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Cost in the United States of FDA-approved small molecule protein kinase inhibitors used in the treatment of neoplastic and non-neoplastic diseases

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ABSTRACT

Because genetic alterations including mutations, overexpression, translocations, and dysregulation of protein kinases are involved in the pathogenesis of many illnesses, this enzyme family is the target of many drug discovery programs worldwide. The FDA has approved 80 small molecule protein kinase inhibitors with 77 drugs orally bioavailable. The data indicate that 69 of these medicinals are approved for the management of neoplasms including solid tumors such as breast and lung cancer as well as non-solid tumors such as leukemia. Moreover, the remaining 11 drugs target non-neoplastic diseases including psoriasis, rheumatoid arthritis, and ulcerative colitis. The cost of drugs was obtained from www.pharmacychecker.com using the FDA label to determine the dosage and number of tablets required per day. This methodology excludes any private or governmental insurance coverage, which would cover the entire cost or more likely a fraction of the stated price. The average monthly cost for the treatment of neoplastic diseases was $17,900 with a price of $44,000 for futibatinib (used to treat cholangiocarcinomas with FGFR2 fusions) and minimum of $5100 for binimetinib (melanoma). The average monthly cost for the treatment of non-neoplastic diseases was $6800 with a maximum of $17,000 for belumosudil (graft vs. host disease) and a minimum of $200 for netarsudil eye drops (glaucoma). There is a negative correlation of the cost of the drugs and the incidence of the targeted disease. Many of these agents are or were designated as orphan drugs meaning that there are fewer than 200,000 potential patients in the United States.

1. The importance of therapeutic protein kinase inhibitors

Because of genetic alterations including mutations, translocations and overexpression, the dysregulation of protein kinase activity plays a pivotal role in the pathogenesis of autoimmune and inflammatory diseases as well as several neoplasms. Consequently, protein kinases are among the most prominent drug targets in the 21st century [1]. Perhaps 25–33% of academic and pharmaceutical drug discovery programs worldwide focus on these enzymes. The therapeutic efficacy of imatinib in the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia in 2001 motivated the pursuit of orally effective therapeutic protein kinase inhibitors [2–4]. This unparalleled achievement resulted from the imatinib inhibition of the activated chimeric BCR-Abl protein-tyrosine kinase, the biochemical defect that produces this leukemia.

About 250 orally effective protein kinase blockers are in clinical trials worldwide [5]. A complete catalogue of these drugs, which is regularly updated, is posted at www.icoa.fr/pkidb/. There are 80 U.S. FDA-approved drugs in use today that target about two dozen different protein kinases (see supplementary material). These targets, however, represent a small fraction of the 518-member protein kinase superfamily. Dozens of medicinals directed against currently targeted and untargeted protein kinases are in clinical trials across the globe [3–5]. During the preparation of this article, the FDA approved three drugs: (i)

Abbreviations: ALK, anaplastic lymphoma kinase; ALL, acute lymphocytic leukemia; AS, activation segment; CDK, cyclin-dependent protein kinase; CML, Chronic myelogenous leukemia; CSF1R, colony stimulating factor-1 receptor; DEMARDs, disease modifying anti-rheumatic drugs; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; FDA, U.S. Food and Drug Administration; FGFR, fibroblast growth factor receptor; GIST, gastrointestinal stromal tumor; HER, human epidermal growth factor receptor; JAK1/2/3, Janus kinases 1/2/3; JM, juxtamembrane; MPN, myeloproliferative neoplasms; NSCLC, non-small cell lung cancer; PDGFR, platelet-derived growth factor receptor; PI, phosphatidylinositol; PKA, protein kinase A; PlGF, placental growth factor; RCC, renal cell carcinoma; RET, rearranged during transfection or the glial-cell derived neurotrophic factor (GDNF) receptor; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; VEGFR, vascular endothelial growth factor receptor.

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capivasertib, a HER2 antagonist used in the treatment of HER2-positive breast cancer, (ii) fruquintinib, a VEGFR inhibitor used for the treatment of colorectal cancer, and (iii) repotrectinib, a ROS1 blocker used for the treatment of ROS1-positive lung cancer. Owing to the newness of these drugs, their prices are not yet available so that all price calculations in this article exclude these three new agents.

Manning et al. found that the human protein kinase family contains 478 typical and 40 atypical members [6] including phosphatidylinositol 3-kinase (PI 3-kinase) [4,7]. Protein kinases mediate the following reaction;.

$$MgATP^{1-} + \text{protein–O:H} \rightarrow \text{protein–O:}PO_3^{2-} + MgADP + H^+$$

Based upon the identity of the protein–OH moiety, these enzymes are divided into protein-serine/threonine kinases (385 members), protein-tyrosine kinases (90), and protein-tyrosine kinase–like enzymes (43). The protein-tyrosine kinase family consists of both transmembrane receptor (58) and intracellular nonreceptor (32) proteins. Moreover, the protein kinase family includes a small group of intracellular proteins such as MEK1/2 that catalyze the phosphorylation of both tyrosine and then threonine residues within the activation segment of their target protein kinases. Owing to this unique property (tyrosine and threonine and not tyrosine or serine/threonine), MEK1/2 and related catalysts are classified as dual specificity (DS) protein kinases. Another indication of the importance of the protein kinase family is 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. These kinases therefore constitute approximately 2.5% of the human genome. Another indication of the importance of protein kinases as drug targets is the finding of Manning et al. that 244 protein kinases map to cancer amplicons and other disease loci [6]. Moreover, as additional research on the pathogenesis of more diseases is performed, it is expected that there will be a significant increase in the number of protein kinase targets.

The U.S. FDA has approved 80 small molecule therapeutic protein kinase antagonists as of November 2023, nearly all of which are orally effective. The exceptions include netarsudil (an eye drop) and temsirolimus and trilaciclib (which are given intravenously). Ruxolitinib is an orally bioavailable JAK1/2 protein kinase inhibitor that was approved for the treatment of polycythemia vera and myelofibrosis in 2011. This medicinal is also topically active and was approved as a cream in 2021 for the treatment of atopic dermatitis. Of the 80 approved drugs, forty-one block receptor protein-tyrosine kinases, twenty-three target nonreceptor protein-tyrosine kinases, twelve are directed against protein-serine/threonine protein kinases, and four target dual specificity protein kinases (MEK1/2) (Table 1).

The data indicate that 69 of these medicinals are approved for the management of neoplasms (58 against solid tumors such as breast, colon, and lung cancers, six against nonsolid tumors such as leukemia, and five against both types of tumors. The oral tablets that constitute protein kinase blockers have many advantages over other types of drug formulations. In comparison with liquids and suspensions, for example, solid forms of oral drugs are more stable during storage [8]. Of greater importance, oral delivery is the patient-preferred method for drug delivery. Compared with intravenous therapy, the patient's quality of life is greater owing to the ability to self-administer at home. This decreases the need for taking time from work to travel to a clinic for treatment with its attendant expenses and loss of income. Although most drugs used in oncology are given intravenously, the preponderance of patients prefers the convenience of oral medicines.

More than two dozen of the FDA-approved drugs are multikinase antagonists. Because the specificity of many of the small molecule protein kinase blockers has not been thoroughly examined, it is likely that additional FDA-approved drugs are multikinase inhibitors. The simultaneous blockade of multiple protein kinases has potential advantages as well as disadvantages. For instance, the therapeutic effectiveness of multikinase antagonists may be related to the blockade of two or more targets. For example, sunitinib and cabozantinib have potent off-target activity against the Axl receptor protein-tyrosine kinase and this property may augment to their clinical effectiveness [9]; Axl is the receptor for GAS6 (growth arrest-specific protein 6). On the other hand, the inhibition of off-target kinases may elicit unwanted side effects. Accordingly, we have the dilemma of whether a magic shotgun should be preferred to Paul Ehrlich's magic bullet [10].

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

[a] NYR, nonreceptor protein-tyrosine kinase; RY, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; Y/T, Dual specificity protein kinase – tyrosine phosphorylation followed by threonine phosphorylation of target kinase activation segments.

Eleven of the FDA-approved protein kinase inhibitors are prescribed for the treatment of non-neoplastic diseases. 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). Moreover, ibrutinib, ruxolitinib, and sirolimus are approved therapeutics for both neoplastic and non-neoplastic diseases.

Of the 80 FDA-approved protein kinase blockers, twenty-one are used in the treatment of more than one disease. Imatinib is the prime example and is approved for the treatment of eight distinct disorders. Imatinib is FDA-approved for the first-line treatment of Philadelphia chromosome-positive (i) chronic myelogenous leukemia, (ii) acute lymphoblastic leukemia, (iii) *KIT* mutation-positive gastrointestinal stromal tumors, (iv) myelodysplastic/myeloproliferative diseases with *PDGFR* gene-rearrangements, (v) dermatofibrosarcoma protuberans, (vi) hypereosinophilic syndrome, (vii) chronic eosinophilic leukemia, and (viii) as a second-line treatment for aggressive systemic mastocytosis without the KIT^{D816V} mutation [11–13]. Furthermore, imatinib is used off-label for the treatment of chordomas, desmoid tumors, advanced *KIT*-mutant melanomas, and chronic myelogenous leukemia

following allogeneic stem cell transplantation. Imatinib is thus a wide-spectrum inhibitor. This broad spectrum of diseases is correlated with the blockade of a large number of kinase targets. It inhibits the nonreceptor protein-tyrosine kinase Abl (and the BCR-Abl chimera – responsible for the pathogenesis of chronic myelogenous leukemia), Abl2, Kit (the stem cell factor receptor), PDGFRα/β, and epithelial discoidin domain-containing receptor-1 (DDR1) and receptor-2 (DDR2). DDR1/2, which are activated by collagen, participate in cell migration, proliferation, differentiation, and the remodeling the extracellular matrix.

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

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

We first consider the overall structure of the active EGFR protein kinase domain as a prototype for all protein kinases. Protein kinases have a small amino-terminal lobe and large carboxyterminal lobe that contains several conserved α-helices and β-strands (Fig. 1 A), first described by Knighton et al. for protein kinase A (PKA) [14,15]. The amino-terminal lobe is dominated by a five-stranded antiparallel β-sheet (β1–β5) and an αC-helix that contains a glutamate that makes a salt bridge with a lysine in the β3-sheet in the active conformation [16]. The N-lobe contains a conserved glycine-rich (GxGxxG) ATP-phosphate-binding loop that links the β1- and β2-strands. The G-rich loop helps position the β- and γ-phosphates of ATP for catalysis. The β1- and β2-strands dock with the adenine component of ATP (not shown). A conserved glutamate occurs near the center of the αC-helix within the amino-terminal lobe of protein kinases. The presence of a salt-bridge between the αC-glutamate and the β3-lysine is a prerequisite for the formation of the active state and corresponds to the "αC_{in} " conformation; by contrast, the β3-lysine and the αC-glutamate of the dormant form of EGFR fail to make contact in the "αC_{out}" conformation (Fig. 1 E). The αC_{in} conformation is necessary, but not sufficient, for the expression of full kinase activity.

The carboxyterminal lobe of protein kinase domains is mainly α-helical with six conserved segments (αD-αI) (Fig. 1 A). The C-terminal lobe also contains four short conserved β-strands (β6-β9) that contain most of the catalytic residues associated with the phosphoryl transfer from ATP to its substrates. The αE-helix is followed by the β6-stand, the catalytic loop, the β7- and β8-strands, and the activation segment, which contains the β9-strand. The activation segment in the active state forms an open structure extending away from the catalytic loop that allows protein/peptide substrate binding. The dormant and the active protein kinase domains contain an additional αEF-helix near the end of the activation segment (Fig. 1 A).

Hanks et al. identified 12 subdomains (I–VIa, VIb–XI) with conserved amino-acid-residue signatures that constitute the catalytic core of protein kinases [17]. Of these, the following four amino acids, which define a K/E/D/D (Lys/Glu/Asp/Asp) signature, illustrate the catalytic properties of protein kinases. As noted above, an invariant β3-strand lysine (the K of K/E/D/D) forms salt bridges with the αC-glutamate (the E of K/E/D/D). The catalytic loop aspartate, which is the first D of K/E/D/D), serves as a base that abstracts a proton from the protein–OH group of the substrate thereby facilitating the nucleophilic attack of the hydroxyl group onto the γ-phosphorous atom of ATP. The second aspartate of the K/E/D/D signature is the first residue of the activation segment. The activation segment of nearly all protein kinases begins with DFG (Asp-Phe-Gly) and ends with APE (Ala-Pro-Glu). The EGFR activation segment begins with DFG, but it ends with ALE (Ala-Leu-Glu). The DFG-D_{in} configuration represents the active conformation. The DFG-D binds Mg^{2+}, which in turn coordinates the α- β- and γ-phosphates of ATP (not shown). The primary structure of the catalytic HRD loop occurs before the β7- and β8-strands, which are followed by the activation segment. The large lobe characteristically binds the peptide/protein substrates at a binding loop within the activation segment. The activation segment in EGFR contains a phosphorylatable tyrosine. Although phosphorylation of one or more residues within the activation segment of most protein kinases is required for activation [18], this phosphorylation is not required for EGFR activation [19,20].

Although the tertiary structure of catalytically active protein kinase

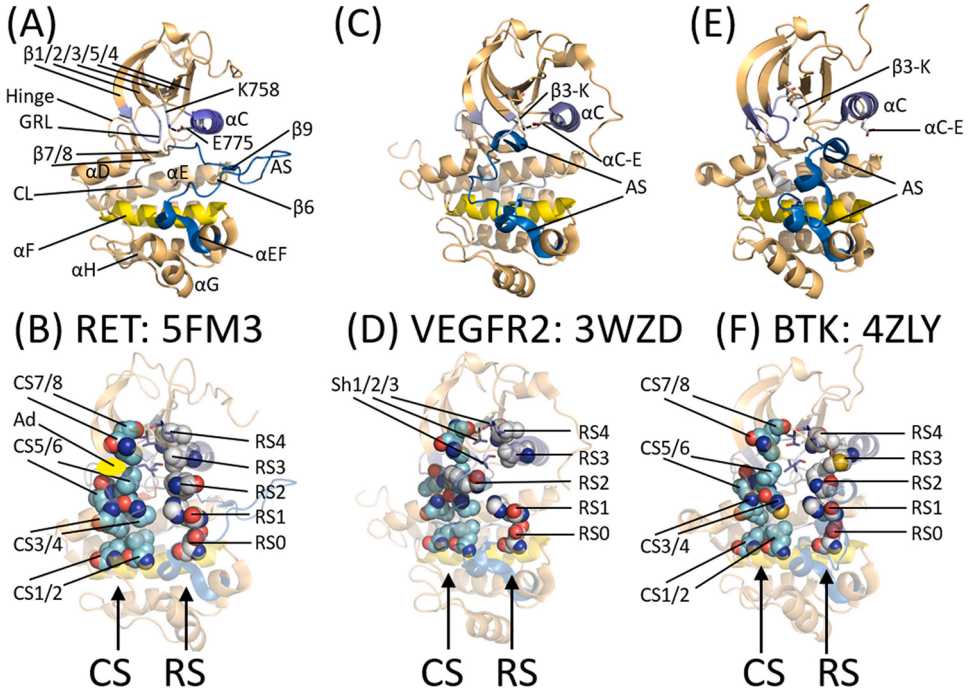

Fig. 1. (A) Overview of active RET and (B) its C-spine and R-spine residues. (C) The AS-closed structure of dormant VEGFR2 and (D) its C-spine, R-spine, and shell residues. (E) Overview of the αC_{out} structure of BTK and (F) its C-spine and R-spine residues. AS, activation segment; CL, catalytic loop. 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 Schrödinger, 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 conformation is the αC-helix out state (Fig. 1E) [22]. Also note that the activation 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}, inactive), and the C-terminal lobe activation segment (AS-open, active; AS-closed, inactive).

Taylor and Kornev [23] and Kornev et al. [24] analyzed the structures 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 histidine of HRD of the catalytic loop. The spinal component from the αC-helix is four residues C-terminal to the conserved αC-glutamate. 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 beginning 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 and CS4 interact with two residues of the αF-helix (CS1 and CS2) to complete the C-spine (Fig. 1B). Using site-directed mutagenesis, 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 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 crystallographic 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].

2.2. 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 inhibitors 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 inhibitors 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 solubilized 170-kDa polypeptide had both EGF binding capacity as well as protein kinase activity [31]. EGFR was also the first receptor that provided evidence for a relationship between mutation, overexpression, and cancer [32]. The EGFR family is among the most investigated receptor 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*) oncogene with which these 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)

Table 2
Classification of small molecule protein kinase inhibitors.

Inhibitor type	Properties
I	Binds in and around the ATP-binding pocket of an active enzyme
I½ A/B	Binds 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

ERBB4/HER4. Although there is a considerable overlap, the HER nomenclature is used more commonly in clinical reports whereas the ErbB nomenclature is associated with the biological sciences. Schechter et al. found that rat neuro/glioblastomas contain the *Neu* oncogene, which is related to the rat *Erbb2* gene of the EGFR family [37]. This finding provided evidence for the potential role of the ErbB family of receptors in the development of cancer and *NEU* is sometimes used in human gene nomenclature. This family of receptors is ubiquitously expressed in epithelial, mesenchymal, and neuronal cells as well as their undifferentiated precursors.

Based upon the primary amino acid sequence of EGFR as determined by cDNA analysis, Ulrich et al. reported that the receptor contains a single hydrophobic transmembrane segment that separates the extracellular ligand-binding domain and the intracellular protein kinase domain [38]. This hypothesis has stood the test of time and applies to nearly all receptor protein kinases. Nine activating ligands bind to the ErbB family of proteins including EGF, amphiregulin, epigen, transforming growth factor-α, betacellulin, epiregulin, heparin-binding EGF-like factor, and neuregulins1/2/3/4. See Ref. [36] for a description of the specificity of ligand and ErbB receptor interactions. ErbB2/HER2 does not bind any of these ligands and ErbB3 lacks protein kinase activity. It is therefore paradoxical that the ErbB2-ErbB3 dimer is the most active of all of the possible homo and heterodimer combinations.

EGFR/ErbB1 plays an important role in the development of many lung cancers [9]. Herbst et al. reported that *EGFR* kinase-domain mutations occur in 10–40% of lung cancer samples [39]. The incidence of *EGFR* kinase-domain mutations is about 10% in Caucasians and about 30–40% in Asian patients. The most common mutations were (i) deletion of five exon-19 residues (^{746}ELREA^{750}) that occur in the small protein kinase lobe and (ii) the exon-21 substitution of an arginine for leucine (L858R) in the large lobe. These two mutations account for greater than 90% of the activating *EGFR* mutations found in NSCLC. However, more than 200 NSCLC *EGFR* mutations have been found [40]. ErbB family blockers used in the treatment of lung cancers are described later.

The ErbB family is also important in the pathogenesis of breast cancers [33,34]. For the purposes of treatment, breast cancers are divided into three categories, which are not mutually exclusive: these include (i) overexpression of *ERBB2/HER2/NEU*, (ii) hormone receptor-positive, and (iii) triple-negative breast cancer. Triple-negative breast cancer refers to those cancers lacking (i) estrogen receptors, (ii) progesterone receptors, and (iii) HER2 overexpression. Wittliff discovered that ErbB2 overexpression is found in 20–30% of breast cancers while 10–20% of breast cancers are of the triple-negative variety and lack hormone receptors and fail to overexpress ErbB2/HER2 [41]. ErbB2 overexpression was correlated with a poor prognosis prior to the advent of ErbB2 targeted therapies, but is now one of the classes of breast cancer that is more amenable to treatment [36]. Wittliff also found that receptors for estrogen, progesterone, or both occur in about 79% of all breast cancers [41]. Furthermore, he found that about 56% of breast cancers contain both the estrogen and progesterone receptors while 14% possess only the estrogen receptor and 9% possess only the progesterone receptor while 21% lack both receptors.

3.2. The Janus kinase (JAK) family

The Janus kinase (JAK) family of nonreceptor protein-tyrosine kinases consists of JAK1/2/3 and TYK2 (Tyrosine Kinase 2) [42,43]. Each of these gene-products contains a JAK homology pseudokinase (JH2) domain that interacts with and regulates the activity of the adjacent protein kinase domain (JH1). Janus is a two-faced Roman God (looking forwards and backwards) whose name was given to this enzyme family because of the presence of two protein kinase domains within a single polypeptide chain. JAK was whimsically conceived as Just Another Kinase [44]. JAK1, JAK2, and TYK2 are expressed in almost all types of cells whereas JAK3 is confined to hematopoietic, myeloid, and lymphoid cells [45]. Numerous cytokines including interferons, interleukins, and hormones (erythropoietin and thrombopoietin) regulate Janus kinase family activity [43]. Ligand binding to various cytokine receptors promotes the activation of their associated Janus kinases, which then mediate the phosphorylation of their receptors. The SH2 domain of signal transducers and activators of transcription (STAT) binds to cytokine receptor phosphotyrosines and thereby promotes STAT phosphorylation and activation by the Janus kinases. The resulting STAT dimers are then translocated into the nucleus where they regulate the expression of hundreds of target proteins. JAK1/3 signaling participates in the pathogenesis of inflammatory disorders while JAK1/2 signaling contributes to the development of myeloproliferative neoplasms. An activating JAK2 V617F mutation occurs in 95% of patients with polycythemia vera and about 50% of cases of myelofibrosis and about 50% of cases of essential thrombocythemia [46]. JAK family gain-of-function mutations are associated with a diverse set of hematological disorders including B and T cell acute lymphoblastic leukemia (B-ALL, T-ALL), acute myelogenous leukemia (AML), and myeloproliferative neoplasms (MPN). JAK family blockers used in the treatment of neoplastic and non-neoplastic disorders are described later.

3.3. VEGFR receptors and ligands

The VEGF family and its receptors play an integral role in angiogenesis, lymphangiogenesis, and vasculogenesis [47–49]. In adults, VEGFR1 and VEGFR2 are found chiefly in vascular endothelial cells while VEGFR3 is localized in lymphatic endothelial cells. The human VEGF family consists of five members: VEGF (or VEGF-A), VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). Each of these proteins contains a signal sequence that is cleaved during biosynthesis. Moreover, alternative splicing of their corresponding pre-mRNAs generates multiple isoforms of VEGF, VEGF-B, and PlGF. VEGF binding sites were identified on vascular endothelial cells corresponding to VEGFR1 (Flt1) and VEGFR2 (Flk1/KDR). VEGF, VEGF-B, and PlGF bind to VEGFR1 while VEGF and VEGF-C bind to VEGFR2 [50,51]. The occurrence of these receptors on vascular endothelial cells accounts for the specificity of action of VEGF, VEGF-B, and PlGF. VEGFR3 (Flt4) binds VEGF-C and VEGF-D. Each of these receptors is a type V (five) protein-tyrosine kinase that consists of an extracellular component containing seven immunoglobulin-like domains, a single transmembrane segment, a juxtamembrane segment, an intracellular protein-tyrosine kinase domain that contains a kinase insert of 70–100 amino acid residues, and a carboxyterminal tail (see ref. [52] for a description of types I–XX receptor protein-tyrosine kinases). The three VEGF receptors are related to the platelet-derived growth factor receptors-α/β, 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), all of which contain extracellular immunoglobulin-like domains and a kinase insert [52].

The important role of angiogenesis in the pathogenesis of renal cell carcinomas and other neoplasms has focused the attention of investigators on the biology of VEGFs and VEGFR1/2/3 and to the development of inhibitors of the intricate and multifaceted angiogenic pathways [49]. VEGF stimulates the phosphorylation of preformed VEGFR2 dimer activation segment tyrosine residues followed by the phosphorylation of additional protein-tyrosines that recruit phosphotyrosine binding proteins thereby leading to signaling by the ERK1/2, FAK, PI3-kinase/AKT, and p38 MAP kinase pathways [50,51]. VEGFR1 modulates the activity of VEGFR2, which is the chief pathway involved in vasculogenesis and angiogenesis. VEGFR3 and its ligands (VEGF-C and VEGF-D) are involved primarily in lymphangiogenesis. A listing of drugs that interact with these growth factors and receptors is given later.

3.4. Anaplastic lymphoma kinase (ALK)

Anaplastic lymphoma kinase was first described in 1994 as the NPM-ALK fusion protein that is expressed in the majority of anaplastic large-cell lymphomas [53]. ALK is a member of the insulin receptor protein-tyrosine kinase superfamily and its ligands are called AUG-α and AUG-β (for augmenter) [54]. About twenty different ALK-fusion proteins have been described that result from various chromosomal rearrangements and they have been implicated in the pathogenesis of several diseases including anaplastic large-cell lymphoma, diffuse large B-cell lymphoma, and inflammatory myofibroblastic tumors [55,56]. The EML4-ALK fusion protein plays a fundamental role in the development in about 5% of non-small cell lung cancers. The formation of dimers by the amino-terminal portion of the ALK fusion proteins results in the activation of the ALK protein kinase domain that plays a key role in the tumorigenic process. Downstream signaling from the ALK fusion protein involves the Ras/RAF/MEK/ERK1/2 cell proliferation module and the JAK/STAT cell survival pathway. The occurrence of oncogenic ALK, particularly in non-small cell lung cancer, has generated considerable interest and effort in developing ALK inhibitors. Crizotinib was the first FDA-approved drug prescribed for the treatment of ALK-positive non--small cell lung cancer [57]. The emergence of crizotinib drug resistance with a median occurrence at about 10 months stimulated the development of second-generation drugs for the treatment of NSCLC and other disorders. About 28% of the cases of crizotinib resistance are related to mutations of ALK in the fusion protein; the others are related to the upregulation of alternative signaling pathways or to undefined mechanisms. [56]. Nearly a dozen different mutations in ALK fusion proteins have been discovered in humans that confer crizotinib resistance. Additional ALK inhibitors are described later.

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

The Philadelphia chromosome occurs in about 95% of chronic myelogenous leukemia cases [58]. Janet Rowley discovered that the Philadelphia chromosome was produced by a reciprocal translocation t (9;22)(q34;q11.2) that results in a shortened chromosome 22 (the Philadelphia chromosome) and a lengthened chromosome 9 [59]. This translocation leads to the formation of the BCR-Abl oncogene where BCR refers to breakpoint cluster region, which was originally on chromosome 22, and Abl is the human ortholog of the murine Abelson leukemia virus, which was originally on chromosome 9 [60,61]. As a result of the formation of the fusion protein, the BCR-Abl kinase exhibits increased activity and is the dominant factor in the pathogenesis of the disease. Imatinib and second and third generation inhibitors have been developed, which bind to the ATP-binding site or an allosteric site of BCR-Abl, as described later.

Alternative splicing of Abl-1 pre-mRNA yields two transcripts: 1a and 1b [58]. The latter protein is 19 residues longer than Abl-1a and it bears a covalently attached myristoyl group that is added post-translationally to a glycine residue immediately following the initiating amino-terminal methionine. The myristoyl group plays a fundamental role in the regulation of Abl-1b activity while the regulation of Abl-1a remains a mystery. The N-terminal and C-terminal lobes of catalytically competent Abl-1b must be able to move (breath) in order to mediate the phosphorylation of its substrates. To keep the Abl-1b kinase in an inactive state, the SH3 domain, the SH2 domain, and the SH2-kinase linker dock tightly to the protein kinase domain and restrict its mobility and inhibit its catalytic activity. Hantschel et al. discovered that the ABL1b glycine-to-alanine mutation at position 2 (*G2A*) led to the biosynthesis of an enzyme with dramatically higher catalytic activity than wildtype Abl-1b [62]. Conversion of glycine to any other residue prevents the myristoylation as catalyzed by N-myristoyltransferase. The first four residues of Abl-1b are MGQQ, which will promote N-myristoyltransferase activity, and those of Abl-1a are MLEI, which will not. Moreover, unlike the wildtype enzyme, the *G2A* mutant protein was highly phosphorylated. These findings indicated that the myristoyl group acts to negatively regulate Abl-1b phosphotransferase activity. The interaction of myristate with Abl-1b induces a bend in the large lobe αI-helix. As a result, the SH3-SH2 complex can dock tightly with the SH1 kinase domain thereby blocking its mobility and catalytic activity. Without the αI-helix–induced bend, the backside of Abl-1b is unable to dock firmly to the protein kinase domain and the enzyme is active. The myristate binding pocket is a type IV allosteric-inhibitor–binding site [58] that interacts with asciminib. Moreover, asciminib is active against the *T315I* (Abl-1a nomenclature) gatekeeper mutant. The drug binds to an allosteric site that is far from the ATP-binding site (28 Å) and is now the best example of an FDA-approved type IV antagonist. See Refs. [63–70] for a description of the type of protein kinase reversible (Groups I, I½, II, III, IV, and V) and targeted covalent irreversible inhibitors (VI). Asciminib is FDA-approved for the third line treatment of Philadelphia chromosome-positive CML and the first line treatment of Philadelphia chromosome-positive CML with the *T315I* gatekeeper mutation.

3.6. The fibroblast growth factors and their receptors

The FGF family is one of the largest, if not the largest, signaling constellation with a total of 22 growth factors, four protein-kinase receptors, and a fifth receptor lacking intracellular enzyme activity [71]. The potential combinations of FGF1–23 and FGFR1–4 interactions numbers in the thousands. This multiplicity increases the difficulty in deciphering specific signaling pathways. Although these are labeled FGF1–23, factors 15 and 19 represent the same molecule that is called FGF(15/19) in this paper; thus, the total number of FGFs is 22. A total of 18 of the 22 growth factors are glycoproteins that are secreted from the cell of origin and they interact with the transmembrane fibroblast growth factor receptors (FGFRs). In contrast, the intracellular factors (FGF11/12/13/14) serve as cofactors for voltage-gated sodium channels. The FGFs range in size from 155 residues (FGF1) to 288 residues (FGF2).

The FGFs are divided into seven subfamilies [72,73]. The first subfamily (FGF1) consists of FGF1 and FGF2. Although these factors lack a traditional signal peptide, they are readily exported from cells by coursing through the plasma membrane. FGF1/2 bind to and activate their cognate FGFRs. These factors have the unusual property of being translocated back into the cell through the plasma membrane and traveling through the cytosol into the nucleus. The second subfamily (FGF4) consists of FGF4, FGF5, and FGF6. The third subfamily (FGF7) consists of FGF3, FGF7, FGF10, and FGF22. These factors possess a signal peptide and are secreted from cells. FGF3/10/22 interact with FGFR1/2 while FGF7 interacts with FGFR2/4. The fourth subfamily (FGF8) consists of FGF8, FGF17, FGF18. These factors are secreted from the cell by the classical signal peptide pathway and FGF8/17 interact with FGFR1/2/3/4 and FGF8 interacts with FGFR2/3/4. The fifth subfamily (FGF9) consists of FGF9, FGF16, and FGF20. These ligands function as homodimers. The sixth subfamily (FGF(15/19)) consists of FGF(15/19), FGF21, and FGF23. These growth factors are secreted from cells by the classical signal peptide process and they interact with FGFR1/2/3/4. All of the previous FGFs function close to the cell that secreted them in an autocrine or paracrine fashion owing to their high affinity for extracellular heparan sulfate glycosaminoglycan chains of heparan sulphate proteoglycans. The paracrine FGFs include the first five subfamilies while the endocrine FGFs consist of the sixth subfamily.

In contrast to the subfamilies 1–5, the FGF(15/19) family is carried by the circulation to their target cells and receptors and they function as endocrine factors; these factors possess low affinity for heparan sulfate, which allows them to diffuse from the site of origin into the circulation and travel to their targets [72,73]. The seventh FGF subfamily (FGF11) consists of FGF11, FGF12, FGF13, and FGF14. These factors are not secreted and occur within the cytosol and nucleus. This subfamily interacts with the cytosolic carboxyterminal tail of voltage-gated sodium

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

3.7. Cyclin-dependent protein-serine/threonine kinases

The replication of every cell in every tissue and organ is stringently controlled during development and throughout the life of the individual [74,75]. In the normal adult, cells replicate as needed. Furthermore, each chromosome must be accurately replicated. The cell cycle consists of G1 (Gap1 and presynthetic growth), the S-phase (DNA synthesis), G2 (Gap 2 or premitotic growth), and the M (mitotic) phase. Cells are preparing for DNA synthesis during G1 and they perform surveillance to establish the integrity of newly synthesized DNA during G2 before initiating mitosis. Chromosomal DNA is replicated during the S-phase and the other cellular components are partitioned between two daughter cells during the M-phase. When cells cease proliferating, they exit the cycle and enter a nondividing quiescent state known as G0. Senescence, in contrast, is an irreversible state of G1 cell cycle arrest in which cells have undergone an irreversible arrest of proliferation and can no longer divide.

Cyclins and their cognate cyclin-dependent protein kinases (CDKs) are required for traversing the cell division cycle [74,75]. Humans possess 20 CDKs (1−20) and 13 cyclin groups (A, B, C, D, E, F, G, H, J, K, L, T, and Y). Cyclins are activated by a two-step process. CDKs interact with cyclins as a first step in protein kinase activation. Following the formation of the CDK-cyclin complex, the CDK activation segment undergoes phosphorylation at a conserved threonine residue that is catalyzed by CDK7 resulting in the full expression of CDK-cyclin enzyme activity. The quantities of the CDKs are more or less constant throughout the cell cycle. The activities of the CDKs that regulate transit through the cell cycle are controlled by the cyclins, proteins whose levels vary during the cell cycle. This oscillation of cyclin levels accounts for their names as they cycle up and down during cell growth and division. CDKs are regulated by a mechanism that involves the biosynthesis (which increases protein kinase activity) and proteolysis (which decreases enzyme activity) of their corresponding cyclins. Using human HeLa cells, Arooz et al. found that the peak quantities of cyclin A2 and cyclin E1, at the G2-phase and G1-phase, respectively, were only about 1/8th of that of their partner enzyme (CDK2) [76]. This result indicates that the CDKs are present in excess and are not maximally stimulated by their regulatory subunits.

The human cyclins are a large family consisting of about 13 groups of proteins with molecular weights ranging from 35 to 90 kDa [74,75]. Cyclins are expressed in distinct stages of the cell cycle and are then degraded by an intricately regulated process that involves interactions with ubiquitin ligases (E3s) and proteasomes. The cyclin family consists of three major groups. Group I or the cyclin B group is made up of A, B, D, E, F, G, and J; group II corresponds to cyclin Y; and group III or the cyclin C group is made up of cyclins C, H, K, L, and T (which are major partners with the transcriptional CDKs). These proteins contain a 100 amino-acid–residue domain consisting of five α-helices called the cyclin box. The A, B, D, E, F, and J cyclins contain two cyclin boxes while the others contain only a single cyclin box.

In order to ensure appropriate advancement through the cell cycle, cells possess a series of checkpoints that block them from progressing into the next phase prematurely or inappropriately before they have successfully finished their current phase [77]. The first checkpoint occurs at G1-S (it is also called start, restriction point, or R-point) where G1-S and S-phase CDK-cyclin complexes are activated during G1. After passing the first checkpoint, completion of the cell cycle is independent of mitogens and growth factors [74,75]. The G1-S enzymes include CDK4, CDK6, and the D-type cyclins (D1/2/3), the various forms of which are expressed in a cell and tissue-specific manner. The CDK2-cyclin E complex is required for the transition to the S-phase. G2-M makes up a second checkpoint as the M-phase CDK1-cyclin A/B complex is activated thereby carrying the cell to metaphase during mitosis. The metaphase-to-anaphase transition makes up the third checkpoint, which leads to sister-chromatid segregation, completion of mitosis, and cytokinesis as a single cell completes cell division and forms two daughter cells. Progression results when the M-phase cyclin-CDK complexes stimulate the anaphase-promoting complex, which results in the proteolytic destruction of proteins that hold the sister chromatids together.

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 phosphorylation 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 hyperphosphorylation of Rb at all 14 sites and (ii) its deactivation. The FDA-approved CDK4/6 blockers are described later.

3.8. Flt3 receptor protein-tyrosine kinase and its ligand (Flt3L)

Work on Flt3 followed the discovery of a feline sarcoma virus in 1971 by McDonough et al. [79]. This viral oncogene is called v-FMS (feline McDonough sarcoma) virus. This led to the discovery of the c-FMS proto-oncogene or colony-stimulating factor-1 receptor (CSF1R). Flt1 (fms-like tyrosine kinase-1) is VEGFR1 and Flt2 is fibroblast growth factor receptor-1 (FGFR1). Flt3 (fms-like tyrosine kinase-3) is a transmembrane receptor protein-tyrosine kinase that plays a crucial role in normal hematopoiesis [80]. This protein, which is expressed by early myeloid and lymphoid progenitor cells, regulates the proliferation and differentiation of hematopoietic cells. Flt3 is not expressed in mature hematopoietic cells. *FLT3* activating mutations occur in about one-third of newly diagnosed acute myelogenous leukemia (AML) patients. *FLT3* internal tandem duplication (ITD) results from a head-to-tail duplication of from one to 412 amino acids within the juxtamembrane domain and such duplication occurs in about 20–25% of patients with AML.

Flt3, Kit, macrophage/colony stimulating factor-1 receptor, PDGFRα/β are type III receptor protein-tyrosine kinases. See Refs. [28,52] for a description of the properties of the 20 types of receptor protein-tyrosine kinases. The type III receptors contain an extracellular portion, a transmembrane segment, an intracellular domain that consists of a juxtamembrane segment, a protein kinase domain that contains an insert of several amino acid residues, and a carboxyterminal tail. The extracellular segment contains five immunoglobulin-like domains (D1–D5). The extracellular domain of human Flt3, which contains 547 amino acid residues, is longer than the intracellular domain, which contains 430 residues. Additionally, the carboxyterminal tail contains 50 amino acids (944−993). The human Flt3L consists of 235 residues, the amino-terminal 26 residues of which make up the signal peptide. Membrane associated Flt3L contains 209 residues. It can undergo proteolysis as catalyzed by ADAM17 (A disintegrin and metalloproteinase) [81] to generate a soluble form consisting of 178 residues that form active dimers. Membrane-associated and soluble Flt3L are equipotent growth factors.

The Flt3 ligand (Flt3L), which promotes dimerization and activation of Flt3, consists of a noncovalent dimer that results from hydrophobic and polar interactions [80]. The dimeric ligand interacts with the D3 portion of two Flt3 receptors with a K_d value of 0.2–0.5 nM. This promotes the phosphorylation of residues in the autoinhibitory JM domain and relieves this inhibition. Additional phosphorylation reactions occur elsewhere that promote the binding of proteins that lead to the

activation of the MAP kinase and PKB/AKT signaling modules that result in cell proliferation and inhibition of programmed cell death (apoptosis). See Ref. [80] for a comprehensive discussion of Flt3-mediated signal transduction. FDA-approved Flt3 inhibitors are described later.

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

We retrieved drug prices in November 2023 from www.pharmacychecker.com for the average patient living in the state of North Carolina (ZIP code 28791). These values represent the retail price of a drug at the pharmacy as determined by negotiations between pharmacies and insurers and reflect both wholesale and retail markups. The pharmacies used in this article include CVS Pharmacy, Walgreens, and Rite Aid Pharmacy – well known national chains in the U.S. CVS accounts for 25.6% of the U.S. prescription drug market, followed by Walgreens (16.5%), and Rite Aid (2.3%) (https://www.statista.com/statistics/734171/pharmacies-ranked-by-rx-market-share-in-us/). After determining the price per tablet, milliliter, or vial, we used the FDA-label to determine the cost per 30-day period based upon the number of tablets or other prescribed dosage units. We multiplied this value by 12 (months) to approximate the yearly price. If the FDA label stated that the dosage was two pills per day, we multiplied the dose per tablet times two to give the daily cost and multiplied this product times 30 to give the fee per month. In the case of axitinib (Inlyta), for example, the dose used for the treatment of renal cell carcinoma is 5 mg twice daily. The price per tablet is $320 or $640 per day times 30 days or $19,200 per month (rounded off to $19,000). If the dosage was for 21 days with a seven-day rest period, we multiplied the daily rate times 21 days and divided by 28 to give the daily cost. In the case of cobimetinib (Cotellic), the dose is 60 mg for the first 21 days of each 28-day cycle. The price of each 20 mg tablet is $117 times three for $351/day for 21 days ($7371) divided by 28 ($263/day) times 30 or about $8000 per month. This methodology excludes any private or governmental insurance coverage, which might cover the entire cost or more likely a fraction of our calculated price. In U.S. Medicare Part D, for example, the patient cost sharing is between 25% and 30% of the list price for drugs costing more than $670 per month. Medicare Part D is a voluntary outpatient prescription drug benefit for people with Medicare provided through private plans that contract with the federal government. A number of drugs have generic equivalents, which can substantially lower the cost. For example, the monthly price of Gleevec (imatinib) is about $4200 while that for its generic version is about $60.

About two-thirds of the FDA-approved protein kinase inhibitors have orphan drug status (Table 3). An orphan drug is a pharmaceutical agent that is developed to treat rare medical conditions. To qualify for orphan drug status in the United States, the total number of potential patients should be less than 200,000. The idea supporting orphan drug status is to stimulate development of drugs for patients with uncommon diseases. The notion behind orphan drug status is that such drugs would not be profitable to produce without government assistance owing to the small population of affected patients. The advantages of orphan-drug status for drug companies include tax credits of 25%, research grants for conducting clinical trials, exemptions from U.S. Food and Drug Administration user fees, and enhanced marketing exclusivity (up to seven years after regulatory approval).

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

The average monthly cost of approved kinase antagonists used in the treatment of neoplastic disorders is $17,900 with a median price of $17,000 (Table 3). One of the more expensive FDA-approved kinase inhibitors is futibatinib ($44,000 per month), which is an irreversible antagonist approved for the treatment of bile duct cancers bearing FGFR2 fusion proteins [82]. An alternative drug prescribed for the treatment of bile duct cancers targeting FGFRs is pemigatinib with a monthly cost of $27,000. Results from clinical trials do not favor one drug over the other [83]; the difference in pricing is thus unrelated to clinical efficacy. Infigratinib had also been approved for the treatment of this uncommon disorder, but the distribution of this FGFR inhibitor has been discontinued in the United States [84]. Erdafitinib is a FGFR1/2/3/4 blocker, which is used for the treatment of urothelial bladder cancers, that costs $21,000 for 30 days and nintedanib, which is an FGFR antagonist prescribed for the treatment of idiopathic pulmonary fibrosis, is priced at $12,000 (Table 4). The mean monthly cost for these four drugs is $18,000.

Nine of the FDA-approved small molecule kinase inhibitors target the EGFR (ErbB) family of receptor protein-tyrosine kinases, one of the most common kinase targets. Lung cancer is one of the most prevalent cancers in the U.S. with an estimated incidence 240,000 new cases in 2023 [85], with about 85% corresponding to NSCLC. Surgery is the primary mode of treatment in patients with localized disease [86]. In patients with advanced or non-localized disease, platinum cytotoxic therapy is used in patients with low expression of PD-L1. With high levels of expression of PD-L1, pembrolizumab (Keytruda) can be prescribed as a single agent. Small molecule kinase inhibitors are used in patients with EGFR mutations. These drugs, which are six in number, include afatinib ($11,000 per month, approved in 2013), erlotinib ($8100, 2004), gefitinib ($7500, 2003), dacomitinib ($17,000, 2018), mobocertinib ($28,000, 2021), and osimertinib ($31,000, 2015) (Table 5). The nearly universal development of drug resistance to gefitinib and erlotinib prompted the development of second- and third-generation inhibitors of EGFR and its drug-resistant mutants (L858R/T790M, C797S, EGFR ex20ins) [87]. The more expensive mobocertinib is recommended for the treatment of patients possessing EGFR exon 20 insertion mutations and osimertinib (an irreversible targeted covalent inhibitor (TCI) [27] is recommended for patients with EGFR exon 19 deletions or exon 21 L858R mutations [88].

Breast cancer is the most common malignancy diagnosed in women in the United States and is a significant cause of morbidity and mortality [85]. The occurrence of breast cancer exceeds that of lung cancer with an incidence of 298,000 new cases per year in women. As noted above, breast cancer is classified into three molecularly and clinically distinct subtypes, which are not mutually exclusive: HR-positive/HER2-negative, HER2-positive/hormone-receptor positive, and triple negative breast cancer (TNBC). The overall survival of patients with metastatic breast cancer continues to improve owing to increasingly effective therapies and supportive care. Patients with breast cancer are treated with surgery, radiation therapy, cytotoxic therapy, and targeted therapies [86]. HER2-positive disease accounts for about 15% of all diagnosed breast cancers. Docetaxel/-trastuzumab/pertuzumab represent the first line therapy and ado-trastuzumab emtansine (T-DM1) is a second-line therapy for HER2-positive disease. T-DM1 is a HER2-antibody drug conjugate linking the microtubule inhibitor (DM1) to a HER2 monoclonal antibody. Tucatinib/trastuzumab/capecitabine is FDA-approved as a third-line treatment. Tucatinib ($12,000/month) is a reversible HER2/ErbB2 antagonist approved in 2020 as a second or third line combination treatment of patients with unresectable HER2-positive breast cancer including those patients with brain metastasis (about one-third of patients). It is also approved (2023) for the second-line combination treatment of HER2-positive metastatic colorectal cancer. Neratinib ($22,000/month) is an irreversible inhibitor of EGFR/-HER2/HER4 that was FDA-approved in 2020 and lapatinib ($9000/month) is a reversible inhibitor of EGFR/HER2 that was approved in 2018 with a black box warning related to hepatotoxicity. These two drugs are approved for third-line treatment of metastatic HER2-positive breast cancer in combination with capecitabine, but they are less commonly used than the tucatinib combination (Table 5).

Both osimertinib (a third-generation blocker) and gefitinib (a first-generation antagonist) are approved 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	PDGFR, 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
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	FGFR1/2/3/ 4	RY	Urothelial bladder cancer	Y	8	$21,000	$252,000	N
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
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	VEGFR1/2/3	RY	Colorectal cancer, hepatocellular carcinoma, gastrointestinal stromal tumor	N	160	$14,000	$168,000	N
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	Y
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
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

[a] NRY, non-receptor protein-tyrosine kinase; RY, receptor protein-tyrosine kinase; S/T, protein-serine/threonine protein kinase; T/Y, dual specificity protein kinase.
[b] Ph^+, Philadelphia-chromosome positive.
[c] N, No; Y, Yes
[d] * indicates that one-half of the prescribed dose should be taken twice daily. ** indicates once weekly.
[e] Representative US drug prices were calculated from Pharmacychecker.com (price per pill or prescription unit) along with the dosage obtained from the FDA label to yield the drug prices per 30-day period. The annual drug cost was approximated by multiplying the 30-day cost times 12 (months).

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

cell lung cancer with exon 19 deletions or exon 21 substitutions (Table 5). The cost of the former ($31,000) is about four times that of the latter ($7500). As a newer third generation EGFR kinase inhibitor, osimertinib ($31,000 per month) has the same clinical effect as gefitinib in the treatment of non-small cell lung cancer with EGFR gene mutations, but progression-free survival is significantly longer than the gefitinib group, and the incidence of adverse reactions is lower [89]. There is also a tendency for more recently approved drugs to cost more than older drugs. The average monthly cost of the nine EGFR family inhibitors is about $16,200.

Nine of the FDA-approved small molecule kinase inhibitors target the JAK family of non-receptor protein-tyrosine kinases, one of the most common kinase targets. The average monthly cost of four of the drugs that are used for the treatment of neoplastic diseases is $19,000 and the monthly cost of the five of the drugs that are used in the treatment of inflammatory diseases, is $4600 (Table 6). Myelofibrosis, polycythemia vera, and essential thrombocythemia are a group of heterogeneous disorders of the hematopoietic system collectively known as Philadelphia chromosome–negative myeloproliferative neoplasms. The prevalence of myelofibrosis, essential thrombocytopenia, and polycythemia vera in the United States is estimated to be approximately 13,000, 134,000, and 148,000, respectively, indicating that they are orphan diseases [90]. Clinical studies do not favor one drug over another. However, fedratinib has a black box warning for the induction of encephalopathy. Although pacritinib was approved recently, its cost is the lowest of the group and this is unusual.

There are three general classes of drugs commonly used in the treatment of rheumatoid arthritis: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs) [91]. NSAIDs and corticosteroids have a short onset of action while DMARDs can take several weeks or months to produce a clinical effect. DMARDs include methotrexate, abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, leflunomide, rituximab, sulfasalazine, and tocilizumab. Methotrexate has been and is the first-line disease modifying anti-rheumatic drug for rheumatoid arthritis since the late 1990s. Methotrexate inhibits dihydrofolate reductase, preventing the reduction of dihydrobiopterin (BH_2) to tetrahydrobiopterin (BH_4), leading to nitric oxide synthase uncoupling and increased sensitivity of T cells to apoptosis, thereby diminishing immune responses. The TNF inhibitors approved by the FDA include adalimumab, certolizumab, etanercept, golimumab, infliximab, and sulfasalazine. Leflunomide is an immunomodulatory drug that may exert its effects by inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase, which plays a key role in the de novo synthesis of uridine monophosphate (UMP). Abatacept binds to the costimulatory molecules CD80 and CD86 on antigen-presenting cells (APC), thereby blocking interaction with CD28 on T cells. By targeting CD20, rituximab promotes cell lysis while sparing hematopoietic and plasma cells without this surface antigen. Anakinra is a recombinant, non-glycosylated form of IL-1Ra that competes with and inhibits IL-1 by binding to the IL-1 receptor; therefore, the administration of this drug reduces the inflammatory response in rheumatoid arthritis patients. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6–mediated signaling through these receptors.

Harrington et al. concluded that there is a role for JAK blockers in younger patients without significant cardiovascular risk and with active disease refractory to multiple classes of DMARDs [91]. However, they propose that it is hard to justify their use as a first-line advanced therapy in the majority of patients, particularly given the greater wealth of safety data about tumor necrosis factor inhibitors, tocilizumab, and abatacept in real world practice. Additionally, in many countries the JAK antagonists will remain a more expensive therapeutic option as it will be some time before generics arrive to the marketplace. The prevalence of rheumatoid arthritis in the United States and Europe is much larger than that of neoplastic diseases with ranges from 0.5% to 1.0% of the total population; the prevalence in Asia is somewhat less.

Renal malignancies have an estimated incidence of about 82,000 per year in the United States [85]. The most common subtypes include clear cell RCC (75%), papillary RCC (10%), and chromophobic RCC (5%). The prognosis of patients with renal cell carcinoma depends upon the clinical stage of cancer with a five-year survival of stage I cancer of about 85%, stage II with about 60%, stage III with about 25%, and stage IV with about 5%. The following targeted agents have been approved for the treatment of metastatic renal cell carcinoma by the U.S. Food and Drug Administration (FDA): sorafenib, sunitinib, pazopanib, axitinib,

Table 6
FDA-approved small molecule JAK family blockers.

Drug	Target	Disease	Cost/30 days	Cost/year	Generic	Approved
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
Upadacitinib	JAK1	Rheumatoid arthritis, psoriatic arthritis, atopic dermatitis	$6000	$72,000	No	2019

cabozantinib, lenvatinib, tivozanib, and bevacizumab [92]. These agents can be classified into the following groups by their mechanism of action. Sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, tivozanib, and lenvatinib are small-molecule protein-tyrosine kinase blockers. These agents inhibit angiogenesis by directly inhibiting receptors such as the vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs) or Fms-like tyrosine kinase receptor-3 (Flt3). Bevacizumab is a monoclonal antibody that binds directly with the vascular endothelial growth factor (VEGF) and prevents its engagement with the VEGF receptors. In addition, the FDA has approved several biologic agents for the treatment of metastatic renal cell carcinoma including (i) nivolumab (Opdivo), which is a PD-1 (programmed cell death 1) immune checkpoint inhibitor, (ii) ipilimumab (Yervoy), which is a monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4 in combination with nivolumab, (iii) the PD-1 immune checkpoint inhibitor pembrolizumab (Keytruda) with axitinib, (iv) and avelumab (Bavencio) with axitinib. For the first-line therapy, cabozantinib was associated with the highest progression free survival followed by avelumab + axitinib and pembrolizumab + axitinib [92]. For second-line therapy, cabozantinib was identified as the most effective treatment option when assessing progression free survival.

Of the six VEGFR blockers used in the treatment of renal cell carcinoma, the average monthly price was $17,300 with a median of ($16,000) (Table 7). Tivozanib was the most expensive ($30,000/month) and cabozantinib was the least expensive ($7000/month). In this situation, an older and less expensive drug (cabozantinib) is more effective that the newer and more expensive drugs. The cost of the frequently prescribed axitinib is $19,000 per month. Krawczyk et al. compared the effectiveness and safety profile of VEGFR inhibitors in the treatment of metastatic renal cell carcinoma [93]. At the first level, there was no difference in the effectiveness of VEGFR protein-tyrosine kinase inhibitors used as monotherapy. When the safety profile and incidence of limiting adverse events is considered, sorafenib ($23,000/month) and tivozanib ($30,000/month) represented the best treatment options. These investigators reported that a targeted protein-tyrosine kinase inhibitor in combination with nivolumab, pembrolizumab, or avelumab (a PD-L1 blocker – Padcev) had lower safety profiles. Nevertheless, these combinations are clinically effective as long as potential adverse effects are closely monitored and treated as necessary.

Chronic myelogenous leukemia is an indolent, or slow-growing, malignant hematological disease characterized by leukocytosis (an elevated white blood cell count) [58]. Chronic myelogenous leukemia accounts for about 15% of all cases of leukemia. The expected incidence of new cases in the United States in 2023 is 8930 (5190 males and 3740 females) and the expected number of fatalities is 1310 (780 males and 530 females) [85]. The natural history of CML, prior to the advent of small molecule protein kinase antagonists, was progression from a stable or chronic phase to an accelerated phase or to a rapidly fatal blast crisis within 3–5 years [58]. The diagnosis of chronic myelogenous leukemia is usually based on detection of the Philadelphia chromosome (Ph) as determined by conventional cytogenetic (karyotyping) analysis or fluorescence in situ hybridization (FISH) analysis of bone marrow samples. Chronic myelogenous leukemia, at least in the stable phase, is unique among malignancies in that the malady appears to be the result of a single major biochemical defect. In contrast, most malignancies are the result of several genetic and biochemical lesions. The BCR-Abl oncoprotein, an activated non-receptor protein-tyrosine kinase, thus represents a unique drug target that differs between normal and leukemic cells. Imatinib was approved by the FDA for the treatment of CML in 2001 and the usefulness of this small molecule protein kinase inhibitor in the treatment of cancer fostered the development of additional protein kinase antagonists [26].

The clinical effectiveness of drugs that are FDA-approved for the treatment of chronic myelogenous leukemia is vastly superior to other protein kinase inhibitors that are used in the treatment of other neoplasms [58,68]. Compared with an age-matched normal group, patients with CML have an annual mortality rate from this disorder of 0.5% or less, which is to say that the drug normalizes the lifespan of these people. Imatinib (first generation), dasatinib, nilotinib, and bosutinib (second generation) have been FDA-approved for frontline therapy, and ponatinib (third generation) is approved for resistant disease with a T315I BCR-Abl gatekeeper mutation or after failure of at least two other protein-tyrosine kinase inhibitors. Asciminib is a STAMP (specifically targeting the Abl myristoyl pocket) inhibitor now approved as a third-line treatment for CML and a first-line treatment in patients with the T315I mutation (the cost of these drugs is given in Table 8). Imatinib and nilotinib are the less expensive agents. Based upon a dosage of 80 mg/day, the cost of asciminib for chronic phase CML is $19,500 per month. However, the dosage prescribed for patients with the T315I mutation is 200 mg twice daily or 10 tablets per day at a cost of $326 per tablet, $3260 per day, $97,800 per month, or $1.17 million per year. With a patient's copayment of 25%, the out-of-pocket costs amount to more than $292,000 per annum. According to U.S. Census data, only 12% of American families have an income greater than $200,000 per year. The drug is prohibitively expensive for the treatment of patients with the T315I mutation.

The aim of current therapy is to (i) promote patient survival or (ii) to achieve treatment-free remission (TFR), whenever possible [94]. Treatment-free remission means that all drugs blocking BCR-Abl are discontinued. For fostering survival, frontline treatment with imatinib, bosutinib, nilotinib, or dasatinib are all effective. If imatinib therapy is used for frontline therapy, a change in therapy at the first evidence of resistant disease is now standard procedure. One reason for using imatinib initially is its availability as a generic drug at a cost lower than that of other agents. The choice of the second-line therapy is guided by an evaluation of possible mutations of the Abl kinase domain and by the patient's comorbidities and age. Adverse events produced by bosutinib include diarrhea (10–30%, which is mild and self-limited) and liver and kidney dysfunction. Dasatinib can produce pleural effusions (10–15%),

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 syndrome, gastrointestinal stromal tumors, myelodysplastic/myeloproliferative disease	$6000	$72,000	Yes	2001
Nilotinib	BCR-Abl	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

myelosuppression (10–20%), and occasional pulmonary hypertension (1–2%). Nilotinib treatment can produce hyperglycemia (10–15%) and exacerbate diabetes mellitus (5–10%) as well as produce pancreatitis (1–3%). Ponatinib produces the most serious side effects including hypertension (20–30%), vasospastic disease (10–15%), skin rashes (5–10%), and pancreatitis (5%). Despite producing the most serious adverse events, ponatinib is the most expensive of the BCR-Abl blockers.

Achieving a treatment-free remission is desirable in younger patients to avoid lifetime therapy. A deep molecular response (DMR), which is defined as a 4–4.5 log reduction in BCR-Abl-1 transcripts on the International Scale (the ratio of BCR-ABL1 transcripts to ABL1 transcripts), is used as a criterion for discontinuing drug treatment. Discontinuing therapy after a deep molecular response lasting two-to-three years is associated with a treatment-free remission rate of 50–60%. When this is done after five years, the probability of achieving a treatment-free remission is greater than 80%. When remission is not achieved, patients respond to the therapy prescribed before drug withdrawal. The concept of treatment-free remission was unthinkable at the beginning of the targeted protein kinase therapy era [58]. In the first decade of the 21st century, the idea that drug treatment for CML could be discontinued and the disease would remain abated was a pipedream. The average cost per month of the six FDA-approved drugs used for the treatment of chronic myelogenous leukemia are given in Table 8. The average value is about $15,400 with the oldest (imatinib) being the least expensive at $6000. This average value ($15,400) is near the average for all small molecule protein-kinase antagonists that are used in the treatment of all neoplastic diseases ($17,900). However, the cost of generic imatinib is $56/month. One advantage for the drug companies is that these BCR-Abl antagonists convert CML into a chronic disease with a steady income for years.

ALK-positive lung cancer patients make up about 5% of all lung cancer patients [95] and this corresponds to about 12,000 new cases in the United States per year [85]. The median survival of patients with these lung cancers is about four and a half years and about one-fifth of them die within two years of diagnosis. The average monthly cost of the five FDA-approved ALK inhibitors is $15,000 (Table 9) with ceritinib being the most expensive and brigatinib being the least expensive. Crizotinib was the first of these drugs to be approved and was therefore the favored drug for first line use. Based upon recent clinical findings, alectinib and brigatinib are now favored as first-line therapies for ALK-positive NSCLC [96]. It is coincidental that these are the least expensive ALK antagonists. There is no set pattern for second-, third-, and following lines of treatment and all five drugs are used. Crizotinib is used for diseases in addition to ALK-positive lung cancer. Moreover, it was initially developed as a MET inhibitor and its broader range of targets may reflect the additional disease targets [55,57].

Table 9
FDA-approved small molecule ALK and Flt3 blockers.

Drug	Disease	Cost/30 days	Cost/ year	Generic	Approved
ALK antagonists					
Alectinib	ALK-positive NSCLC	$8400	$100,800	No	2015
Brigatinib	ALK-positive NSCLC	$6000	$72,000	No	2017
Ceritinib	ALK-positive NSCLC resistant to crizotinib	$21,000	$252,000	No	2014
Crizotinib	ALK- or ROS1-positive NSCLC, anaplastic large cell lymphoma, inflammatory myofibroblastic tumor	$20,000	$240,000	No	2011
Lorlatinib	ALK-positive NSCLC	$19,000	$228,000	No	2018
Flt3 antagonists					
Gilteritinib	*FLT3*-mutation positive acute myeloid leukemia	$26,000	$312,000	No	2018
Midostaurin	*FLT3*-mutation positive acute myeloid leukemia in combination with cytarabine and daunorubicin	$22000	$264,000	No	2017
Quizartinib	*FLT3* internal tandem duplication positive acute myelogenous leukemia in combination with cytarabine and daunorubicin	$17,000	$204,000	No	2023

Non-receptor CDK4/6 protein-serine/threonine kinase inhibitors

were added to the breast cancer armamentarium in 2015 with the approval of palbociclib (Table 10). Abemaciclib and ribociclib were added in 2017. The average cost of these three drugs is about $17,000 monthly, which is near the average cost of all FDA-approved small molecule protein kinase inhibitors used for the treatment of neoplasms. In this "real-world" population of patients with $HR^+/HER2^-$ metastatic breast cancer, palbociclib in combination with endocrine therapy was associated with improved progression-free survival outcomes (20.0 months) compared with patients treated with letrozole alone in the first-line setting (11.9 months) [97]. Although palbociclib failed to improve overall survival, both ribociclib and abemaciclib with endocrine therapy improved overall survival. Such findings suggest that the latter two drugs should be used in preference to palbociclib.

Siegel et al. estimate that the number of new cases of in situ melanoma of the skin in 2023 will be 89,070 (58,120 male, 39,490 female) and the number of deaths will be 7990 (5420 male, 2520 female) [85]. About one in 25 cases of melanoma (3600) will have metastasis or spread to distant parts of the body, and these are the types of cases that can be treated with a combination of MEK1/2 and B-RAF inhibitors (Table 11). About half the cases of melanoma bear *BRAF* mutations [98]. The effectiveness of the three drug combinations is about equal and the cost of the combinations of the drugs is nearly the same: binimetinib and encorafenib ($21,100 per month), cobimetinib and vemurafenib ($19, 500), and trametinib and dabrafenib ($20,800). Note that each of these combinations is the product of a single drug company (Table 11), thus facilitating clinical trials with a combination of drugs. Genentech became a member of the Roche group in 2009.

The Bruton non-receptor protein-tyrosine kinase (BTK), a deficiency of which leads to X-linked agammaglobulinemia, plays a central role in B cell antigen receptor signaling [99]. Owing to the exclusivity of this enzyme in B cells, the acronym could represent B cell tyrosine kinase. BTK is activated by the Lyn and SYK protein kinases following activation of the B cell receptor. BTK in turn catalyzes the phosphorylation and activation of phospholipase Cγ2 leading to the downstream activation of the Ras/RAF/MEK/ERK pathway and the NF-κB pathways. Both pathways participate in the maturation of antibody-producing B cells. Dysregulation of B cell receptor signaling occurs in several B cell neoplasms including mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström macroglobulinemia. Acalabrutinib, ibrutinib, and zanubrutinib are targeted covalent inhibitors that react with BTK C481 while pirtobrutinib is a reversible BTK blocker (www.brimr.org/PKI/PKIs.htm).

Ibrutinib, which was the first of this quartet to be approved, is promiscuous with many side effects [100]. This agent is a potent inhibitor of ITK, TXK, BMX, EGFR, Blk, and JAK. The most common adverse reactions (≥20%) in patients with B-cell malignancies were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia. Zanubrutinib is also a potent blocker of TXK, BMX, EGFR, and BLK. Its most common adverse reactions (≥ 20%) include neutropenia, thrombocytopenia, decreased white blood cell count, anemia, upper respiratory tract infection, rash, bruising, diarrhea, and cough. Acalbrutinib appears to be less promiscuous and fails to inhibit the kinases that are adventitious targets of ibrutinib and zanubrutinib. The average monthly cost of the four FDA-approved BTK antagonists is $14,750; zanubrutinib is the least expensive and the newest drug (pirtobrutinib) is the most expensive (Table 8). Although all are effective in the treatment of mantle cell lymphoma, pirtobrutinib may have fewer side effects than the others.

About one-third of leukemia cases are of the acute myeloid type [85]. The estimated incidence of acute myeloid leukemia in the United States in 2023 is 20,380 (11,410 male and 8970 female) and the estimated number of deaths is 11,310 (6440 male and 4870 female) [85]. The five-year survival of patients with AML is about 30%. Mutations in the *FLT3* gene occur in about 30% of AML cases. These mutations include internal tandem duplications in the JM domain (25%) and point mutations in the tyrosine kinase domain (5%) [101]. The average cost of three FDA-approved drugs exclusively targeting mutant *FLT3* is about $21,700 (Table 9). At the present time, the three drugs have about equal clinical effectiveness. In addition to these three drugs, pacritinib, sorafenib, and sunitinib are also used to treat this hematological malignancy and there is a place for each of them in the treatment of *FLT3*-mutation positive AML.

Gastrointestinal stromal tumor (GIST) is a rare sarcoma of the digestive tract typically driven by mutations of *KIT* (80%) or *PDGFRA* (5–10%) [102]. Imatinib is FDA-approved for the first-line treatment of patients with *KIT*-mutation positive GIST, sunitinib is the standard second-line treatment, and regorafenib is the preferred third-line treatment [103]. Because imatinib has a generic version, it is the least expensive of the drugs. Owing to mutations that occur during these treatments, there is a need for additional lines of treatment. This has led to the development and approval of avapritinib and ripretinib in 2020 [102,104]. The monthly cost of these drugs is relatively high (near $40, 000 monthly, Table 12). Unfortunately, neither drug improves the outcome of GIST patents in comparison with standard care in earlier times. Imatinib-resistant GIST represents an on-going therapeutic challenge using new protein kinase inhibitors or immune-oncology agents [103].

Larotrectinib and entrectinib were FDA-approved for the treatment of solid tumors with NTRK fusion proteins in 2018 and 2019, respectively [105]. *NTRK1*, *NTRK2*, and *NTRK3* genes encode the tropomyosin receptor kinase (TRK) family (TRKA, TRKB, and TRKC), which are transmembrane receptors that bind the neurotrophins and activate downstream signaling cascades through phosphatidylinositol 3–kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR), RAS/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and phospholipase Cγ pathways. Abnormalities in the TRK pathway, principally *NTRK* gene fusions, are involved in cancer pathogenesis since they produce a constitutive activation of downstream pathways. NTRK fusions are rare events in the most common cancers (prevalence of NTRK fusions < 5%) but are rather frequent in some rare cancers such as infantile fibrosarcoma and secretory breast carcinoma (prevalence of *NTRK* fusions > 90%). In both cases, *NTRK* fusions have demonstrated a driver role in tumorigenesis and progression, making NTRK an optimum agnostic biomarker for targeted therapy with TRK inhibitors. The agnostic designation means that the type of solid tumor is not relevant as long as it bears an NTRK

Table 10
FDA-approved small molecule CDK4/6 antagonists.

Drug	Target	Disease	Cost/30 days	Cost/ year	Generic	Approved
Abemaciclib	CDK4/ 6	HER2-positive breast cancer, both monotherapy and combination therapy	$15,000	$180,000	Yes	2017
Palbociclib	CDK4/ 6	Breast cancer (HER2-positive or negative) combination therapy	$16,000	$192,000	Yes	2015
Ribociclib	CDK4/ 6	Breast cancer (HER2-postitive or negative) combination therapy	$20,000	$240,000	No	2017
Trilaciclib	CDK4/ 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

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
Pralsetinib	RET	RET-fusion protein NSCLC, RET mutant medullary thyroid cancer, RET fusion thyroid cancer	$23,000	$276,000	No	2020
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	$276000	No	2019

fusion protein. The cost of larotrectinib is more than twice that of entrectinib, and there is no clinical evidence of the superiority of one compared with the other (Table 12). In addition to blocking TRK, entrectinib also inhibits the action of ROS1 leading to its use in the treatment of ROS-1 positive NSCLC. See Ref. [105] for a summary of other FDA-approved tissue-agnostic therapies and a summary of the clinical trials that led to the approval of entrectinib and larotrectinib.

As reported in 1985, Takahashi et al. transformed murine NIH 3T3 fibroblasts with sonicated human lymphoma DNA [106]. They determined that the transforming sequence encompassed 34 kilobases and was made up of a rearrangement of two normal but unlinked DNA segments. Because this transforming sequence was the product of gene rearrangement during transfection, they named it "REarranged during Transfection," or RET. RET was subsequently identified as the receptor for the glial-cell derived neurotrophic factor (GDNF) [107]. Besides GDNF, this family of ligands includes artemin (ARTN), neurturin (NRTN), and persephin (PSPN) [108]. RET is a transmembrane receptor protein-tyrosine kinase that is required for the normal development of the brain, the peripheral sympathetic and parasympathetic nervous systems, the neuroendocrine thyroid calcitonin producing C-cells, thyroid, lung as well as hematopoietic progenitors and other tissues. [108].

About 1–2% of patients with NSCLC harbor activated RET-fusion proteins [108]. The incidence of new cases of RET-fusion protein lung cancer is about 2000–4000 per year. KIF5B-RET is the most common RET-fusion protein identified in NSCLC. RET point mutations occur in a large percentage of patients with medullary thyroid carcinomas that are derived from thyroid C-cells as well as metastatic thyroid cancer (non-parafollicular). Patients with RET-driven cancers were formerly treated with broad spectrum RET antagonists including cabozantinib and vandetanib for the treatment of medullary thyroid cancers and lenvatinib and sorafenib for differentiated thyroid cancers [108]. In 2020, pralsetinib and selpercatinib, which more specifically target RET, have been FDA-approved for the treatment of RET-fusion protein NSCLC, *RET*-mutant medullary thyroid cancer, and *RET*-mutant differentiated thyroid cancer (Table 12). The monthly cost of these two drugs is comparable at about $23,000. See Ref. [109] for a description of the clinical trials that lead to the approval of pralsetinib and selpercatinib for *RET*-mutant medullary and non-medullary thyroid cancers and RET-fusion protein NSCLC.

6. Discussion

The average monthly cost for the treatment of neoplastic diseases with FDA-approved small molecule protein-kinases antagonists was $17,900 corresponding to an annual cost of about $215,000. Futibatinib was near the high end with a maximum monthly cost of $44,000 and an annual cost of about $528,000 (used to treat cholangiocarcinomas with FGFR2 fusions). Binimetinib was at the low end with a monthly cost of $5100 and an annual cost of $61,200 (melanoma). Because binimetinib is usually given concurrently with encorafenib ($21,100 monthly and $253,000 annually together) the $5100 figure is somewhat off. As noted above, the monthly cost of asciminib for the treatment of mutant BCL-Abl T315I is $97,800 per month, or $1.17 million per year. The average monthly cost for the treatment of non-neoplastic diseases was $6800 and $81,600 per annum. Belumosudil was at the high end with a maximum of $17,000 per month or $204,000 per annum (graft vs. host disease). Netarsudil eye drops were at the low end with a monthly cost of $200 and $2400 per annum (glaucoma).

According to the U.S. Census Bureau, the average U.S. household income in 2022 was $105,555, while the median U.S. household income was $74,580. Without private or public health insurance, the kinase inhibitor costs are prohibitive. The above data reflect drug costs in the United States in the second half of 2023. Drug manufacturers typically increase their prices in January and July. Accordingly, the actual drugs

prices in the United States in 2024 will be higher than reported here. Moreover, the increase is usually greater than the rate of inflation.

The above data show that the cost of small molecule FDA-approved protein kinase inhibitors is quite expensive and contributes to their financial toxicity. Financial toxicity refers to the financial hardship experienced by patients taking these drugs, which is especially so with cancer patients [110]. The problem of financial toxicity is increasing since the costs of care is increasing with newer treatments, the prevalence of cancer is growing, and many survivors live with cancer as a chronic disease. Depending on the country and thus the healthcare system, financial toxicity prevalence varies widely, but studies have shown consistently that its presence is associated with lower quality of life, poorer adherence to or delay of care, and early mortality. High costs of cancer care are a recognized cause of financial toxicity through medical costs (such as the cost of new treatments), non-medical costs (e.g., cost of travel to hospitals in distant cities), or indirect costs (e.g., lost wages resulting from time off work for cancer treatment). Even if healthcare is available to everyone via universal health insurance coverage, patients have out-of-pocket (OOP) expenses in relation to their disease and its treatment. Since many cancer survivors experience long-term symptoms and side effects, these costs can continue for years after diagnosis.

Data indicate that up to three-quarters of cancer patients reported financial toxicity [110]. Predictors of financial toxicity included younger age, female gender, and a more recent diagnosis. Moreover, there is a relationship between financial toxicity and symptom burden and psychiatric symptoms including depression. While the focus on financial toxicity has historically been on the costs of cancer care, especially in light of the significant rise in the cost of cancer medicines, limitations in or inability to work are also likely to contribute to financial toxicity. Similarly, reduced income and missed days of work due to illness are associated with financial hardship. Data on employment after cancer show that as many as 40% of employed cancer survivors do not return to work after cancer diagnosis and inability to work is associated with greater financial hardship and reduced quality of life. Those more likely to return to work after diagnosis are individuals with a higher educational level, male gender, those with less invasive surgery, those with longer sick leaves, and those with provision of workplace accommodations such as flexible hours and rehabilitation services.

In 2021, the U.S. spent 17.8% of gross domestic product (GDP) on health care, nearly twice as much as the average Organization for Economic Co-operation and Development (OECD) country (www.healthsystemtracker.org). OECD is a unique forum where the governments of 37 democracies with market-based economies collaborate to develop policy standards to promote sustainable economic growth. Health spending per person in the U.S. was nearly two times higher than that in the closest country, Germany, and four times higher than that in South Korea. Health spending per person in the U.S. was $12,914 in 2021, which was over $5,000 more than any other high-income nation. Despite having the most expensive health care system, the United States ranks last overall compared with six other industrialized countries—Australia, Canada, Germany, the Netherlands, New Zealand, and the United Kingdom—on measures of quality, efficiency, access to care, equity, and the ability to lead long, healthy lives (aspe.hhs.gov). Moreover, the U.S. spends twice as much on prescription drugs as other comparatively wealthy nations, on average. In 2022, private insurers and government health programs spent about $963 per capita on prescription drugs while comparable countries spent an average of about $466.

The way that medicines are paid for in the U.S. is so convoluted and byzantine that some drugmakers set two prices for the same drug—and many health plans are choosing to cover the more expensive version. The decisions mean some patients are paying hundreds or thousands of dollars more in out-of-pocket charges to fill a prescription for an identical medicine made by the same company. Health-insurance plans that pay for many medicines often use middlemen, called pharmacy-benefit managers, to negotiate how much the plans will pay. Usually, the pharmacy-benefit managers ask for rebates from manufacturers in exchange for putting a drug on their list of covered medicines, called a formulary. A higher-priced drug can result in a larger rebate to the pharmacy-benefit manager, an inherent conflict of interest.

Drug manufacturers claim that they must offer the costlier versions to gain a favorable place on the formulary because the pharmacy-benefit managers prefer the higher rebates and fees of costlier drugs. The manufacturers state that their drugs' lower-priced twins appeal to hospitals and health systems that purchase the medicines themselves. Pharmacy-benefit managers assert that the rebates lower their plans' final costs for drugs. Some plans use the rebate money to help keep a lid on premiums for all their members. Pharmacy-benefit managers suggest that drug companies set their own prices and plans sometimes choose to cover the higher list price of a drug because manufacturers' rebates make them cheaper even than the versions with lower list price. It will continue to be difficult to decrease drug costs in the U.S. despite passage of the U.S. Inflation Reduction Act in 2022 owing to the role of legislators in the United States in drug pricing. The pharmaceutical industry spends more on lobbyists that curry favor with members of the U.S. House of Representatives and U.S. senators than any other industry, a total of about $240 million annually. The lobbyists in turn make contributions to the legislator's election campaign.

The profit margins of large pharmaceutical companies average about 21% (www.forbes.com); this calculation is based on net profit/revenues $\times$ 100% where net profit represents revenues minus cost (including research, development, clinical trials, and advertising). In contrast, the median profit margin of all large companies in the United States is about 6.5% (www.aei.org). This 300% greater profit margin of drug companies is one component that contributes to the excessive cost of many prescription drugs in the United States. The salaries of lawyers and personnel of contract research organizations that have inserted themselves as necessary brokers between pharmaceutical companies and consumers contribute to the excessive cost of drugs and drug development. The salaries of pharmacy-benefit managers and the fees that these for-profit companies extract for services rendered are additional factors adding to the overall price of pharmaceutics to the patient.

The drug companies state that decreasing the cost of drugs will stymie drug development. However, drug companies spend more money on advertising than they do on drug development. If they need more funds for development, advertise less. The prices of new anticancer agents seem to be decided by pharmaceutical companies according to what the market will bear [111]. There is little correlation between the actual efficacy of a new protein kinase blocker and its price as measured by cost-efficacy, prolongation of patient life in months-to-years, or improved quality of life. Moreover, there is no evidence that more expensive kinase inhibitors, on average, are more effective than their lower priced counterparts.

After the passage of the U.S. Inflation Reduction Act in 2022, Medicare will be able to negotiate drug prices for expensive drugs [112]. This includes 10 drugs in 2026, 15 drugs in 2027, and 15 drugs in 2028. The drugs that are under negotiation for 2026 include ibrutinib ($2.9 trillion in annual costs in 2020) and palbociclib ($2.1 billion in annual costs in 2020). Ruxolitinib may be under negotiation for 2027 ($1.3 billion in annual costs in 2020) and tofacitinib may be under negotiation for 2028 ($575 million in annual costs in 2020) [113]. Note that tofacitinib is an anti-inflammatory medicine. The Inflation Reduction Act also promises to lower the out-of-pocket expenses to $2000 in 2025 [114] Owing to the large amount of money involved, the implementation of this act will face legal challenges [115]. The U.S. Judiciary and the U.S. Supreme Court have favored big business for several decades and we believe that parts of the Inflation Reduction Act related to drug pricing will be overturned.

The development of small molecule protein kinase antagonists represents a bona fide medical breakthrough [68]. As the FDA approves new kinase antagonists, companies seem to analyze the market response

to similar previously approved drug(s) and they set the price of the new one somewhat higher. In the oncology setting, there seems to be little correlation between the benefit of a new drug and its price. Owing to the current high cost of co-payments in the United States, health insurance does not eliminate this financial worry among cancer patients. Medical debt is the most common cause of personal bankruptcy in the United States. Because of financial distress, patients become noncompliant and may take less than the prescribed amount of a medication or none-at-all [110]. If the patient fails to take the medication, it helps neither the patient nor the drug company. Owing to the work of thousands of investigators worldwide in developing targeted cancer therapies, more must be done to fairly distribute the fruits of this research to any patient worldwide who might benefit from the end result.

CRediT authorship contribution statement

Roskoski Robert: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The author is unaware of any affiliations, memberships, or financial holdings that might be perceived as affecting the objectivity of this review.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.107036.

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