Lecture 9: Cell Growth Inhibitors

1. Tyrosine kinase inhibitors (TKIs) – totally independent of cell cycle

These agents are cytostatic, not cytotoxic. They mainly inhibit cancer cell growth rather than kill cells. They are also known as cell signal modulators and they commonly target other enzymes that signal through phosphorylation.

Phosphorylation is the addition of a phosphate group to a substrate (another enzyme or protein). If the site that is phosphorylated is a tyrosine amino acid, then the enzyme is a tyrosine kinase. Enzymes that cause phosphorylation are also known as kinases. Enzymes that remove the phosphate groups are called phosphatase enzymes, per the equations below:

Kinase: Substrate-Tyr-OH + ATP → Substrate-Tyr-O-PO_3^{-2} + ADP

Phosphatase: Substrate-Tyr-O-PO_3^{-2} → Substrate-Tyr-OH + PO_4^{-3}

Notice that the addition of a phosphate group adds two negative charges to the tyrosine (neutral) reside. This is a major change to the amino acid in a protein, yet can be removed easily. This makes for a good on/off switch. Most tyrosine kinases utilize ATP as the source of phosphate but some use GTP instead. Signaling pathways are very complex and cascading (see Figure 1).

All the tyrosine kinase inhibitors are designed to occupy the binding site of ATP (see Figure 2). Notice their names all end with 'nib'.

Many TKIs are substrates for (or inhibitors of) CYP3A4, but other CYP enzymes commonly involved too.

Figure 2. Example of a tyrosine kinase inhibitor (imatinib) and the residues it binds to in the active site. Interacting amino acids in purple. Thr-315 is commonly mutated to isoleucine.

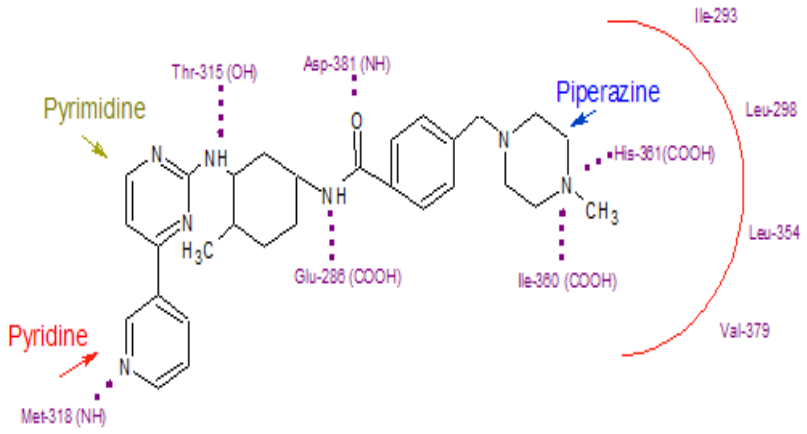
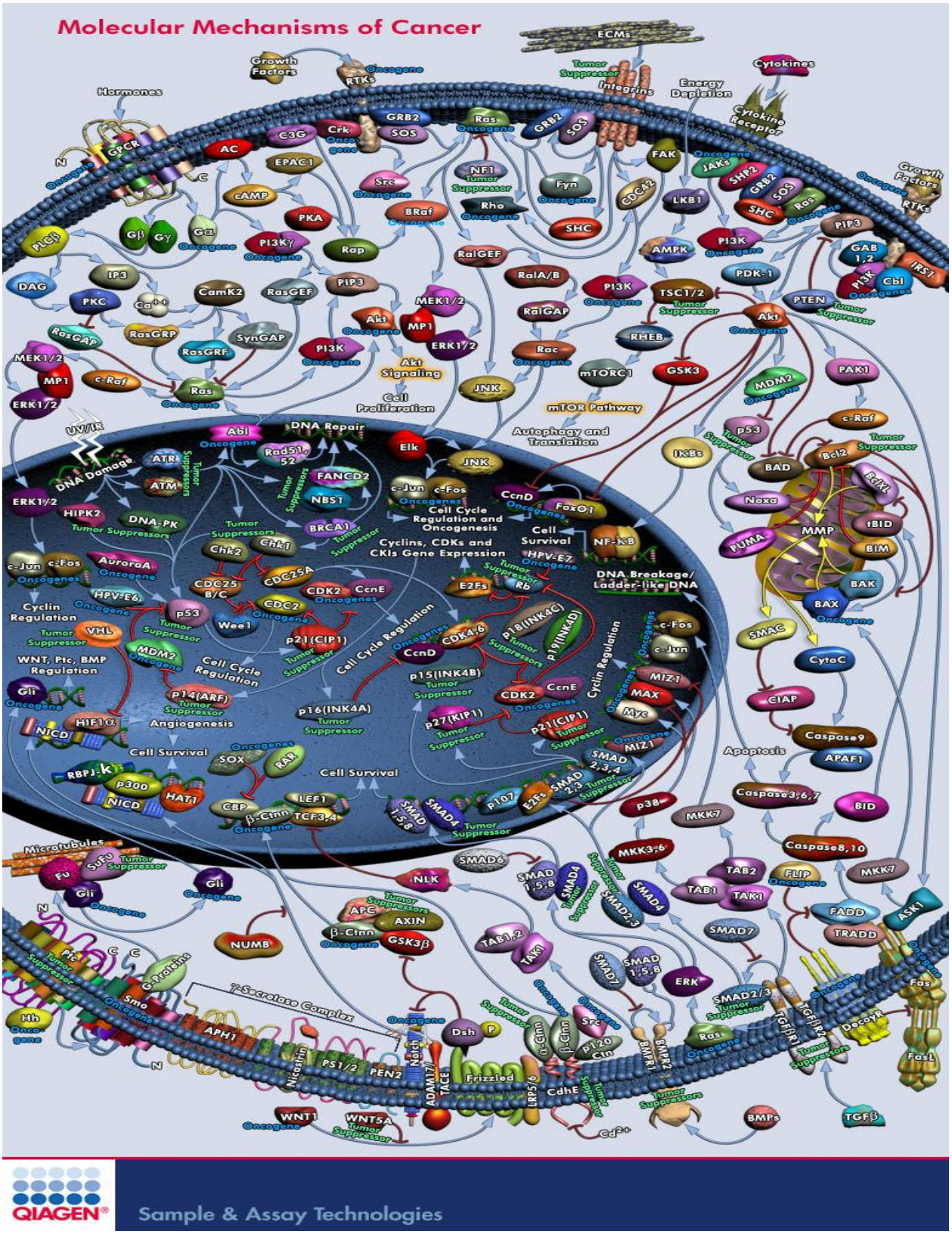
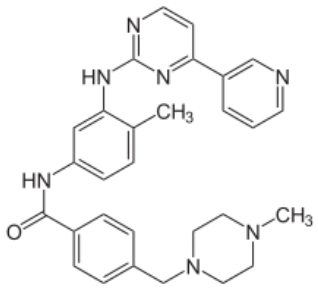


Figure 1. Signaling pathways are complex within cells (both normal and cancer cells).



For leukemias:

Imatinib (Gleevec): approved 2001; everyone should know the story about imatinib!



Uses: Mainly Ph+ chronic myelogenous leukemia (CML), Ph+ acute lymphocytic leukemia (ALL); also c-Kit+ cancers of gastrointestinal stromal tissue (GIST), also myelodysplastic syndromes with gene rearrangements that code for platelet derived growth factor (PDGF). Although extremely effective in some patients, resistance to imatinib can develop somewhat quickly. Administered PO with a meal. Formulated as mesylate salt (CH_3S04^-).

Mechanism: Specifically targets several tyrosine kinases (esp. bcr-abl, c-kit). A very important one is expressed in most CML cancers and is a product of the Philadelphia chromosome translocation. The Philadelphia chromosome is a consequence of the bcr-abl transloction (see Figure 3) because it involves the breakpoint cluster region (bcr) and the Abelson gene (abl). The abl gene encodes the actual TK activity. The chimeric bcr-abl fusion is a constitutively active tyrosine kinase.

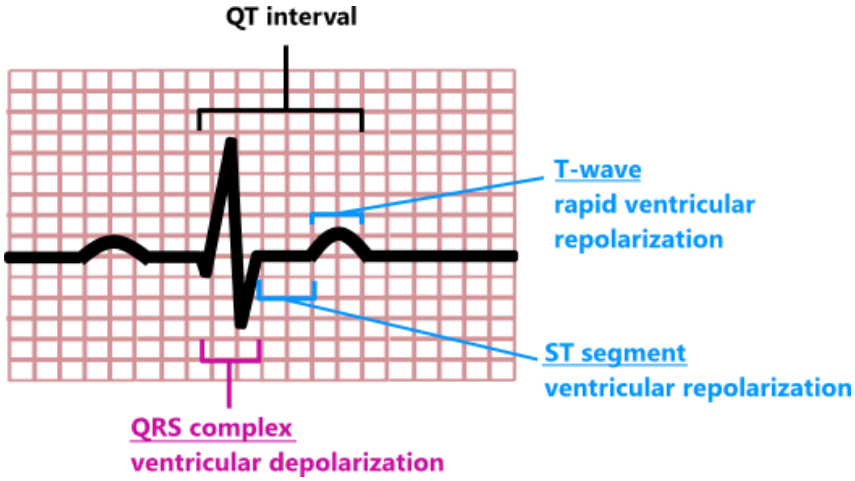
An important mutation (T315-I) in the abl gene can exist which causes resistance to imatinib. This is a point mutation and involves replacement of threonine 315 with isoleucine, which is much more bulky. This mutation prevents access of imatinib to the ATP binding site.

Toxicities: Weight gain, headache, some myelosuppression, hepatotoxicity, rash, nausea, musculoskeletal pain, some possible QT prolongation (see Figure 3).

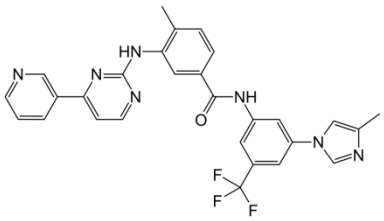
ADME: Elimination t1/2 values of imatinib and main metabolite are about 18 and 40 hrs, respectively. The main metabolite (N-desmethyl) is formed by CYP3A4. It retains activity but less than parent. Imatinib is metabolized by other isozymes (1A2, 2C9, 2C19, 2D6) participate. Strong inhibitors and inducers of CYP3A4 should be avoided.

Note(s): Imatinib is the prototype TK inhibitor. Developed in the early 1990s and Oregon Health & Science University (OHSU). It holds the record for the fastest approval by FDA of a new agent. The agent showed marked efficacy in phase 1 clinical trials. Its success ushered in the era of "targeted therapy". In reality, targeted therapy had started long ago (for example with the antimetabolites) but the TKs caused so much excitement the new term "targeted therapy" was coined.

Figure 3. The QT interval with definitions of its components.



Nilotinib (Tasigna): approved June, 2010



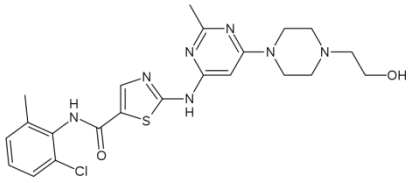
Uses: Ph+ leukemias but after resistance to imatinib has developed. Administered PO. Absorption shows a large positive food effect; must be taken while fasting or AUC can increase and be variable.

Mechanism: As for imatinib but structural changes in the molecule cause it to bind the bcr-abl TK better. About 30-50 times more potent than imatinib. Also more potent than imatinib against both resistant bcr-abl TK and non-resistant bcr-abl TK. Nilotinib can inhibit both the bcr-abl TK and c-kit TK. Not active against tumors with the T315-I mutation.

Toxicities: Myelosuppression, QT prolongation*, hepatotoxicity.

ADME: Also a better substrate of CYP3A4 so drug interactions can occur. Also because of QT prolongation issue, more attention to food effect.

Dasatinib (Sprycel): approved Oct, 2010



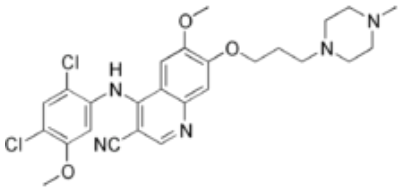
Uses: Ph+ leukemias but after resistance to imatinib has developed. Administered PO, 100 mg daily. Absorption has a modest food effect (increased AUC); should be taken while fasting.

Mechanism: As for imatinib and nilotinib, but structural changes in the molecule cause it to bind the bcr-abl TK better. Also more potent than imatinib and nilotinib against both resistant bcr-abl TK and non-resistant bcr-abl TK. About 300 times more potent than imatinib for bcr-abl TK. Also inhibits TKs in the SRC family (SRC, LCK, YES, FYN), and other TKs: c-KIT, EPHA2, and PDGFR-β. Not active against tumors with the T315-I mutation.

Toxicities: Myelosuppression, edema, QT prolongation*, hepatotoxicity.

ADME: Dasatinib is extensively metabolized by the liver. CYP3A4 is the primary enzyme responsible metabolism. Flavin-containing monooxygenase 3 (FMO-3) and glucuronidation are also involved in the formation and clearance of dasatinib metabolites. Imatinib can also cause a small amount of irreversible inhibition of CYP3A4.

Bosutinib (Bosulif): approved Sept 2012

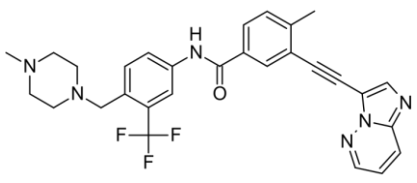


Uses: Ph+ leukemias after resistance to imatinib and dasatinib has developed. Still not effective for tumors with the T315-1 mutation. Administered PO with food.

Note(s): A substrate of CYP3A4 so drug interactions can occur. No apparent QT prolongation issue.

Ibrutinib (Imbruvica): approved 2013; MCL (targets BTK: Bruton's tyrosine kinase); hemorrhage, nephrotoxicity.

Ponatinib (Iclusig): approved Dec 2012 (targets Ph+ leukemias)



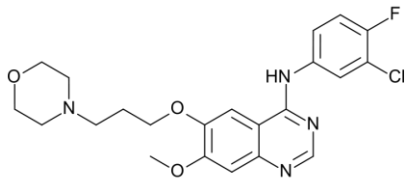
Uses: Ph+ leukemias (CML or ALL) after resistance to imatinib and dasatinib has developed. Effective for tumors with the T315-1 mutation. Administered PO with food.

Toxicities: Thrombosis, hepatotoxicity, cardiotoxicity*.

Note(s): A substrate of CYP3A4/5, 2C8, and 2D6. So drug interactions can occur. *Minimal QT prolongation issue.

For NSCLC:

Gefitinib (Iressa): approved May, 2003 but withdrawn April, 2012



Uses: Advanced or metastatic non-small cell lung cancer after platinum and docetaxel therapy. Administered PO. No large food effect. Initially it was approved by "accelerated approval mechanism" based on objective response rate, not survival benefit. Later survival studies did not show benefit. Also, lack of activity in many patients (yet still toxic) led to more restricted use; now withdrawn.*

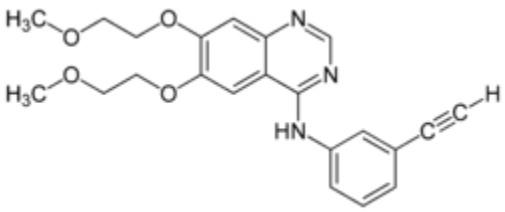
Mechanism: Inhibits the intracellular TK linked to the epidermal growth factor receptor (EGFR). EGFR is the starting point of the Ras signaling cascade (which is anti-apoptotic). Thus, inhibition of the TK that activates the cascade will inhibit the cascade and consequently apoptosis can proceed more normally.

Toxicities: Diarrhea, rash, nausea, interstitial pneumonitis* (rare but serious lung toxicity).

ADME: Gefitinib is metabolized extensively by the liver and mainly by CYP2D6 and CYP3A4, and some CYP1A1. Drug interactions are possible. Strong inhibitors and inducers of CYP3A4 should be avoided. CYP1A1 in lung can generate reactive quinone imine metabolites. *Smokers can generate much more of the reactive metabolites.

Note(s): Mutations is EGFR tend to be activating, thus greater TK activity. These mutations tend to be more common in Asians, women, and non-smokers. The response to gefitinib is better than chemotherapy (platinum + docetaxel) in EGFR mutation+ patients. For EGFR mutation- patients, chemotherapy is superior. Also, in spite of being targeted at the EGFR TK, there is not a good correlation between overall expression of EGFR and efficacy of gefitinib.

Erlotinib (Tarceva): approved Nov, 2004



Uses: Like iressa for advanced or metastatic non-small cell lung cancer after platinum and docetaxel therapy. Administered PO; fasting. Has replaced gefitinib in this use, especially with the withdrawal of iressa. Also for advanced or metastatic pancreatic cancer, in combination with gemcitabine.

Mechanism: Inhibits the intracellular TK linked to the epidermal growth factor receptor (EGFR). The EGFR is the starting point of the Ras signaling cascade (which is anti-apoptotic). Thus, inhibition of the TK that activates the cascade will inhibit the cascade and consequently apoptosis can proceed more normally.

Toxicities: Diarrhea, rash, fatigue, anorexia, lung toxicity* and some liver toxicity^.

ADME: Elimination t1/2 of about 36 hrs. Erlotinib is metabolized extensively by the liver and mainly by CYP3A4 and CYP1A1/2. The terminal t1/2 can be shortened dramatically by smoking. Drug interactions with CYP3A4 are possible. Strong inhibitors and inducers of CYP3A4 should be avoided. CYP1A1 in lung can generate reactive quinone imine metabolites. *Smokers can generate much more of the reactive metabolites.

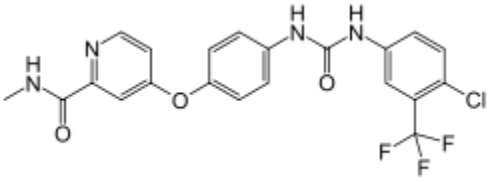
Note(s): ^Data indicate that the lung and liver toxicities might be caused by formation of reactive quinone intermediates.

Crizotinib (Xalkori): approved Nov, 2013; NSCLC; TKI (targets ALK but also HGFR, c-Met, ROS1 (c-ros), and Recepteur d'Origine Nantais (RON); QTc, hepatotoxicity, lung toxicity.

Ceritinib (Zykadia): approved Nov, 2014; NSCLC following or if intolerant to crizotinib; TKI (targets ALK: anaplastic lymphoma kinase); QTc, hepatotoxicity, lung toxicity.

For liver and renal cell cancer:

Sorafenib (Nexavar): approved Dec, 2005



Uses: Liver cancer and renal cell carcinoma. Administered PO; fasting.

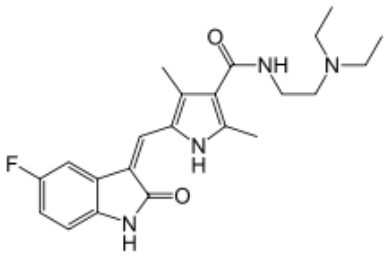
Mechanism: Inhibits multiple intracellular cell surface TKs (c-KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß) and RAF TKs (CRAF, BRAF and mutant BRAF). The contribution of the inhibition of each of these enzymes to the overall activity of sorafenib is difficult to determine.

Toxicities: Diarrhea, rash, fatigue, anorexia, QT prolongation, hand-foot syndrome. Also rare reports of cardiac ischemia, hemorrhage, and hypertension.*

ADME: Elimination t1/2 of sorafenib is about 30-50 hrs. Sorafenib is metabolized extensively by CYP3A4 so drug interactions are possible. Data indicate that sorafenib can competitively inhibit (moderately) CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. However, the clinical consequence of this appears to be minimal. Sorafenib also undergoes glucuronidation by UGT1A1. Sorafenib also inhibits glucuronidation activity of UGT1A1 and UGT1A9 in vitro. It can increase the systemic exposure of concomitantly administered drugs that are UGT1A1 or UGT1A9 substrates.

Note(s): It has been proposed that the numerous but rare toxicities caused by sorafenib are due to the multiple TKs that sorafenib inhibits.

Sunitinib (Sutent): approved Jan, 2006



Uses: Renal cell carcinoma, GIST that is resistant to imatinib (simultaneously); also pancreatic neuroendrocrine tumors. Administered PO. No food effect so can be taken with or without food.

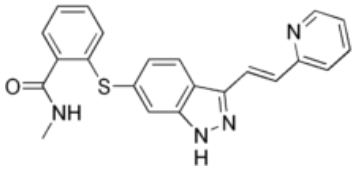
Mechanism: Inhibits multiple cell surface TKs (PDGF-R, VEGF-R, c-KIT, RET, FLT-3, CSF-1R). Some of these TKs are known to be important in renal cell cancer signaling (e.g. VEGF-R, RET).

Toxicities: Diarrhea, nausea, anorexia, mucositis, skin discoloration, hand-foot syndrome, and rare but possible severe hepatotoxicity that has caused deaths (again perhaps from reactive intermediates); also QT prolongation.

ADME: Sunitinib is metabolized primarily by CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The elimination t1/2 of sunitinib is about 50 hrs, while that of the active metabolite is about 100 hrs. Strong inhibitors and inducers of CYP3A4 should be avoided. If sunitinib must be administered with a strong inhibitor or inducer, then dosage adjustments should be made.

Note(s): Interestingly, in spite of targeting many TKs, sunitinib has failed in several late stage trials for cancers such as breast, colorectal, non-small cell lung, and prostate cancer.

Axitinib (Inlyta): approved Jan 2012



Uses: Renal cell carcinoma that has become resistant to other agents. Administered PO. No food effect so can be taken with or without food. *Dosed twice daily.

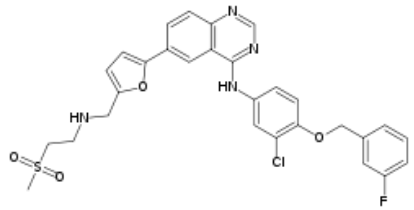
Mechanism: Inhibits several VEGF TK enzymes including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR. Note that this agent is more specific than sunitinib.

Toxicities: Hypertension, diarrhea, thromboembolic events, no apparent QT prolongation.

ADME: Axitinib is metabolized primarily in the liver by CYP3A4 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. *The elimination t1/2 is short and ranges from 3-6 hrs. Strong inhibitors or inducers of CYP3A4 should be avoided.

For breast cancer:

Lapatinib (Tykerb): approved Mar, 2007



Uses: Advanced breast cancer in combination with capecitabine for patients with HER2+ breast cancer; also in combination with letrazole for postmenapausal patients that have ER+ and HER2+ breast cancer. Administered PO. Has a substantial food effect and should be dosed without a meal. Not especially potent as dose is 1250-1500 mg/day.

Mechanism: A dual inhibitor and targets EGFR-1 and HER2/neu TKs. HER2/neu is the same as EGFR-2.

Toxicities: Diarrhea, nausea, anorexia, fatigue, rash, QT prolongation; rare but potentially serious hepatotoxicity*.

ADME: Lapatinib is metabolized extensively by CYP3A4 so drug interactions are possible. CYP2C8 and CYP2C19 participate but only in minor ways.

Note(s): *Hepatotoxicity might be caused by quinone imine reactive intermediates.

Alectinib (Alecensa): Used for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Accelerated approval in late 2015.

Lenvatinib (Lenvima): For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC (differentiated thyroid cancer) LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced RCC following one prior anti-angiogenic therapy. Targets tyrosine kinases associated with VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Approved May 2016.

Carbozantinib (Cabometyx): For the treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy. Targets tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. Approved April 2016.

PI3K (phosphoinositide 3-kinase) inhibitors; tend to be serine/threonine kinases which specifically phophorylate serine or threonine residues.

PI3K converts PIP2 to PIP3 (extra phosphate added).

Note: The tumor suppressor PTEN codes for a protein that reverses this reaction.

Idelalisib (Zydelig): approved 2014; was being developed locally by Calistoga Pharmaceuticals (as CAL101) but company bought by Gilead.

Uses: Chronic lymphocytic leukemia (CLL), in combination with rituximab. Administered PO.

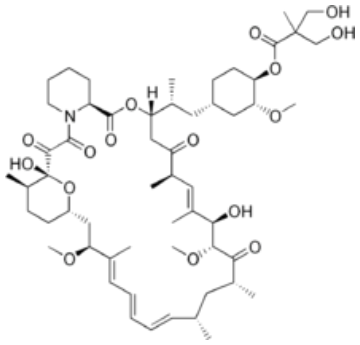
Mechanism: Inhibitor of the PI3 kinase delta (PI3Kδ) WHICHinhibits several cell signaling pathways, including B-cell receptor (BCR) signaling and the CXXR4 and CXCR5 signaling,

Toxicities: Hepatoxicity, severe diarrhea, colitis, pneumonitis, intestinal performation. No QT.

ADME: Metabolized to its major metabolite via aldehyde oxidase and CYP3A.

2. Mammalian target of rapamycin (mTOR) inhibitors – end in 'mus'

Temsirolimus (Torisel): approved May, 2007



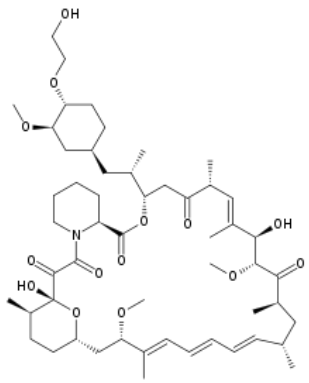
Uses: Renal cell carcinoma (RCC). Administered IV. Formulated in ethanol/vitamin E/ polyethylene glycol which can cause allergic reactions. Premedication with antihistamines is advised.

Mechanism: Inhibitor of the kinase of mTOR. This kinase is actually a serine-threonine kinase. Downstream of mTOR are several proteins involved in cell growth and proliferation cascade such as cyclin D1, HIF-1α and VEGF. In RCC, the mTOR signaling was well established as an important pathway, therefore the development of temsirolimus was rationally driven. Other forms of cancer can utilize mTOR signaling to some extent, and therefore temsirolimus may be of use (e.g. triple negative breast cancer).

Toxicities: Immune/allergic reactions; fatigue, rash, infections (due to immunosuppression) myelosuppression; rare but serious lung toxicity.

ADME: Temsirolimus is metabolized extensively by CYP3A4 and a good substrate for the efflux transported Pgp. Therefore drug interactions are possible.

Everolimus (Afinitor): approved March 2009 for RCC; July 2012 for BC



Uses: RCC but after failure of sorafenib or sunitinib; also pancreatic neuroendocrine tumors, and ER+ but HER2- breast cancer in combination with exemestane. Administered PO.

Mechanism: Inhibitor of the kinase of mTOR (mTOR1 specifically). This kinase is actually a serine-threonine kinase. Downstream of mTOR are several proteins involved in cell growth and proliferation cascade such as cyclin D1, HIF-1α and VEGF. Everolimus is also strongly immunosuppressive and even used for this purpose (Zortress).

Toxicities: Fatigue, rash, mucositis, infections (due to immunosuppression), myelosuppression, and rare but serious lung toxicity.

ADME: Everolimus is metabolized by CYP3A4 and a good substrate for the efflux transported Pgp. Therefore drug interactions are possible. Avoid co-administration of strong inducers and inhibitors of CYP3A4.

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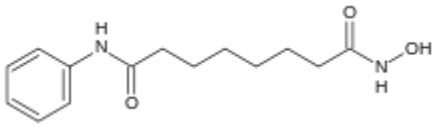
3. Histone deacetylase (HDAC) inhibitor

Vorinostat (Zolinza): approved Oct, 2006



Uses: Cutaneous T-cell lymphoma. Administration is PO with food.

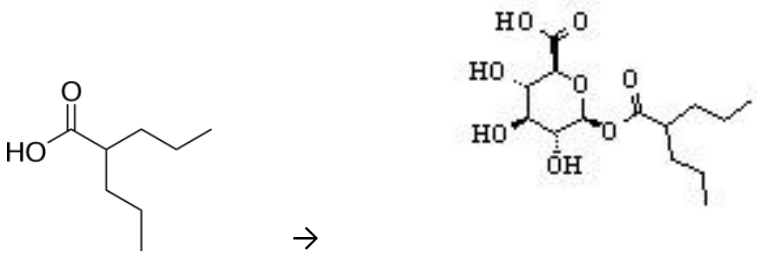
Mechanism: Vorinostat inhibits the enzymatic activity of histone deacetylases (HDACs). HDAC1, HDAC2 and HDAC3 and HDAC6 are inhibited at nanomolar concentrations. HDACs catalyze the removal of acetyl groups from lysine residues in proteins such as histones and some transcription factors. Vorinostat causes the accumulation of acetylated histones which leads to apoptosis.

Toxicities: Diarrhea, nausea, weight decrease, fatigue, and rare but potentially serious pulmonary embolism and anemia.

ADME: Major pathway of metabolism involve glucuronidation of vorinostat. Also, hydrolysis of hydroxyl amide, followed by β-oxidation to form 4-anilino 4-oxobutanoic acid (inactive) and glucuronide of metabolite. Elimination t1/2 is short at about 2 hrs for both vorinostat and the O-glucuronide metabolite (Figure 4), while that of the 4-anilino-4-oxobutanoic acid metabolite is about 11 hours. CYP enzymes do not play a large role in the metabolism of vorinostat.

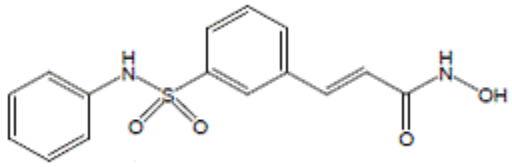
Note(s): The anticonvulsant valproic acid (VPA) is a weak HDAC inhibitor and is also glucuronidated. There can be severe thrombocytopenia and/or GI bleeding if vorinostat is administered with VPA, due to competition for glucuronidation. VPA is dosed at gram levels per day. Finally, the lung toxicity might be formed by reaction quinone imine.

Figure 4. Structure of valproic acid and glucuronide metabolite.



→ Glucuronide metabolite

Belinostat (Beleodaq): approved 2014



Uses: Relapsed or refractory peripheral T-cell lymphoma (PTCL). Administration is IV.

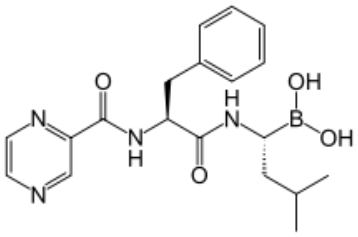
Mechanism: Like vorinostat, it inhibits the enzymatic activity of histone deacetylases (HDACs). HDAC1, HDAC2 and HDAC3 and HDAC6 are inhibited at nanomolar concentrations.

Toxicities: Pneumonia, rupyrexia, infection, anemia, increased creatinine, thrombcyopenia.

ADME: Primarily metabolized by hepatic UGT1A1. Strong UGT1A1 inhibitors are expected to increase exposure to belinostat. Belinostat also undergoes hepatic metabolism CYP2A6, CYP2C9, and CYP3A4. Because belinostat is primarily (80 -90%) metabolized by UGT1A1, the clearance of belinostat could be decreased in patients with reduced UGT1A1 activity (e.g., patients with UGT1A1*28 allele). Dose reduce in patients known to be homozygous for the UGT1A1*28 allele to minimize dose limiting toxicities.

4. Proteozome inhibitors – note they end with 'mib'

Bortezomib (Velcade): approved May, 2003



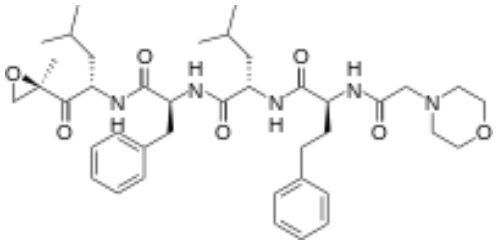
Uses: Multiple myeloma and mantle cell lymphoma. Administration is IV by bolus injection over 3-5 seconds.

Mechanism: Inhibit the action of proteasomes; bortezomib causes accumulation of damaged proteins which signals for an increase in apoptosis. For unknown reasons, multiple myeloma and mantle cell lymphoma cells are more sensitive to proteosome inhibition than normal cells. Bortezomib contains a boron atom and it binds the catalytic site of the chymotrypsin like activity in the 26S proteasome. Proteasomes regulates protein expression and function. They are important in the degradation of ubiquitinylated proteins. Proteins become ubiquitinylated when they are damaged or misfolded. Hence, proteasomes help rid cells of damaged proteins.

Toxicities: Myelosuppression, peripheral neuropathy, diarrhea, nausea, asthenia, higher rate of shingles.

ADME: Multiple CYP enzymes participate in the metabolism of bortezomib; drug interactions are not expected except for strong inducers (e.g. rifampin, phenytoin) or strong inhibitors (e.g. ketoconazole, ritonavir) are co-administered. CYP enzymes even catalyzed the removal of boron from the molecule.

Carfilzomib (Kyprolis): approved July 2012



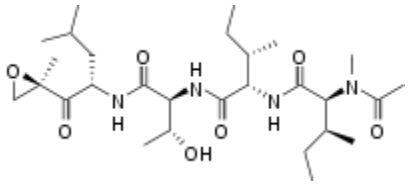
Uses: Multiple myeloma following progression after use of two prior therapies including bortezomib and an immunomodulating agent. Administration is IV, over 2-10 minutes. Formulation includes sulfobutylether β- cyclodextrin. Premedication (dexamethasone) to minimize infusion reactions is recommended. Hydrate patients to reduce renal toxicity risk.

Mechanism: Synthetic analog of the natural toxin epoxomicin (Figure 5). Irreversibly binds to and inhibits the chymotrypsin-like activity of the 20S proteasome. Has selectivity for the N-terminal threonine in active site.*

Toxicities: Quite toxic; sudden cardiac arrest; myelosuppresion, cardiotoxicity, tumor lysis syndrome, pulmonary hypertension, hepatotoxic, renal toxicity.

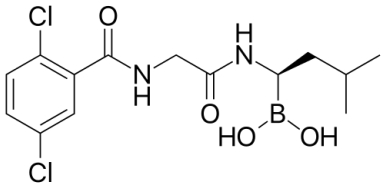
ADME: High renal excretion; very short t1/2 of 1 hr or shorter; rapidly and extensively metabolized into peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis are the principal pathways of metabolism; CYP enzymes play only minor role in overall metabolism; metabolites have no known biologic activity.

Figure 5. Structure of epoxomicin.



Note(s): *The reaction is complex but believed to involve 5 steps, ultimately leading to attack of enzyme threonine on the carbon of the epoxide group of epoxomicin, accompanied by the epoxide ring-opening (SN2) nucleophilic substitution.

Ixazomib (Ninlaro): approved Nov, 2015



Uses: Mulitple myeloma; in combination with lenalidomide and dexamethasone for the treatment of patients who have received at least one prior therapy. Ixazomib is the first approved oral proteasome inhibitor.

Mechanism: Reversibly inhibits the protein subunit beta type-5 (PSMB-5) which is part of the 20S proteasome complex.

Toxicities: Thrombocytopenia, N/V, peripheral neuropathy, hepatocotxicity, hepatotoxicity, peripheral edema, evidence of teratogenicity. No QT effects.

ADME: Substrate of CYP3A4; avoid use with strong CP3A4 inducers.

5. BCL-2 inhibitors – BCL-2 protein is anti-apoptotic

Venetoclax (Venclexta): approved Apr, 2016

Uses: Chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy. Patients must have the 17p deletion as detected by an FDA-approved test. Small molecule and orally bioavailable.

Mechanism: Inhibitor of BCL-2 and over-expression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and has been associated with resistance to various chemotherapeutics.

Toxicities: The most frequent serious adverse reactions are pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia (AIHA), anemia, and tumor lysis syndrome (TLS).

ADME: Substrate of CYP3A4/5; avoid use with strong CP3A4 inducers.

Note: Venetoclax is subject to a positive food effect. Administration with a high-fat meal can increase venetoclax exposure by 5.1-to 5.3-fold compared to fasting conditions. Venetoclax should be administered with a meal.

6. Cyclin inhibitors – Cyclins (cell cycle control proteins)

Palbociclib (Ibrance): approved Feb 2016

Uses: HR-positive, HER2-negative advanced or metastatic breast cancer in combination with letrozole as initial endocrine based therapy in postmenopausal women, or with fulvestrant in women with disease progression following endocrine therapy. The indication in combination with letrozole is approved under accelerated approval based on progression-free survival (PFS). *Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*

Mechanism: Inhibits cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. *In vitro*, palbociclib reduces cellular proliferation of estrogen receptor (ER)-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle.

Toxicities: The most common adverse reactions (≥ 10%) of any grade reported in patients in the IBRANCE plus letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis.

ADME: Several metabolic pathways for palbociclib: oxidation (CYP3A4) and sulfation (SULT2A1), with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma (23%).

Note: Palbociclib is subject to a positive food effect. Venetoclax should be administered with a meal.