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Protein Kinase Inhibitors

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OVERVIEW

The kinase inhibitors are a large group of unique and potent antineoplastic agents which specifically target protein kinases that are altered in cancer cells and that account for some of their abnormal growth. Protein kinases are ubiquitous intracellular and cell surface proteins that play critical roles in cell signaling pathways involved in metabolism, injury responses, adaption, growth and differentiation. They act by adding a phosphate group to a protein (phosphorylation), usually on a specific amino acid which often makes the protein or enzyme "active". The human genome has more than 500 protein kinases and they can be classified as (1) tyrosine, (2) serine-theonine or (3) nonspecific (both), based upon their amino acid specificity. Many protein kinases are cell surface receptors and act to initiate an intracellular pathway of activation, after the receptor is engaged by its ligand, typically a cytokine or growth factor. Inhibitors of these kinases are called protein kinase receptor inhibitors. Other kinases are intracellular and take part in cell signaling. These kinases can be targeted by "non-receptor" protein kinases. Finally, some kinase inhibitors have specificity for multiple kinases and are called "multi-kinase inhibitors."

Protein kinases can be specifically involved in cell growth, proliferation and differentiation and mutations may lead to unregulated growth and proliferation that is typical of cancerous cells. These mutated protein kinases represent an attractive target for anticancer agents. The potent activity and lack of generalized toxicity of the kinase inhibitors relate to the specificity of antagonist for the mutated protein. In like manner, their toxicity often relates to off-target activity, either to the unmutated kinase or to closely related, normal kinases.

The protein kinases can be categorized based upon the amino acid that they phosphorylate: either serine, threonine or tyrosine. The tyrosine kinase receptor inhibitors were the initial and are perhaps the best characterized kinase inhibitors. The protein kinase inhibitors are relatively recently developed agents, all having been introduced since 2001. They are unique and represent a major advance in cancer chemotherapy, away from broadly cytotoxic agents and towards drugs that specifically target the molecular abnormalities of cancer cells. The initial tyrosine kinase inhibitor approved for use in the United States was imatinib (Gleevec: 2001) which is used to treat Philadelphia chromosome positive chronic lymphocytic leukemia, which has a mutated kinase receptor (BCR-ABL) that is created by the specific translocation that creates the Philadelphia chromosome. Imatinib is a specific inhibitor of the BCR-ABL kinase. The introduction of this first protein kinase inhibitor was followed by more than a dozen others within the next 10 years.

While most kinase inhibitors are antineoplastic agents, a few are also used for benign conditions including macular degeneration (pegaptanib), rheumatoid arthritis (tofacitinib) and idiopathic pulmonary fibrosis (nintedanib). Generally, however, the side effect profile of kinase inhibitors are such that they are reserved for severe, progressive, debilitating or potentially fatal conditions.

The protein kinase inhibitors all have some degree of hepatotoxicity and many have been linked to cases of clinically apparent liver injury which can be severe and even fatal. Interestingly, some of the cases of liver injury attributed to the protein kinase antagonists had features of autoimmunity, so that the liver injury may be caused by an immunologic reaction to metabolic products of the agent itself, rather than off-target activity of the inhibitor. In addition, at least two protein kinase inhibitors (imatinib and nilotinib) have been linked to instances of reactivation of hepatitis B. It is not clear whether this relates to a specific activity of the kinase inhibitor on hepatitis B virus replication or whether it is due to immunosuppression. Other kinase inhibitors have been linked to cases of rare and idiosyncratic liver injury, which can be hepatocellular or cholestatic and is typically self-limited but may be fatal.

The Table below lists the protein kinase inhibitors discussed in LiverTox, their brand name, predominant protein kinase (PK) specificity, year of approval in the United States, likelihood score, and major clinical uses.

PROTEIN KINASE INHIBITORS

Underlined Generic Names link to a LiverTox record.

CANCER				
Generic Name **Brand Name**	**Kinase Target**	**Approval**	Likelihood Score†	**Major Uses††**
Abemaciclib Verzenio	Cyclin dependent kinase 4/6	2017	E*	Breast cancer
Acalabrutinib Calquence	Bruton kinase	2017	D	Mantel cell lymphoma
Afatinib Gilotrif	EGFR, HER2	2013	D	NSCLC
Alectinib Alecensa	ALK	2015	D	NSCLC
Axitinib Inlyta	VEGFR 1-3	2012	E	Renal cell cancer
Binimetinib Mektovi	BRAF	2018	E*	Melanoma
Bortezomib Velcade	Proteasome	2003	C	Multiple myeloma, Mantle cell lymphoma
Bosutinib Bosulif	BCR-ABL, scr	2012	E*	CML, resistant
Brigatinib Alunbrig	ALK	2017	E*	NSCLC
Cabozantinib Cometriq, Cabometyx	MET, VEGFR-2	2012	E*	Medullary thyroid cancer, Renal cell cancer
Carfilzomib Kyprolis	Proteasome	2012	E*	Multiple myeloma, resistant
Ceritinib Zykadia	ALK	2014	D	NSCLC
Cobimetinib Cotellic	MEK	2015	D	Melanoma
Copanlisib Aliqopa	PI3Kα/δ	2017	E*	Follicular lymphoma

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Crizotinib Xalkori	ALK	2011	D	NSCLC
Dabrafenib Tafinlar	BRAF	2013	E*	Melanoma
Dacomitinib Vizimpro	HER1,2,3	2018	E*	NSCLC
Dasatinib Sprycel	BCR-ABL, src	2006	D	CML, resistant
Duvelisib Copiktra	PI3K	2018	E*	CLL, Small cell lymphoma
Enasidenib IDHIFA	Mutant IDH-2	2017	E*	AML
Encorafenib Braftovi	BRAF	2018	E*	Melanoma
Erlotinib Tarceva	EGFR, HER1	2004	C	NSCLC, Pancreatic cancer
Gefitinib Iressa	EGFR	2009	C	NSCLC
Gilteritinib Xospata	FLT3	2018	E*	AML
Glasdegib Daurismo	Hedgehog	2018	E*	AML
Ibrutinib Imbruvica	Bruton kinase	2013	D	Mantle cell lymphoma, CLL
Idelalisib Zydelig	PI3Kδ	2014	D	CLL, Non-Hodgkin lymphoma
Imatinib Gleevec	BCR-ABL, c-Kit	2001	B	CML, GIST
Ivosidenib Tibsovo	Mutant IHD-1	2018	E*	AML
Ixazomib Ninlaro	26S Proteasome	2015	E*	Multiple myeloma
Lapatinib Tykerb	EGFR, HER2	2007	D	Breast cancer, HER2 positive
Larotrectinib Vitrakvi	NTRK	2018	E*	Solid tumors
Lenvatinib Lenvima	VEGFR 1-3, FGF 1-4, PDGF, c-Kit, RET	2015 2016 2018	D	Thyroid cancer Renal cell cancer Hepatocellular cancer
Lorlatinib Lorbrena	ALK	2018	E*	NSCLC
Midostaurin Rydapt	FLT3	2018	E*	AML
Neratinib Nerlynx	HER2	2017	E*	Breast cancer

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Nilotinib Tasigna	BCR-ABL	2007	E*	CML, resistant
Niraparib Zejula	PARP	2017	E*	Ovarian cancer
Olaparib Lynparza	PARP	2014 2018	E	Ovarian cancer Advanced breast cancer
Osimertinib Tagrisso	EGFR	2015	E*	NSCLC, refractory
Palbociclib Ibrance	ER+, HER2	2015	E*	Breast cancer, HER2 negative
Pazopanib Votrient	VEGFR 1-3	2009	C	Renal cell cancer
Ponatinib Iclusig	BCR-ABL	2013	E*	CML, ALL
Regorafenib Stivarga	VEGFR 1-3, PDGF	2012	D	Colorectal cancer, GIST
Ribociclib Kisqali	Cyclin dependent kinase 4/6	2017	C	Breast cancer
Rucaparib Rubraca	PARP	2016	D*	Ovarian cancer, advanced
Ruxolitinib Jakafi	Janus kinase	2011	E*	Myelofibrosis
Sonidegib Odomzo	Hedgehog	2015	E*	Basal cell skin cancer
Sorafenib Nexavar	VEGFR 1-3	2005 2007 2013	C	Renal cell cancer Hepatocellular cancer Thyroid cancer
Sunitinib Sutent	PDGF, c-Kit	2006	D	CML, resistant; GIST, renal cell cancer
Talazoparib Talzenna	PARP	2018	E*	Breast cancer
Trametinib Mekinist	MEK 1-2	2013	E*	Melanoma
Vandetanib Caprelsa	VEGFR 2	2011	E*	Medullary thyroid cancer
Vemurafenib Zelboraf	BRAF	2011	E*	Melanoma
Vismodegib Erivedge	Hedgehog	2012	D	Basal cell skin cancer
MISCELLANEOUS				
Generic Name Brand Name	**Kinase Target**	**Approval**	Likelihood Score†	**Major Uses††**
Baricitinib Olumiant	Janus kinase	2018	E*	Rheumatoid arthritis
Fostamatinib Tavalisse	Spleen tyrosine kinase	2017	E*	Immune thrombocytopenia

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Nintedanib Ofev	VEGFR, FGFR, PDGFR	2014	E*	Pulmonary fibrosis
Pegaptanib Macugen	VEGFR 1-3	2004	E	Macular degeneration
Tofacitinib Xeljanz	Janus kinase	2012	E*	Rheumatoid arthritis

† Likelihood Score indicates the likelihood of association with drug induced liver injury, based upon the known potential of the drug to cause such injury.

†† Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer.