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REVIEWS

TYROSINE KINASE INHIBITORS IN MODERN ONCOTHERAPY

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ABSTRACT

The widespread prevalence and increasing incidence of cancer has imposed the introduction of new therapeutic approaches and medications. The elucidation of the key role of receptor tyrosine kinases (RTKs) in intercellular signaling and their involvement in fundamental processes, replication, growth, differentiation, and apoptosis, has provided substantial evidence linking their altered functionality to tumorigenesis.

This review aims to briefly discuss the role of RTKs in tumorigenesis and characterize tyrosine kinase inhibitors (TKIs), focusing on their mechanisms of action, pharmacodynamics, and pharmacokinetics as essential drugs in modern targeted cancer therapy.

Two primary mechanisms inhibit mutated or overexpressed RTKs. The first involves monoclonal antibodies targeting the extracellular domains of RTKs or their ligands, inhibiting RTK dimerization and activation, thus forming the group of extracellular TKIs. The second mechanism involves small-molecule TKIs targeting the intracellular tyrosine kinase domain of the receptors or other intracellular tyrosine kinases mediating their signaling pathways. Numerous mono- and multi-targeted TKIs have been developed, addressing one or more signaling pathways. Identifying specific mutations in individual patients and applying specific TKIs have introduced the principles of personalized cancer therapy. Most TKIs are well-tolerated and significantly improve patient survival. The selectivity of TKIs toward their targets determines their efficacy and safety profile.

Despite their advantages, TKI therapy is associated with significant toxic effects and high variability due to their pharmacokinetic features. Literature discusses the potential of therapeutic drug monitoring to optimize dosing, thereby enhancing efficacy and minimizing adverse side effects.

In summary, TKIs are pivotal medications in modern oncology that have revolutionized the treatment paradigm for numerous cancers.

Keywords: *receptor tyrosine kinases (RTKs), tyrosine kinase inhibitors (TKIs), targeted therapy*

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INTRODUCTION

In recent decades, the incidence of cancer has been steadily increasing, making it a global health challenge. According to the World Health Organization, about 20 million new cancer cases and nearly 9.7 million deaths were recorded in 2022. Approximately one in five people develops cancer during their lifetime. Of the total number of new cases registered, the most common are lung cancer (12.4%) and

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colorectal cancer (9.6%). In women, breast cancer is the leading cause of cancer (11.5%), while in men, it is prostate cancer (7.3%) (1). These data highlight the need not only for screening and early diagnosis of neoplastic diseases but also for new therapeutic approaches to improve prognosis and quality of life for patients affected by these diseases. One of the most innovative approaches in this direction is the development of targeted therapies that focus on specific molecular targets in tumor cells.

Since the discovery of receptor tyrosine kinases (RTKs) in the 1960s, their key role in various aspects of cell biology such as intercellular communication, replication, growth, differentiation, and apoptosis has been revealed. At the same time, data have accumulated on how alterations in their normal function lead to tumorigenesis. The development of new drugs that can specifically block these receptors and their signaling pathways represents a significant part of the oncology-focused pharmaceutical industry. In the current treatment of a substantial number of cancers, tyrosine kinase inhibitors (TKIs) have been established as an important therapeutic strategy. A wide variety of new TKIs have been included in the therapeutic algorithm for various hematological and solid tumors, which also provides an opportunity for personalized treatment tailored to the patient's genetic profile.

AIM

The aim of this review is to briefly discuss the role of RTKs in tumorigenesis and to characterize the main representatives of TKIs, their mechanism of action, pharmacodynamics, and pharmacokinetics as essential drugs used in modern targeted therapy in oncology.

TYROSINE KINASE RECEPTORS

More than 90 tyrosine kinases have been identified in the human genome. Of these, about 60 are membrane receptors, grouped according to their structure and ligands into 20 different families (2), and 32 enzymes, grouped into 11 families, are expressed intracellularly (3).

Receptor tyrosine kinases are transmembrane proteins with a key role in signal transduction. Structurally, they are composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain (TKD), rich in

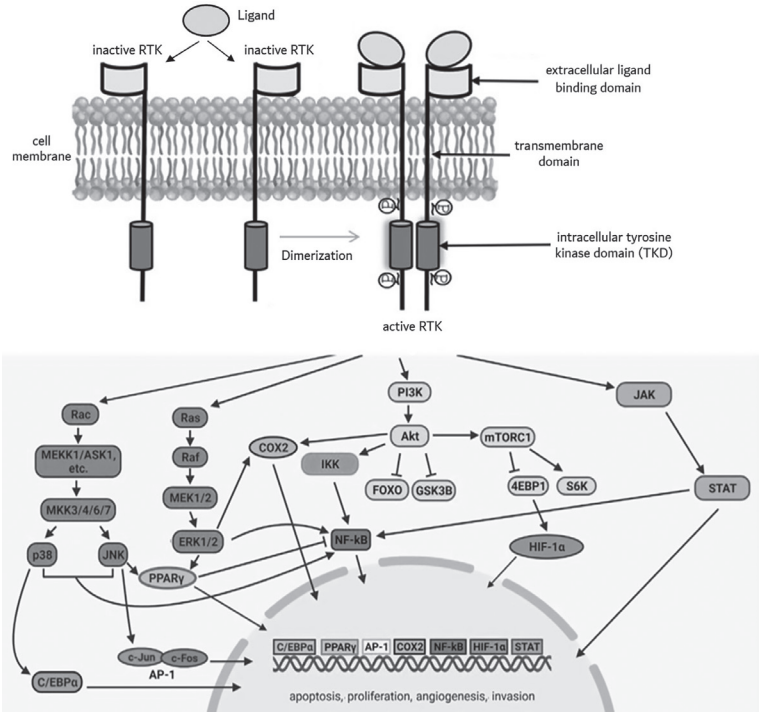


Fig. 1. Mechanisms of receptor tyrosine kinase activation and intracellular signal transduction.
RTK—receptor tyrosine kinase; TKD—tyrosine kinase domain

tyrosine residues. The TKD is in a state of cis-autoinhibition, maintained by specific intramolecular interactions characteristic of each receptor. The extracellular domain recognizes specific ligands such as growth factors, hormones, and cytokines. Upon binding to the ligand, the receptors dimerize and/or oligomerize, which removes cis-autoinhibition, allowing the receptor to activate itself through trans-autophosphorylation of tyrosine residues. In turn, phosphotyrosine residues serve to attract and bind to a variety of intracellular proteins rich in Src homology-2 (SH2) and phosphotyrosine-binding (PTB) domains. This way, activated RTKs acquire the ability to cluster around their intracellular domain a variety of signaling intracellular molecules and activate signaling cascades such as rat sarcoma/mitogen-activated protein kinase (RAS/MAPK), phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT), and Janus activated kinase/signal transducer and activator of transcription (JAK2/STAT), responsible for fundamental processes such as replication, growth, differentiation, apoptosis, motility, and intercellular communication (4) (Fig. 1).

These processes, which are strictly regulated under physiological conditions, can be compromised by mutations (often gain-of-function mutations), abnormal autocrine and paracrine stimulation, or overexpression of RTKs (through DNA amplification or chromosomal rearrangement of RTK genes). This leads to the constant activation of oncogenic signaling cascades, triggering uncontrolled cell proliferation, promoting angiogenesis and metastasis, i.e., activating the basic processes characteristic of tumorigenesis. The cell's apoptotic mechanisms are also suppressed, ensuring its "immortality". Altered activation of RTKs can be achieved through various mechanisms—increased affinity for ligands, increased activity of TKDs, and stimulated dimerization due to the absence of cis-inhibitory interactions. Mutations or overexpression of RTKs have been found in approximately 30% of all human cancers (5).

TYROSINE KINASE INHIBITORS

The discovery of the molecular mechanisms by which RTKs participate in cell-to-cell signaling and their role in tumor biology has led to the identification of various targets and the development of promising new drugs for the treatment of a range of solid tumors and hematological neoplasms. In the last two decades, TKIs have been successfully introduced into the therapeutic protocols for these diseases. By specifically blocking the activity of mutated or overexpressed RTKs, as well as intracellular peptides and proteins with tyrosine kinase activity, TKIs prevent the transduction of oncogenic signals. TKIs are a significant part of modern targeted therapy and are classified into two groups: monoclonal antibodies directed against the extracellular domain of RTKs or their ligands, and small molecule TKIs, capable of crossing the cell membrane and blocking the intracellular TKD domain of RTKs, as well as those of intracellular peptides with tyrosine kinase activity (6). Fig. 2 illustrates the main strategies used to block oncogenic tyrosine kinase signaling through the development of various types of drugs within the TKI group—monoclonal antibodies against growth factors interacting with RTKs; monoclonal antibodies targeting the receptors themselves; soluble receptors for growth factors interacting with RTKs, and small molecule TKIs.

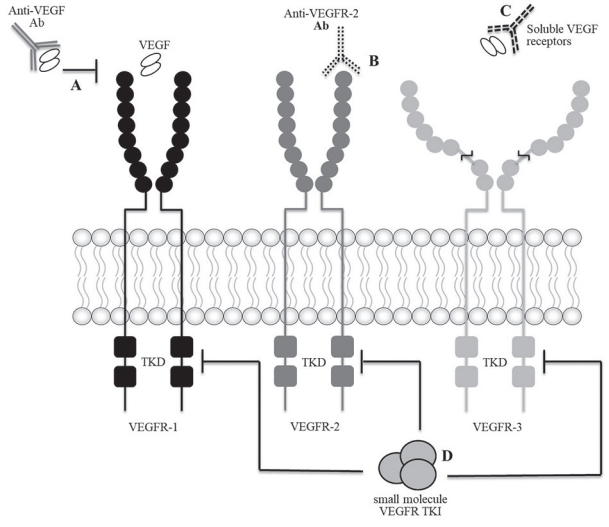


Fig. 2. Blocking the VEGFR signaling pathway by different types of TKIs.

A. Monoclonal antibody against VEGF (e.g., bevacizumab); **B.** Monoclonal antibody against VEGFR-2 (e.g., ramucirumab); **C.** Soluble receptors for VEGF (e.g., aflibercept); **D.** Small molecule TKIs against VEGFR (e.g., sunitinib, sorafenib, regorafenib, apatinib) (VEGF—vascular endothelial growth factor; VEGFR—tyrosine kinase receptor for VEGF; TKD—tyrosine kinase domain; Ab—antibody; TKI—tyrosine kinase inhibitor)

As large molecules, monoclonal antibodies cannot enter cells. Instead, they interact with cell surface receptors expressed on tumor cells. They are typically named with the suffix *-mab*. Overexpression of the human epidermal growth factor receptor 2 (HER2) gene, also known as erbB2 receptor tyrosine kinase 2 (ERBB2), is observed in some breast and gastric neoplasms that are positive for HER2 mutations. Approximately 20% of breast cancers overexpress HER2, representing a particularly aggressive subtype of the disease with an increased risk of developing systemic and brain metastases. The use of monoclonal antibodies such as trastuzumab and pertuzumab, which target different regions of HER2 and prevent receptor dimerization, has significantly improved the prognosis of the disease (7,8). The treatment of colorectal carcinoma may include bevacizumab, a monoclonal antibody that, by binding to vascular endothelial growth factor (VEGF), suppresses the growth of tumor blood vessels (9). Metastatic, inoperable colorectal carcinoma (mCRC) has a poor prognosis, and most patients receive primarily palliative systemic chemotherapy. Genomic profiling is used to detect specific mutations, which allows for the possibility of providing targeted therapy to selected patients. For example, patients with mCRC expressing wild-type KRAS/NRAS/BRAF can benefit from inhibition of the epidermal growth factor receptor (EGFR) with cetuximab or panitumumab in combination with chemotherapy (10). Targeted therapy is promising in patients with non-small cell lung cancer (NSCLC). However, most patients develop resistance, highlighting the need for the development of new drugs. For example, the prognostic value of AXL levels (from the Greek word *anexelekto*, meaning uncontrolled), a member of the TAM receptor tyrosine kinase family, is being intensively studied in NSCLC. The potent anti-tumor activity of the monoclonal antibody enapotamab, conjugated with vedotin and directed against AXL, has been demonstrated in various NSCLC subtypes (11). Ramucirumab is a new IgG1 monoclonal antibody that binds specifically and with high affinity to the extracellular domain of VEGFR-2. This blocks the interaction between VEGFR-2 and its ligands, and inhibits receptor activation and subsequent signal transduction in the cell, leading to a reduction in neovascularization and tumor growth (12). Ramucirumab is the first angiogenesis-targeted monoclonal antibody that improves overall survival (OS) and progression-free survival (PFS) observed in advanced gastric cancer, NSCLC, and colorectal carcinoma, but not in breast

Table 1. Examples of small molecule TKIs, their targets, and application in clinical oncology.

TKIs	TYROSINE KINASE TARGET	NEOPLASM(S) TARGETED	CLINICAL STATUS
EGFR and HER2 Inhibitors			
Ibrutinib	BTK	B cell malignancies	Approved: 2013 (14)
Gefitinib	EGFR	NSCLC	Approved: 2002 (15)
Erlotinib	EGFR	NSCLC	Approved: 2004 (16)
Osimertinib	EGFR	NSCLC	Approved: 2015 (17)
Afatinib	ErbB1/2/4	NSCLC	Approved: 2013 (18)
Icotinib	EGFR	NSCLC	Approved: 2011 (19)
Lapatinib	EGFR/HER2	HER2+ breast cancer	Approved: 2007 (20)
Neratinib	EGFR, HER2, HER4	HER2+ breast cancer	Approved: 2017 (21)
Pyrotinib	EGFR, HER2, HER4	HER2+ breast cancer	Approved: 2018 (22)

Anti-Angiogenic Inhibitors			
Sunitinib	VEGFR1/2/3, PDGFRα/β, Kit, FLT3	imatinib-resistant GIST	Approved: 2006 (23)
Sorafenib	VEGFR1-3, PDGFR, FGFR, BRAF, c-KIT, FLT-3	mRCC HCC DTC	Approved: 2005 (24) Approved: 2007 (25) Approved: 2013 (26)
Vandetanib	EGFR, VEGFR2-3, RET	MTC	Approved: 2011 (27)
Regorafenib	VEGFR1-3, TIE2, PDGFR, FGFR, BRAF, RET	CRC imatinib- and sunitinib-resistant GIST sorafenib-resistant HCC	Approved: 2012 (28) Approved: 2013 (29) Approved: 2017 (30)
Axitinib	VEGFR1-3, c-KIT	RCC	Approved: 2012 (31)
ALK/ROS1 Inhibitors			
Crizotinib	ALK, ROS1, MET	ALK+ NSCLC	Approved: 2011 (32)
Brigatinib	ALK	ALK+ NSCLC	Approved: 2017 (33)
Lorlatinib	ALK, ROS1	ALK+ NSCLC	Approved: 2018 (34)
FGFR Inhibitors			
Erdafitinib	FGFR1-4	urothelial carcinoma	Approved: 2019 (35)
Pemigatinib	FGFR1-3	CCA	Approved: 2020 (36)
c-KIT/PDGFR Inhibitors			
Imatinib	Bcr-Abl, KIT, PDGFR	Ph+ CML GIST	Approved: 2001 (37) Approved: 2002 (38)
Avapritinib	KIT, PDGFR	GIST	Approved: 2020 (39)
MET Inhibitors			
Capmatinib	MET	METex14 + NSCLC	Approved: 2020 (40)
Tepotinib	MET	METex14 + NSCLC	Approved: 2021 (40)
RET Inhibitors			
Selpercatinib	RET	RET+ NSCLC	Approved: 2020 (41)
Pralsetinib	RET	RET+ NSCLC RET+ thyroid cancer MTC	Approved: 2020 (42)

ALK—anaplastic lymphocyte kinase; BRAF—v-raf murine sarcoma viral oncogene homolog B; BTK—Bruton's tyrosine kinase; CCA—cholangiocarcinoma; c-KIT—mast/stem cell growth factor receptor kit; CML—chronic myeloid leukemia; DTC—differentiated thyroid cancer; EGFR (ErbB1/HER1)—epidermal growth factor receptor; FLT3—FMS-like tyrosine kinase-3; GIST—gastrointestinal stromal tumors; HCC—hepatocellular carcinoma; MET—mesenchymal-epithelial transition factor; METex14—MET exon14 skipping alterations; mRCC—metastatic renal cell carcinoma; MTC—medullary thyroid cancer; NSCLC—non-small cell lung cancer; PDGFR—platelet-derived growth factor receptor; RET—rearranged during transfection; ROS1—ROS proto-oncogene 1; TIE2—angiopoietin receptor; VEGFR—vascular endothelial growth factor receptor

cancer or hepatocellular carcinoma (HCC), as established in phase III trials of the drug (13).

Compared to monoclonal antibodies, small molecule TKIs are much more numerous. They are typically named with the suffix *-nib*. Due to their low molecular weight, they can cross the cell membrane and bind to the TKD of RTKs or other intracellular tyrosine kinases. This interrupts the signaling pathway and leads to a slowing of proliferation and death of tumor cells. Table 1 lists selected representatives of small molecule TKIs targeting various targets.

For both types of TKIs, there is also a different way of administration. While most small molecule TKIs can be manufactured in tablet or capsule form and are available for oral administration, most monoclonal antibodies are administered intravenously. However, some monoclonal antibodies, such as trastuzumab, can also be administered subcutaneously, which could shorten patients' hospital stay 43.

MONO- AND MULTI-TARGET THERAPY WITH TKIs—EFFICIENCY AND SIDE EFFECTS OF THEIR APPLICATION

After the US Food and Drug Administration (FDA) approved imatinib for the treatment of chronic myeloid leukemia in 2001, numerous TKIs (over 50) emerged, contributing to significant advances in the treatment of oncological diseases (44). Most solid tumors exhibit dysregulation of multiple signaling pathways. This contributed to the idea that multi-target therapy, which targets several signaling pathways simultaneously, could be more effective than mono-target therapy. Drug resistance is the main challenge in oncological practice (45). Cancer cells are dependent not only on the presence of an activated oncogene but also on the cells in the microenvironment. In advanced cancers, inhibition of a single target usually leads to mutations that stimulate the survival of cancer cells (46). By inhibiting not only the proliferation of cancer cells but also blocking the microenvironment that favors oncogenesis, a multi-target therapy can achieve greater effectiveness than a mono-target therapy. The synergistic effect of inhibiting multiple targets would contribute to a lower risk of developing resistance and, consequently, enhance efficacy (47). In this context, there is also the question of which strategy is better—whether to use several monotarget inhibitors simultaneously or to apply monotherapy with inhibitors that act on more than one target. It should be noted that some of the multi-target TKIs, such as those associated with VEGFR, were initially conceived as highly selective, but later it turned out that they also attack other unexpected targets (3,48). The selectivity of binding of different TKIs to their targets determines not only the efficacy and mechanism of action but also their safety profile (49). Only a few TKIs exhibit selectivity for specific protein kinases, while most TKIs inhibit multiple kinases (~10–100), which leads to an increased risk of toxicity (50). For example, studies report a ~5% frequency of discontinuation of therapy with the multi-kinase inhibitor imatinib due to adverse events (51). Toxicity may result not only from excessive inhibition of the targeted tyrosine kinase (on-target effect) but also from the simultaneous inhibition of multiple other kinases (off-target effect) due to the limited selectivity of most TKIs (49,52,53). There is a close relationship between the effectiveness of therapy and the occurrence of toxic reactions. The adverse event profile is often used as a monitoring tool to identify the desired effects of therapy (54). A positive correlation has also been established between the number of inhibited kinases and the degree of toxic potential of TKIs (55).

In the development of targeted therapy, there were also expectations that it would be accompanied by fewer adverse side effects compared to traditional chemotherapy. Unfortunately, significant toxic effects are still observed with the use of TKIs, although they vary depending on the specific inhibitor used. On-target effects usually cause adverse reactions such as hypertension, hypothyroidism, skin reactions, and proteinuria (56). Skin problems are common with EGFR inhibitors and manifest as an acneiform rash (drug acne), changes in nails and nail bed (paronychia and pyogenic granuloma), hair graying, dryness, and/or yellowing of the skin (57,58). Congestive heart failure is observed with the use of trastuzumab (59). Adverse events such as hypertension, thromboembolism, impaired wound healing, and increased risk of bleeding (including tumor-related hemorrhage) are associated with the use of VEGF and VEGFR inhibitors (60).

PHARMACOKINETIC CHARACTERISTICS OF TKIs

There are two prominent trends in the development of anti-tumor drugs. The first involves the creation of new targeted drugs that meet the requirements of personalized medicine. The second trend concerns the method of drug administration and is also called the transition from intravenous to oral treatment. Thus, over the past decade, there has been a significant increase in the number of anti-tumor drugs administered orally (61). In this regard, TKIs are no exception. On the one hand, they are the main representatives of targeted medicine, and on the other hand, the number of small molecule TKIs, which are administered exclusively orally, is growing exponentially. It should be noted, however, that in terms of pharmacokinetics and pharmacodynamics, these drugs show high (about 30–35%) inter-individual variability (62). Although the bioavailability of small molecule TKIs, which depends on their absorption, distribution, metabolism, and excretion, is highly variable in individual patients, they continue to be administered according to a strictly defined predetermined dose regimen. These features, often overlooked in the literature, pose risks for patients exposed to either extremely low or, conversely, high drug exposure (61).

The bioavailability and effectiveness of TKIs are determined by various pharmacokinetic factors. For example, their combination with proton pump inhibitors, which increase gastric pH, reduces their absorption, which is optimal at low pH values (63). Food is another factor that affects the absorption of TKIs—in some cases, it reduces the solubility of the drug, and in others it increases it, thereby enhancing bioavailability and reducing the risk of adverse gastrointestinal side effects. In terms of volume of distribution (Vd) and plasma half-life, TKIs also show considerable variability due to differences in their tissue distribution and affinity for binding to plasma proteins. Most TKIs are metabolized by cytochrome P450 (CYP)3A4. Some of them, such as imatinib, gefitinib, lapatinib, and nilotinib, are enzymatic CYP inhibitors, which alter their metabolism and lead to significant drug interactions. Genetic variations in CYP3A4 can lead to increased systemic concentrations, which can improve the therapeutic effect but also increase side effects. Studies have shown that patients who are poor metabolizers of CYP2C9 substrates are at increased risk of toxicity (64).

The elimination of TKIs is primarily extrarenal (through feces) and a very small amount is eliminated through the kidneys. A significant portion of TKIs remain unchanged in the feces, and this may be the result of either ineffective metabolism or a high amount of unabsorbed drug excreted immediately (63,65). Another feature is that TKIs are substrates and inhibitors of ATP-binding cassette (ABC) transporters B1 and G2. They can also interact with organic cation transporters (OCT1). ATP-binding cassette transporters (ABCB1 and ABCG2) are involved in the efflux of TKIs from cells, and OCT1—in their influx (66).

All these features of the pharmacokinetics and pharmacogenetics of TKIs determine the high degree of variability in terms of response to therapy and the occurrence of adverse side effects, which in turn necessitates the idea of introducing therapeutic drug monitoring to optimize the dose and achieve a complete cytogenetic response or a large/deep molecular response. For example, some studies highlight the role of drug monitoring as a new strategy in patients with chronic myeloid leukemia treated with imatinib, nilotinib, or dasatinib, where the dose is adjusted based on plasma drug concentrations to increase efficacy and minimize the frequency of adverse events (67).

CONCLUSION

Fundamental studies on RTKs have provided invaluable information on the principles of intercellular signaling and their role in processes such as cell proliferation, differentiation, survival, and apoptosis. Disrupted mechanisms in all these processes underlie tumorigenesis. The accumulated knowledge in this area has laid the foundation for the development and introduction into the clinical practice of TKIs. Currently, these drugs are being used with increasing success in oncological practice. By providing the opportunity to apply the principles of targeted therapy and personalized medicine, they have changed the paradigm and revolutionized the treatment of many tumor diseases.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63. doi: 10.3322/caac.21834.
2. Esteban-Villarrubia J, Soto-Castillo JJ, Pozas J, San Román-Gil M, Orejana-Martín I, Torres-Jiménez J, et al. Tyrosine Kinase Receptors in Oncology. Int J Mol Sci. 2020 Nov 12;21(22):8529. doi: 10.3390/ijms21228529.
3. Broekman F. Tyrosine kinase inhibitors: Multitargeted or single-targeted? World J Clin Oncol. 2011;2(2):80. doi: 10.5306/wjco.v2.i2.80.
4. Du Z, Lovly CM. Mechanisms of receptor tyrosine kinase activation in cancer. Mol Cancer. 2018 Dec;17(1):58. doi: 10.1186/s12943-018-0782-4.
5. Ebrahimi N, Fardi E, Ghaderi H, Palizdar S, Khorram R, Vafadar R, et al. Receptor tyrosine kinase inhibitors in cancer. Cell Mol Life Sci CMLS. 2023 Mar 22;80(4):104. doi: 10.1007/s00018-023-04729-4.
6. Wilkes GM. Targeted Therapy: Attacking Cancer with Molecular and Immunological Targeted Agents. Asia-Pac J Oncol Nurs. 2018;5(2):137–55. doi: 10.4103/apjon.apjon_79_17.
7. Dempsey N, Sandoval A, Mahtani R. Metastatic HER2-Positive Breast Cancer: Is There an Optimal Sequence of Therapy? Curr Treat Options Oncol. 2023 Sep;24(9):1120–37. doi: 10.1007/s11864-023-01108-w.
8. Keating GM. Pertuzumab: in the first-line treatment of HER2-positive metastatic breast cancer. Drugs. 2012 Feb 12;72(3):353–60. doi: 10.2165/11209000-000000000-00000.
9. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020 Jun;86:102017. doi: 10.1016/j.ctrv.2020.102017.
10. Sakata S, Larson DW. Targeted Therapy for Colorectal Cancer. Surg Oncol Clin N Am. 2022 Apr;31(2):255–64. doi: 10.1016/j.soc.2021.11.006.
11. Koopman LA, Terp MG, Zom GG, Janmaat ML, Jacobsen K, Gresnigt-van den Heuvel E, et al. Enapotamab vedotin, an AXL-specific antibody-drug conjugate, shows preclinical antitumor activity in non-small cell lung cancer. JCI Insight. 2019 Nov 1;4(21):e128199, 128199. doi: 10.1172/jci.insight.128199.
12. Aprile G, Bonotto M, Ongaro E, Pozzo C, Giuliani F. Critical appraisal of ramucirumab (IMC-1121B) for cancer treatment: from benchside to clinical use. Drugs. 2013 Dec;73(18):2003–15. doi: 10.1007/s40265-013-0154-8.
13. Chan MM, Sjoquist KM, Zalcberg JR. Clinical utility of ramucirumab in advanced gastric cancer. Biol Targets Ther. 2015;9:93–105. doi: 10.2147/BTT.S62777.
14. Cameron F, Sanford M. Ibrutinib: first global approval. Drugs. 2014 Feb;74(2):263–71. doi: 10.1007/s40265-014-0178-8.
15. Singh S, Sadhukhan S, Sonawane A. 20 years since the approval of first EGFR-TKI, gefitinib: Insight and foresight. Biochim Biophys Acta BBA - Rev Cancer. 2023 Nov 1;1878(6):188967. doi: 10.1016/j.bbcan.2023.188967.
16. Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA Drug Approval Summary: Erlotinib (Tarceva®) Tablets. Oncologist. 2005 Aug 1;10(7):461–6. doi: 10.1634/theoncologist.10-7-461.
17. Yin Y, Shu Y, Zhu J, Li F, Li J. A real-world pharmacovigilance study of FDA Adverse Event Reporting System (FAERS) events for osimertinib. Sci Rep. 2022 Nov 15;12:19555. doi: 10.1038/s41598-022-23834-1.
18. Roskoski R. Orally effective FDA-approved protein kinase targeted covalent inhibitors (TCIs). Pharmacol Res. 2021 Mar;165:105422. doi: 10.1016/j.phrs.2021.105422.
19. Tan F, Shi Y, Wang Y, Ding L, Yuan X, Sun Y. Icotinib, a selective EGF receptor tyrosine kinase inhibitor, for the treatment of non-small-cell lung cancer. Future Oncol Lond Engl. 2015;11(3):385–97. doi: 10.2217/fon.14.249.
20. Ryan Q, Ibrahim A, Cohen MH, Johnson J, Ko C wen, Sridhara R, et al. FDA Drug Approval Summary: Lapatinib in Combination with Capecitabine for Previously Treated Metastatic Breast Cancer That Overexpresses HER-2. Oncologist. 2008 Oct 1;13(10):1114–9. doi: 10.1634/theoncologist.2008-0816.
21. Research C for DE and. FDA approves neratinib for extended adjuvant treatment of early stage HER2-positive breast cancer. FDA [Internet]. 2024 Aug 9; Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ne-

ratinib-extended-adjuvant-treatment-early-stage-her2-positive-breast-cancer

22. Blair HA. Pyrotinib: First Global Approval. Drugs. 2018 Nov;78(16):1751–5. doi: 10.1007/s40265-018-0997-0.

23. Goodman VL, Rock EP, Dagher R, Ramchandani RP, Abraham S, Gobburu JVS, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. Clin Cancer Res Off J Am Assoc Cancer Res. 2007 Mar 1;13(5):1367–73. doi: 10.1158/1078-0432.CCR-06-2328.

24. Kane RC, Farrell AT, Saber H, Tang S, Williams G, Jee JM, et al. Sorafenib for the treatment of advanced renal cell carcinoma. Clin Cancer Res Off J Am Assoc Cancer Res. 2006 Dec 15;12(24):7271–8. doi: 10.1158/1078-0432.CCR-06-1249.

25. Kane RC, Farrell AT, Madabushi R, Booth B, Chattopadhyay S, Sridhara R, et al. Sorafenib for the Treatment of Unresectable Hepatocellular Carcinoma. Oncologist. 2009 Jan 1;14(1):95–100. doi: 10.1634/theoncologist.2008-0185.

26. Sussman M, Munsell M, Valderrama A, Seal BS, Wen L. Estimating the Economic Impact of Sorafenib in Treatment of Locally Recurrent or Metastatic, Progressive, Differentiated Thyroid Carcinoma (DTC) That is Refractory to Radioactive Iodine (RAI) Treatment. Value Health. 2014 Nov;17(7):A621. doi: 10.1016/j.jval.2014.08.2200.

27. Thornton K, Kim G, Maher VE, Chattopadhyay S, Tang S, Moon YJ, et al. Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary. Clin Cancer Res Off J Am Assoc Cancer Res. 2012 Jul 15;18(14):3722–30. doi: 10.1158/1078-0432.CCR-12-0411.

28. Goel G. Evolution of regorafenib from bench to bedside in colorectal cancer: Is it an attractive option or merely a 'me too' drug? Cancer Manag Res. 2018;10:425–37. doi: 10.2147/CMAR.S88825.

29. Ferraro D, Zalcberg J. Regorafenib in gastrointestinal stromal tumors: clinical evidence and place in therapy. Ther Adv Med Oncol. 2014 Sep;6(5):222–8. doi: 10.1177/1758834014544892.

30. Pelosof L, Lemery S, Casak S, Jiang X, Rodriguez L, Pierre V, et al. Benefit-Risk Summary of Regorafenib for the Treatment of Patients with Advanced Hepatocellular Carcinoma That Has Progressed on Sorafenib. Oncologist. 2018 Apr;23(4):496–500. doi: 10.1634/theoncologist.2017-0422.

31. Tyler T. Axitinib: Newly Approved for Renal Cell Carcinoma. J Adv Pract Oncol. 2012;3(5):333–5. doi: 10.6004/jadpro.2012.3.5.7.

32. Kazandjian D, Blumenthal GM, Chen HY, He K, Patel M, Justice R, et al. FDA approval summary: crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. Oncologist. 2014 Oct;19(10):e5-11. doi: 10.1634/theoncologist.2014-0241.

33. Markham A. Brigatinib: First Global Approval. Drugs. 2017 Jul;77(10):1131–5. doi: 10.1007/s40265-017-0776-3.

34. Liu G, Lam VK. Podcast on Lorlatinib as a First-Line Treatment Option for Patients with ALK-Positive Metastatic NSCLC with Brain Metastasis. Adv Ther. 2023 Oct;40(10):4117–26. doi: 10.1007/s12325-023-02606-x.

35. Markham A. Erdafitinib: First Global Approval. Drugs. 2019 Jun;79(9):1017–21. doi: 10.1007/s40265-019-01142-9.

36. Patel TH, Marcus L, Horiba MN, Donoghue M, Chatterjee S, Mishra-Kalyani PS, et al. FDA Approval Summary: Pemigatinib for Previously Treated, Unresectable Locally Advanced or Metastatic Cholangiocarcinoma with FGFR2 Fusion or Other Rearrangement. Clin Cancer Res Off J Am Assoc Cancer Res. 2023 Mar 1;29(5):838–42. doi: 10.1158/1078-0432.CCR-22-2036.

37. Cohen MH, Johnson JR, Pazdur R. U.S. Food and Drug Administration Drug Approval Summary: conversion of imatinib mesylate (STI571; Gleevec) tablets from accelerated approval to full approval. Clin Cancer Res Off J Am Assoc Cancer Res. 2005 Jan 1;11(1):12–9.

38. Kumar V, Doros L, Thompson M, Mushti SL, Charlab R, Spehalski EI, et al. FDA Approval Summary: Ripretinib for advanced gastrointestinal stromal tumor (GIST). Clin Cancer Res Off J Am Assoc Cancer Res. 2023 Jun 1;29(11):2020–4. doi: 10.1158/1078-0432.CCR-22-2400.

39. Research C for DE and. FDA approves avapritinib for gastrointestinal stromal tumor with a rare mutation. FDA [Internet]. 2020 Jan 9; Available from: https://www.fda.gov/drugs/resources-information-

approved-drugs/fda-approves-avapritinib-gastrointestinal-stromal-tumor-rare-mutation

40. Mathieu LN, Larkins E, Akinboro O, Roy P, Amatya AK, Fiero MH, et al. FDA Approval Summary: Capmatinib and Tepotinib for the Treatment of Metastatic NSCLC Harboring MET Exon 14 Skipping Mutations or Alterations. Clin Cancer Res Off J Am Assoc Cancer Res. 2022 Jan 15;28(2):249–54. doi: 10.1158/1078-0432.CCR-21-1566.

41. Duke ES, Bradford D, Marcovitz M, Amatya AK, Mishra-Kalyani PS, Nguyen E, et al. FDA Approval Summary: Selpercatinib for the treatment of advanced RET fusion-positive solid tumors. Clin Cancer Res Off J Am Assoc Cancer Res. 2023 Sep 15;29(18):3573–8. doi: 10.1158/1078-0432.CCR-23-0459.

42. Kim J, Bradford D, Larkins E, Pai-Scherf LH, Chatterjee S, Mishra-Kalyani PS, et al. FDA Approval Summary: Pralsetinib for the Treatment of Lung and Thyroid Cancers With RET Gene Mutations or Fusions. Clin Cancer Res Off J Am Assoc Cancer Res. 2021 Oct 15;27(20):5452–6. doi: 10.1158/1078-0432.CCR-21-0967.

43. Shuel SL. Targeted cancer therapies: Clinical pearls for primary care. Can Fam Physician Med Fam Can. 2022 Jul;68(7):515–8. doi: 10.46747/cfp.6807515.

44. Huang L, Jiang S, Shi Y. Tyrosine kinase inhibitors for solid tumors in the past 20 years (2001-2020). J Hematol OncolJ Hematol Oncol. 2020 Oct 27;13(1):143. doi: 10.1186/s13045-020-00977-0.

45. Nikolaou M, Pavlopoulou A, Georgakilas AG, Kyrodimos E. The challenge of drug resistance in cancer treatment: a current overview. Clin Exp Metastasis. 2018 Apr;35(4):309–18. doi: 10.1007/s10585-018-9903-0.

46. Khamisipour G, Jadidi-Niaragh F, Jahromi AS, Zandi K, Hojjat-Farsangi M. Mechanisms of tumor cell resistance to the current targeted-therapy agents. Tumour Biol J Int Soc Oncodevelopmental Biol Med. 2016 Aug;37(8):10021–39. doi: 10.1007/s13277-016-5059-1.

47. Potapova O, Laird AD, Nannini MA, Barone A, Li G, Moss KG, et al. Contribution of individual targets to the antitumor efficacy of the multitargeted receptor tyrosine kinase inhibitor SU11248. Mol Cancer Ther. 2006 May;5(5):1280–9. doi: 10.1158/1535-7163.MCT-03-0156.

48. Krug M, Hilgeroth A. Recent advances in the development of multi-kinase inhibitors. Mini Rev Med Chem. 2008 Nov;8(13):1312–27. doi: 10.2174/138955708786369591.

49. Grossman M, Adler E. Protein Kinase Inhibitors - Selectivity or Toxicity? In: Kumar Singh R, editor. Biochemistry [Internet]. IntechOpen; 2021. Available from: https://www.intechopen.com/books/protein-kinases-promising-targets-for-anticancer-drug-research/protein-kinase-inhibitors-selectivity-or-toxicity-

50. Hantschel O. Unexpected off-targets and paradoxical pathway activation by kinase inhibitors. ACS Chem Biol. 2015 Jan 16;10(1):234–45. doi: 10.1021/cb500886n.

51. Lamore SD, Kohnken RA, Peters MF, Kolaja KL. Cardiovascular Toxicity Induced by Kinase Inhibitors: Mechanisms and Preclinical Approaches. Chem Res Toxicol. 2020 Jan 21;33(1):125–36. doi: 10.1021/acs.chemrestox.9b00387.

52. Chen ZI, Ai DI. Cardiotoxicity associated with targeted cancer therapies. Mol Clin Oncol. 2016 May;4(5):675–81. doi: 10.3892/mco.2016.800.

53. González-Medina M, Miljković F, Haase GS, Drueckes P, Trappe J, Laufer S, et al. Promiscuity analysis of a kinase panel screen with designated p38 alpha inhibitors. Eur J Med Chem. 2020 Feb 1;187:112004. doi: 10.1016/j.ejmech.2019.112004.

54. Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. Lung Cancer Amst Neth. 2012 Oct;78(1):8–15. doi: 10.1016/j.lungcan.2012.06.009.

55. Jabbour E, Deininger M, Hochhaus A. Management of adverse events associated with tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. Leukemia. 2011 Feb;25(2):201–10. doi: 10.1038/leu.2010.215.

56. Shah DR, Shah RR, Morganroth J. Tyrosine kinase inhibitors: their on-target toxicities as potential indicators of efficacy. Drug Saf. 2013 Jun;36(6):413–26. doi: 10.1007/s40264-013-0050-x.

57. Lee WJ, Lee JL, Chang SE, Lee MW, Kang YK, Choi JH, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib.

Br J Dermatol. 2009 Nov;161(5):1045–51. doi: 10.1111/j.1365-2133.2009.09290.x.

58. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. Ann Oncol Off J Eur Soc Med Oncol. 2005 Sep;16(9):1425–33. doi: 10.1093/annonc/mdi279.

59. Riccio G, Coppola C, Piscopo G, Capasso I, Maurea C, Esposito E, et al. Trastuzumab and target-therapy side effects: Is still valid to differentiate anthracycline Type I from Type II cardiomyopathies? Hum Vaccines Immunother. 2016 May 3;12(5):1124–31. doi: 10.1080/21645515.2015.1125056.

60. Totzeck M, Mincu RI, Rassaf T. Cardiovascular Adverse Events in Patients With Cancer Treated With Bevacizumab: A Meta-Analysis of More Than 20 000 Patients. J Am Heart Assoc. 2017 Aug 10;6(8):e006278. doi: 10.1161/JAHA.117.006278.

61. Herbrink M, Nuijen B, Schellens JHM, Beijnen JH. Variability in bioavailability of small molecular tyrosine kinase inhibitors. Cancer Treat Rev. 2015 May;41(5):412–22. doi: 10.1016/j.ctrv.2015.03.005.

62. Sarah A, Dondi E, De Francia S. Tyrosine kinase inhibitors: the role of pharmacokinetics and pharmacogenetics. Expert Opin Drug Metab Toxicol. 2023;19(11):733–9. doi: 10.1080/17425255.2023.2277758.

63. van Erp NP, Gelderblom H, Guchelaar HJ. Clinical pharmacokinetics of tyrosine kinase inhibitors. Cancer Treat Rev. 2009 Dec;35(8):692–706. doi: 10.1016/j.ctrv.2009.08.004.

64. Gay F, Oliva S, Petrucci MT, Conticello C, Catalano L, Corradini P, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol. 2015 Dec;16(16):1617–29. doi: 10.1016/S1470-2045(15)00389-7.

65. Zhao Q, Wu ZE, Li B, Li F. Recent advances in metabolism and toxicity of tyrosine kinase inhibitors. Pharmacol Ther. 2022 Sep;237:108256. doi: 10.1016/j.pharmthera.2022.108256.

66. Kaehler M, Cascorbi I. Pharmacogenomics of Impaired Tyrosine Kinase Inhibitor Response: Lessons Learned From Chronic Myelogenous Leukemia. Front Pharmacol. 2021;12:696960. doi: 10.3389/fphar.2021.696960.

67. Miura M. Therapeutic drug monitoring of imatinib, nilotinib, and dasatinib for patients with chronic myeloid leukemia. Biol Pharm Bull. 2015;38(5):645–54. doi: 10.1248/bpb.b15-00103.