



Tasigna: An Innovative TKI from Novartis for Patients with CML



by Dianne S. Pena

On October 30 the FDA approved Novartis Oncology's Tasigna®, thus giving physicians and CML patients another treatment option. We cover this innovative TKI, how it is differentiated from Gleevec®, and where it may fit in the CML market alongside its sister blockbuster, and its fastest-growing competitor, Sprycel®.

On October 30, Novartis Oncology announced the Food and Drug Administration's approval of Tasigna [nilotinib], for treatment of chronic phase and accelerated phase Philadelphia-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included Gleevec [imatinib mesylate]. Based on the reputation of its predecessor, Gleevec, which achieved FDA approval in 2001, Tasigna bears the weight of great expectations.

With Gleevec, Novartis revolutionized first-line therapy for most patients with CML, however, there are a number of patients who either don't respond to the drug or lose responsiveness over time. "The number of these patients is very small, but it is a true medical need," said Rainer Boehm, Senior Vice President and North American Region Head of Oncology—Tasigna addresses this need.

Approximately 95-100 percent of patients with CML have the abnormal Philadelphia chromosome. This mutated chromosome leads to the production of a faulty tyrosine kinase (TK), a specialized protein normally responsible for turning cell division on and off. This rogue TK—known as BCR-ABL—causes white

blood cells to produce at an abnormal rate, and is the target for both Gleevec and Tasigna.

Armed with the knowledge gained during the development of Gleevec, researchers at Novartis Oncology were able to design an even more targeted assault on BCR-ABL. Of the 33 BCR-ABL kinase mutations associated with Ph+ CML, Tasigna is able to overcome the resistance resulting from all but one of these mutations. "With Tasigna," said Boehm, "we knew what we were looking for."

Without effective treatment, patients with CML typically progress from the initial (chronic) phase through a transition period (accelerated phase) to a rapidly fatal form (blast crisis), usually within 3 to 5 years. Although recent long-term studies show a nearly 90 percent five-year survival rate for chronic-phase patients who receive Gleevec, some Ph+ CML patients fail to respond initially or develop resistance during treatment, and a small cohort cannot tolerate it. Because the stakes are so high, finding new treatments for these patients has been essential.

With Tasigna, Novartis is clearly eager to hold onto the franchise it has established in the CML market. Last year, Gleevec was Novartis's second largest-selling drug, with worldwide sales of \$2.6 billion. Until the introduction of Sprycel® [dasatinib, Bristol-Myers Squibb] in June 2006, Novartis held a virtual lock on the CML market.

Sprycel, like Tasigna, is presently indicated for second-line use in patients resistant or intolerant to Gleevec, and is active against certain BCR-ABL mutations. Sprycel is considered a broad-spectrum kinase inhibitor and binds to a different site on the BCR-ABL molecule



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(compared with Gleevec and Tasigna, which more specifically target BCR-ABL). Approval of Sprycel for second-line CML was based on results from the Phase 2 START-R trial, which compared the agent (70 mg twice daily) with high-dose Gleevec (800 mg twice daily) in Gleevec-resistant patients. Results showed higher rates of major cytogenetic response and complete cytogenetic response with Sprycel in this patient population.

Ultimately, Sprycel may pose a threat to both Tasigna and Gleevec. According to BMS, Sprycel sales for the first three quarters of 2007 were \$102 million. In addition, the same week that Novartis reported the approval of Tasigna, BMS announced that the FDA had approved revised labeling for Sprycel which included reducing the starting dose from 70 mg twice a day to 100 mg once daily. The dose reduction is based on data that show decreased adverse events but comparable efficacy at the lower dose. As yet, Sprycel lacks long-term survival data, and there is insufficient information to determine whether resistance will be a problem. A Phase 3 study of Sprycel versus standard-dose Gleevec is currently being conducted for first-line use in patients with CML.

Tasigna Pricing and Availability

The price of Tasigna is approximately \$5700 per month—similar to Gleevec (800 mg) which is \$5844 per month, according to Novartis (the AWP for 400 mg is \$2844 per month). According to the Journal of the National Cancer Institute, (Feb. 2007) the average wholesale price for one month of therapy with Sprycel is \$3900. This apparent pricing advantage for Sprycel may play a role in therapeutic decision making if efficacy and safety are seen as comparable between the two products.

Novartis has made good on its promise to make Tasigna available within days of its approval. Because it is an oral agent, Tasigna is currently available through regular distribution channels and is not limited to specialty pharmacies. Boehm does not foresee any bar-

riers to reimbursement, and sees no major hurdles to formulary adoption and uptake.

Asked about the potential for Tasigna to cannibalize sales of Gleevec, Boehm expects to see little erosion in Gleevec market share in the immediate future, because the compounds are likely to be used sequentially. “Gleevec is still clearly first line, with proven safety and efficacy for this patient population, and until data show that Tasigna is better than Gleevec for first line, Gleevec will keep its place.” Novartis is testing Tasigna now as first-line therapy. For the time being, however, Boehm sees great value in being able to address the needs of more CML patients by offering both Gleevec and Tasigna.



Tasigna Product and Packaging

Clinical Support for Tasigna

The approval of Tasigna is based on results from an open-label, Phase 2 multicenter study of 280 patients with chronic phase Ph+ CML and 105 patients with accelerated-phase Ph+ CML who were resistant or intolerant to Gleevec. Both cytogenetic responses—reduction or elimination of the Philadelphia chromosome—and hematologic responses—normalization of white cell counts—were measured. All of the patients in this study had previously received Gleevec; 77 percent had received doses of 600 mg or higher. After a minimum follow up of 6 months, 40 percent of 232 chronic-phase patients evaluated for efficacy had a major cytogenetic response (MCyR). Complete cytogenetic response—elimination of Ph+ cells—occurred in 28 percent. For accelerated-phase patients, the primary endpoint was confirmed hematological response (HR). At follow up (after a minimum of 4 months of treatment) Tasigna achieved complete HR in

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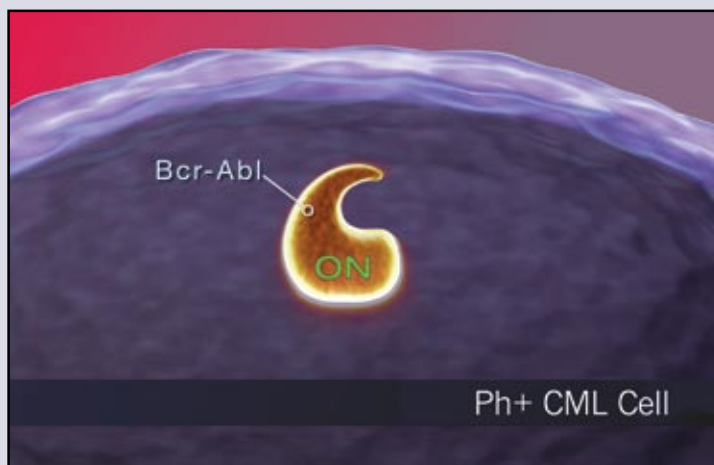
18 percent of accelerated-phase patients. Further data are needed to determine whether Tasigna prolongs survival.

The principal safety concern with Tasigna is QT interval prolongation; for this reason, it is contraindicated in patients with pre-existing long QT syndrome or hypokalemia or hypomagnesemia, which may predispose patients to QT interval prolongation. Cross-tolerance between Tasigna and Gleevec is minimal—in clinical studies many patients who had experienced serious side effects with Gleevec, such as grade 3/4 skin rash, gastrointestinal intolerance, fluid retention, and liver toxicity, were able to tolerate Tasigna.

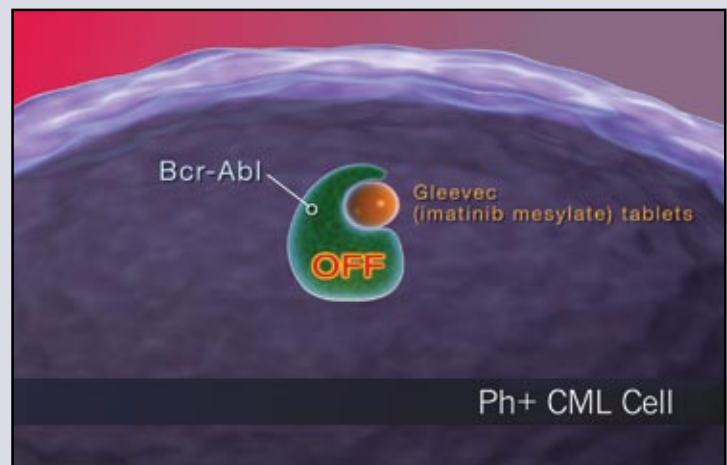
In Conclusion

Physicians now have the option of increasing the dosage of Gleevec or switching to Tasigna or Sprycel for patients who fail to respond to initial therapy with Gleevec. Novartis is hoping that the stellar reputation of Gleevec, the relationships they've established with hematologist-oncologists, and their presence in the CML marketplace will smooth the transition from Gleevec to Tasigna. It is not clear how recent developments with Sprycel will affect the adoption of Tasigna. A longer-term question is whether Sprycel or Tasigna will ultimately overtake Gleevec as the agent of choice for first-line therapy, or how treatment paradigms for CML will shift now that hematologist-oncologists have three effective TK inhibitors to deploy. **DSP**

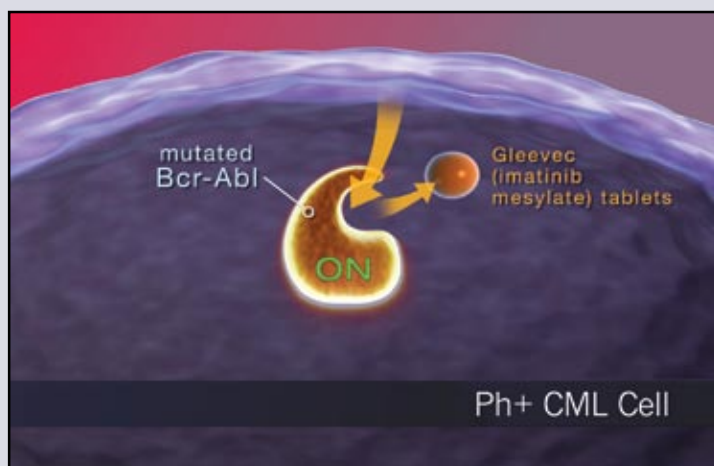
TASIGNA MECHANISM OF ACTION



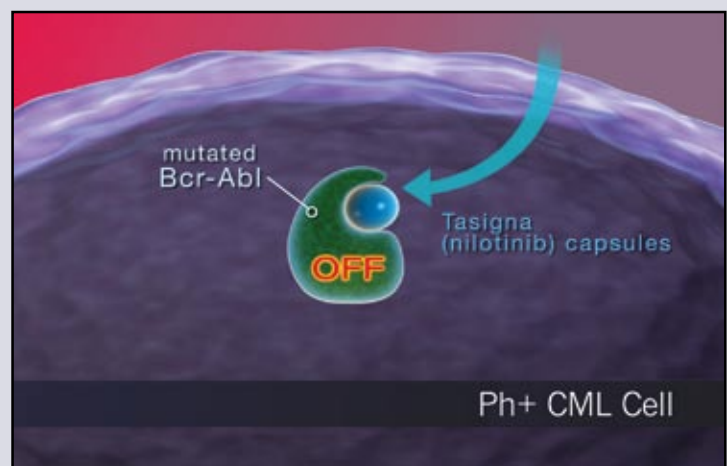
1) Bcr-Abl switches are stuck at the "on" position.



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



3) Ph+ CML cells can protect themselves by mutating.



4) Tasigna is designed to work where Gleevec does not.

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