylation of the retinoblastoma (Rb) protein at only one site among 14 potential phosphorylation sites to yield monophosphorylated Rb that exists for several hours in the G1-phase [78]. CDK4 and CDK6 are protein kinases that exhibit narrow substrate specificity; these enzymes catalyze the phos- phorylation of Rb (RB1) and two other Rb-like family proteins (RBL1 or p107 and RBL2 or p130) [74,75]. The generation of cyclin D proteins is followed by the production of cyclin E, cyclin A, and cyclin B along with the activation of their associated CDKs. The biosynthesis of cyclin E activates CDK2 later in the G1-phase thereby leading to (i) the hyper- phosphorylation of Rb at all 14 sites and (ii) its deactivation. The FDA-approved CDK4/6 blockers are described later. 3.8. Tyrosine kinase of the Flt3 receptor and its ligand (Flt3L) After McDonough et al. discovered a feline sarcoma virus in 1971, work on Flt3 began [79]. The feline McDonough sarcoma virus, or v-FMS virus, is the name of this viral oncogene. As a result, the colony-stimulating factor-1 receptor (CSF1R), also known as the c-FMS proto-oncogene, was discovered. VEGFR1 is Flt1 (fms-like tyrosine kinase-1), while fibroblast growth factor receptor-1 (FGFR1) is Flt2. A trans-membrane receptor protein-tyrosine kinase, Flt3 (fms-like tyrosine kinase-3) is essential for healthy hematopoiesis [80]. This protein controls the growth and differentiation of hematopoietic cells and is expressed by early myeloid and lymphoid progenitor cells. When hematopoietic cells develop, Flt3 is not expressed. Approximately one-third of individuals with newly diagnosed acute myelogenous leukemia (AML) have FLT3 activating mutations. About 20–25% of AML patients have FLT3 internal tandem duplication (ITD), which is caused by a head-to-tail duplication of one to 412 amino acids inside the juxtamembrane domain. The protein-tyrosine kinases Flt3, Kit, PDGFRα/β, and macrophage/colony stimulating factor-1 receptor are type III receptors. The characteristics of the 20 kinds of receptor protein-tyrosine kinases are described in Refs. [28, 52]. A carboxyterminal tail, a protein kinase domain with an insert of several amino acid residues, an intracellular domain including a juxtamembrane segment, an extracellular part, and a transmembrane segment are all present in type III receptors. There are five immunoglobulin-like domains (D1–D5) in the extracellular region. With 547 amino acid residues, the extracellular domain of human Flt3 is longer than the intracellular domain, which has 430 residues. 50 amino acids are also present in the carboxyterminal tail (944–993). The signal peptide is composed of the 26 amino-terminal residues of the 235 residues that make up the human Flt3L. There are 209 residues in the membrane-associated Flt3L. ADAM17 (A disintegrin and metalloproteinase) may catalyze proteolysis of it, resulting in a soluble version with 178 residues that form active dimers [81]. Flt3L is a soluble and membrane-associated equipotent growth factor. A noncovalent dimer that arises from hydrophobic and polar contacts makes up the Flt3 ligand (Flt3L), which facilitates dimerization and Flt3 activation [80]. The dimeric ligand has a Kd value of 0.2–0.5 nM and interacts with the D3 region of two Flt3 receptors. This reduces this inhibition by promoting the phosphorylation of residues in the autoinhibitory JM domain. Other phosphorylation processes take place in other locations, encouraging the binding of proteins that result in the PKB/AKT signaling module and MAP kinase activation, which promotes cell division and prevents programmed cell death (apoptosis). For a detailed description of Flt3-mediated signal transduction, see Ref. [80]. The description of FDA-approved Flt3 inhibitors follows.

Indo-American Journal of Life Sciences and Biotechnology

## 4. Estimating the cost of FDA-approved small molecule protein kinase inhibitors in the United States

In November 2023, we obtained medicine costs for the typical patient in the state of North Carolina (ZIP code 28791) from www.pharmacychecker.com. These figures include both wholesale and retail markups and indicate the retail price of a medication at the pharmacy as agreed upon by pharmacies and insurance. The well-known national chains in the United States, Rite Aid Pharmacy, Walgreens, and CVS Pharmacy, are among the pharmacies used in this article. The U.S. prescription medicine market is dominated by CVS with 25.6%, followed by Rite Aid with 2.3% and Walgreens with 16.5% (https://www.statista.com/statistics/7 34171/pharmacies-ranked-by-rx-market-share-in-us/). We utilized the FDA label to calculate the cost per 30-day period based on the quantity of tablets or other specified dose units after determining the price per tablet, milliliter, or vial. To estimate the annual cost, we multiplied this figure by 12 (months). The daily cost would be calculated by multiplying the dosage per tablet by two, as shown on the FDA label, and the monthly charge would be calculated by multiplying this product by thirty. For instance, 5 mg twice day of axitinib (Inlyta) is the dosage used to treat renal cell carcinoma. Each pill costs $320 or $640 per day for 30 days, which adds up to $19,200 per month (rounded to $19,000). To calculate the daily cost, we multiplied the daily rate by 21 days and divided the result by 28 if the dose was for 21 days with a seven-day rest interval. For the first 21 days of every 28-day cycle, the dosage of cobimetinib (Cotellic) is 60 mg. $117 times three is $351/day for 21 days ($7371), which is then divided by 28 ($263/day) times 30, or around $8000 each month. Any private or government insurance coverage, which might cover the whole cost or, more likely, a portion of our estimated price, is not included in our technique. For instance, under Medicare Part D in the United States, patients must pay between 25% and 30% of the list price for medications that cost more than $670 per month. For those with Medicare, Medicare Part D is an optional outpatient prescription medication coverage offered by commercial companies under a contract with the federal government. Generic versions of some medications are available, which may significantly reduce the price. For instance, Gleevec (imatinib) costs over $4200 each month, although its generic equivalent costs only $60. Approximately two-thirds of protein kinase inhibitors that have received FDA approval are classified as orphan drugs (Table 3). A pharmaceutical product created to address uncommon medical disorders is known as an orphan medication. In order to be eligible for orphan medication classification in the US, there must be less than 200,000 prospective patients overall. The goal of orphan drug classification is to encourage the development of medications for people with rare illnesses. The idea behind orphan drug classification is that because of the tiny number of patients afflicted, it would not be economical to create such treatments without government aid. The benefits of being classified as an orphan medicine for pharmaceutical firms include improved commercial exclusivity (up to seven years following regulatory approval), exemptions from U.S. Food and medicine Administration user fees, research funding for completing clinical studies, and a 25% tax credit.

## 5. Cost of FDA-approved small molecule protein kinase blockers

According to Table 3, the median monthly cost of authorized kinase antagonists used to treat neoplastic diseases is $17,000, with an average of $17,900. Futibatinib ($44,000 a month), an irreversible antagonist authorized for the treatment of bile duct tumors containing FGFR2 fusion proteins, is among the priciest FDA-approved kinase inhibitors [82]. A different medication administered for the Pemigatinib is used to treat bile duct tumors that target FGFRs; it costs $27,000 a month. Clinical trial results do not prefer one medication over another [83], hence the price difference has nothing to do with clinical effectiveness. Although the sale of this FGFR inhibitor has been stopped in the United States, infigratinib was also authorized for the treatment of this rare condition [84]. The cost of nintedanib, a FGFR antagonist used to treat idiopathic pulmonary fibrosis, is $12,000, while erafitinib, a FGFR1/2/3/4 blocker used to treat urothelial bladder malignancies, is $21,000 for 30 days (Table 4). These four medications have an average monthly cost of $18,000. One of the most prevalent kinase targets, the EGFR (ErbB) family of receptor protein-tyrosine kinases, is the target of nine of the FDA-approved small molecule kinase inhibitors. With an expected 240,000 new cases in 2023 [85], lung cancer is one of the most common diseases in the United States, with around 85% of those instances being non-small cell lung cancer (NSCLC). For individuals with limited illness, surgery is the main therapy option [86]. Platinum cytotoxic treatment is utilized in individuals with low expression of PD-L1 who have advanced or non-localized illness. When PD-L1 expression is high, pembrolizumab (Keytruda) may be administered alone. Patients with EGFR mutations are treated with small molecule kinase inhibitors. There are six of these medications: osimertinib ($31,000, 2015), dacomitinib ($17,000, 2018), mobocertinib ($28,000, 2021), erlotinib ($8100, 2004), gefitinib ($7500, 2003), and afatinib ($11,000 a month, approved in 2013) (Table 5). Second- and third-generation inhibitors of EGFR and its drug-resistant mutations (L858R/T790M, C797S, EGFR ex20ins) were developed in response to the almost universal development of drug resistance to gefitinib and erlotinib [87]. For patients with EGFR exon 20 insertion mutations, the more costly mobocertinib is advised for therapy; for patients with EGFR exon 19 deletions or exon 21 L858R mutations, osimertinib, an irreversible targeted covalent inhibitor (TCI) [27], is advised [88]. In the US, breast cancer is the most prevalent disease to be diagnosed in women and is a major source of

Indo-American Journal of Life Sciences and Biotechnology

morbidity and death [85]. With an incidence of 298,000 new cases in women annually, breast cancer is more common than lung cancer. Triple negative breast cancer (TNBC), HER2-positive/hormone-receptor positive, and HR-positive/HER2-negative are the three molecularly and clinically different subtypes of breast cancer that are not mutually exclusive, as previously mentioned. Patients with metastatic breast cancer are continuing to live longer because to supportive care and more effective treatments. Surgery, radiation treatment, cytotoxic therapy, and targeted therapies are used to treat patients with breast cancer [86]. About 15% of all breast cancers that are diagnosed are HER2-positive. Ado-trastuzumab emtansine (T-DM1) is a second-line treatment for HER2-positive illness, whereas docetaxel/-transtuzumab/pertuzumab is the first-line treatment. T-DM1 is a HER2-antibody drug combination that binds a HER2 monoclonal antibody to the microtubule inhibitor (DM1). The FDA has authorized tucatinib/trastuzumab/capecitabine as a third-line therapy. Tucatinib, a reversible HER2/ErbB2 antagonist that costs $12,000 per month, was authorized in 2020 as a second or third line combination therapy for patients with HER2-positive breast cancer that cannot be cured, including those who have brain metastases, which affect around one-third of patients. Additionally, it has been authorized in 2023 for the second-line combination treatment of metastatic colorectal cancer that is HER2-positive. Lapatinib ($9000/month) is a reversible inhibitor of EGFR/HER2 that was authorized in 2018 with a black box warning about hepatotoxicity, and neratinib ($22,000/month) is an irreversible inhibitor of EGFR/- HER2/HER4 that was FDA-approved in 2020. Though less often used than the tucatinib combination, these two medications are authorized for third-line therapy of metastatic HER2-positive breast cancer when combined with capecitabine (Table 5). Gefitinib, a first-generation antagonist, and osimertinib, a third-generation blocker, are both authorized for the treatment of non-small

**Table 3**

Monthly and yearly cost of FDA-approved targeted small molecule protein kinase inhibitors.

| **Neoplastic Diseases** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Drug | Target | [a]Kinase family | Therapeutic indications[b] | [c]Orphan | [d]Dose/ mg per day | [e]Cost/ 30 days | Cost/ year | Generic |
| Abemaciclib | CDK4/6 | S/T | HER2-positive breast cancer, both monotherapy and combination therapy | N | 400* | $15,000 | $180,000 | Y |
| Acalabrutinib | BTK | NRY | Mantle cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma | Y | 200* | $14,000 | $168,000 | N |
| Afatinib | ErbB1/2/4 | RY | NSCLC (non-small cell lung cancer) and squamous NSCLC | Y | 40 | $11,000 | $132,000 | Y |
| Alectinib | ALK, RET | RY | ALK-positive NSCLC | Y | 1200* | $8400 | $100,800 | N |
| Asciminib | Bcr-Abl | NRY | Third-line Ph⁺ chronic myelogenous leukemia (CML) and CML with *T315I* mutations | Y | 80 | $10,000 | $120,000 | N |
| Avapritinib | PDGFRR, Kit | RY | GIST (gastrointestinal stromal tumors) with *PDGFRA* exon 18 mutations | Y | 300 | $37,000 | $444,000 | N |
| Axitinib | VEGFR1/2/3 | RY | Advance renal cell carcinoma | N | 300 | $19,000 | $228,000 | Y |
| Binimetinib | MEK1/2 | T/Y | Melanoma with *BRAF V600E* or *V600K* mutations with encorafenib | Y | 90* | $5100 | $61,200 | N |

Indo-American Journal of Life Sciences and Biotechnology

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Bosutinib | BCR-Abl | NRY | Chronic myelogenous leukemia | Y | 500 | $19,000 | $228,000 | N |
| Brigatinib | ALK | RY | ALK-positive NSCLC | Y | 180 | $6000 | $72,000 | N |
| Cabozantinib | VEGFR1/2/3, RET | RY | Advanced medullary thyroid cancer, renal cell and hepatocellular carcinomas | Y | 40 | $7000 | $84,000 | N |
| Capivasertib | AKT | RY | Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer | N | 800 * | ? | ? | N |
| Capmatinib | MET | RY | NSCLC with *MET* exon 14 skipping mutations | Y | 800* | $23,000 | $276,000 | N |
| Ceritinib | ALK | RY | ALK-positive NSCLC resistant to crizotinib | Y | 750 | $21,000 | $252,000 | N |
| Cobimetinib | MEK1/2 | T/Y | Melanoma with *BRAF V600E* or *V600K* mutations with vemurafenib | Y | 60 | $8000 | $96,000 | N |
| Crizotinib | ALK, MET | RY | ALK- or ROS1-postive NSCLC, anaplastic large cell lymphoma, inflammatory myofibroblastic tumor | Y | 500* | $20,000 | $240,000 | N |
| Dabrafenib | B-Raf | S/T | *BRAF*-mutation positive melanoma; NSCLC with *BRAF V600E* mutations; anaplastic thyroid cancer with *BRAF V600E* mutations | Y | 300* | $6800 | $81,600 | N |
| Dacomitinib | ErbB1/2/4 | RY | *EGFR*-mutant NSCLC | Y | 45 | $17,000 | $204,000 | N |
| Dasatinib | BCR-Abl | NRY | Ph+ chronic myelogenous leukemia or acute lymphoblastic leukemia | Y | 100 | $17,000 | $204,000 | Y |
| Encorafenib | B-Raf | S/T | *BRAF V600E* or *V600K* mutation positive melanoma with binimetinib; *BRAF V600E* mutation positive colorectal cancer with cetuximab | Y | 450 | $16,000 | $192,000 | N |
| Entrectinib | TRKA/B/C, ROS1, ALK | RY | Solid tumors with NTRK fusion proteins, ROS1-positive NSCLC | Y | 600 | $18,000 | $216,000 | N |
| Erdafitinib | FGFR 1/2/3/4 | RY | Urothelial bladder cancer | Y | 8 | $21,000 | $252,000 | N |

Indo-American Journal of Life Sciences and Biotechnology

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Erlotinib | EGFR | RY | NSCLC, pancreatic cancer | N | 150 | $8100 | $97,200 | Y |
| Everolimus | FKBP12/ mTOR | S/T | HER2-negative breast cancer, pancreatic neuroendocrine tumors, renal cell carcinoma, angiomyolipoma, subependymal giant cell astrocytoma | N | 10 | $19,000 | $228,000 | N |
| Fedratinib | JAK2 | NRY | Myelofibrosis | Y | 400 | $25,000 | $300,000 | N |
| Fruquintinib | VEFGR1/2/3 | RY | Metastatic colorectal cancer | N | 5 | ? | ? | N |
| Futibatinib | FGFR2 | RY | Cholangiocarcinoma (bile duct cancer) with FGFR2 fusion proteins or other rearrangements | Y | 20 | $44,000 | $528,000 | N |
| Gefitinib | EGFR | RY | NSCLC with exon 19 deletions or exon 21 substitutions | Y | 250 | $7500 | $90,000 | Y |
| Gilteritinib | Flt3 | RY | *FLT3*-mutation positive acute myeloid leukemia | Y | 120 | $26,000 | $312,000 | N |
| Ibrutinib | BTK | NRY | Chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma, graft vs. host disease | N | 560 | $16,000 | $192,000 | Y |
| Imatinib | BCR-Abl, Kit, PDGFR | NRY | $Ph^+$ chronic myelogenous leukemia or acute lymphoblastic leukemia, aggressive systemic mastocytosis, chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, gastrointestinal stromal tumors, myelodysplastic/ myeloproliferative disease | N | 400 | $4200 | $50,400 | Y |
| Infigratinib | FGFR2/1/3/4 | RY | Cholangiocarcinoma with FGFR2 fusions or other rearrangements | Y | 125 | $12,000 | $144,000 | N |
| Lapatinib | ErbB1/2/ HER2 | RY | HER2-positive breast cancer | N | 1250 | $9,000 | $108,000 | N |
| Larotrectinib | TRKA/B/C | RY | Solid tumors with NTRK fusion proteins | N | 200* | $39,000 | $468,000 | N |
| Lenvatinib | VEGFR, RET | RY | Differentiated thyroid cancer, hepatocellular carcinoma, renal cell carcinoma, endometrial carcinoma | N | 24 | $23,000 | $276,000 | Y |
| Lorlatinib | ALK | RY | ALK-positive NSCLC | Y | 100 | $19,000 | $228,000 | N |

Indo-American Journal of Life Sciences and Biotechnology

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Midostaurin | Flt3, PDGFRs | RY | *FLT3*-mutation positive acute myeloid leukemia in combination with cytarabine and daunorubicin | Y | 200* | $22,000 | $264,000 | N |
| Mobocertinib | EGFR | RY | NSCLC bearing exon 20 insertions | Y | 160 | $28,000 | $336,000 | N |
| Momelotinib | JAK2 | NRY | Myelofibrosis patients with anemia | Y | 200 | $25,000 | $300,000 | N |
| Neratinib | ErbB2/HER2 | RY | HER2-positive breast cancer | N | 240 | $22,000 | $264,000 | N |
| Nilotinib | BCR-Abl | NRY | Ph⁺ chronic myelogenous leukemia | Y | 600* | $9600 | $115,200 | N |

(*continued on next page*)

**Table 3** (*continued*)

| **Neoplastic Diseases** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Osimertinib | EGFR T970M | RY | NSCLC with exon 19 deletions or exon 21 substitutions | Y | 80 | $31,000 | $372,000 | N |
| Pacritinib | JAK2 | NRY | Myelofibrosis | Y | 100 | $12,000 | $144,000 | N |
| Palbociclib | CDK4/6 | S/T | Breast cancer (HER2-positive or negative) combination therapy | N | 125 | $16,000 | $192,000 | Y |
| Pazopanib | VEGFR1/2/3 | RY | Renal cell carcinoma, soft tissue sarcomas | N | 800 | $16,000 | $192,000 | Y |
| Pemigatinib | FGFR2/1/3 | RY | Cholangiocarcinoma with FGFR2 fusions or other rearrangements | Y | 13.5 | $27,000 | $324,000 | N |
| Pexidartinib | CSF1R, Kit | RY | Tenosynovial giant cell tumors | Y | 800* | $23,000 | $276,000 | N |
| Pirtobrutinib | BTK | NRY | Mantle cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma | Y | 200 | $22,000 | $264,000 | N |
| Ponatinib | BCR-Abl | NRY | Ph⁺ chronic myelogenous leukemia or acute lymphoblastic leukemia | N | 45 | $21,000 | $252,000 | N |
| Pralsetinib | RET | RY | RET-fusion protein NSCLC, RET mutant medullary thyroid cancer, RET fusion thyroid cancer | Y | 400 | $23,000 | $276,000 | N |
| Quizartinib | Flt3 | RY | *FLT3* internal tandem duplication positive acute myelogenous leukemia in combination with cytarabine and daunorubicin | Y | 35.4 | $34,000 | $408,000 | N |
| Regorafenib | VEGFR1/2/ | RY | Colorectal cancer, hepatocellular carcinoma, gastrointestinal | N | 160 | $14,000 | $168,000 | N |

Indo-American Journal of Life Sciences and Biotechnology

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 | | stromal tumor | | | | | |
| Repotrectinib | ROS1 | RY | ROS1-postive lung cancer | N | 320 * | ? | ? | N |
| Ribociclib | CDK4/6 | S/T | Breast cancer (HER2-positive or negative) combination therapy | N | 600 | $20,000 | $240,000 | N |
| Ripretinib | KIT/PDGFR | RY | Gastrointestinal stromal tumor | Y | 150 | $41,000 | $492,000 | N |
| Ruxolitinib | JAK1/2/3, TYK2 | NRY | Myelofibrosis, polycythemia vera, atopic dermatitis (applied topically) | Y | 20* | $18,000 | $216,000 | N |
| Selpercatinib | RET | RY | RET gene fusion NSCLC, thyroid cancer, and solid tumors | Y | 320 * | $22,000 | $264,000 | N |
| Selumetinib | MEK1/2 | T/Y | Neurofibromatosis type 1 | Y | 80* | $14,000 | $168,000 | N |
| Sorafenib | VEGFR1/2/3 | RY | Hepatocellular carcinoma, renal cell carcinoma, differentiated thyroid cancer | Y | 800* | $23,000 | $276,000 | N |
| Sunitinib | VEGFR2, et al. | RY | Gastrointestinal stromal tumor, renal cell carcinoma, pancreatic neuroendocrine tumor | N | 50 | $15,000 | $180,000 | Y |
| Temsirolimus | FKBP12/mTOR | S/T | Advanced renal cell carcinoma | Y | 25++ | $6400 | $76,800 | |
| Tepotinib | MET | RY | *MET* mutant NSCLC | Y | 450 | $24,000 | $288,000 | N |
| Tivozanib | VEGFR2 | RY | Renal cell carcinoma | Y | 1.34 | $30,000 | $360,000 | N |
| Trametinib | MEK1/2 | T/Y | Melanoma with *BRAF V600E* or *V600K* mutations with dabrafenib; NSCLC with BRAF V600E mutations with dabrafenib | Y | 2 | $14,000 | $168,000 | N |
| Trilaciclib | CDK4/6 | S/T | Chemotherapy-induced myelosuppression when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer | N | 960 | $24,000 | $244,000 | N |
| Tucatinib | ErbB2/HER2 | RY | HER2-positive breast cancer and colon cancer | Y | 600* | $12,000 | $144,000 | N |
| Vandetanib | VEGFR2 | RY | Medullary thyroid cancer | N | 300 | $9000 | $108,000 | N |
| Vemurafenib | B-Raf | S/T | *BRAF V600E* or *V600K* mutation positive melanoma with cobimetinib; Chester-Erdheim disease | Y | 1920* | $12,000 | $144,000 | N |
| Zanubrutinib | BTK | NRY | Mantle cell lymphoma | Y | 320* | $7000 | $84,000 | N |

Indo-American Journal of Life Sciences and Biotechnology

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Non-neoplastic Diseases | | | | | | | | |
| Abrocitinib | JAK1 | NRY | Atopic dermatitis | N | 100 | $5600 | $67,200 | N |
| Baricitinib | JAK2/1 | NRY | Rheumatoid arthritis | N | 2 | $2500 | $30,000 | Y |
| Belumosudil | ROCK2 | S/T | Graft vs. host disease | Y | 200 | $17,000 | $204,000 | N |
| Deucravacitinib | TYK2 | NRY | Psoriasis | N | 0.01 | $6500 | $78,000 | N |
| Fostamatinib | SYK | NRY | Chronic immune thrombocytopenia | Y | 300* | $14,000 | $168,000 | N |
| Netarsudil | ROCK1/2 | S/T | Glaucoma | N | 0.2 | $200 | $2400 | N |
| Nintedanib | FGFR1/2/3 | RY | Idiopathic pulmonary fibrosis | Y | 300* | $12,000 | $144,000 | Y |
| Ritlecitinib | JAK3 | NRY | Alopacia areata | Y | 50 | $4200 | $50,400 | N |
| Sirolimus | FKBP12/mTOR | S/T | Kidney transplant, lymphangioleiomyomatosis | N | 2 | $2,000 | $24,000 | Y |
| Tofacitinib | JAK3 | NRY | Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis | N | 10* | $5,000 | $60,000 | Y |
| Upadacitinib | JAK1 | NRY | Rheumatoid arthritis, psoriatic arthritis, atopic dermatitis | N | 15 | $6,000 | $72,000 | N |

Protein-serine/threonine protein kinase (S/T); dual specificity protein kinase (T/Y); receptor protein-tyrosine kinase (RY); and non-receptor protein-tyrosine kinase (NRY). b Ph+, positive for the Philadelphia chromosome. * denotes that half of the recommended dosage should be taken twice day; c N, No; Y, Yes. ** denotes once every seven days. The medication costs for a 30-day period were derived by combining the dose information from the FDA label with representative US pharmacy prices from Pharmacychecker.com (price per pill or prescription unit). The 30-day cost was multiplied by 12 (months) to get the yearly medicine cost.

**Table 4**

FDA-approved small molecule FGFR family blockers.

| Drug | Target | Disease | Cost/30 days | Cost/year | Generic | Approved |
|---|---|---|---|---|---|---|
| Erdafitinib | FGFR1/2/3/4 | Urothelial bladder cancer | $21,000 | $252,000 | No | 2019 |
| Infigratinib | FGFR2/1/3/4 | Cholangiocarcinoma with FGFR2 fusions or other rearrangements | $12,000 | $144,000 | No | 2021 |
| Nintedanib | FGFR1/2/3 | Idiopathic pulmonary fibrosis | $12,000 | $144,000 | Yes | 2014 |
| Pemigatinib | FGFR2/1/3 | Cholangiocarcinoma with FGFR2 fusions or other rearrangements | $27,000 | $324,000 | No | 2020 |

**Table 5**

FDA-approved small molecule EGFR family blockers.

| Drug | Target | Disease | Cost/30 days | Cost/year | Generic | Approved |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| Afatinib | ErbB1/2/4 | NSCLC and squamous NSCLC | $11,000 | $132,000 | Yes | 2013 |
| Capivasertib | AKT | HER2-positive breast cancer | ? | ? | No | 2023 |
| Dacomitinib | ErbB1/2/4 | *EGFR*-mutant NSCLC | $17,000 | $204,000 | No | 2018 |
| Erlotinib | EGFR | NSCLC, pancreatic cancer | $8100 | $97,200 | Yes | 2004 |
| Gefitinib | EGFR | NSCLC with exon 19 deletions or exon 21 substitutions | $7500 | $90,000 | Yes | 2003 |
| Lapatinib | ErbB1/2 | HER2-positive breast cancer | $9000 | $108,000 | No | 2007 |
| Mobocertinib | EGFR | NSCLC bearing exon 20 insertions | $28,000 | $336,000 | No | 2021 |
| Neratinib | ErbB2/HER2 | HER2-positive breast cancer | $22,000 | $264,000 | No | 2017 |
| Osimertinib | EGFR T790M | NSCLC with exon 19 deletions or exon 21 substitutions | $31,000 | $372,000 | No | 2015 |
| Tucatinib | ErbB2/HER2 | HER2-positive breast cancer and colorectal cancer | $12,000 | $144,000 | No | 2020 |

exon 19 deletions or exon 21 changes in cell lung carcinoma (Table 5). The former costs $31,000, which is almost four times as much as the later, which costs $7500. When treating non-small cell lung cancer with EGFR gene mutations, osi-mertinib ($31,000 per month), a more recent third-generation EGFR kinase inhibitor, has the same clinical effect as gefitinib; however, its progression-free survival is noticeably longer than that of the gefitinib group, and its adverse reaction rate is lower [89]. Additionally, newly authorized medications often have higher prices than previously approved medications. The nine EGFR family inhibitors cost around $16,200 per month on average.

One of the most prevalent kinase targets, the JAK family of non-receptor protein-tyrosine kinases, is the target of nine of the FDA-approved small molecule kinase inhibitors. According to Table 6, the average monthly cost of the five medications used to treat inflammatory disorders is $4600, whereas the average monthly cost of the four medications used to treat neoplastic diseases is $19,000. Philadelphia chromosome–negative myeloproliferative neoplasms are a collection of diverse hematopoietic system illnesses that include myelofibrosis, polycythemia vera, and essential thrombocythemia. According to estimates, the prevalence of essential thrombocytopenia, polycythemia vera, and myelofibrosis in the US is around 13,000, 134,000, and 148,000, respectively, making them orphan illnesses [90]. There is no preference for one medication over another in clinical trials. Fedratinib does, however, include a black box warning for causing encephalopathy. Despite its recent approval, pacritinib has the lowest cost among the bunch, which is remarkable.

Corticosteroids, disease-modifying anti-rheumatic medications (DMARDs), and non-steroidal anti-inflammatory medicines (NSAIDs) are the three major pharmacological groups that are often used to treat rheumatoid arthritis [91]. DMARDs might take weeks or months to show a clinical impact, while NSAIDs and corticosteroids work quickly. Anakinra, certolizumab pegol, etanercept, golimumab, infliximab, leflunomide, rituximab, sulfasalazine, tocilizumab, abatacept, adalimumab, and methotrexate are examples of DMARDs. Since the late 1990s, the first-line disease-modifying anti-rheumatic medication for rheumatoid arthritis has been methotrexate. Nitric oxide synthase is produced when methotrexate inhibits dihydrobiopterin reductase, which stops dihydrobiopterin (BH2) from being reduced to tetrahydrobiopterin (BH4).

T cell uncoupling and heightened apoptosis sensitivity, which reduces immunological responses. Adalimumab, certolizumab, etanercept, golimumab, infliximab, and sulfasalazine are among the TNF inhibitors that the FDA has authorized. The immunomodulatory medication leflunomide may work by preventing the mitochondrial enzyme dihydroorotate dehydrogenase, which is essential for the de novo production of uridine monophosphate (UMP), from doing its job. Abatacept inhibits interaction with CD28 on T cells via binding to the costimulatory molecules CD80 and CD86 on antigen-presenting cells (APC). Rituximab increases cell lysis by targeting CD20, preserving hematopoietic and plasma cells that do not have this surface antigen. By binding to the IL-1 receptor, the recombinant, non-glycosylated version of IL-1Ra anakinra suppresses and competes with IL-1, therefore lowering the inflammatory response in individuals with rheumatoid arthritis. Particularly binding to soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), tocilizumab has been shown to block IL-6-mediated signaling via these receptors. Younger patients with active illness who are resistant to many types of DMARDs and who do not have a substantial cardiovascular

risk may benefit from JAK blockers, according to Harrington et al. [91]. However, they contend that, given the increased abundance of safety data on tumor necrosis factor inhibitors, tocilizumab, and abatacept in actual clinical practice, it is difficult to defend their usage as a first-line advanced treatment in the majority of patients. Furthermore, since generic versions won't be available for a while, JAK antagonists will continue to be a more costly treatment choice in many nations. With a frequency of 0.5% to 1.0% of the population, rheumatoid arthritis is much more common in the US and Europe than neoplastic illnesses; in Asia, the incidence is somewhat lower.

In the United States, an estimated 82,000 cases of renal cancers occur annually [85]. The three most prevalent subtypes are chromophobic RCC (5%), papillary RCC (10%), and clear cell RCC (75%). Patients with renal cell carcinoma have a five-year survival rate of around 85% for stage I cancer, 60% for stage II, 25% for stage III, and 5% for stage IV, depending on the clinical stage of the malignancy. The U.S. Food and Drug Administration (FDA) has authorized the following targeted medicines for the treatment of metastatic renal cell carcinoma: axitinib, pazopanib, sunitinib, sorafenib,

**Table 6**

FDA-approved small molecule JAK family blockers.

| Drug | Target Generic | Disease Approved | Cost/30 days | Cost/year | | |
|---|---|---|---|---|---|---|
| Neoplastic Diseases | | | | | | |
| Fedratinib | JAK2 | Myelofibrosis | $25,000 | $300,000 | No | 2019 |
| Momelotinib | JAK2 | Myelofibrosis patients with anemia | $25,000 | $300,000 | No | 2023 |
| Pacritinib | JAK2 | Myelofibrosis | $12,000 | $144,000 | No | 2022 |
| Ruxolitinib | JAK1/2/3, TYK2 | Myelofibrosis, polycythemia vera, atopic dermatitis (applied topically) | $18,000 | $216,000 | No | 2011 |
| Non-neoplastic Diseases | | | | | | |
| Abrocitinib | JAK1 | Atopic dermatitis | $5600 | $67,200 | No | 2022 |
| Baricitinib | JAK2/1 | Rheumatoid arthritis | $2500 | $30,000 | Yes | 2018 |
| Ritlecitinib | JAK3 | Alopecia areata | $4200 | $50,400 | No | 2023 |
| Tofacitinib | JAK3 | Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis | $5000 | $60,000 | Yes | 2012 |

Jak1 Upadacitinib Atopic dermatitis, psoriatic arthritis, and rheumatoid arthritis No. 2019: $6000 $72,000 Bevacizumab, tivozanib, lenvatinib, and cabozantinib [92]. Based on their mode of action, these agents may be divided into the following classes. Small-molecule protein-tyrosine kinase blockers include lenvatinib, tivoza-nib, cabozantinib, axitinib, sunitinib, pazopanib, and sorafenib. By directly blocking receptors like the vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), or Fms-like tyrosine kinase receptor-3 (Flt3), these substances prevent angiogenesis. A monoclonal antibody called bevacizumab binds directly to vascular endothelial growth factor (VEGF) and stops it from binding to VEGF receptors. Furthermore, the FDA has authorized a number of biologic agents for the treatment of metastatic renal cell carcinoma, including (i) avelumab (Bavencio) with axitinib, (ii) ipilimu-mab (Yervoy), a monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4 in combination with nivolumab, (iv) the PD-1 immune checkpoint inhibitor pembrolizumab (Keytruda), and (iv) nivolumab (Opdivo), both of which are PD-1 immune checkpoint inhibitors. Cabozantinib was linked to the greatest progression-free survival for the first-line treatment, followed by pembrolizumab + axitinib and avelumab + axitinib [92]. When evaluating progression-free survival for second-line therapy, cabozantinib was shown to be the most successful treatment choice. The average monthly cost of the six VEGFR blockers used to treat renal cell carcinoma was $17,300, with a median of $16,000

Indo-American Journal of Life Sciences and Biotechnology

(Table 7). The most costly drug was tivozanib ($30,000/month), while cabozantinib ($7000/month) was the least expensive. Cabozantinib, an older and less costly medication, works better in this case than the more recent and costly ones. Axitinib, which is often recommended, costs $19,000 a month. VEGFR inhibitors' efficacy and safety profile in treating metastatic renal cell cancer were compared by Krawczyk et al. [93]. The efficacy of VEGFR protein-tyrosine kinase inhibitors used as monotherapy was the same at the first level. The best treatment alternatives were tivozanib ($30,000/month) and sorafenib ($23,000/month) when taking into account the incidence of limiting adverse events and the safety profile. These researchers found that the safety profiles were poorer when a targeted protein-tyrosine kinase inhibitor was used in conjunction with nivolumab, pembrolizumab, or avelumab (a PD-L1 blocker, Padcev). However, as long as any possible negative effects are properly monitored and addressed as needed, these combinations are clinically successful.
Leukocytosis, or an increased white blood cell count, is a hallmark of chronic myelogenous leukemia, a malignant hematological illness that progresses slowly [58]. About 15% of all leukemia cases are chronic myelogenous leukemia. According to estimates, there will be 8930 new cases (5190 males and 3740 females) and 1310 deaths (780 men and 530 females) in the US in 2023 [85]. Prior to the development of small molecule protein kinase antagonists, CML progressed naturally over three to five years, either from a stable or chronic phase to an accelerated phase or to a swiftly lethal blast crisis [58]. Chronic myelogenous leukemia diagnosis

is often predicated on the identification of the Philadelphia chromosome (Ph), as established by fluorescence in situ hybridization (FISH) examination of bone marrow samples or traditional cytogenetic (karyotyping) analysis. Among cancers, chronic myelogenous leukemia is distinct in that, at least during the stable phase, it seems to be caused by a single significant biochemical flaw. On the other hand, a number of genetic and biochemical abnormalities cause the majority of cancers. Therefore, the activated non-receptor protein-tyrosine kinase, or BCR-Abl oncoprotein, is a distinct therapeutic target that varies between leukemic and normal cells. After the FDA authorized imatinib in 2001 for the treatment of CML, the development of further protein kinase antagonists was encouraged by the effectiveness of this small molecule protein kinase inhibitor in the treatment of cancer [26]. Compared to other protein kinase inhibitors used to treat other neoplasms, FDA-approved medications for the treatment of chronic myelogenous leukemia have much greater clinical efficacy [58,68]. Patients with CML have a yearly death rate from the condition of 0.5% or less when compared to an age-matched normal population; in other words, the medication normalizes these individuals' lifespans. In addition to ponatinib (third generation), which is approved for resistant disease with a T315I BCR-Abl gatekeeper mutation or after at least two other protein-tyrosine kinase inhibitors have failed, the FDA has approved imatinib (first generation), dasatinib, nilotinib, and bosutinib (second generation) for frontline therapy. Now licensed as a third-line therapy for CML and a first-line treatment for individuals with the T315I mutation, asciminib is a STAMP inhibitor that specifically targets the Abl myristoyl pocket (Table 8 lists the cost of these medications). The less costly agents include imatinib and nilotinib. The monthly cost of asciminib for chronic phase CML is $19,500, assuming a daily dose of 80 mg. For individuals with the T315I mutation, however, the recommended dose is 200 mg twice day or 10 pills daily, which comes at a cost of $326 every tablet, $3260 per day, $97,800 per month, or $1.17 million annually. The annual out-of-pocket expenses, including a 25% patient copayment, exceed $292,000. A mere 12 percent of American households earn more than $200,000 annually, according to figures from the U.S. Census. For individuals with the T315I mutation, the cost of the medication is unaffordable.
Whenever feasible, current therapy seeks to either (i) increase patient survival or (ii) achieve treatment-free remission (TFR) [94]. In order to achieve treatment-free remission, all medications that inhibit BCR-Abl must be stopped. Frontline therapy with dasatinib, nilotinib, bosutinib, or imatinib is helpful for promoting survival. It is currently routine practice to switch therapies as soon as resistant illness is observed if imatinib treatment is used as frontline therapy. The fact that imatinib is a generic medication that is less expensive than other medicines is one justification for its early use. The patient's age and comorbidities, as well as an assessment of potential mutations in the Abl kinase domain, inform the selection of the second-line treatment. Bosutinib side effects include liver and renal problems, as well as diarrhea (10–30%, moderate, self-limited). Pleural effusions may result with dasatinib (10–15%),

Indo-American Journal of Life Sciences and Biotechnology

**Table 7**
FDA-approved small molecule VEGFR family blockers.

| Drug | Target | Disease | Cost/30 days | Cost/year | Generic | Approved |
|---|---|---|---|---|---|---|
| Axitinib | VEGFR1/2/3 | Advanced renal cell carcinoma | $19,000 | $228,000 | Yes | 2012 |
| Cabozantinib | VEGFR1/2/3, RET | Advanced medullary thyroid cancer, renal cell and hepatocellular carcinomas | $7000 | $84,000 | No | 2012 |
| Fruquintinib | VEGFR1/2/3 | Metastatic colorectal cancer | ? | ? | No | 2023 |
| Lenvatinib | VEGFR, RET | Differentiated thyroid cancer, hepatocellular, renal cell, and endometrial carcinoma | $23,000 | $276,000 | Yes | 2015 |
| Pazopanib | VEGFR1/2/3 | Renal cell carcinoma, soft tissue sarcomas | $16,000 | $192,000 | Yes | 2009 |
| Regorafenib | VEGFR1/2/3 | Colorectal cancer, hepatocellular carcinoma, gastrointestinal stromal tumor | $14,000 | $168,000 | No | |
| Sorafenib | VEGFR1/2/3 | Hepatocellular carcinoma, renal cell carcinoma, differentiated thyroid cancer | $23,000 | $276,000 | No | 2005 |
| Sunitinib | VEGFR2 et al. | Gastrointestinal stromal tumor, renal cell carcinoma, pancreatic neuroendocrine tumors | $15,000 | $180,000 | Yes | 2006 |
| Tivozanib | VEGFR2 | Renal cell carcinoma | $30,000 | $360,000 | No | 2021 |
| Vandetanib | VEGFR2 | Medullary thyroid cancer | $9000 | $108,000 | No | 2011 |

**Table 8**
FDA-approved small molecule Abl and BTK blockers.

| Drug | Target | Disease | Cost/30 days | Cost/year | Generic | Approved |
|---|---|---|---|---|---|---|
| **Abl Antagonists** | | | | | | |
| Asciminib | BCR-Abl | Third-line Ph⁺ chronic myelogenous leukemia (CML) and CML with *T315I* mutations | $19,500 | $234,000 | No | 2021 |
| Bosutinib | BCR-Abl | Chronic myelogenous leukemia | $19,000 | $228,000 | No | 2012 |
| Dasatinib | BCR-Abl | Ph⁺ chronic myelogenous leukemia or acute lymphoblastic leukemia | $17,000 | $204,000 | Yes | 2006 |
| Imatinib | BCR-Abl | Ph⁺ chronic myelogenous leukemia or acute lymphoblastic leukemia, aggressive systemic mastocytosis, chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, hypereosinophilic | $6000 | $72,000 | Yes | 2001 |

Indo-American Journal of Life Sciences and Biotechnology

| | | | | | |
|---|---|---|---|---|---|
| | | syndrome, gastrointestinal stromal tumors, | | | |
| Nilotinib | BCR-Abl | myelodysplastic/myeloproliferative disease Ph⁺ chronic myelogenous leukemia | $9600 | $115,200 | No 2007 |
| Ponatinib | BCR-Abl | Ph⁺ chronic myelogenous leukemia or acute lymphoblastic leukemia | $21,000 | $252,000 | No 2012 |
| **BTK Antagonists** | | | | | |
| Acalbrutinib | | Mantle cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma | $14,000 | $168,000 | No 2017 |
| Ibrutinib | | Chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma, graft vs. host disease | $16,000 | $192,000 | Yes 2013 |
| Pirtobrutinib | | Mantle cell lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma | $22,000 | $264,000 | No 2023 |
| Zanubrutinib | | Mantle cell lymphoma | $7000 | $84,000 | No 2019 |

sporadic pulmonary hypertension (1–2%) and myelosuppression (10–20%). Treatment with nilotinib may result in pancreatitis, hyperglycemia (10–15%), and worsen diabetes mellitus (5–10%).

**Table 9**

FDA-approved ALK and Flt3 blockers are tiny molecules. (1–3%). The most significant adverse effects of ponatinib are skin rashes (5–10%), pancreatitis (5%), vasospastic disease (10–15%), and hypertension (20–30%). Even though it produced the most severe

Authorized Generic negative side effects, ponatinib is the priciest BCR-Abl blocker. Younger patients should aim for a treatment-free remission in order to prevent lifelong therapy. The threshold for stopping medication therapy is a deep molecular response (DMR), which is characterized as a 4–4.5 log decrease in BCR-Abl-1 transcripts on the International Scale (the ratio of BCR-ABL1 transcripts to ABL1 transcripts). After two to three years of a profound molecular response, stopping medication is linked to a 50–60% treatment-free remission rate. A treatment-free remission is more than 80% likely to be achieved when this is done five years later. Patients react to the treatment recommended prior to medication discontinuation when remission is not attained. When targeted protein kinase therapy first emerged, the idea of remission without treatment was unimaginable [58]. The notion that CML might be treated with medication and kept at a low level was a pipe dream in the first ten years of the twenty-first century. Table 8 lists the average monthly cost of the six FDA-approved medications used to treat chronic myelogenous leukemia. The oldest (imatinib) is the least costly, costing $6000, while the average is almost $15,400. The average price of $15,400 is comparable to the average of $17,900 for all small molecule protein-kinase antagonists used to treat neoplastic disorders. However, generic imatinib costs $56 a month. The fact that these BCR-Abl antagonists turn CML into a chronic illness with a consistent revenue stream for years is advantageous to the pharmaceutical corporations. Approximately 5% of all lung cancer patients have ALK-positive lung cancer [95], which translates to 12,000 new cases in the US annually [85]. About one-fifth of patients with these lung tumors pass away within two years of diagnosis, and their median survival is about four and a half years. The five FDA-approved ALK inhibitors have an average monthly cost of $15,000 (Table 9), with brigatinib being the least costly and ceritinib being the most expensive. Cri-zotinib was the preferred medication for first-line usage since it was the first of these medications to get approval. In light of current clinical results,

As first-line treatments for ALK-positive NSCLC, alectinib and brigatinib are now preferred [96]. The fact that they are the least costly ALK antagonists is only a coincidence. All five medications are taken, and there is no predetermined schedule for the second, third, and subsequent lines of therapy. The drug crizotinib is utilized for conditions other than lung cancer that is ALK-positive. Furthermore, it was first created as a MET inhibitor, and the new disease targets may be reflected in its wider spectrum of targets

[55,57].

CDK4/6 protein-serine/threonine kinase inhibitors that are not receptors were approved in 2015 together with palbociclib, adding them to the arsenal against breast cancer (Table 10). In 2017, ribociclib and bemaciclib were introduced. These three medications have an average monthly cost of around $17,000, which is comparable to the average cost of all FDA-approved small molecule protein kinase inhibitors used to treat neoplasms. Palbociclib in conjunction with endocrine therapy was linked to better progression-free survival outcomes (20.0 months) in this "real-world" population of patients with HR+/HER2-metastasized breast cancer when compared to patients treated with letrozole alone in the first-line setting (11.9 months) [97]. Both ribociclib and abemaciclib combined with endocrine treatment increased overall survival, despite palbociclib's failure to do so. These results imply that the latter two medications need to be used instead of palbociclib. According to Siegel et al., there will be 89,070 new cases of in situ melanoma of the skin in 2023 (58,120 males and 39,490 females), and 7990 fatalities (5420 males and 2520 females) [85]. A combination of MEK1/2 and B-RAF inhibitors may be used to treat the about one in 25 instances of melanoma (3600) that will develop metastases, or spread to other regions of the body (Table 11). BRAF mutations are present in around half of melanoma cases [98]. All three medicine combinations—binimetinib and encorafenib ($21,100 per month), cobimetinib and vemurafenib ($19,500), and trametinib and dabrafenib ($20,800)—are almost equally effective and cost around the same. Clinical studies using a combination of medications are made easier by the fact that each of these combinations is the product of a single pharmaceutical firm (Table 11). In 2009, Genentech joined the Roche organization. A key player in B cell antigen receptor signaling is the Bruton non-receptor protein-tyrosine kinase (BTK), a lack of which causes X-linked agammaglobulinemia [99]. The term can stand for B cell tyrosine kinase since this enzyme is only found in B cells. After the B cell receptor is active, the Lyn and SYK protein kinases activate BTK. The Ras/RAF/MEK/ERK and NF-κB pathways are subsequently activated as a result of BTK's catalysis of phospholipase Cγ2 phosphorylation and activation. Both pathways contribute to the development of B cells that produce antibodies. A number of B cell neoplasms, such as Waldenstrom macroglobulinemia, chronic lymphocytic leukemia, and mantle cell lymphoma, exhibit dysregulation of B cell receptor signaling. Pirtobrutinib is a reversible BTK blocker, while acalabrutinib, ibrutinib, and zanu-brutinib are targeted covalent inhibitors that interact with BTK C481 (www.brimr.org/PKI/PKIs. htm). The first of these quartet to get approval, ibrutinib, is promiscuous and has a lot of adverse effects [100]. This substance is a strong inhibitor of Blk, JAK, EGFR, BMX, TXK, and ITK. Neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal discomfort, rash, nausea, bruises, exhaustion, bleeding, and pyrexia were the most frequent adverse reactions (≥20%) in patients with B-cell malignancies. Additionally, zanubrutinib is a strong inhibitor of BLK, EGFR, BMX, and TXK. Neutropenia, thrombocytopenia, reduced white blood cell count, anemia, upper respiratory tract infection, rash, bruises, diarrhea, and cough are among its most frequent side effects (≥ 20%). It seems that acalbrutinib is less effective at inhibiting the kinases that are accidental targets of both zanubrutinib and ibrutinib. The four FDA-approved BTK antagonists have an average monthly cost of $14,750; the newest medication, pirtobrutinib, is the most costly, while zanubrutinib is the least expensive (Table 8). Pirtobrutinib may have less negative effects than the other medications, despite the fact that they are all successful in treating mantle cell lymphoma.

Acute myeloid leukemia accounts for around one-third of all leukemia cases [85]. According to estimates, there will be 20,380 cases of acute myeloid leukemia in the US in 2023 (11,410 men and 8970 women), and 11,310 fatalities (6440 men and 4870 women) [85]. About 30% of AML patients survive for five years. About 30% of AML patients had mutations in the FLT3 gene. Among these alterations are point mutations in the tyrosine kinase domain (5%) and internal tandem duplications in the JM domain (25%). [101]. Three FDA-approved medications that only target mutant FLT3 had an average price of $21,700 (Table 9). The three medications now have almost comparable clinical efficacy. Apart from these three medications, sunitinib, sor-afenib, and pacritinib are also used to treat this hematological malignancy, and each has a role in treating AML that has a FLT3 mutation. Rare sarcomas of the digestive system, gastric stromal tumors (GIST) are usually caused by mutations in either PDGFRA (5–10%) or KIT (80%) [102]. For patients with KIT-mutation positive GIST, imatinib is the FDA-approved first-line therapy, sunitinib is the recommended second-line treatment, and regorafenib is the recommended third-line treatment [103]. Imatinib is the least priced medication since it is available in a generic form. Additional lines of therapy are required because of the mutations that take place throughout these therapies. As a result, avapritinib and ripretinib were developed and approved in 2020 [102,104]. These medications have a comparatively high monthly cost (about $40,000 per month, Table 12). Regretfully, neither medication enhances GIST patent outcomes as compared to prior conventional therapy. A persistent treatment challenge with novel protein kinase inhibitors or immune-oncology medicines is imatinib-resistant GIST [103].

**Table 10**

FDA-approved small molecule CDK4/6 antagonists.

| Drug | Target | Disease | Cost/30 | Cost/ | Generic | Approved |
|---|---|---|---|---|---|---|

Indo-American Journal of Life Sciences and Biotechnology

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | days | year | | |
| Abemaciclib | CDK 4/6 | HER2-positive breast cancer, both monotherapy and combination therapy | $15,000 | $180,000 | Yes | 2017 |
| Palbociclib | CDK 4/6 | Breast cancer (HER2-positive or negative) combination therapy | $16,000 | $192,000 | Yes | 2015 |
| Ribociclib | CDK 4/6 | Breast cancer (HER2-postitive or negative) combination therapy | $20,000 | $240,000 | No | 2017 |
| Trilaciclib | CDK 4/6 | Chemotherapy-induced myelosuppression when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer | $12,000 | $144,000 | No | 2021 |

Indo-American Journal of Life Sciences and Biotechnology

**Table 11**
FDA-approved small molecule MEK1/2 and B-RAF antagonists.

| Drug | Disease | Cost/30 days | Cost/year | Generic | Approved | Company |
|---|---|---|---|---|---|---|
| MEK1/2 Blockers | | | | | | |
| Binimetinib | Melanoma with *BRAF V600E* or *V600K* mutations with encorafenib | $5100 | $61,200 | No | 2018 | Array Pharm |
| Cobimetinib | Melanoma with *BRAF* V600E or V600K mutations with vemurafenib | $7500 | $90,000 | No | 2015 | Genentech |
| Selumetinib | Neurofibromatosis type I | $14,000 | $168,000 | No | 2020 | AstraZeneca |
| Trametinib | Melanoma with *BRAF* V600E or V600K mutations with dabrafenib; NSCLC with *BRAF* V600E mutations with dabrafenib | $14,000 | $168,000 | No | 2013 | GSK |
| B-RAF Blockers | | | | | | |
| Dabrafenib | *BRAF*-mutation positive melanoma with trametinib; NSCLC with *BRAF* V600E mutations; anaplastic thyroid cancer with *BRAF* V600E mutations | $6800 | $81,600 | No | 2013 | GSK |
| Encorafenib | *BRAF V600E or V600K* mutation positive melanoma with binimetinib; *BRAF* V600E mutation positive colorectal cancer with cetuximab | $16,000 | $192,000 | No | 2018 | Array Pharm |
| Vemurafenib | *BRAF V600E or V600K* mutation positive melanoma with cobimetinib; Erdheim-Chester disease | $12,000 | $144,000 | No | 2011 | Genentech / Hoffman La Roch |

Table 12
Miscellaneous FDA-approved small molecule antagonists.

| Drug | Targets | Disease | Cost/30 days | Cost/year | Generic | Approved |
|---|---|---|---|---|---|---|
| Avapritinib | PDGFR/Kit | GIST (gastrointestinal stromal tumors) with PDGFRA exon 18 mutations | $37,000 | $444,000 | No | 2020 |
| Ripretinib | Kit/PDGFRA | Gastrointestinal stromal tumor | $41,000 | $492,000 | No | 2020 |
| Capmatinib | MET | NSCLC with MET exon 14 skipping mutations | $23,000 | $276,000 | No | 2020 |
| Tepotinib | MET | Met exon 14 skipping NSCLC | $24,000 | $288,000 | No | 2021 |
| Entrectinib | TRKA/B/C, ROS1 | Solid tumors with NTRK fusion proteins, ROS1-positive NSCLC | $18,000 | $216,000 | No | 2019 |
| Larotrectinib | TRKA/B/C | Solid tumors with NTRK fusion proteins, | $39,000 | $468,000 | No | 2018 |
| Pralsetin | RET | RET-fusion protein NSCLC, RET mutant | $23,00 | $276,00 | No | 2020 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ib | | medullary thyroid cancer, RET fusion thyroid cancer | 0 | 0 | | |
| Selpercatinib | RET | RET gene fusion NSCLC, thyroid cancer, and solid tumors | $22,000 | $264,000 | No | 2020 |
| Pexidartinib | CSF1R, Kit | Tenosynovial giant cell tumors | $23,000 | $27600 0 | No | 2019 |

protein fusion. Larotrectinib is more than twice as expensive as entrectinib, yet there is no clinical proof that one is better than the other (Table 12). Entrectinib is used to treat ROS-1 positive NSCLC because it not only blocks TRK but also reduces ROS1 activity. For an overview of the clinical studies that resulted in the approval of entrectinib and larotrectinib, as well as a description of other FDA-approved tissue-agnostic treatments, see Ref. [105]. In 1985, Takahashi et al. used sonicated human cancer DNA to change murine NIH 3T3 fibroblasts [106]. They discovered that the changing sequence consisted of a rearrangement of two normal but unlinked DNA segments, and that it covered 34 kilobases. They called this transforming sequence "REarranged during Transfection," or RET, since it was the result of gene rearrangement during transfection. Later, it was shown that RET is the receptor for GDNF, or glial-cell derived neurotrophic factor [107]. This family of ligands comprises persephin (PSPN), neurturin (NRTN), and artemin (ARTN) in addition to GDNF [108]. The brain, peripheral sympathetic and parasympathetic nervous systems, neuroendocrine thyroid calcitonin-producing C-cells, thyroid, lung, hematopoietic progenitors, and other tissues all depend on RET, a transmembrane receptor protein-tyrosine kinase. [108]. Activated RET-fusion proteins are present in 1% to 2% of NSCLC patients. Between 2000 and 4000 new cases of RET-fusion protein lung cancer are reported each year. The most prevalent RET-fusion protein found in NSCLC is KIF5B-RET. A significant proportion of individuals with metastatic thyroid cancer (non-parafollicular) and medullary thyroid carcinomas originating from thyroid C-cells have RET point mutations. Broad spectrum RET antagonists, such as lenvatinib and sorafenib for differentiated thyroid tumors and cabozantinib and vandetanib for medullary thyroid cancers, were previously used to treat patients with RET-driven malignancies [108]. In 2020, selpercatinib and pralsetinib, which target RET more precisely,

have received FDA approval to treat RET-fusion protein non-small cell lung cancer, RET-mutant differentiated thyroid carcinoma, and RET-mutant medullary thyroid cancer (Table 12). These two medications have similar monthly costs of almost $23,000. The clinical studies that resulted in the licensure of pralsetinib and selpercatinib for RET-mutant medullary and non-medullary thyroid malignancies as well as RET-fusion protein non-small cell lung cancer are described in Ref. [109].

## 6. Discussion

FDA-approved small molecule protein-kinase antagonists for the treatment of neoplastic illnesses cost an average of $17,900 a month, or roughly $215,000 per year. Futibatinib, which was used to treat cholangiocarcinomas with FGFR2 fusions, was on the expensive side, with a maximum monthly cost of $44,000 and an annual cost of almost $528,000. With a monthly cost of $5100 and an annual cost of $61,200 (melanoma), binimetinib was the least expensive option. The $5100 amount is a little wrong since binimetinib is often administered together with encorafenib ($21,100 monthly and $253,000 yearly combined). As previously mentioned, asciminib costs $97,800 per month, or $1.17 million annually, to treat mutant BCL-Abl T315I. Non-neoplastic illness therapy averaged between $6800 per month and $81,600 annually. At a maximum of $17,000 a month or $204,000 annually, Belumosudil was at the top end of the graft vs. host disease spectrum. Netarsudil eye drops were inexpensive, costing between $200 to $2400 each month for glaucoma. The median household income in the United States in 2022 was $74,580, while the average family income was $105,555, according to the U.S. Census Bureau. The expense of kinase inhibitors is exorbitant if you don't have private or public health insurance. Drug prices in the US during the second half of 2023 are shown in the data above. In January and July, drug makers usually raise their prices. Consequently, the real medications

Prices in the United States will surpass those shown below in 2024. Furthermore, the increase often outpaces the rate of inflation. The aforementioned data indicates that FDA-approved small molecule protein kinase inhibitors are expensive, which contributes to their financial toxicity. The financial problems experienced by individuals taking these treatments, especially those with cancer, are referred to as "financial toxicity" [110]. The problem of financial toxicity is growing in importance as a result of increased cancer prevalence, the fact that many survivors have cancer as a chronic condition, and increasing healthcare expenditures brought on by better treatments. Although the prevalence of financial toxicity varies widely by country and, therefore, by healthcare system, studies have consistently shown that its presence is associated with worse quality of life, poorer adherence to or postponement of treatment, and early mortality. The high cost of cancer care, which can be ascribed to direct costs (such as the cost of new medications), indirect

costs (such as lost wages from taking time off work for cancer treatment), or non-direct costs (such as the cost of traveling to hospitals in remote areas), is one known source of financial harm. Even when everyone has access to healthcare due to universal health insurance, consumers still have to pay out-of-pocket (OOP) expenses for their disease and its treatment. Since many cancer survivors have persistent symptoms and side effects, these costs may continue for years following a diagnosis. According to data, up to 75% of cancer patients experienced financial hardship [110]. Younger age, female gender, and more recent diagnosis were associated with financial toxicity. Furthermore, psychological disorders like depression are linked to financial toxicity and symptom load. Even while the expenses of cancer treatment have traditionally received the most attention, limitations or incapacity to work are equally likely to contribute to financial toxicity, particularly given the recent sharp increase in cancer treatment costs. Financial issues are also linked to decreased income and lost work days because of sickness. Up to 40% of employed cancer survivors do not return to work after receiving a cancer diagnosis, per research on employment after cancer. This inability to work is linked to a worse quality of life and greater financial difficulties. Males, those with more education, those who have had less invasive surgery, those who have taken more sick days, and those who have access to workplace accommodations like flexible scheduling and rehabilitation programs are more likely to return to work after a diagnosis. According to www.healthsystemtracker.org, the United States spent 17.8% of its GDP on health care in 2021, which is more than twice as much as the average Organization for Economic Co-operation and Development (OECD) nation. The governments of 37 democracies with market-based economies work together in the OECD, a special forum, to advocate policies that support steady, long-term economic development. The United States spent four times as much on health care per person as South Korea and almost twice as much as Germany, the next-ranking nation. In 2021, the United States spent $12,914 per person on health care, more than $5,000 more than any other high-income country. In terms of quality, efficiency, access to care, equity, and the capacity to live long, healthy lives, the United States ranks last among six other developed nations—Australia, Canada, Germany, the Netherlands, New Zealand, and the United Kingdom—despite having the most costly health care system (aspe.hhs.gov). Additionally, on average, the United States spends twice as much on prescription pharmaceuticals as other equally rich countries. In 2022, government health programs and commercial insurers spent about $963 per person on prescription medications, compared to the average of around $466 in similar nations. Some pharmaceutical companies establish two rates for the same prescription due to the complicated procedure of paying for pharmaceuticals in the United States, and many health insurance plans are opting to cover the more costly version. Because to the rulings, some patients now have to spend hundreds or thousands extra out of pocket to complete a prescription for a drug manufactured by the same business. Pharmacy-benefit intermediaries are often used by health insurance plans that cover a large number of medications. Drug makers argue that since pharmacy-benefit administrators prefer the higher rebates and fees of more expensive medications, they must provide the more expensive versions of their medications in order to secure a favorable spot on the formulary. The producers claim that hospitals and health systems that buy their medications are drawn to their less expensive relatives. Pharmacy-benefit administrators claim that the reimbursements reduce the total cost of prescription medications for their plans. Some plans utilize the rebate money to reduce rates for all of their subscribers. Pharmacy benefit managers believe that pharmaceutical businesses should choose their own pricing, and plans may choose to pay for a drug's higher list price since manufacturer rebates make it even more inexpensive than comparable medications with lower list costs. It will be difficult to reduce prescription expenses in the country even after the U.S. Inflation Reduction Act was passed in 2022 since American politicians have significant influence on pharmaceutical prices. At about $240 million a year, the pharmaceutical business spends more than any other industry on lobbyists who have sway over U.S. senators and members of the U.S. House of Representatives. The legislator's election campaign then receives funding from the lobbyists.

According to www.forbes.com, the average profit margin for major pharmaceutical firms is about 21%. This figure is calculated by dividing net profit by sales, where net profit is the sum of revenues less costs (including advertising, clinical trials, R&D, and costs). On the other hand, according to www.aei.org, the median profit margin for all significant corporations in the United States is around 6.5%. One factor contributing to the exorbitant cost of many prescription medications in the US is the 300% higher profit margin of pharmaceutical companies. The exorbitant cost of medications and drug development is partly caused by the wages of attorneys and staff members of contract research firms that have established themselves as essential middlemen between pharmaceutical corporations and customers. The fees that these for-profit businesses charge for services delivered and the wages of pharmacy-benefit administrators are two further elements that raise the total cost of pharmaceuticals for the patient. medicine manufacturers claim that lowering medicine prices would impede the development of new medications. Drug corporations, however, invest more in advertising than in developing new drugs. Reduce their advertising if they need more funding for development. Pharmaceutical corporations seem to set the pricing of novel anticancer drugs based on what the market will bear [111]. A novel protein kinase blocker's cost-effectiveness, length of patient life in months to years, or enhanced quality of life all show minimal relationship with the drug's real effectiveness. Furthermore, there is little proof that kinase inhibitors with higher prices are often more effective than those with lower prices. The U.S. Inflation Reduction Act, which was passed in 2022, would allow Medicare to bargain for lower prescription costs [112]. Ten medications in 2026, fifteen in 2027, and fifteen in 2028 are

Indo-American Journal of Life Sciences and Biotechnology

included in this. Ibrutinib ($2.9 trillion in 2020 annual prices) and palbociclib ($2.1 billion in 2020 annual costs) are among the medications being negotiated for 2026. Negotiations may be underway for tofacitinib for 2028 ($575 million in 2020 annual expenses) and ruxolitinib for 2027 ($1.3 billion in 2020 annual costs). [113]. Keep in mind that tofacinib is an anti-inflammatory drug. Additionally, the Inflation Reduction Act pledges to reduce out-of-pocket costs to $2000 by 2025 [114]. Due of the substantial financial stakes, there will be legal obstacles to this act's implementation [115]. We think that portions of the Inflation Reduction Act pertaining to medicine prices will be overturned since the U.S. Supreme Court and the U.S. Judiciary have supported big business for many years. One real medicinal advance is the creation of small molecule protein kinase antagonists [68]. Businesses seem to assess the market reaction when the FDA licenses novel kinase antagonists. a comparable previously authorized medication or medications, and they set the new one's price a little higher. There seems to be no relationship between a new drug's price and benefit in the cancer context. Health insurance does not remove this financial concern for cancer sufferers since co-payments are now quite expensive in the US. In the US, medical debt is the leading cause of personal bankruptcy. Patients who experience financial hardship may stop taking their medications as directed or stop taking them altogether [110]. Neither the patient nor the pharmaceutical firm benefit if the patient skips doses. More has to be done to equitably share the results of this study to any patient globally who could benefit from the final product, given the efforts of thousands of participants worldwide in the development of targeted cancer medicines.

**References**

[1] P. Cohen, Protein kinases – the major drug targets of the twenty-first century? Nat. Rev. Drug Discov. 1 (2002) 309–315,

[2] P. Cohen, D. Cross, P.A. J¨anne, Kinase drug discovery 20 years after imatinib: progress and future directions, Nat. Rev. Drug Discov. 20 (2021) 551–569.

[3] M.M. Attwood, D. Fabbro, A.V. Sokolov, S. Knapp, H.B. Schio¨th, Trends in kinase drug discovery: targets, indications and inhibitor design, Nat. Rev. Drug Discov. 20 (2021) 839–861. Author correction. Nat Rev Drug Discov 2021;20:798. doi: 10.1038/s41573-021-00303- 4.

[4] G.K. Kanev, C. de Graaf, I.J.P. de Esch, R. Leurs, T. Würdinger, B.A. Westerman, A.J. Kooistra, The landscape of atypical and eukaryotic protein kinases, Trends Pharm. Sci. 40 (2019) 818–832, F. Carles, S. Bourg, C. Meyer, P. Bonnet, PKIDB: a curated, annotated and updated database of protein kinase inhibitors in clinical trials, pii: E908, Molecules 23 (2018), G. Manning, D.B. Whyte, R. Martinez, T. Hunter, S. Sudarsanam, The protein kinase complement of the human genome, Science 298 (2002) 1912–1934, R. Roskoski Jr, Properties of FDA-approved small molecule phosphatidylinositol 3-kinase inhibitors prescribed for the treatment of malignancies, Pharm. Res 168 (2021), 105579, B.C. Doak, B. Over, F. Giordanetto, J. Kihlberg, Oral druggable space beyond the rule of 5: insights from drugs and clinical candidates, Chem. Biol. 21 (2014) 1115–1142.

[5] S.H. Myers, V.G. Brunton, A. Unciti-Broceta, AXL inhibitors in cancer: a medicinal chemistry perspective, J. Med Chem. 59 (2016) 3593–3608,

[6] B.L. Roth, D.J. Sheffler, W.K. Kroeze, Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia, Nat. Rev. Drug Discov. 3 (2004) 353–359,

[7] R. Roskoski Jr, Properties of FDA-approved small molecule protein kinase inhibitors: a 2020 update, Pharm. Res 152 (2020), 104609.

[8] R. Roskoski Jr, Properties of FDA-approved small molecule protein kinase inhibitors: a 2021 update, Pharm. Res 165 (2021), 10546.

[9] R. Roskoski Jr., Properties of FDA-approved small molecule protein kinase inhibitors: a 2022 update, Pharm. Res 175 (2022), 106037,.

[10] D.R. Knighton, J.H. Zheng, L.F. Ten Eyck, V.A. Ashford, N.H. Xuong, S.S. Taylor, J.M. Sowadski, Crystal structure of the catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase, Science 253 (1991) 407–414.

[11] D.R. Knighton, J.H. Zheng, L.F. Ten Eyck, N.H. Xuong, S.S. Taylor, J.M. Sowadski, Structure of a peptide inhibitor bound to the catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase, Science 253 (1991) 414–420.

Indo-American Journal of Life Sciences and Biotechnology

[12] S.S. Taylor, M.M. Keshwani, J.M. Steichen, A.P. Kornev, Evolution of the eukaryotic protein kinases as dynamic molecular switches, Philos. Trans. R. Soc. Lond. B Biol. Sci. 367 (2012) 2517–2528,
[13] S.K. Hanks, A.M. Quinn, T. Hunter, The protein kinase family: Conserved features and deduced phylogeny of the catalytic domains, Science 241 (1988) 42–52,
[14] B. Nolen, S. Taylor, G. Ghosh, Regulation of protein kinases; controlling activity through activation segment conformation, Mol. Cell 15 (2004) 661–675.
[15] N. Gotoh, A. Tojo, M. Hino, Y. Yazaki, M. Shibuya, A highly conserved tyrosine residue at codon 845 within the kinase domain is not required for the transforming activity of human epidermal growth factor receptor, Biochem Biophys. Res Commun. 186 (1992) 768–774.
[16] D.A. Tice, J.S. Biscardi, A.L. Nickles, S.J. Parsons, Mechanism of biological synergy between cellular Src and epidermal growth factor receptor, Proc. Natl. Acad. Sci. USA 96 (1999) 1415–1420,
[17] M. Huse, J. Kuriyan, The conformational plasticity of protein kinases, Cell 109 (2002) 275–282,
[18] H.S. Meharena, P. Chang, M.M. Keshwani, K. Oruganty, A.K. Nene, N. Kannan, S. S. Taylor, A.P. Kornev, Deciphering the structural basis of eukaryotic protein kinase regulation, PLoS Biol. 11 (2013), e1001680
[19] A.P. Kornev, N.M. Haste, S.S. Taylor, L.F. Ten Eyck, Surface comparison of active and inactive protein kinases identifies a conserved activation mechanism, Proc. Natl. Acad. Sci. USA 103 (2006) 17783–17788,
[20] A.P. Kornev, S.S. Taylor, L.F. Ten Eyck, A helix scaffold for the assembly of active protein kinases, Proc. Natl. Acad. Sci. USA 105 (2008) 14377–14382
[21] R. Roskoski Jr, Hydrophobic and polar interactions of FDA-approved small molecule protein kinase inhibitors with their target enzymes, Pharm. Res 169 (2021), 105660,.
[22] R. Roskoski Jr, Properties of FDA-approved small molecule protein kinase inhibitors: a 2023 update, Pharm. Res 187 (2023), 106552,
[23] R. Roskoski Jr, Orally effective FDA-approved protein kinase targeted covalent inhibitors (TCIs), Pharm. Res 165 (2021), 105422,
[24] W.J. Fantl, D.E. Johnson, L.T. Williams, Signaling by receptor tyrosine kinases, Annu Rev. Biochem 62 (1993) 453–481,.
[25] S.P. Kennedy, J.F. Hastings, J.Z. Han, D.R. Croucher, The under-appreciated promiscuity of the epidermal growth factor receptor family, Front Cell Dev. Biol. 4 (2016) 88,