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Medicinal Chemistry of Tyrosine Kinase Inhibitor Drug: A Review

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A B S T R A C T

Tyrosine kinases are a part of many cell functions, including cell signaling, growth, and division. These enzymes may be too active or found at high levels in some types of cancer cells, and blocking them may help keep cancer cells from growing. Some tyrosine kinase inhibitors are used to treat cancer. They are a type of targeted therapy. Numerous TKIs aiming at various tyrosine kinases have been generated by the originators of these compounds and proven to be effective anti-tumor agents and anti-leukemic agents. Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Sorafenib, Sunitinib drugs approved by the FDA in 2016, appears to be on its way to the standard of care in regards to TKIs.

Keywords: Tyrosine kinases, Dasatinib, Erlotinib, Gefitinib, Imatinib

A R T I C L E I N F O

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1. Introduction

A substance that blocks the action of enzymes called tyrosine kinases. Tyrosine kinases are a part of many cell functions, including cell signaling, growth, and division. These enzymes may be too active or found at high levels in some types of cancer cells, and blocking them may help keep cancer cells from growing. Some tyrosine kinase inhibitors are used to treat cancer. They are a type of targeted therapy. A tyrosine kinase inhibitor (TKI) is a pharmaceutical drug that inhibits tyrosine kinases. Tyrosine kinases are enzymes responsible for the activation of many proteins by signal transduction cascades. The proteins are activated by adding a phosphate group to the protein (phosphorylation), a step that TKIs inhibit. TKIs are typically used as anticancer drugs. For example, they have

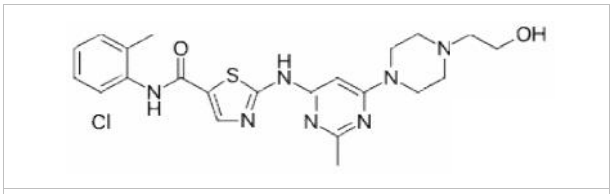
substantially improved outcomes in chronic myelogenous leukemia. They are also called tyrphostins, the short name for "tyrosine phosphorylation inhibitor", originally coined in a 1988 publication, [1]which was the first description of compounds inhibiting the catalytic activity of the epidermal growth factor receptor (EGFR).

The 1988 study was the first demonstration of a systematic search and discovery of small-molecular-weight inhibitors of tyrosine phosphorylation, which do not inhibit protein kinases that phosphorylateserine or threonine residues, can discriminate between the kinase domains of the EGFR and that of the insulin receptor. It was further shown that in spite of the conservation of the tyrosine-kinase domains one can design and synthesize tyrphostins that discriminate between even closely related protein tyrosine kinases such as EGFR and its close relative HER2.[3] Numerous TKIs aiming at various tyrosine kinases have been generated by the originators of these compounds and proven to be effective anti-tumor agents and anti-leukemic agents. [4] [5] Based on this work imatinib was developed against chronic myelogenous leukemia (CML)[6] and later gefitinib and erlotinib aiming at the EGF receptor. Sunitinib, an inhibitor of the receptors for FGF, PDGF and VEGF is also based on early studies on TKIs aiming at VEGF receptors.[7] Cabozantinib, developed by Exelixis and approved by the FDA in 2016, appears to be on its way to the standard of care in regards to TKIs.

2. Tyrosine Kinase Inhibitors (TKIs)

Dasatinib:

Dasatinib previously known as BMS-354825 is a cancer drug produced by Bristol-Myers Squibb and sold under the trade name Sprycel (4). Dasatinib is an oral Bcr-Abl tyrosine kinase inhibitor (inhibits the "Philadelphia chromosome") and Src family tyrosine kinase inhibitor approved for first line use in patients with chronic myelogenous leukemia (CML)[1] and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). It is being evaluated for use in numerous other cancers, including advanced prostate cancer.

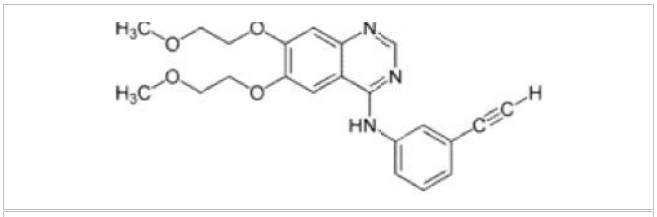


Systematic (IUPAC) name
2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide monohydrate

Dasatinib Anhydrous is an orally bioavailable synthetic small molecule-inhibitor of SRC-family protein-tyrosine kinases. Dasatinib binds to and inhibits the growth-promoting activities of these kinases. Apparently because of its less stringent binding affinity for the BCR-ABL kinase, dasatinib has been shown to overcome the resistance to imatinib of chronic myeloid leukemia (CML) cells harboring BCR-ABL kinase domain point mutations. SRC-family protein-tyrosine kinases interact with variety of cell-surface receptors and participate in intracellular signal transduction pathways; tumorigenic forms can occur through altered regulation or expression of the endogenous protein and by way of virally-encoded kinase genes.

Erlotinib

Erlotinib hydrochloride (trade name Tarceva) is a drug used to treat non-small cell lung cancer (NSCLC), pancreatic cancer and several other types of cancer. It is a receptor tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor (EGFR). It is marketed in the United States by Genentech and OSI Pharmaceuticals and elsewhere by Roche. In the United States as of 2015 one 150 mg pill costs between 200 and 242 USD.[5]

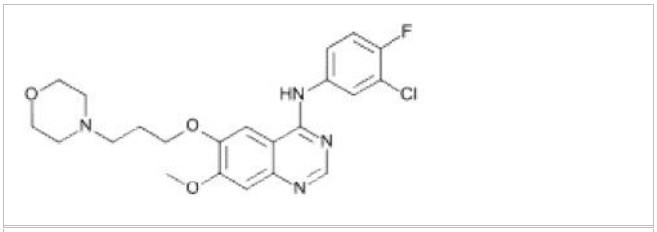


Systematic (IUPAC) name
3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine

Erlotinib Base is a quinazoline derivative with antineoplastic properties. Competing with adenosine triphosphate, erlotinib reversibly binds to the intracellular catalytic domain of epidermal growth factor receptor (EGFR) tyrosine kinase, thereby reversibly inhibiting EGFR phosphorylation and blocking the signal transduction events and tumorigenic effects associated with EGFR activation.

Gefitinib:

Gefitinib trade name **Iressa**, marketed by Astra Zeneca and Teva), is a drug used for certain breast, lung and other cancers. Gefitinib is an EGFR inhibitor, like erlotinib, which interrupts signaling through the epidermal growth factor receptor (EGFR) in target cells. Therefore, it is only effective in cancers with mutated and overactive EGFR [6].



Systematic (IUPAC) name
(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine

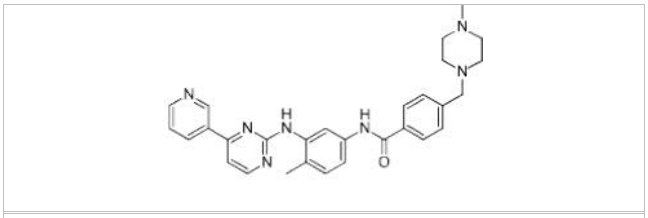
Gefitinib inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the epidermal growth factor receptor

(EGFR-TK). EGFR is expressed on the cell surface of many normal cells and cancer cells. Gefitinib is an anilinoquinazoline with antineoplastic activity.

Gefitinib inhibits the catalytic activity of numerous tyrosine kinases including the epidermal growth factor receptor (EGFR), which may result in inhibition of tyrosine kinase-dependent tumor growth. Specifically, this agent competes with the binding of ATP to the tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and resulting in inhibition of signal transduction. Gefitinib may also induce cell cycle arrest and inhibit angiogenesis.

Imatinib:

Imatinib (INN), marketed by Novartis as **Gleevec** (Canada, South Africa and the USA) or **Glivec** (Australia, Europe and Latin America), investigational name **STI-571**, is a tyrosine-kinase inhibitor used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML).[6] Imatinib kills cancer cells by turning off tyrosine kinases. In order to survive, cells need signaling through proteins (signal cascade) to keep them alive. Some of the proteins in this cascade use a phosphate group as an "on" switch. This phosphate group is added by a tyrosine kinase enzyme. In healthy cells, these tyrosine kinase enzymes are turned on and off as needed. In Ph-positive CML cells, one tyrosine kinase enzyme, BCR-Abl, is stuck on the "on" position, and keeps adding phosphate groups. Imatinib blocks this BCR-Abl enzyme, and stops it from adding phosphate groups. As a result, these cells stop growing, and even die by a process of cell death (apoptosis). [6]

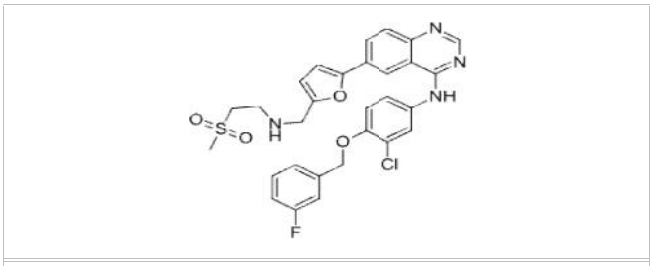


Systematic (IUPAC) name
4-[(4-methylpiperazin-1-yl)methyl]-*N*-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2 yl] amino}phenyl) benzamide

Imatinib is an antineoplastic agent used to treat chronic myelogenous leukemia. Imatinib is a 2-phenylamino pyrimidine derivative that functions as a specific inhibitor of a number of tyrosine kinase enzymes. In chronic myelogenous leukemia, the Philadelphia chromosome leads to a fusion protein of Abl with Bcr (breakpoint cluster region), termed Bcr-Abl. As this is now a continuously active tyrosine kinase, Imatinib is used to decrease Bcr-Abl activity. Imatinib Base is an antineoplastic agent that inhibits the Bcr-Abl fusion protein tyrosinekinase, an abnormal enzyme produced by chronic myeloid leukemia cells that contain the Philadelphia chromosome. Imatinib also inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF)/c-kit; the SCF/c-kit receptor tyrosine kinase is activated in gastrointestinal stromal tumor (GIST). This agent inhibits proliferation and induces apoptosis in cells that overexpress these oncoproteins.

Lapatinib:

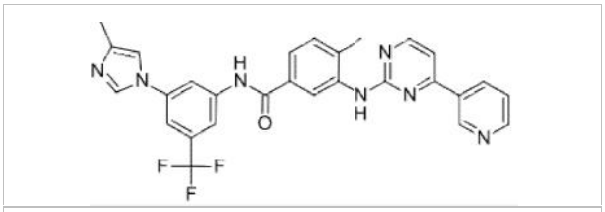
Lapatinib (INN), used in the form of lapatinibditosylate, (USAN) (Tykerb / Tyverb, GSK) is an orally active drug for breast cancer and othersolidtumours. [1] It is a dual tyrosine kinase inhibitor which interrupts the HER2/neu and epidermal growth factor receptor (EGFR) pathways.(7] It is used in combination therapy for HER2-positive breast cancer. It is used for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2).[7]



Systematic (IUPAC) name
3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[(2-methylsulfonylethylamino)methyl]-2-furyl]quinazolin-4-amine

GW572016 is a synthetic, orally-active quinazoline with potential antineoplastic properties. Lapatinib reversibly blocks phosphorylation of the epidermal growth factor receptor (EGFR), ErbB2, and the Erk-1 and-2 and AKT kinases; it also inhibits cyclin D protein levels in human tumor cell lines and xenografts. EGFR and ErbB2 have been implicated in the growth of various tumor types. Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase inhibitors. An anti-cancer drug, lapatinib was developed by GlaxoSmithKline (GSK) as a treatment for solid tumours such as breast and lung cancer. It was approved by the FDA on March 13, 2007, for use in patients with advanced metastatic breast cancer in conjunction with the chemotherapy drug capecitabine.

Nilotinib:



Systematic (IUPAC) name
4-methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)- 5 (trifluoromethyl)phenyl]-3-[(4-pyridin -3-ylpyrimidin-2-yl) amino]benzamide

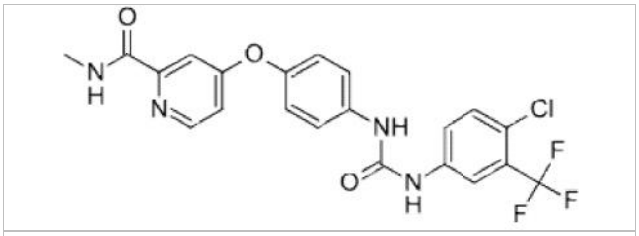
Nilotinib (AMN107, trade name Tasigna, in the form of the hydrochloride monohydrate salt, is a small-molecule tyrosine kinase inhibitor approved for the treatment of imatinib-resistant chronic myelogenous leukemia. Structurally related to imatinib, it was developed based on the structure of the Abl-imatinib complex to address

imatinib intolerance and resistance. Nilotinib is a selective Bcr-Abl kinase inhibitor that is 10-30 folds more potent than imatinib in inhibiting Bcr-Abl tyrosine kinase activity and proliferation of Bcr-Abl expressing cells.[8]

AMN107 is an orally bioavailable aminopyrimidine-derivative Bcr-Abl tyrosine kinase inhibitor with antineoplastic activity. Designed to overcome imatinib resistance, nilotinibbinds to and stabilizes the inactive conformation of the kinase domain of the Abl protein of the Bcr-Abl fusion protein, resulting in the inhibition of the Bcr-Abl-mediated proliferation of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) cells. This agent also inhibits the receptor tyrosine kinases platelet-derived growth factor receptor (PDGF-R) and c-kit, a receptor tyrosine kinase mutated and constitutively activated in most gastrointestinal stromal tumors (GISTs). With a binding mode that is energetically more favorable than that of imatinib, nilotinib has been shown to have an approximately 20-fold increased potency in kinase and proliferation assays compared to imatinib.

Sorafenib

Sorafenib (co-developed and co-marketed by Bayer and Onyx Pharmaceuticals as Nexavar), is a kinase inhibitor drug approved for the treatment of primary kidney cancer (advanced renal cell carcinoma), advanced primary liver cancer (hepatocellular carcinoma), and radioactive iodine resistant advanced thyroid carcinoma.

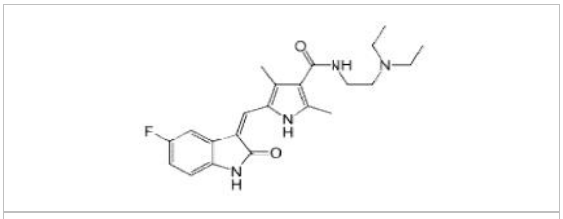


Systematic (IUPAC) name
4-[4-[[4-chloro-3-(trifluoromethyl) phenyl]carbamoylamino] phenoxy]-*N*-methyl-pyridine-2-carboxamide

Sorafenib is a synthetic compound targeting growth signaling and angiogenesis. Sorafenib blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation; in addition, sora fenib inhibits the VEGFR-2/PDGFR-beta signaling cascade, thereby blocking tumor angiogenesis. (8) No large changes in QTc interval were observed. After one 28-day treatment cycle, the largest mean QTc interval change of 8.5 ms (upper bound of two-sided 90% confidence interval, 13.3 ms) was observed at 6 hours post-dose on day 1 of cycle 2.

Sunitinib:

Sunitinib (marketed as Sutent by Pfizer, and previously known as SU11248) is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor that was approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) on January 26, 2006. Sunitinib was the first cancer drug simultaneously approved for two different indications.[9]



Systematic (IUPAC) name
2-diethylaminoethyl)-5-[(*Z*)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide

Sunitinib is an indolinone derivative and tyrosine kinase inhibitor with potential antineoplastic activity. Sunitinib blocks the tyrosine kinase activities of vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor b (PDGFRb), and c-kit, thereby inhibiting angiogenesis and cell proliferation. This agent also inhibits the phosphorylation of Fms-related tyrosine kinase 3 (FLT3), another receptor tyrosine kinase expressed by some leukemic cells.

Table 1: Summary of Food and Drug Administration (FDA)-Approved Tyrosine Kinase Inhibitors (TKIs)

Drug (Trade Name)	Target	FDA-Approved Indications	Toxicities, Side Effects and Precautions	Monitoring
Dasatinib (Sprycel)	BCR-ABL, SRC family, c-KIT, PDGFR	Chronic myeloid leukemia, acute lymphocytic leukemia	Rash; diarrhea; pleural effusion; fluid retention; mucositis; myelosuppression; QT interval prolongation	CBC; EKG; LFTs; weight; signs and symptoms of fluid retention
Erlotinib (Tarceva)	EGFR	Non-small cell lung cancer, pancreatic cancer	Acneiform rash; diarrhea; loss of appetite; nausea and vomiting; fatigue; conjunctivitis; elevated LFTs	LFTs; signs of inflammatory or infectious sequelae in patients with dermatologic toxicity
Gefitinib (Iressa)	EGFR	Non-small cell lung cancer	Acneiform rash; diarrhea; loss of appetite; interstitial lung disease (rare); elevated LFTs; patients cannot smoke while on	LFTs; signs of inflammatory or infectious sequelae in patients with dermatologic toxicity

			treatment	
Imatinib (Gleevec)	BCR-ABL, c-KIT, PDGFR	Acute lymphocytic leukemia, chronic myeloid leukemia, gastrointestinal stromal tumors,hypereosinophilic syndrome, systemic mastocytosis	Rash; weight gain; edema; pleural effusion; cardiac toxicity (depression of LVEF); nausea and vomiting; arthralgias and myalgias; myelosuppression	CBC; LFTs; weight; signs and symptoms of fluid retention
Lapatinib (Tykerb)	HER2/neu, EGFR	Breast cancer with HER2/neu overexpression	Cardiac toxicity (depression of LVEF; QT prolongation); acneiform rash; palmar-plantar erythrodysesthesia (hand-foot syndrome); diarrhea; nausea, vomiting and dyspepsia; elevated LFTs	LVEF; EKG; electrolyte levels; LFTs
Nilotinib (Tasigna)	BCR-ABL, c-KIT, PDGFR	Chronic phase or accelerated Ph- positive CML for patients resistant/intolerant of prior imatinib therapy	Rash; nauseas and vomiting; myelosuppression; QTc prolongation; sudden death; electrolyte abnormalities; hepatic dysfunction; avoid in patients with hypokalemia, hypomagnesemia, long QT syndrome	CBC; LFTs; Serum lipase; baseline and periodic EKGs
Sorafenib (Nexavar)	BRAF, VEGFR, EGFR, PDGFR	Renal cell cancer, hepatocellular carcinoma	Hypertension; alopecia; bleeding; rash; palmar-plantar erythrodysesthesia (hand-foot syndrome); hypophosphatemia; diarrhea; nausea and vomiting.	Blood pressure; dermatologic toxicity (see left); amylase, lipase, and phosphate levels; CBC
Sunitinib (Sutent)	VEGFR, PDGFR, c-KIT, FLT3	Renal cell cancer, gastrointestinal stromal tumor	Nausea and vomiting; yellow discoloration of skin; hypothyroidism; depression of LVEF; adrenal function abnormalities; diarrhea; myelosuppression; mucositis; elevated lipase and creatinine levels; elevated LFTs; increased uric acid levels	Adrenal function in patients with trauma or severe infection, or in those undergoing surgery; blood pressure; EKG; LVEF; CBC; electrolyte levels (magnesium,potassium); phosphate levels;

Note: All small molecule inhibitors are administered orally. Most small molecule inhibitors undergo cytochrome P450 metabolism and are therefore subject to multiple potential interactions (e.g., with anticonvulsants, azole antifungals, dexamethasone, isoniazid [Nydrazid], macrolide antibiotics, nefazodone [Serzone, brand no longer available in the United States], protease inhibitors, rifampin [Rifadin], St. Johnâ€™s wort, verapamil [Calan], and warfarin [Coumadin]). **Abbreviations**: FDA = U.S. Food and Drug Administration; CBC = complete blood count; BCR-ABL = breakpoint cluster region-Abelson; PDGFR = platelet-derived growth factor receptor; EKG = electrocardiography; EGFR = epidermal growth factor receptor; LVEF = left ventricular ejection fraction; LFTs = liver function tests; Ph = Philadelphia chromosome; DVT = deep venous thrombosis; VEGFR = vascular endothelial growth factor receptor.

4. Conclusion

Tyrosine kinase inhibitors are a valuable addition of the therapeutic armamentarium. Especially in certain haematologic diseases, i.e. chronic myeloid leukemia (CML)-therapy, TKI have revolutionized pharmacotherapy with survival rates not significantly different from healthy matched population. Tyrosine kinases have been generated by the originators of these compounds and proven to be effective anti-tumor agents and anti-leukemic agents.

5. References

[1] Yaish P, Gazit A, Gilon C, Levitzki A."Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors". Science. 1988, **242** (4880): 933–935

[2] Gazit A, Osherov N, Posner I, Yaish P, Poradosu E, Gilon C, Levitzki A "Tyrphostins Heterocyclic and alpha-substituted benzylidenemalononitrile tyrphostins as potent inhibitors of EGF receptor and ErbB2/neu tyrosine kinases". J Med Chem. 1991, **34** (6): 1896–907.

[3] Osherov N, Gazit A, Gilon C, Levitzki A (1993). "Selective inhibition of the epidermal growth factor and HER2/neu receptors by tyrphostins". J Biol Chem. **268** (15): 11134–42

[4] FDA. "FDA approves additional medical indication for Sprycel 5-Raymond E, Faivre S, Armand JP: Epidermal growth factor receptor tyrosine kinase as a target for anticancer therapy.

[5] PaoW, Miller V, Zakowski M, et al. (September 2004). "EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib". Proceedings of the National Academy of Sciences of the United States of America. **101**

[6] Higa GM, Abraham J. "Lapatinib in the treatment of breast cancer". Expert Review of Anticancer Therapy (log in required). Future Drugs. 2007, **7** (9): 1183–92.

[7] Manley, P.; Cowan-Jacob, S.; Mestan, J. (2005). "Advances in the structural biology, design and clinical development of Bcr-Abl kinase inhibitors for the treatment of chronic myeloid leukaemia. Biochimica Biophysica Acta. **1754**

[8] Smalley KS, Xiao M, Villanueva J, Nguyen TK, Flaherty KT, Letrero R, Van Belle P, Elder DE, Wang Y, Nathanson KL, Gastrointestinal stromal tumor: a clinical overview". Hematol. Oncol. Clin. North Am. 2009, **23** (1): 69–78,