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Previous

Issue Content

Next


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## RESEARCH

# A Cancer Drug with Fan Mail

## A new type of drug makes chronic myelogenous leukemia patients very happy

By Tom Hollon

"I feel so good that sometimes I forget I have leukemia," writes **Gay Bratton** of her experience with STI571, Novartis Pharma's experimental drug for treatment of chronic myelogenous leukemia (CML). Bratton, a high school math teacher and grandmother, started taking STI571 at Houston's M.D. Anderson Cancer Center last December as a participant in a Phase I trial of the drug. With STI571, her white blood cell counts are under control and her anemia is gone, giving her the energy to function normally.

**Judy Orem** was the ninth person to take STI571 for CML at Oregon Health Sciences University (OHSU) in Portland. After more than a year on the drug, she has some puffiness around the eyes and has learned to eat before taking her pill to avoid an upset stomach. Her real side effects, she writes, are "getting my taste back, being able to be active again, having energy, having my mind back, and enjoying life."

**Jerry Mayfield** is not taking STI571. Unlike Bratton and Orem, his CML can still be controlled with interferon-\* (IFN-\*), the current front-line treatment; for that reason, he was not eligible to enroll in the Phase I trial. But Mayfield, a retired Louisiana state trooper, is so passionate about STI571 that he operates, at his own expense, a Web site to spread the word ([www.newcmldrug.com](http://www.newcmldrug.com)).

"It's just so amazing to hear things like that," says **Brian Druker**, the OHSU physician who is principal investigator of the STI571 clinical trial. "If you heard that from one patient, that would be one thing," he says enthusiastically, "but those are the sorts of things I hear from every single one of my patients."

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**The crystal structure of AMP-PNP bound to Lck was used to make a model of the Abl kinase domain. Left, the general architecture of the Abl kinase domain; top**



Lydon's team at Ciba laboratories in Basel, Switzerland, including **Juerg Zimmermann, Elizabeth Buchdunger, Peter Traxler, and Helmut Mett**, screened compound libraries at random, looking for inhibitors of cancer-associated kinases. Eventually they found a 2-phenylaminopyrimidine that was a weak inhibitor of the kinase activity of the platelet-derived growth factor (PDGF) receptor (PDGF-R). Their interest turned to CML when they discovered derivatives that were potent dual inhibitors of PDGF-R and Bcr-Abl; their compounds killed Philadelphia chromosome-positive (Ph+) cells in vitro and in vivo when implanted into nude mice.

At that point, around 1995, they began collaborating with Druker, a CML specialist. But it wasn't a logical next step to start a CML drug development program. CML represented a very small market--only about 4,500 Americans are annually diagnosed with CML, according to the Leukemia and Lymphoma Society of America. To a big drug company, numbers like that often mean a drug isn't going to be profitable. But Druker and Lydon argued that their best drug, STI571, should be developed to validate the concept of protein kinase inhibitors. As they point out in a recent paper,<sup>1</sup> CML made a good test case for a new drug class. The heart of their argument was that if a protein kinase inhibitor could have a big effect on a cancer, it might be more likely with CML, caused by just one mutation, than with other cancers, which nearly always arise after damage to multiple genes. Eventually, Novartis committed to clinical trials, and the preclinical team, including **Peter Graff, Ulrika Pfaar, and Hans Michael Buerger**, formulated STI571 into pill form and got it ready.

## Response: 31/31

Phase I began in June 1998, with Druker coordinating tests in Portland, Houston, and Los Angeles. Enrolling patients were essentially in the latter part of the chronic phase; they either had rising Ph+ cell counts in spite of interferon, or were unable to tolerate interferon's side effects. "It became evident very early on," says Lydon, "that there were some spectacular effects. Once we reached the target dose that in animals and cell-based studies killed off the leukemic cells, we saw normalization of blood cell counts in all the patients." As Druker recently reported at a meeting of the American Association for Cancer Research, at 300 mg/day, 31 of 31 patients responded, with minimal side effects. "We are doing better than with previous treatments," Druker says. "All the people in the study were people who had failed interferon. And we now have them back with normal blood counts, and half of them are having a decrease in the percentage of cells that have the Philadelphia chromosome. They are tolerating their therapy very well; not only do they feel better than when they were on interferon, but their disease is under better control than when they were on interferon."

Some of the patients have been on STI571 daily for a year with no apparent side effects. It is, however, too early to say the drug is delaying progression to blast crisis, "although there are some hints of that," Druker says. He adds that he does not consider anyone cured. Although 10- 20 percent of the patients show no Philadelphia chromosomes in cell counts, RT-PCR assays show they have low levels of Bcr-Abl mRNA transcripts. If they get down to none and stay that way for a couple of years, Druker might consider taking them off STI571.

The mildness of STI571 side effects is immensely surprising, since indirect data suggest it is also inhibiting c-Abl, the c-kit tyrosine kinase, and PDGF-R. While imperfect selectivity was worrisome prior to clinical trials, Druker argued that the plight of CML patients made the risk worth taking. The apparent short-term safety of STI571 will be encouraging if it is now used in clinical trials for glioblastoma, where

