

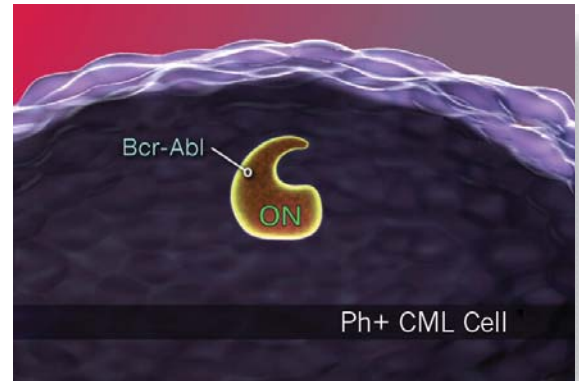
Targeting the Key Cause and Driver of Ph+ CML

Healthy cells make specialized proteins called tyrosine kinases, or TK, which normally turn cell division on and off. The cells of some cancers, like chronic myeloid leukemia (CML), develop a genetic abnormality which results in the production of a malfunctioning TK protein. Bcr-Abl is a malfunctioning TK and the key cause and driver of Philadelphia Chromosome Positive CML (or Ph+ CML). Bcr-Abl switches are stuck at the “on” position and tells the body to continue producing white blood cells. These forces drive the Ph+ CML cells to continually divide.

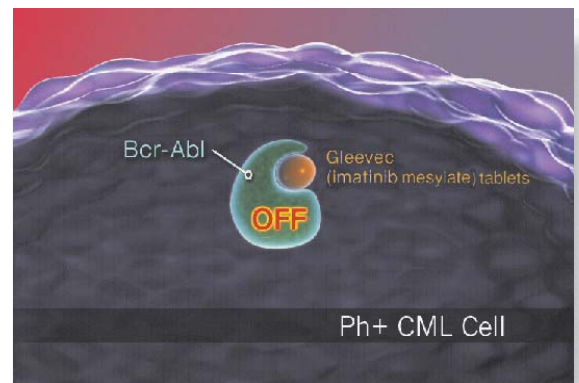
Traditional chemotherapy typically kills dividing cells, good or cancerous. Gleevec® (imatinib mesylate) tablets* is designed to target the Ph+ CML cells. By attaching to Bcr-Abl, Gleevec turns off the switch that signals the body to continue producing white blood cells.

Cancer cells can protect themselves by mutating when challenged. Ongoing studies have shown a small percentage of cases where Ph+ CML cells never respond to, or stop responding to, Gleevec. In addition, a small subset of patients cannot tolerate therapy with Gleevec.

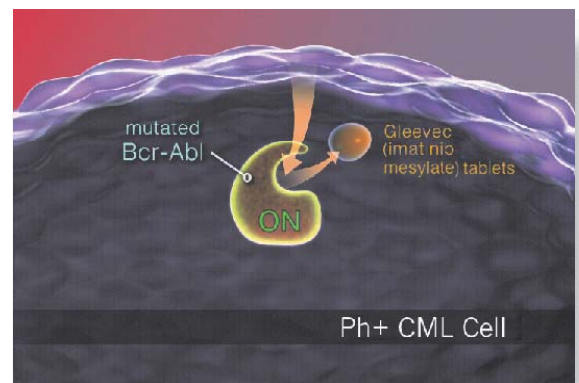
Building on the vast knowledge and experience gained during the development of Gleevec, Novartis has developed Tasigna (nilotinib) capsules, a next generation TK inhibitor. Tasigna was specifically designed to target the Bcr-Abl protein more preferentially than Gleevec without adding new targets. In preclinical studies, the medicine was able to overcome resistance resulting from Bcr-Abl kinase mutations in 32 of 33 cell lines commonly associated with Ph+ CML. Tasigna has been approved for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included Gleevec.



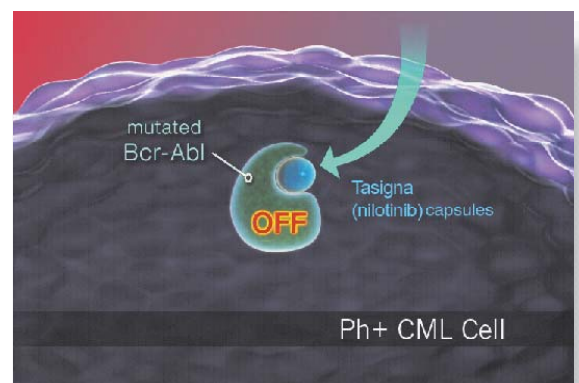
Bcr-Abl switches are stuck at the “on” position.



Gleevec turns off the switch that signals the body to continue producing white blood cells.



Ph+ CML cells can protect themselves by mutating.



Tasigna is designed to work where Gleevec does not.

* Known as Glivec® (imatinib) outside the U.S., Canada and Israel.

Tasigna important safety information

WARNING: QT PROLONGATION AND SUDDEN DEATHS

TASIGNA prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. TASIGNA should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. Use with caution in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

Myelosuppression

Treatment with Tasigna is associated with Grade 3/4 neutropenia, thrombocytopenia, and anemia. Complete blood counts should be performed every 2 weeks for the first 2 months, then monthly thereafter as clinically indicated. Myelosuppression with Tasigna was generally reversible and usually managed by withholding Tasigna temporarily or dose reduction.

QT prolongation

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Sudden deaths

There were sudden deaths reported in the safety population and the expanded access program. Ventricular repolarization abnormalities may have contributed to their occurrence.

Elevated serum lipase

Caution is recommended in patients with history of pancreatitis. Check serum lipase periodically.

Liver function abnormality

Serum bilirubin and hepatic transaminases

The use of Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Check hepatic function tests periodically.

Electrolyte abnormalities

Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, hyponatremia and hypocalcemia. Correct electrolyte abnormalities prior to initiating Tasigna and monitor periodically during therapy.

Hepatic impairment

Metabolism of Tasigna is mainly hepatic. Tasigna has not been investigated in patients with hepatic impairment. Caution is recommended in these patients and QT interval should be monitored closely.

Drug interactions

The concomitant use of QT prolonging drugs and strong inhibitors or inducers of CYP3A4 should be avoided as they may affect serum concentration of Tasigna.

Concomitant strong CYP3A4 inhibitors

The concomitant use of strong CYP3A4 inhibitors should be avoided (including, but not limited to, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted. If interruption of treatment with Tasigna is not possible, patients who require treatment with a drug that prolongs QT or strongly inhibits CYP3A4 should be closely monitored for prolongation of the QT interval, and a dose reduction to ½ the daily dose is recommended (400 mg once daily). If the strong inhibitor is discontinued, a washout period should be allowed before Tasigna is adjusted upward to the indicated dose. Close monitoring for prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors. Grapefruit products and other foods that are known to inhibit CYP3A4 should also be avoided.

Concomitant strong CYP3A4 inducers

The concomitant use of strong CYP3A4 inducers should be avoided (including, but not limited to, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital). Patients should also refrain from taking St John's Wort. If patients must be co-administered a strong CYP3A4 inducer, the dose of Tasigna may need to be increased, depending on patient tolerability. If the strong inducer is discontinued, the Tasigna dose should be reduced to the indicated dose. Tasigna is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1. Since warfarin is metabolized by CYP2C9 and CYP3A4, it should be avoided if possible. Tasigna inhibits human P-glycoprotein. If Tasigna is administered with drugs that are substrates of Pgp, increased concentrations of the substrate are likely and caution should be exercised. Tasigna may also induce CYP2B6, CYP2C8, and CYP2C9. Therefore, Tasigna may alter serum concentration of other drugs.

Food effects

Food increases blood levels of Tasigna. Patients should avoid food 2 hours before and 1 hour after taking dose.

Lactose

Since the capsules contain lactose, Tasigna is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency, or of glucose-galactose malabsorption.

Pregnancy

Fetal harm can occur when Tasigna is administered to a pregnant woman. Women should be advised not to become pregnant when taking Tasigna.

Adverse reactions

In chronic phase patients, the most commonly reported adverse reactions (>10%) were rash (33%), pruritus (29%), nausea (31%), fatigue (28%), headache (31%), constipation (21%), diarrhea (22%), and vomiting (21%). The most common (>10%) Grade 3/4 adverse reactions were thrombocytopenia (28%), neutropenia (28%), elevated lipase (15%), and hyperglycemia (11%). In accelerated phase patients, the most commonly reported adverse reactions (>10%) were rash (28%), pruritus (20%), and constipation (18%). The most common (>10%) Grade 3/4 adverse reactions were thrombocytopenia (37%), neutropenia (37%), anemia (23%), and elevated lipase (17%). Other serious adverse reactions included pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, and pyrexia (Grade 3/4: 2%).

Dose adjustments or modifications

Tasigna may need to be temporarily withheld and/or dose reduced for QT prolongation, hematological toxicities that are not related to underlying leukemia, clinically significant moderate or severe nonhematologic toxicities, laboratory abnormalities, or concomitant use of strong CYP3A4 inhibitors. With concomitant use of strong CYP3A4 inducers, the dose of Tasigna may need to be increased, depending on patient tolerability.

Other patients in whom Tasigna should be used with caution

Tasigna should not be used during pregnancy. Sexually active female patients should use effective contraception during treatment. Women should not breast feed while taking Tasigna. There are no data to support the use of Tasigna in pediatric patients. Use with caution in patients with hepatic impairment.