Various Protein Kinase Inhibitors as Anticancer Agents

Subjects: Oncology

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Protein kinases (PTKs) are enzymes that regulate the biological activity of proteins by phosphorylation of certain amino acid residues. This reaction causes a conformational change from an inactive to an active form of the protein, which is one of the most important regulatory mechanisms of the cell cycle and transduction of external signals. Dysregulation of protein kinases activity is implicated in the processes of carcinogenesis and the progression of various solid cancers. Therefore, protein kinases are prime targets for the development of selective anticancer drugs.

Protein kinases Anticancer agents Small molecule inhibitors

1. Tyrosine Kinase (TK) Inhibitors

Tyrosine kinases (RTKs) are enzymes that selectively phosphorylate the hydroxyl groups of a tyrosine residue in different proteins with adenosine triphosphate (ATP) as the source of phosphate. They have a share in the regulation of the most fundamental cellular processes, such as growth, differentiation, proliferation, survival, migration and metabolism of cells or programed cell death in response to extracellular and intracellular stimuli [1]. There are two types of tyrosine kinases, namely receptor tyrosine kinases (RTKs) and nonreceptor tyrosine kinases (NRTKs) [2]. A lot of RTKs and NRTKs are associated with cancers, thus a significant number of tyrosine kinase inhibitors (TKIs) are currently in clinical development. Since 2011, the FDA approved eleven new anticancer drugs that are inhibitors of anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR or HER1), human epidermal growth factor receptor 2 (HER2), human epidermal growth factor receptor 4 (HER4), fibroblast growth factor receptors (FGFRs), vascular endothelial growth factor receptors (VEGFRs), mesenchymal-epithelial transition factor (MET) or receptor tyrosine kinase rearranged during transfection (RET) (**Table 1**). These drugs show anticancer activity by blocking multiple molecular signal transduction pathways (**Figure 1**).

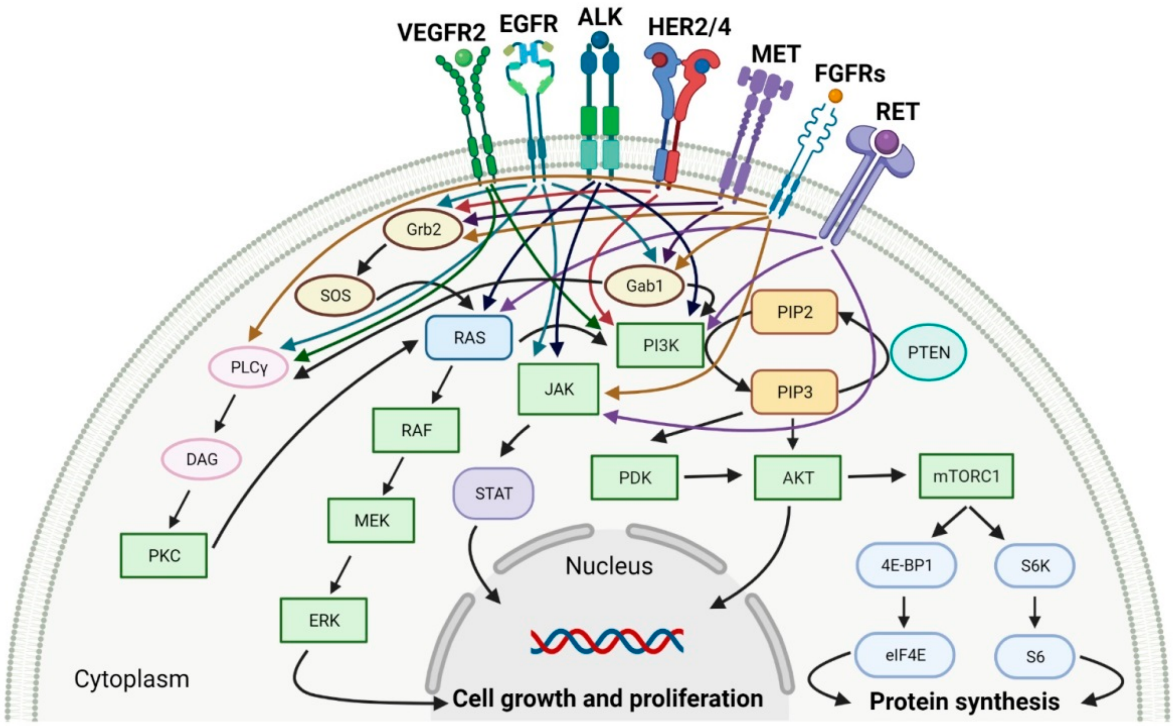

Figure 1. Molecular signal transduction pathways for specific receptor tyrosine kinases (RTKs). **VEGFR2**: vascular endothelial growth factor receptor 2. **EGFR**: epidermal growth factor receptor. **ALK**: anaplastic lymphoma kinase. **HER2/4**: human epidermal growth factor receptor 2 and 4. **MET**: mesenchymal-epithelial transition factor. **FGFRs**: fibroblast growth factor receptors. **RET**: tyrosine kinase rearranged during transfection receptor. **Gab1**: Grb2-associated-binding protein 1. **Grb2**: growth factor receptor-bound protein 2. **SOS**: Son of sevenless. **PLCγ**:. phospholipase C gamma. **DAG**: diacylglycerol. **PKC**: protein kinase C. **RAS**: rat sarcoma viral oncogene homolog. **RAF**: proto-oncogene serine/threonine-protein kinase. **MEK**: mitogen-activated protein kinase kinase. **ERK**: mitogen-activated protein kinase. **PI3K**: phosphatidylinositol 3-kinase. **PIP2**: phosphatidylinositol 4,5-bisphosphate. **PIP3**: phosphatidylinositol-3,4,5-trisphosphate. **PTEN**: phosphatase and tensin homolog deleted on chromosome ten. **PDK**: 3-phosphoinositide-dependent protein kinase. **AKT**: protein kinase B. **mTORC1**: mammalian target of rapamycin complex 1. **4E-BP1**: 4E-binding protein 1. **eIF4E**: eukaryotic translation initiation factor 4E. **S6K**: p70S6 kinase. **S6**: S6 protein. **JAK**: Janus kinase. **STAT**: signal transducer and activator of transcription. Created with BioRender.com based on information in [3][4][5][6][7][8][9].

The oncogenic driver mutations identified in non-small-cell lung cancer (NSCLC) include ALK gene rearrangements, ROS1 gene rearrangements, EGFR mutations, MET mutations and RET rearrangements [10]. In NSCLC harboring ALK gene rearrangements are observed ALK fusion proteins with potent transforming activity as oncogenic drivers of tumor growth [11]. **Ceritinib** is the second-generation AKL inhibitor that blocks autophosphorylation of ALK and ALK-mediated phosphorylation of signal transducer and activator of transcription 3 (STAT3), which is a downstream signaling protein [12][13]. Hence, this drug inhibits the cell cycle in the G1 phase and the proliferation of ALK-dependent cancer cells. Among the existing therapies targeting EGFR-mutated NSCLC, there have been two FDA-approved medicaments during the last eleven years, i.e., **osimertinib** and **mobocertinib**. **Osimertinib** is a third-generation, irreversible TK inhibitor of both EGFR TKI-sensitizing mutations

and a secondary EGFR mutation in exon 20, namely T790M [14]. **Mobocertinib**, on the other hand, is a first-in-class irreversible EGFR TK inhibitor, which was specifically developed to selectively inhibit oncogenic variants containing EGFR exon 20 insertion (EGFRex20ins) mutations. Both drugs form a covalent bond with cysteine 797 in EGFR with high-affinity binding resulting in sustained EGFR activity inhibition [15][16]. The difference in the structure of these drugs is the presence of an isopropyl ester group on the pyrimidine ring of **mobocertinib,** leading to increased selectivity for the EGFRex20ins mutant compared with **osimertinib** [16]. In NSCLC, MET and its mutant variants produced by gene mutation, amplification and overexpression are attractive targets for a blockade. For example, MET and variant with exon 14 skipping mutation are targets for **capmatinib** and **tepotinib** activity. The drugs act by inhibition of MET phosphorylation and the activation of key downstream effectors in MET-dependent cancer cell lines [17][18]. The cancers harboring RET alterations, particularly NSCLC, can be treated with **pralsetinib**. It selectively inhibits RET autophosphorylation and proliferation of RET-mutant cancer cells [9].

Overexpression of HER2 occurs approximately in 15 to 20% of breast cancers. **Neratinib** and **tucatinib** are inhibitors of the human epidermal growth factor receptors (HERs) that are used for the treatment of HER2-positive breast cancer (HER2 + BC). **Neratinib** irreversibly inhibits EGFR, HER2 and HER4 kinases, while **tucatinib** reversibly and highly selectively blocks HER2. The drugs have shown to be effective in monotherapy or in combination chemotherapy with **capecitabine** [19][20]. Patients with HER2 + BC who have disease progression after prior therapy with multiple HER2-targeted drugs may benefit from these TKIs used with or without **trastuzumab** [21][22]. The mechanism of action of both drugs includes binding to the ATP pocket of the HER2, which results in decreased receptor autophosphorylation and inhibition of downstream mitogen-activated protein kinase (MAPK) and phosphatidylinositol triphosphate kinase (PI3K) signaling. This leads to cell cycle arrest at the G1-S phase, thereby reducing cell proliferation [23][24].

FGFR2 fusion or rearrangements are present in 10–16% of intrahepatic cholangiocarcinomas. Treatment options, which improve clinical outcomes of patients with cholangiocarcinoma (CCA) harboring FGFR2 gene fusions, have been extended to the first two targeted therapies, i.e., **pemigatinib** and **infigratinib** [25][26]. The FDA approval of these TKIs includes the indication for adults with previously treated, unresectable, locally advanced or metastatic CCA. Their mechanism of action is a selective, ATP-competitive inhibition of fibroblast growth factor receptors (FGFRs). Both drugs potently inhibit FGFR1, FGFR2 and FGFR3 kinases and also demonstrate weaker activity against FGFR4 [27][28].

Renal cell carcinoma (RCC) is the most common type of kidney cancer. From a pathologist's point of view, RCC tends to be a highly vascular tumor. The prominent vascularization is due to the increased production of proangiogenic growth factors, such as vascular endothelial growth factor receptors (VEGFRs) [29]. **Tivozanib** is a quinoline-urea derivative that inhibits VEGFRs in an ATP-competitive manner. In particular, the drug shows inhibitory activity against VEGFR-1, VEGFR-2 and VEGFR-3 at picomolar concentrations. The analysis of the mechanism of action indicates that **tivozanib** produced a significant inhibition of the ligand-induced phosphorylation of VEGFRs causing direct anticancer activity as well as suppression of angiogenesis and vascular permeability [30]. In clinical trials, this agent used as third-line or fourth-line therapy in patients with RCC improved progression-free survival and was better tolerated than sorafenib [31]. The promising results of **tivozanib** led to its

approval by the FDA for the treatment of adult patients with relapsed or refractory advanced RCC following two or more prior systemic therapies [32].

Table 1. Features of the tyrosine kinase inhibitors approved as drugs by the Food and Drug Administration (FDA) from 2011 to 2022. The order of drugs is tabulated in order of most recent to oldest registration date. A generic name of a drug is an international nonproprietary name (INN).

No	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
1	Mobocertinib	EXKIVITY Takeda Pharmaceuticals America, Inc., Deerfield, IL, USA	FDA: 15 September 2021 EMA: Not approved		EGFR [1]	Oral	Non-Small Cell Lung Cancer	Diarrhea, rash, stomatitis, vomiting, decreased appetite, nausea, paronychia, musculoskeletal pain, dry skin, fatigue, decreased hemoglobin, decreased lymphocytes, increased creatinine, amylase, and lipase, decreased potassium, and magnesium	[33]
2	Infigratinib	TRUSELTIQ BridgeBio Pharma, Inc., Palo Alto, CA, USA	FDA: 28 May 2021 EMA: 21 August 2020		FGFRs [2]	Oral	Cholangiocarcinoma	Nail toxicity, stomatitis, dry eye, fatigue, increased creatinine, phosphate, alkaline phosphate, and alanine aminotransferase, decreased phosphate, and hemoglobin	[34] [35]
3	Tivozanib	FOTIVDA AVEO Oncology, Boston, MA, USA; Eusa Pharma (Netherlands) B.V., Schiphol-Rijk	FDA: 10 March 2021 EMA: 24 August 2017		VEGFRs [3]	Oral	Renal Cell Carcinoma	Fatigue, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough, stomatitis, sodium decreased, lipase increased, and phosphate decreased	[32] [36] [37]
4	Tepotinib	TEPMETKO EMD Serono, Inc., Darmstadt, Germany.	FDA: 3 February 2021 EMA:		MET [4]	Oral	Non-Small Cell Lung Cancer	Peripheral edema, diarrhea, fatigue, nausea, decreased appetite, increased	[38]

No	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
			Not approved					blood creatinine levels, hypoalbuminemia, increased amylase levels	
5	Pralsetinib	GAVRETO Genentech, Inc., South San Francisco, CA, USA	FDA: 4 September 2020 EMA: 18 November 2021		RET [5]	Oral	Non-Small Cell Lung Cancer	Fatigue, constipation, musculoskeletal pain, hypertension	[39] [40]
6	Capmatinib	TABRECTA Novartis Pharmaceuticals Corporation, Basel, Switzerland	FDA: 6 May 2020 EMA: Not approved		MET [4]	Oral	Non-Small Cell Lung Cancer	Peripheral edema, nausea, fatigue, vomiting, dyspnea, decreased appetite	[41]
7	Pemigatinib	PEMAZYRE Incyte Corporation, Wilmington, DE, USA	FDA: 17 April 2020 EMA: March 26, 2021		FGFRs [2]	Oral	Cholangiocarcinoma	Hyperphosphatasemia, alopecia, diarrhea, fatigue, dyspepsia	[42] [43]
8	Tucatinib	TUKYSA Seattle Genetics, Inc., Bothell, WA, USA	FDA: 17 April 2020 EMA: 11 February 2021		HER2 [6]	Oral	Breast Cancer	Diarrhea, palmar–plantar erythrodysesthesia syndrome, decreased hemoglobin or phosphate, nausea	[44] [45]
9	Neratinib	NERLYNX Puma Biotechnology, Inc., Los Angeles, CA, USA	FDA: 17 July 2017 EMA: 31 August 2018		EGFR [1], HER2 [6], HER4 [7]	Oral	Breast Cancer	Diarrhea	[46] [47]
10	Osimertinib	TAGRISSO AstraZeneca, Cambridge, UK	FDA: 13 November 2015 EMA:		EGFR [1]	Oral	Non-Small Cell Lung Cancer	Diarrhea, rash, dry skin, nail toxicity	[48] [49]

nd other genome through their oscillating level during the cell cycle [52]. The CDKs have been grouped into cell cycle related subfamilies (CDK1, 4 and 5) and transcriptional subfamilies (CDK7, 8, 9, 11 and 20). Dysregulating the CDKs and cyclins level leads to abnormal cell proliferation and tumor growth. Owing to the role of CDKs in cancer cells, their inhibition is an important target for novel anticancer drugs. The suppression of CDK4 and CDK6 activity is now being investigated to treat various solid tumors, including lung, prostate and ovarian cancers. The CDK4/6 inhibitors, i.e., **palbociclib**, **ribociclib** and **abemaciclib**, demonstrated promising clinical activity in the treatment of advanced breast cancer, thereby being recently FDA approved (**Table 2**) [53][54]. The approval of **abemaciclib** (as VERZENIO) includes using it for monotherapy or in combination with **fulvestrant,** which is an estrogen receptor antagonist. **Palbociclib** (as IBRANCE) was registered for combination therapy with **fulvestrant** or an aromatase inhibitor (**letrozole**). **Ribociclib** (as KISQALI) was approved only in combination with an aromatase inhibitor (**letrozole**) for initial endocrine-based therapy. All of these drugs are selective inhibitors of cyclin-dependent kinase 4 (CDK4) and 6 (CDK6). They inhibit Rb protein phosphorylation in the early G1 phase, thereby blocking cell-cycle

No	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
			24 April 2017						
11	Ceritinib	ZYKADIA Novartis Pharmaceuticals Corporation, Basel, Switzerland [59][60]	FDA: 29 April 2014 EMA: 6 May 2015		ALK [8]	Oral	Non-Small Cell Lung Cancer	Diarrhea, nausea, vomiting, abdominal pain	[50] [51]

[55][56][57][58]

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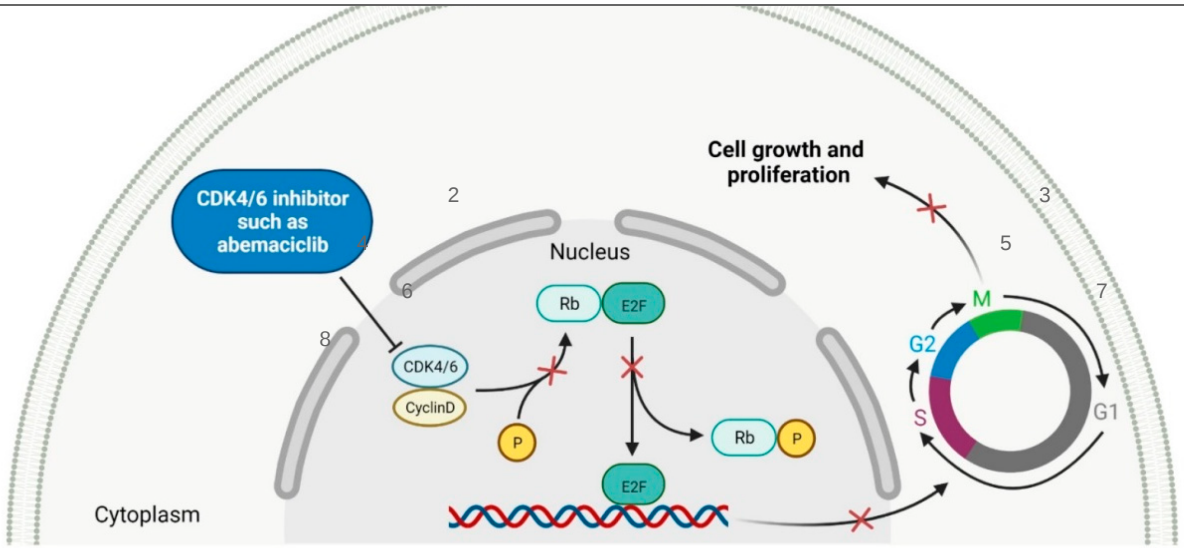


Figure 2. Mechanism of action of CDK4/6 inhibitors (the "x" on the arrows indicates process inhibition). **CDK4/6**: cyclin-dependent kinase 4/6. **P**: phosphate group. **Rb**: retinoblastoma protein. **E2F**: E2 factor. **G1**: first growth phase. **S**: synthesis phase. **G2**: second growth phase. **M**: mitotic phase. Created with BioRender.com based on information in Ref. [54].

Table 2. Features of the cyclin-dependent kinase inhibitors approved as drugs by the Food and Drug Administration (FDA) from 2011 to 2022. The order of drugs is tabulated in order of most recent to oldest registration date. A generic name of a drug is an international nonproprietary name (INN).

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
1	Abemaciclib	VERZENIO Eli Lilly and Company, Indianapolis, IN, USA	FDA: 28 September 2017 EMA: 27 September 2018		CDK4 [1], CDK6 [2]	Oral	Breast Cancer	Diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache,	[61] [62]

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
								thrombocytopenia, leucopenia	
2	Ribociclib	KISQALI Novartis Pharmaceuticals Corporation, Basel, Switzerland	FDA: 13 March 2017 EMA: 22 August 2017		CDK4 [1], CDK6 [2]	Oral	Breast Cancer	Neutropenia, nausea, infections, fatigue, diarrhea	[63] [64]
3	Palbociclib	IBRANCE Pfizer Inc., New York City, NY, USA	FDA: 3 February 2015 EMA: 9 November 2016		CDK4 [1], CDK6 [2]	Oral	Breast Cancer	Neutropenia, leukopenia, fatigue, anemia, nausea, arthralgia, alopecia, diarrhea, hot flush	[65] [66]

s by the hyperactivation of several different kinases (**Figure 3**). Multi-kinase inhibitor is one agent that targets a set of structurally related kinases leading to simultaneous blocking of their activity [67]. The use of one multi-kinase inhibitor is preferred to two single agents, since drug–drug interactions can trigger changing metabolism and activities against particular kinases. Multi kinase drugs become the second choice when their pharmacokinetic properties are worse. Besides, multi-kinase inhibitors are less specific and can consequently result in more side effects. The disadvantage during treatment with multi-kinase inhibitors is acquired resistance [68]. The approval characteristics of FDA-registered multi-kinase inhibitors are presented in **Table 3**.

[1] **CDK4**: cyclin-dependent kinase 4. [2] **CDK6**: cyclin-dependent kinase 6.

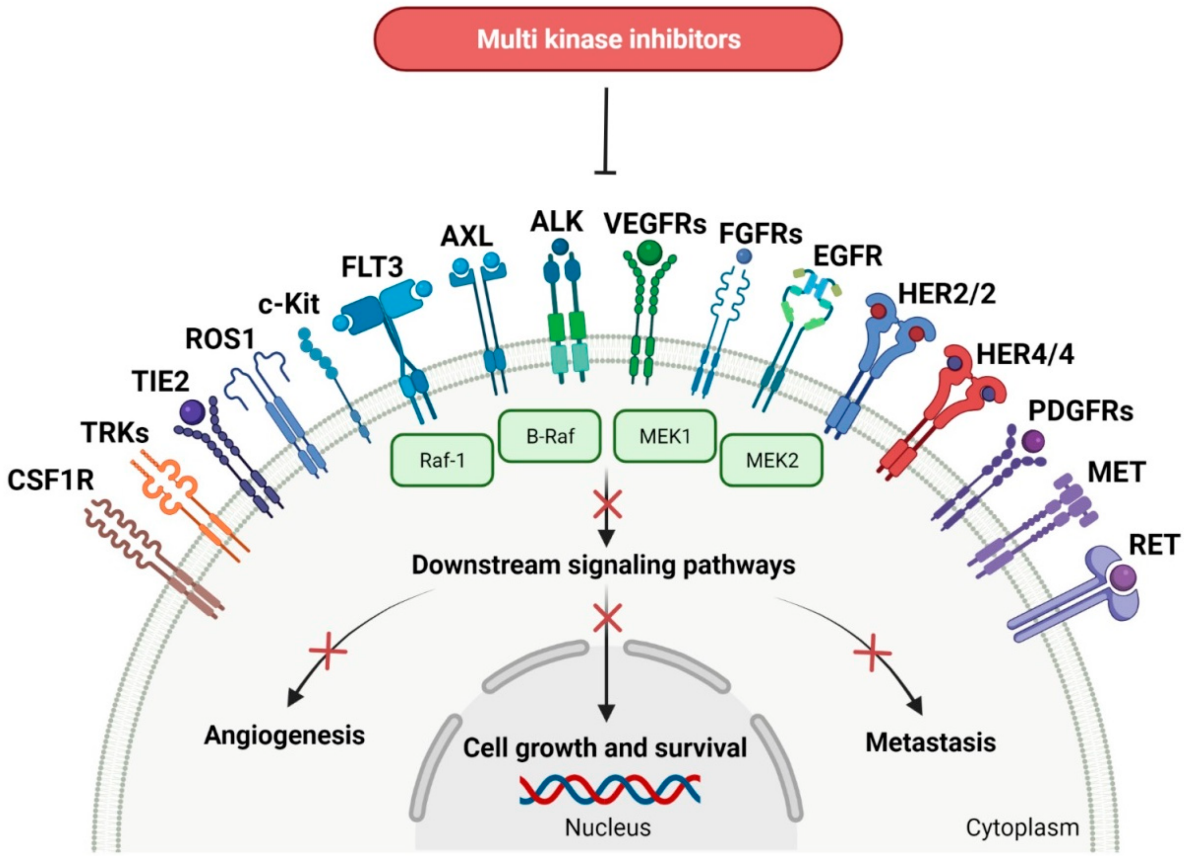


Figure 3. Schematic representation of mode of action of multi-kinase inhibitors that target a set of various related kinases (the “x” on the arrows indicates process inhibition). **CSF1R**: colony-stimulating factor 1 receptor. **TRKs**: tropomyosin receptor tyrosine kinases. **TIE2**: tunica interna endothelial cell kinase 2. **ROS1**: proto-oncogene tyrosine-protein kinase ROS. **c-Kit**: mast/stem cell growth factor receptor. **FLT3**: FMS-like tyrosine kinase-3. **AXL**: AXL receptor tyrosine kinase. **ALK**: anaplastic lymphoma kinase. **VEGFRs**: vascular endothelial growth factor receptors. **FGFRs**: fibroblast growth factor receptors. **EGFR**: epidermal growth factor receptor. **HER2/2**: human epidermal growth factor receptor 2 and 2. **HER4/4**: human epidermal growth factor receptor 4 and 4. **PDGFRs**: platelet-derived growth factor receptors. **RET**: receptor tyrosine kinase rearranged during transfection. **B-Raf**: serine/threonine-protein kinase B-Raf. **Raf-1**: RAF serine/threonine-protein kinase. **MEK1**: mitogen-activated protein kinase kinase 1. **MEK2**: mitogen-activated protein kinase kinase 2. **MET**: mesenchymal-epithelial transition factor. Created with BioRender.com.

Patients with NSCLC receiving the first-generation TKIs, e.g., **crizotinib**, **geftinib** and **erlotinib**, experienced issues related to acquired resistance. This resistance can develop by various mechanisms, such as **crizotinib**-resistant mutations in the anaplastic lymphoma kinase (ALK) domain. In addition, patients’ treatment with **crizotinib** often develops CNS metastases, likely due to the poor CNS penetration of **crizotinib**. However, **crizotinib** exhibits higher clinical response rates than standard chemotherapy and is recommended both for first-line therapy in NSCLC, as well as next-line therapy in patients who have not been treated with **crizotinib** previously. The next-generation multi-kinase inhibitors are designed to overcome TKI-resistant mutations. **Alectinib**, **brigatinib** and **entrectinib**, which are the second-generation ALK inhibitors, possess activity against treatment-resistant ALK mutants, whereas **lorlatinib**, which belongs to the third-generation drug, is highly selective proto-oncogene tyrosine-protein kinase ROS (ROS1) and ALK inhibitor and has the ability of robust brain penetration [69]. The second-generation EGFR TKIs, namely **dacomitinib** and **afatinib**, are characterized by their broader activity against HER family members and irreversibility, covalently binding to their targets of the kinases domain. They have the potential for anticancer activity against receptors with acquired mutations that are resistant to first-generation inhibitors. For example, **dacomitinib** specifically inhibits EGFR with exon 19 deletion or exon 21 L858R substitution mutations but also inhibits HER2, HER4 and transphosphorylation of HER3 [70].

Fibroblast growth factor receptor (FGFR) mutations are frequently observed in a variety of malignancies, e.g., FGFR2/3 alternations are common in urothelial carcinoma. **Erdafitinib**, a pan-FGFR inhibitor, is a promising therapy for cancers harboring these mutations. **Erdafitinib** obtained its first global approval in 2019 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma with FGFR alterations. The response to treatment was fast and independent of the number of previous therapies, the presence of visceral metastasis or tumor location [71]. The ongoing clinical trials show that **erdafitinib** demonstrated anticancer activity against other cancers, including cholangiocarcinoma, liver cancer, non-small cell lung cancer, prostate cancer, lymphoma and esophageal cancer [72]. The next drug approved by the FDA in 2019 is **pexidartinib**, which is used in the therapy of symptomatic tenosynovial giant cell tumor (TGCT). The drug is a selective inhibitor of the colony-stimulating factor 1 (CSF1) receptor, mast/stem cell growth factor receptor (c-Kit or CD117) and FMS-like tyrosine kinase 3 harboring an internal tandem duplication mutation (FLT3-ITD). The action mechanism of **pexidartinib** is to

arrest the kinase in the autoinhibited state by interacting with the CSF1R juxtamembrane region, which prevents an ATP and substrate binding [73].

The multi-kinase inhibitors that already obtained approval for the treatment of metastatic melanoma, an aggressive form of skin cancer with a high mortality rate, are second-generation serine/threonine-protein kinase B-Raf (B-Raf) inhibitors, such as **vemurafenib**, **dabrafenib** or **encorafenib** and mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitors, such as **trametinib**, **cobimetinib** or **binimetinib**. They are the most promising treatment strategies for melanoma consisting of selective inhibition of the active conformation of the B-Raf, especially with V600E mutation [74]. Furthermore, **dabrafenib** and **encorafenib** are also used in the therapy of cancers with several other mutated forms of B-Raf, e.g., V600K-mutated melanomas and V600K/D-mutated melanoma, respectively. The B-Raf inhibitors are characterized by high response rates, a mild, manageable toxicity profile and improved progression-free survival (PFS) as compared with chemotherapy, but their use is limited by the rapid development of resistance [75]. **Encorafenib** is distinguished among the other second-generation B-Raf kinase inhibitors by increasing its inhibitory effect with a shorter off-rate [76]. Currently, monotherapy with B-Raf inhibitor for the treatment of BRAF-mutated melanoma is subsequently replaced by combination therapy with B-Raf and MEK inhibitors, which target key enzymes in the MAPK signaling pathway (RAS-RAF-MEK-ERK). The approved combination of active anticancer ingredients, such as **vemurafenib** plus **cobimetinib**, **dabrafenib** plus **trametinib** or **encorafenib** plus **binimetinib**, is a more effective therapy than B-Raf inhibitor monotherapy and is recommended as a first-line therapeutic option in treating melanoma [77]. What is more, **encorafenib** and **binimetinib** combination therapy is already ongoing clinical development for the treatment of colorectal cancer (CRC). **Selumetinib**, the next inhibitor of MEK 1 and 2, is approved in children with neurofibromatosis type 1 and inoperable plexiform neurofibromas. The long-term treatment with **selumetinib** has meaningful benefits, such as a high level of clinical response and absence of cumulative toxic effects [78].

In 2020, the combination of **encorafenib** and monoclonal antibody (**cetuximab**) received its first approval for treating metastatic colorectal cancer (mCRC) [79]. CRC can also be treated with **regorafenib**, which is an inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3, tunica interna endothelial cell kinase 2 (TIE2), PDGFRB, c-Kit, FGFR1, RET, RAF proto-oncogene serine/threonine-protein kinase (RAF-1) and B-Raf, including wild-type B-Raf and B-Raf V600E [80]. The inhibitor possesses antiangiogenic activity due to the inhibition of TIE2. Moreover, it has anticancer activity against gastrointestinal stromal tumor (GIST), hepatocellular carcinoma and is ongoing clinical development for various malignant tumors. Another two drugs, which were approved in 2020 for GIST, are **avapritinib** and **ripretinib**. They inhibit mast/stem cell growth factor receptor (c-Kit) and platelet-derived growth factor receptor α (PDGFRA). **Avapritinib** is a therapy only for GIST harboring a PDGFRA exon 18 mutations, including PDGFRA D842V mutations, whereas ripretinib inhibits wild-type c-Kit and PDGFRA mutations, as well as multiple primary and secondary resistance mutations in GIST [81]. **Ripretinib** is an appropriate treatment for patients who were resistant to other approved tyrosine kinase inhibitors, such as **regorafenib** or **imatinib**. The mechanism of its action involves durably binding to both the switch pocket in the intracellular juxtamembrane domain and the activation loop in the kinase domain to prevent from adopting an active state of kinase and locking it in the inactive conformation, thereby inhibiting cell proliferation [82].

A total of six drugs, which have been approved by the FDA since 2011 for thyroid cancer treatment, are antiangiogenic multi-kinase inhibitors, including **vandetanib**, **cabozantinib** and **lenvatinib** or mutation-specific inhibitors, including **dabrafenib** for BRAF-mutated anaplastic thyroid cancer (ATC), **larotrectinib** for NTRK-fusion thyroid cancer and **selpercatinib** for RET-mutant medullary thyroid cancer (MTC). **Vandetanib** and **cabozantinib** are registered for the treatment of advanced MTC. The drugs inhibit EGF, RET and VEGF receptors or the MET, RET and VEGF receptors, respectively. Thus, their action involves blocking the sustaining proliferative signaling mediated by tyrosine kinase receptors, angiogenesis and apoptosis. **Cabozantinib**, due to downregulation of the MET pathway, may prevent invasiveness and metastatic spread of cancer cells and the development of acquired resistance. Hence, it induces more prolonged clinical responses than those to other TKIs. What is more, it displays stronger antiangiogenic activity than **vandetanib** [83]. However, the use of **cabozantinib** and **vandetanib** is at least partially limited by their adverse events. In contrast, next-generation drug **selpercatinib**, which is a highly potent and selective RET inhibitor, shows durable efficacy with a more satisfactory safety profile [84]. The first FDA-approved treatment for patients with anaplastic thyroid carcinomas (ATCs), a highly aggressive and undifferentiated cancer, is **dabrafenib** (B-Raf inhibitor) plus **trametinib** (MEK inhibitor). This dual inhibition improves overall response frequency and achieves better clinical results compared with B-Raf inhibitor monotherapy [85].

Larotrectinib is a highly selective TRK inhibitor that was developed for the therapy for cancers with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion in adults and children [86]. All patients undergoing the **larotrectinib** treatment were characterized by advanced solid tumors, including salivary gland tumors, infantile fibrosarcoma, thyroid cancer, NSCLC and other cancers. **Larotrectinib** also has potential efficacy against CNS tumors because of its ability to cross the blood–brain barrier [87]. The only other registered TRK inhibitor apart from **larotrectinib** is **entrectinib**, with activity against ALK, TRK and ROS1. In clinical trials, responses to **entrectinib** treatment were observed in the following diseases: NSCLC, mammary analog secretory carcinoma (MASC), colorectal cancer, melanoma, glioneuronal tumor and renal cell carcinoma (RCC) [88]. **Lenvatinib** is also used in therapy for RCC, as well as radioiodine-refractory differentiated thyroid cancer (RR-DTC), hepatocellular carcinoma and endometrial cancer. The inhibitor targets VEGFR-1, VEGFR-2, VEGFR-3, FGFR1-3, RET, mast/stem cell growth factor receptor (c-Kit) and platelet-derived growth factor receptor β (PDGFRB), thereby resulting in broad spectrum of direct antitumor activity and significant antiangiogenic effects [89]. Another drug for RCC is **axitinib**, which is approved for monotherapy in the second-line treatment and in combination with **pembrolizumab** or **avelumab** for first-line therapy [90][91]. It inhibits both proliferation and angiogenesis through blocking receptors, such as c-Kit and PDGFR on the one hand, and proangiogenic receptors VEGFR-1, VEGFR-2 and VEGFR-3 on the other. **Axitinib** has demonstrated promising activity in other solid tumors as well, including metastatic breast cancer, advanced NSCLC, pancreatic and thyroid cancers [92].

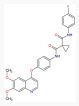
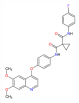
Table 3. Features of the multi-kinase inhibitors approved as drugs by the Food and Drug Administration (FDA) from 2011 to 2022. The order of drugs is tabulated in order of most recent to oldest registration date. A generic name of a drug is an international nonproprietary name (INN).

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
1	Ripretinib	QINLOCK Deciphera Pharmaceuticals, Inc., Waltham, MA, USA	FDA: 15 May 2020 EMA: 18 November 2021		c-Kit [1], PDGFRA [2]	Oral	Gastrointestinal Stromal Tumor	Alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar–plantar erythrodysesthesia syndrome, vomiting	[93] [94]
2	Selpercatinib	RETEVMO Eli Lilly and Company, Indianapolis, IN, USA	FDA: 8 May 2020 EMA: 11 February 2021		RET [3]	Oral	Non-Small Cell Lung Cancer, Thyroid Cancer	Increased AST levels, increased glucose levels, decreased albumin levels, decreased leukocyte levels, decreased calcium levels, increased creatinine levels, dry mouth, diarrhea, increased alkaline phosphatase levels, hypertension, fatigue, decreased platelet levels, edema, increased total cholesterol levels, decreased sodium levels, rash, constipation, decreased magnesium levels, increased potassium levels, increased bilirubin levels, headache, decreased glucose levels, nausea, abdominal pain, cough, prolonged QT interval, dyspnea, vomiting, hemorrhage	[95] [96]
3	Selumetinib	KOSELUGO AstraZeneca, Cambridge, UK	FDA: 13 April 2020 EMA: 17 June 2021		MEK1 [4], MEK2 [5]	Oral	Neurofibromatosis Type 1	Vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, musculoskeletal pain, fatigue, pyrexia, stomatitis, acneiform rash, headache,	[97] [98]

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
								paronychia, pruritus, dermatitis, constipation, hair changes, epistaxis, hematuria, proteinuria, decreased appetite, decreased cardiac ejection fraction, edema, sinus tachycardia, skin infection	
4	Avapritinib	AYVAKIT Blueprint Medicines Corporation, Cambridge, MA, USA	FDA: 9 January 2020 EMA: 24 September 2020		c-Kit [1], PDGFRA [2]	Oral	Gastrointestinal Stromal Tumor	Edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, increased lacrimation, abdominal pain	[99] [100]
5	Entrectinib	ROZLYTREK Genentech, Inc., South San Francisco, CA, USA	FDA: 15 August 2019 EMA: 31 July 2020		TRK [6], ROS1 [7], ALK [8]	Oral	Solid Tumors, Non-Small Cell Lung Cancer	Dysgeusia, fatigue, dizziness, constipation, nausea, diarrhea, increased weight, paresthesia, increased blood creatinine, myalgia, peripheral edema, vomiting, anemia, arthralgia, increased aspartate aminotransferase (AST)	[101] [102]
6	Pexidartinib	TURALIO Daiichi Sankyo, Tokyo, Japan	FDA: 2 August 2019 EMA: Not approved		CSF1R [9], c-Kit [1], FLT3 [10]	Oral	Tenosynovial Giant Cell Tumor	Hair color changes (depigmentation), fatigue, increased AST, increased alanine aminotransferase (ALT), dysgeusia, vomiting, periorbital edema, abdominal pain, decreased appetite, pruritus, hypertension, increased alkaline phosphatase	[103] [104]

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
7	Erdafitinib	BALVERSA Janssen Pharmaceuticals, Inc., Raritan (HQ), NJ, USA	FDA: 12 April 2019 EMA: Not approved		FGFRs [11] (1, 2, 3, 4)	Oral	Urothelial Carcinoma	Increased phosphate levels, stomatitis, fatigue, diarrhea, dry mouth, onycholysis, decreased appetite, dysgeusia, dry skin, dry eye, alopecia, palmar–plantar erythrodysaesthesia syndrome, constipation, abdominal pain, nausea, musculoskeletal pain	[72]
8	Larotrectinib	VITRAKVI Loxo Oncology, Inc., Stamford, CT, USA	FDA: 26 November 2018 EMA: 19 September 2019		TRK [6]	Oral	TRK Fusion Cancers	Fatigue, nausea, dizziness, vomiting, anemia, increased transaminase levels, cough, constipation, diarrhea	[105] [106]
9	Lorlatinib	LORBRENA Pfizer Inc., New York City, NY, USA	FDA: 2 November 2018 EMA: 6 May 2019		ALK [8], ROS1 [7]	Oral	Non-Small Cell Lung Cancer	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy	[107] [108]
10	Dacomitinib	VIZIMPRO Pfizer Inc., New York City, NY, USA	FDA: 27 September 2018 EMA: 2 April 2019		EGFR [12], HER2 [13], HER4 [14]	Oral	Non-Small Cell Lung Cancer	Diarrhea, paronychia, dermatitis acneiform, stomatitis, decreased appetite	[109] [110]
11	Encorafenib	BRAFTOVI Pfizer Inc., New York City, NY, USA	FDA: 27 June 2018 EMA: 20 September 2018		B-Raf [15]	Oral	Melanoma Metastatic, Colorectal Cancer	Nausea, diarrhea, vomiting, fatigue, arthralgia	[111] [112]

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
12	Binimetinib	MEKTOVI Array BioPharma Inc., Boulder, CO, USA	FDA: 27 June 2018 EMA: 20 September 2018		MEK1 [4], MEK2 [5]	Oral	Melanoma Metastatic	Nausea, diarrhea, vomiting, fatigue, arthralgia	[111] [113]
13	Brigatinib	ALUNBRIG Takeda Pharmaceuticals America, Inc., Deerfield, IL, USA	FDA: 28 April 2017 EMA: 22 November 2018		ALK [8], EGFR [12]	Oral	Non-Small Cell Lung Cancer	Nausea, diarrhea, fatigue, cough, headache, CPK elevation, pancreatic enzyme elevation, hyperglycemia	[114] [115]
14	Alectinib	ALECENSA Genentech, Inc., South San Francisco, CA, USA	FDA: 11 December 2015 EMA: 16 February 2017		ALK [8]	Oral	Non-Small Cell Lung Cancer	Constipation, nausea, diarrhea, vomiting, edema, increased levels of bilirubin, AST and ALT, myalgia, rash, anemia, increase in bodyweight	[116] [117]
15	Cobimetinib	COTELLIC Genentech, Inc., South San Francisco, CA, USA	FDA: 10 November 2015: EMA: 20 November 2015.		MEK1 [4], MEK2 [5]	Oral	Melanoma Metastatic	Diarrhea, nausea, rash, arthralgia, fatigue, increased creatine phosphokinase levels	[118] [119]
16	Lenvatinib	LENVIMA Eisai Inc., Tokyo, Japan, U.S. Corporate Headquarters in Nutley, NJ, USA	FDA: 13 February 2015 EMA: 28 May 2015		VEGFRs [16] (1, 2, 3), FGFR [11] (1, 2, 3, 4), PDGFRA [2], RET [3], c-Kit [1]	Oral	Thyroid Cancer, Renal Cell Carcinoma, Hepatocellular Carcinoma, Endometrial Cancer	Hypertension, diarrhea, fatigue or asthenia, decreased appetite, bodyweight decreased, nausea, stomatitis, palmar–plantar erythrodysesthaesia syndrome, proteinuria	[120] [121]
17	Afatinib	GILOTRIF Boehringer Ingelheim	FDA: 12 July 2013		EGFR [12], HER2	Oral	Non-Small Cell Lung Cancer	Diarrhea, rash/acne, stomatitis/mucositis, paronychia, dry skin,	[122] [123]

No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
		Pharmaceuticals, Inc., Ingelheim, Germany	EMA: 25 September 2013		[13], HER4 [14]			decreased appetite, pruritus, nausea, fatigue, vomiting, epistaxis, cheilitis	
18	Trametinib	MEKINIST GlaxoSmithKline, London, UK	FDA: 29 May 2013 EMA: 30 June 2014		MEK1 [4], MEK2 [5]	Oral	Melanoma, Metastatic, Non-Small Cell Lung Cancer, Thyroid Cancer	Rash, diarrhea, fatigue, nausea/vomiting, peripheral edema	[124] [125]
19	Dabrafenib	TAFINLAR GlaxoSmithKline, London, UK	FDA: 29 May 2013 EMA: 26 August 2013		B-Raf [15]	Oral	Melanoma, Metastatic, Non-Small Cell Lung Cancer, Thyroid Cancer	Alopecia, arthralgia, back pain, constipation, cough, erythrodysaesthesia, fever, headache, hyperkeratosis, muscle pain, nasopharyngitis, papilloma, squamous cell cancer	[126] [127]
20	Cabozantinib	CABOMETYX Exelixis, Inc., Alameda, CA, USA	FDA: 25 April 2016 EMA: 9 September 2016		MET [17], RET [3], VEGFRs [16] (1, 2, 3), c-Kit [1], FLT-3 [10], TIE2 [18], TRKB [19], AXL [20]	Oral	Renal Cell Carcinoma, Hepatocellular Carcinoma	Diarrhea, fatigue, nausea, vomiting, decreased appetite, hypertension, palmar–plantar erythrodysesthesia syndrome	[128] [129] [130]
21	Cabozantinib	COMETRIQ Exelixis, Inc., Alameda, CA, USA	FDA: 29 November 2012 EMA: 21 March 2014		MET [17], RET [3], VEGFRs [16] (1, 2, 3), c-Kit [1], FLT-3 [10], TIE2 [18], TRKB [19], AXL [20]	Oral	Thyroid Cancer	Diarrhea, stomatitis, palmar–plantar erythrodysesthesia syndrome, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, constipation, increased AST, increased ALT,	[131] [132] [133]

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No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
								lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia	
22	Regorafenib	STIVARGA Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA	FDA: 27 September 2012 EMA: 26 August 2013		VEGFRs [16] (1, 2, 3), RET [3], c-Kit [1], PDGFRs [21] (A, B), FGFRs [11] (1, 2), TIE2 [18], B-Raf [15], RAF-1 [22]	Oral	Colorectal Cancer, Gastrointestinal Stromal Tumor, Hepatocellular Carcinoma	Asthenia/fatigue, decreased appetite and food intake, hand-foot skin reaction, palmar–plantar erythrodysesthesia, diarrhea, mucositis, weight loss, infection, hypertension, dysphonia	[134] [135] [136]
23	Axitinib	INLYTA Pfizer Inc., New York City, NY, USA	FDA: 27 January 2012 EMA: 3 September 2012		VEGFRs [16] (1, 2, 3), c-Kit [1], PDGFRs [21] (A, B)	Oral	Renal Cell Carcinoma	Diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar–plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, constipation	[137] [138] [139]
24	Crizotinib	XALKORI Pfizer Inc., New York City, NY, USA	FDA: 26 August 2011 EMA: 23 October 2012		ALK [8], MET [17], ROS1 [7]	Oral	Non-Small Cell Lung Cancer	Vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, neuropathy	[140] [141] [142]
25	Vemurafenib	ZELBORAF Genentech, Inc., South San Francisco, CA, USA	FDA: 17 August 2011 EMA: 17		B-Raf [15]	Oral	Melanoma Metastatic	Arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea,	[143] [144] [145]

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No.	Generic Name of Drug	Brand Name and Company	First FDA/EMA Approval Date	Structure	Molecular Target	Route of Administration	Indication	Adverse Effects	Ref.
			February 2012						
26	Vandetanib	CAPRELSA AstraZeneca, Cambridge, UK	FDA: 6 April 2011 EMA: 17 February 2012		VEGFR-2 [23], EGFR [12], RET [3]	Oral	Thyroid Cancer	Diarrhea, rash, nausea, hypertension, fatigue, headache, decreased appetite, acne, dermatitis acneiform, dry skin, photosensitivity reaction, erythema	[146] [147]

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[1] **c-Kit**: mast/stem cell growth factor receptor. [2] **PDGFRA**: platelet-derived growth factor receptor α. [3] **RET**: receptor tyrosine kinase. [4] **MEK**: mitogen-activated protein kinase kinase. [5] **MEK2**: mitogen-activated protein kinase kinase 2. [6] **TRK**: tropomyosin receptor kinase. [7] **ROS1**: proto-oncogene tyrosine-protein kinase ROS. [8] **ALK**: anaplastic lymphoma kinase. [9] **CSF1R**: colony-stimulating factor 1 receptor. [10] **FLT3**: Fms-like tyrosine kinase 3. [11] **FGFRs**: fibroblast growth factor receptors. [12] **EGFR**: epidermal growth factor receptor. [13] **HER2**: human epidermal growth factor receptor 2. [14] **TEK**: tunica interna endothelial cell kinase. [15] **B-Raf**: proto-oncogene serine/threonine-protein kinase B-raf. [16] **VEGFRs**: vascular endothelial growth factor receptors. [17] **MET**: mesenchymal epithelial transition factor. [18] **SUE2**: [19] **TRKB**: [20] **AXL**: [21] **PDGFRs**: platelet-derived growth factor receptors. [22] **RAF-1**: [23] **VEGFR-2**: vascular endothelial growth factor receptor-2

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