

Activating Neutrophils to Attack Cancer Cells

Daniel Conners, Chairman and President, Biothera Pharmaceutical Group

Based in Eagan, Minnesota, Biothera is conducting clinical trials of Imprime PGG®, the company's lead compound, in a variety of cancer indications, including one Phase III trial in colorectal cancer. Daniel Conners, Biothera's founder, president, and chairman, answered questions about the company's development programs and partnering strategy.

Please describe the background to the establishment of Biothera.

Conners: Biothera, originally named Biopolymer Engineering, Inc., was founded in 1997 as a material sciences company specializing in carbohydrate chemistry. During the next several years, the company acquired technology patent portfolios that enabled it to develop novel immune health and pharmaceutical compounds. Biothera's own research led to major discoveries about

the mechanism of action of its beta glucan compounds, as well as new applications in pharmaceuticals, specifically in oncology, as well as numerous non-pharmaceutical uses, such as in food, beverages, supplements, cosmetics, animal nutrition ingredients. The company established two business groups to commercialize the technology: the Pharmaceutical Group and the Healthcare Group.

Please briefly explain the underlying science for Imprime PGG.

Conners: The immune system's two arms, the innate and the adaptive, are very effective at protecting the body against pathogenic challenges like bacteria and virus. Cancer, however, is a "self" cell, and the immune system does not naturally attack self. To some extent, therapeutic monoclonal antibodies' attempt to replace the natural adap-

tive immune mechanism -- in addition to ligand binding or receptor inhibition effects -- can mobilize small cellular subsets of the innate immune system to target cancer cells.

Biothera's technology is based on the concept that activating both arms of the immune system against cancer will result in better treatments. Imprime PGG selectively binds to a specific receptor on the largest population of immune cells in the body, called neutrophils, and activates them to kill monoclonal antibody targeted cancer cells. About 15 trillion neutrophils circulate throughout the body at any one time. Mobilizing this army of innate immune cells will, in combination with monoclonal antibody treatments, engage both arms of the immune system against cancer and should result in dramatically improved cancer treatments.

What are the differences between Imprime PGG, which is yeast-derived glucan, and those derived from a fungus or from algae?

Conners: Glucans derived from yeast, cereal grains, mushrooms and algae have different molecular structures. Biothera's extensive research demonstrates that molecular differences exist that affect the mechanism of action, and ultimately the effectiveness, of these glucans. Yeast and mushroom glucans are the only types known to demonstrate immunotherapeutic properties. However, these glucans have important differences in molecule structures. In particular, mushroom glucans lack the branched side chains of yeast glucans. These differences are essential to the significantly superior biological activity of yeast glucans and Imprime PGG, in particular.

We understand that Imprime PGG-bound neutrophils can mobilize neutrophils toward the inflammatory condition at the tumor site created by a monoclonal antibody drug, harnessing the pathogen killing ability of neutrophils. How do you identify the monoclonal antibody drug to be used in combination with Imprime PGG?

Conners: We have demonstrated that the complement system plays a key role in the mechanism of action of Imprime PGG. In particular, most monoclonal antibodies are of a type that activates the complement cascade when they bind to their cell surface antigen. This activation results in complement components being deposited on the cancer cell as well as the release of soluble complement components that are chemoattractants. When primed with Imprime PGG, neutrophils recognize these chemoattractants, and when they reach the cancer cells, they also recognize the cell surface complement components. This process triggers the killing mechanism. The mechanism of action of the antibody itself is of little relevance to the activity of Imprime PGG.



Daniel Conners

You initiated a Phase III trial evaluating Imprime PGG in recurrent or progressive KRAS wild-type colorectal cancer patients. When do you expect to announce the results?

Conners: Biothera began dosing patients in a Phase III trial in metastatic colorectal cancer in May 2011. The study is evaluating the combination therapy of Imprime PGG and Erbitux. This multi-centered trial eventually will have approximately 50 clinical sites in the U.S., Canada, France and Germany. We expect to be able to review PFS within 18-24 months. We have an opportunity for accelerated approval in the US as early as 2013-14 if trial recruitment targets and PFS endpoints are met. Biothera previously performed a Phase II clinical trial in KRAS-mutant colorectal cancer with Imprime PGG in combination with Erbitux. The trial demonstrated strong proof of concept, with a significantly improved clinical benefit in overall response, median overall survival, and the one-year survival rate. Our intention is to present the data to the FDA and seek guidance for accelerated development and approval of Imprime PGG in this indication.

Please describe the status of your development programs for Imprime PGG in other indications.

Conners: In addition to the Phase III trial for metastatic colorectal cancer, we are conducting three phase II clinical trials, two of which are in nonsmall cell lung cancer and another in chronic lymphocytic leukemia. The trials in nonsmall cell lung cancer are both 90-patient Phase IIb trials, one testing patients being treated with Avastin with and without Imprime PGG, the other testing patients treated with Erbitux with and without Imprime PGG. The trials are both over 50% completed and the preliminary data is positive.

In collaboration with the Mayo Clinic, Imprime PGG is being tested in high risk chronic lymphocytic leukemia patients in combination with two monoclonal antibodies, Rituxan and Campath. Preliminary data from this trial are very promising.

Please describe your partnering strategy.

Conners: Our strategy is to continue to advance Imprime PGG through the FDA clinical development process while working to license the drug to one or more pharmaceutical companies that will help complete the regulatory approval process and market the drug worldwide. We are currently engaged in licensing discussions with several pharmaceutical companies.

Profile

Daniel Conners

Mr. Conners founded the company in 1997 and has led the company's development at every stage. Mr. Conners previously founded and managed Techtel, the first digital wireless communication company in Ukraine, and Metropolitan Investment Group, Inc., a private investment firm.