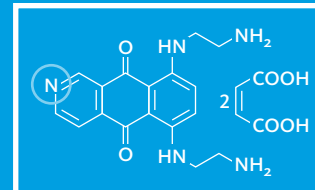


#### Mitoxantrone

In designing the pixantrone structure, scientists removed the OH groups in mitoxantrone that are thought to be the cause of free-radical production and cardiotoxicity.



#### Pixantrone

A nitrogen atom in this position in the pixantrone structure provides an improvement in pre-clinical anti-tumor activity and safety. This atom may be involved in maintaining the molecule in a planar configuration and allowing intercalation into DNA.

# Pixantrone

**Pixantrone is an investigational drug designed to improve the safety and activity of anthracyclines, a family of chemotherapeutic agents that are a mainstay for treating breast cancer and a variety of hematologic malignancies.** Although high response rates have been observed following first-line treatment with anthracyclines, the class is associated with significant irreversible damage to the heart. As a result, there is a maximum cumulative dosage of anthracyclines beyond which continued or repeat therapy with these drugs is not recommended. Thus, patients treated with first-line anthracycline therapy may have limited options if their disease progresses or returns.

As a company committed to making cancer more treatable, we have great interest in developing an anthracycline derivative that provides similar or superior efficacy to the parent compound, while reducing or eliminating treatment-limiting toxicities. Pixantrone was identified as a promising replacement for approved anthracyclines following extensive analysis of a large number of derivative compounds. A growing body of preclinical and clinical data supports the safety and efficacy of pixantrone, and we are evaluating this investigational drug as a treatment for non-Hodgkin's lymphoma (NHL) and other cancers.

In November 2005, we presented positive data from a randomized clinical trial of pixantrone in combination with rituximab compared with rituximab alone in patients with relapsed or refractory indolent NHL. Although this study was closed in 2004 due to a change in strategy and slow enrollment, 38 patients were evaluable for safety and efficacy endpoints. The results demonstrated an 87 percent improvement in time to disease progression (TTP), the study's primary endpoint, for patients treated with pixantrone and rituximab compared with rituximab alone. The median TTP

for patients treated with combination therapy was 13.2 months, compared with 8.1 months for rituximab alone. One- and two-year progression-free survival rates were 66 percent and 44 percent for patients in the combination arm, compared with zero percent for the rituximab arm at both time points.

The study also met its secondary endpoint, demonstrating a significant improvement in objective responses, defined as a 50 percent or greater reduction in tumor size. In the combination arm, 75 percent of patients achieved a major response, with 35 percent achieving a complete response, compared with 33 percent and 11 percent, respectively, in the rituximab arm. Pixantrone was generally well tolerated, and no cases of drug-related grade 3 or 4 cardiac toxicity were reported, even though 80 percent of patients in the study had previously received anthracyclines.

We are currently conducting a pivotal phase III trial of pixantrone as a single-agent therapy in patients with relapsed aggressive NHL who have failed at least one second-line, multi-agent chemotherapy regimen. The trial is designed to assess complete response rate, TTP, and overall survival, and we expect to conduct an interim analysis of the study in the first half of 2006.

A trial evaluating pixantrone as a component of first-line, multi-agent regimens also is ongoing in patients with relapsed aggressive NHL. In this trial, pixantrone is used to replace doxorubicin, the anthracycline used in standard treatment regimens for NHL.

# Colin Murnane

**In 2002, my wife Judy and I were on vacation with several other couples when I discovered a lump on my neck.** On our return, I had the lump examined. It turned out to be non-Hodgkin's lymphoma. We couldn't believe it. We were having a house built in Florida. We were planning on moving there from New York and were looking forward to enjoying our retirement playing golf in the sun. But all that had to wait once I was diagnosed with cancer.

Initially, I was treated with a standard regimen of CHOP chemotherapy in combination with rituximab, which seemed to work for a while, but then the cancer came back. I underwent second-line chemotherapy, but I still didn't achieve remission. Finally in late 2005, my doctor suggested that I enter a clinical trial for pixantrone. I went through four cycles of pixantrone treatment and felt really good while I was on it. The pixantrone treatment took much less time than my previous chemotherapy regimens, and the excellent nurses at the Lakeland Center for Cancer Care and Research helped make the hour pass quickly. While on pixantrone, I was able to get back to playing golf — and I even played my best round ever while on pixantrone!

I was very encouraged by the first several CT scans, which suggested the treatment was working. Unfortunately, my cancer appears to be progressing again, so I have started a new chemotherapy treatment. Judy and I remain hopeful that I will achieve remission. We are just taking everything one day at a time.

All I want is to have time to enjoy my retirement with Judy and our wonderful family and friends and to see our beautiful grandson grow up. Judy has been my source of strength through all of this, and we are looking forward to getting on with the plans that we made for our life together. I'm not ready to give up on our dream. I'm glad that I found doctors and nurses who aren't ready to give up either. Even at the age of 65, I still believe I can knock a few strokes off my golf game.



“When I was first diagnosed with non-Hodgkin’s lymphoma, my wife and I were very discouraged about what the future would bring. Today, we feel that with all the treatment options, it’s okay to be more optimistic about our long-term prospects.”

Colin Murnane, pixantrone clinical trial patient (pictured with wife Judy)