GleevecTM (STI571) belongs to a new class of antiproliferative agents called signal transduction inhibitors (STIs). The therapeutic efficacy of gleevec is based on its specific inhibition of bcr/abl oncogen protein (IC50=0.25 µM), which is a widely expressed tyrosine kinase in transformed chronic myeloid leukemia (CML) cells.

Two human bcr/abl positive (+/+) and one negative (-/-) cell lines were incubated with different concentrations of gleevec (range: 0.05 to 10 µM) for 96 hours. To evaluate the metabolic changes after gleevec treatment by MRS, 5 mmol/l [1-13C] labeled glucose was added to the cells for the last 4 hours of incubation. The water soluble and lipid extract fractions were analyzed by 13C-, 1H-, and 31P-MRS at a Bruker 600 DRX spectrometer.

To assess the metabolic changes of gleevec, the cells were incubated with 0.1 µM gleevec for 96 hours. This gleevec concentration corresponds to the IC25 values (concentration required for 25% inhibition of cell growth) for both bcr/abl +/+ cell lines. There was no change in the metabolic homeostasis in bcr/abl -/- cells after gleevec incubation. The metabolic changes in both bcr/abl +/+ cells showed the same cellular response. Surprisingly, these cells had higher concentrations of ATP after gleevec incubation. Addition of gleevec strongly suppressed lactate production from [1-13C] labeled glucose as has been seen from the intensity of [3-13C] labeled lactate in 13C-MRS as well as from the integrals of lactate satellite peaks in 1H-MRS spectra. Simultaneously, gleevec led to an increased production of 13C-labeled glutamate especially for C4-labeled glutamate. The analysis of incubation media indicated that gleevec treated cells utilized less glucose than control cells. The lipid extracts of gleevec treated bcr/abl +/+ cells contained less fatty acids.

Summary: Gleevec led to a specific inhibition of glycolitic activity with the subsequent stimulation of the Krebs cycle in the bcr/abl positive cells. Since the energy metabolism was elevated after treatment, gleevec, unlike standard chemotherapeutics, stimulates differentiation of bcr/abl positive leukemic cells without killing them.