INITIAL PROJECT CASE STUDY

Discovery and Development of the Anti-cancer Drug
Gleevec for Chronic Myeloid Leukemia (CML) and other cancers

Background
Imatinib (Gleevec® in the USA) is a breakthrough therapeutic, providing targeted anti-cancer therapy, which has transformed the prognosis for patients with chronic myeloid leukemia (CML). Unlike previous anti-cancer agents that have broadly cytotoxic effects, imatinib targets a specific tyrosine kinase (Ber-abl tyrosine kinase), which is the causative agent of cancer in 95% of CML patients. Imatinib was discovered by scientists at Ciba-Geigy (now Novartis), and approved for sale by the FDA in the US in May 2001 for treatment of CML that is refractory to interferon therapy, and in February 2002 for treatment of gastrointestinal stromal tumors. Since 2001, the prognosis for patients with CML diagnosis has changed from a median survival of 5 years to 95% survival at 5 years in the most recent followup study [Druker, et al. (2006)]. While initially approved for patients that failed other therapies, Gleevec® is now the first-line therapy for patients diagnosed with CML.

Traditional anti-cancer therapies are generally cytotoxic drugs and radiation, both of which cause death of cells that are actively growing and dividing. For this reason, traditional chemotherapy causes hair loss (hair growth and retention requires active growth of cells in the hair follicles), and immunosuppression (blood cells are continuously replaced by the differentiation and cell division of hemopoietic stem cells) among other side effects. The effects on patients can be devastating and can actually limit the efficacy of the cancer treatment by causing severe, sometimes life-threatening infections.

Since the discovery of specific gene alterations that cause the malignant character of cancer cells, it has been the dream of researchers to find targeted therapies that key on just the specific molecular changes in cancer cells. The discovery of oncogenes (genes that cause cancer) in the early 1980’s initiated the hope for a new generation of highly effective, targeted cancer therapeutics. After more than two decades of research since the discovery of oncogenes, Gleevec® was the first, and is still the most successful, targeted chemotherapeutic agent brought to the market.

Before the introduction of Gleevec®, CML therapy involved bone marrow transplants, when an appropriate donor could be found, or chemotherapy in the form of hydroxyurea and interferon-alpha. Bone marrow transplants require the killing of all the patient’s hemopoietic cells by massive irradiation and then replacement by transplantation of a donor’s bone marrow, which will include hemopoietic stem cells. This is a difficult procedure, with significant morbidity and mortality, and cannot always be done because of the lack of a well-matched donor. From experience, bone marrow transplantations work best with patients less than 20 years old, yet the average age of onset of CML is 50-60 years of age. Treatment with interferon-alpha is not well-tolerated by many patients, and is effective in only two-thirds of patients. CML was almost always a fatal disease before the introduction of Gleevec®.
Protein kinases are a large family (nearly 1200 identified in the human genome) of enzymes in eukaryotes that use ATP to phosphorylate proteins. The family is divided into numerous structural groups and three basic functional groups – enzymes that phosphorylate proteins on their tyrosine residues (thus, “tyrosine protein kinases”), enzymes that phosphorylate serine or threonine residues (“serine-threonine protein kinases”) and enzymes that phosphorylate histidine kinases (“histidine protein kinases”). There is usually great specificity in the protein target of a particular protein kinase – e.g., a particular serine-threonine protein kinase will phosphorylate a particular protein on particular serine and threonine residues. Typically, phosphorylation of the target enzyme changes the activity or substrate specificity of the phosphorylated enzyme. Often, the phosphorylated proteins are part of a chain of kinase enzymes, so that one kinase will phosphorylate another kinase, that will phosphorylate another, in a “signal transduction cascade”. Many of these enzymes are involved in regulating cellular activities, such as steps the cell cycle.

In cancer cells of CML patients, a chromosome abnormality fuses two genes usually widely separated – the BCR and ABL genes. The BCR-ABL fusion results from a reciprocal translocation between the long arms of chromosomes 9 and 22. Because of this dramatic change, the cancer cells can be recognized by cytology, looking at chromosomes. The t(9;22) translocation, or “Philadelphia chromosome” was recognized in 1960 as a unique characteristic associated with the cancerous blood cells in 95% of CML patients. However, it wasn’t until the mid-1980’s that the Philadelphia chromosome was recognized as a BCR-ABL fusion, and it wasn’t until preclinical testing of imatinib that there were hints that the BCR-ABL fusion might actually cause CML disease.

The ABL gene is a tyrosine kinase that is typically tightly regulated, and in adult cells, typically silent. However the Philadelphia chromosome causes fusion of the BCR gene to the ABL gene, resulting in a BCR-ABL fusion protein that is highly expressed in the CML cancer cells. It is expression of the ABL kinase that causes the uncontrolled growth of leukemic cells in CML.

A kinase inhibitor must be highly specific to be effective. A non-specific inhibitor will invariably wreak havoc and cause damage to normal cellular functions, making it no more effective as a therapeutic than broadly cytotoxic drugs.

A small molecule inhibitor of tyrosine kinases was found by scientists at the pharmaceutical company Ciba-Geigy in the early 1990s. A team led by Brian Druker of the Oregon Health Sciences University in Portland, Oregon, demonstrated that the Ciba-Geigy inhibitor (then known as STI-571) was highly specific to the BCR-ABL kinase and another kinase called c-kit, but STI-571 did not significantly inhibit the activity of other kinases. The academic clinical team has subsequently coordinated many of the clinical trials for STI-571/imatinib/Gleevec® showing its efficacy in CML patients. These studies included early Phase 1 trials (which provided the first exciting evidence of amazing efficacy in CML patients), to followup Phase IV studies (which have showed the long-term benefits, making CML a “manageable” cancer) [Druker, et al. (2001); O’Brien, et al. (2003); Druker, et al. (2006)]. Other articles that may be of interest include the following [Druker (2001); Savage, et al. (2002); Stone (2004)] Fabbro, et al. (2002).
Gleevec was first made available to patients with Chronic Myeloid Leukemia (CML) in May of 2001. Gleevec was initially indicated for the treatment of patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. The effectiveness of Gleevec in clinical trials was based on a “surrogate marker”, the hematologic and cytogenetic response, which is the loss of the Philadelphia-chromosome from the blood cell population. Approval of Gleevec was made in the absence of controlled trials that demonstrated a clear clinical benefit, such as improvement in disease-related symptoms or increased survival.

Currently, the yearly sales of Gleevec® provides over $2B in revenue to Novartis.

Nonetheless, Gleevec® was almost shelved. The timing was bad – Ciba-Geigy and Sandoz were in merger discussions and then reorganizing, after the merger was finalized in 1996, so the kinase inhibitor project was in danger of getting lost in the shuffle. The market for CML appeared limited – only 5000 patients each year get CML in the US. There was liver toxicity in early animal tests, and coupled with the general sentiment that it was unlikely to achieve sufficient selectivity in kinase enzymes, the safety of the molecule for use as a human therapeutic was questioned.

Timeline:

![Timeline](Figure from: [Wong, et al. (2004)])

Novartis

Novartis is a large, international pharmaceutical company headquartered in Basel, Switzerland. They were formed from the merger of two major Swiss pharmaceutical companies, Sandoz and Ciba-Geigy in 1996. Their therapeutic areas include all the major diseases including cardiovascular, metabolic, cancer and autoimmune disease. They also do business in eye-care and animal health. Novartis operates in over 140 countries and has sales revenues worldwide of about $20 billion. They had a research budget in 2000 of about $2.4 billion with research
centers all over the world, from Basel to LaJolla, California. Cancer therapy is a major focus of
the programs of several of the largest pharmaceutical companies as well, each of which has
programs that intend to compete with Novartis in cancer treatments, if not specifically in CML or
GIST therapy.

India now allows patents on drugs discovered after 1995, but Gleevec was discovered before
then. In 2007, Novartis challenged India’s refusal to honor the patent on imatinib. In a recent
ruling, India’s courts decided that imatinib would not be protected in India, allowing “generic”
versions of the drug to be manufactured and sold in India.

**Expert Resources:**
Brian Druker, MD of Oregon Health Sciences University (Portland OR). Make sure to read the
provides some of the historical background, and this biography:
Druker obtained his bachelor’s degree from the University of California, San Diego, in 1977 and his medical degree
from UCSD four years later. He went on to do an internship and residency in Barnes Hospital at the Washington
University School of Medicine and then a three-year fellowship in Medical Oncology at the Dana-Farber Cancer
Center. Between 1987 and 1993 he was an instructor at Harvard Medical School, and then moved on to Oregon
Health & Sciences University, where he is now a professor of medicine and director of the OHSU Cancer Institute
Leukemia Center. Last year, Druker became a Howard Hughes Medical Institute investigator.

**Analyzing the Case**
The discovery and development of Gleevec® provide a number of opportunities for in-depth
exploration of what went right in a drug discovery and development program. While typical
drug discovery and development programs take over 15 years, the discovery and development of
Gleevec was remarkably fast – about 5 years from demonstration of cellular activity to approval
of the drug by the FDA. Furthermore, the approval was based on a “surrogate endpoint” – the
elimination of leukemic cells from the blood, rather than increased survival or improvement in
symptoms, which allowed a greatly shortened clinical trial design.

The discovery and development of Gleevec® also provides an opportunity to look at what almost
gone wrong.

Your job is to find an interesting aspect of this case, investigate it and create general learnings
from analyzing the history.

The questions listed below are intended as guidelines in the investigations and analysis of data,
not as items to be specifically answered by the team in their report. Do not make the mistake of
using them as a check-list for going through the project analysis. You may wish to use them,
however, as guidance and as part of the input in crafting your own plan for the conduct of the
work based on your team’s judgment. You could consider the case from the point of view of
possible alternative histories.

Questions that the team might want to consider include the following:
1. Many in the pharmaceutical industry believe that it is important to have a “champion” for
   a molecule, in order to progress through the difficulties encountered during discovery and
development of a drug. What was the role of Brian Druker – was he a real champion for
the compound? When was his influence most important? What did he do to influence Novartis decision-makers? How did he achieve “champion” status as a company outsider?

2. Was Gleevec® a clear “star” from the start? What were the unique features of the molecule, and when were they known?

3. A paradigm in drug discovery project management is “fail early-fail fast”. By stopping projects early, when they are destined to fail, costs can be minimized. Do you think Ciba-Geigy/Novartis were practicing a strong “fail early-fail fast” project management strategy? Why or why not?

4. What was the value of the Philadelphia chromosome to the clinical development plan?

5. What were the unique features of the molecule and the disease that allowed such a rapid timeline for approval of Gleevec®?

6. The market for Gleevec® was initially estimated to be sales of $100M per year, or less. Only 5000 patients per year are diagnosed with CML. Currently, Gleevec® has sales of $2B per year. How did the Novartis market analysts make such a large mistake? What were the likely assumptions in the market analysis? With the benefit of hindsight, which assumptions were wrong?

**Evaluation of the Team’s Performance:**

An important aspect of the team’s performance will be the organization of the final report and the presentation of results. The presentation and report are ultimately the only way the effectiveness of the team’s work can be judged.

The team’s performance will be judged by the faculty from the presentation and the report. Some of the critical issues the faculty will consider are: did the team focus on the important issues, did they research these points well, picking up important details in the forest of unimportant details, analyze the case logically and carefully, and present their results clearly and briefly, with good supporting materials, and did the team pull together well. The results of this project will not be included in the grades for the coming semester. Rather, the faculty and students will gain an impression of the teams and their members from this exercise. More importantly, success of the project team from the faculty’s point of view might be defined as having the team learn about themselves as individuals and as a team, how to approach real problems and to juxtapose diverse and difficult issues (e.g. science, healthcare policy, ethics, the law and business), to learn some important things about what the industry is like and how to present in an effective way the results of a complex analysis, and how to deal with imperfect knowledge about the subject at hand.

It may be useful to put yourself in the position of a project team that has been charged by the Board of Directors of a company to do a critical analysis of a situation and make a presentation to them at a specific, scheduled meeting. This has all the right feel for the criteria of your initial project - a short deadline, a critical audience for your presentation that wants to understand a complex situation and make the right decisions based on your analysis. The board would expect you to pick out the key points, do a thorough analysis and give an incisive presentation that can provide them with some options based on a comfortable familiarity with the critical elements of the case. You may want to think about your team’s objectives in these terms.
**Organizing the project and the team**

The team will first need to organize itself. You may wish to appoint a project leader, or you may wish to act as a committee of the whole to make the decisions that will be needed. You should decide how you will make decisions and how you will make work assignments among team members; how you will pull together the results and how you will collectively analyze and report on the work you’ve done. How well you organize will determine in large part the project team’s cohesion and performance level and how quickly you’re able to make progress.

Don’t procrastinate – the time will go by quickly. Don’t underestimate how long it will take to write good summaries of what you’ve learned, and turn those learnings into Powerpoint slides. Write as you go, whenever you can.

The diverse experiences and talents of the team should be used effectively to maximize performance. Analyze the unique strengths among your team members in light of the project needs, and assign roles accordingly. There is not much time to do the project: organize the team and breakdown the task, do the research, do the analysis, prepare the results for oral and written report, and finally make your presentation to the faculty and to your classmates. This project reflects the prevalent situation in the real world (and for the rest of your time at KGI!). Time is too short to do a perfect job, but the key points must be engaged and analyzed, so prioritization is key to your performance. You will have to manage the time available, set goals and milestones and keep your team on schedule. Don’t forget to set aside some time to get to know one another, and have some fun.

**Resources**

Your team will have a place to meet, access to computers, copiers and internet resources, and access to the library. One or more faculty advisors will be available to answer certain procedural questions, and to meet with the team periodically to provide some guidance. On-line journals are available from the library.

The expert resource person(s) will be available to answer some of your questions about what happened in the history of your case, some of their personal views of the situation etc. To interview these expert resource people effectively you will need to outline or define carefully what you want to know from them, have organized your questions and your method for conducting the interview. The resource people are busy people who have volunteered to play this role, use them well but carefully and sparingly. You should plan to interview them only once, so prepare for that interview, and have at least a general understanding of the focus of your team’s project.

**Reporting your Analysis**

The team’s performance on the initial project will be judged entirely on the basis of the oral and written report. The oral report will be presented by the team to the faculty and students and a few guests (the presentation date, but not the detailed schedule is available). While the specific structure of the presentation is completely up to the team, there are some guidelines that might prove useful.

- You might think of it as a presentation to the board of directors, as mentioned.
• Know what you want to accomplish, the points you want to get across
• Structure the presentation to include all the essentials and the time allotted to them; e.g. technical and historical background, technical issues and integration, business issues, IP, ethics and particularly your analysis and judgments
• Make the slides clear, to the point, uncluttered and professional
• Be prepared to answer detailed questions about anything you present, or to justify any opinions you express

The written report is the product of the team’s analysis whose structure and format is therefore part of the choices made by the team to convey their results most effectively. *This report should be absolutely not longer than 10 pages, including the summary.* A typical report would have the following general structure listed below, but the team should feel free to create the structure they feel most comfortable with. (Standards of written English should be high – you may want to refer to Strunk and White, *The Elements of Style.*)

- Executive Summary [containing an overview of the report and a brief summary of the conclusions and recommendations – keep in mind that there will always be directors (and faculty members?) who only read the executive summary]
- A statement of the problem or situation and enough background material to enable the critical reader to understand the critical issues, scientific, medical and business, that the team decided to focus upon
- Analysis [this section will have multiple sections that scrutinize the critical components of the problem at hand, from the scientific issues, ethical problems, to the economic viability of the product.]
- Conclusions and recommendations [this section would state the conclusions, supported by the above analysis, and describe succinctly, but incisively the reasoning behind each of the conclusions]

**References:**

*European Journal of Cancer, Volume 38, Supplement 5, Pages S1-S87 (September 2002) – entire issue devoted to the discovery & development of imatinib.*


*Case written by Molly Schmid, 2007*