

Named Patient Program
Pixantrone is available in Europe as an investigational drug on a named-patient basis. It is supplied by IDIS to healthcare professionals who request it for the treatment of individual patients with relapsing aggressive non-Hodgkin lymphoma. The program was initiated May 2009.

Regulatory Status
Pixantrone is currently under review for approval in the EU. Pixantrone will be resubmitted to the FDA in 2011, and could obtain FDA approval in the first half of 2012.

The safety of pixantrone has been evaluated in 348 patients, which included 278 patients with NHL, nearly all of whom had extensive prior anthracycline exposure. Throughout its clinical development, the safety profile of pixantrone has demonstrated that it is well tolerated with manageable toxicities.

The primary source for the safety assessment of pixantrone was the well-controlled PIX301 trial, the first randomized controlled trial in this patient population. In that study, pixantrone, administered at a weekly dose of 85 mg/m² on days 1, 8 and 15 of a 28-day cycle, was well tolerated in heavily pretreated patients with relapsed or refractory aggressive NHL.

Pixantrone recipients had a low incidence of febrile neutropenia (7.4%). Pixantrone patients also experienced a low incidence of hair loss (13.2%), a very common side effect of other drugs in this class. Overall, the incidence of serious adverse events was similar between pixantrone and the control arm. The pixantrone patients had a higher incidence of leucopenia and neutropenia and numerically more serious cardiac events (6 vs. 3) including both events reported as related or unrelated to the study drug by the

investigator. Disease progression reported as an adverse event was less frequent in the pixantrone than in the control arm (1.5% vs. 13.4%).

References

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- Pettengell R, et al. Phase III trial of pixantrone cimaleate compared with other agents as thir-line, single-agent treatment of relapsed aggressive non-Hodgkin's lymphoma (EXTEND): Results from the treatment and follow-up periods. Poster presented ASH 2009.
- Data on file



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Pixantrone

Pixantrone dimaleate for injection (BBR 2778) is a next generation antitumor aza-anthracenedione with a molecular structure similar to other topoisomerase II inhibitors, such as anthracyclines like doxorubicin. It is under development for the treatment of aggressive non-Hodgkin lymphoma (NHL).

Anthracyclines are the cornerstone therapeutic for the treatment of lymphoma, leukemia, breast cancer and other diseases. Although anthracyclines are effective for use as first-line (initial) treatment, they can cause cumulative heart damage that may result in congestive heart failure many years later. As a result, there is a lifetime limit of anthracycline doses and most patients who previously have been treated with an anthracycline are not able to receive further anthracycline treatment if their disease returns.¹⁻³

Unlike other drugs in this class that cause serious tissue necrosis if they pass through the walls of vessels into surrounding tissue, pixantrone can be given through a peripheral vein and does not require a central implanted catheter.

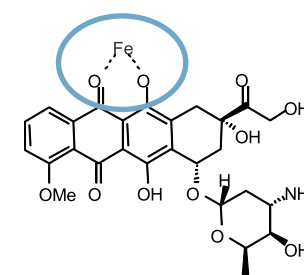
Proposed Target Product Profile

- Efficacy as a single agent in relapsed or refractory aggressive non-Hodgkin lymphoma
- Ease of administration—can be administered through a peripheral vein rather than a central catheter

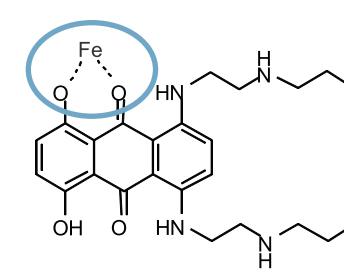
PIXANTRONE: RATIONALLY DESIGNED

Pixantrone, the first aza-anthracenedione to reach advanced clinical development, was rationally designed to improve the efficacy and reduce the toxicity associated with anthracyclines and anthracenediones. Its structural changes do this by increasing the stability of deoxyribonucleic acid (DNA) adduct formation while reducing the potential to form oxygen-free radicals and toxic drug-

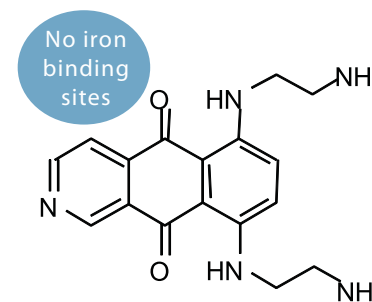
metal complexes. Unlike mitoxantrone, an anthracenedione, pixantrone lacks the 5,8-dihydroxy-substitution of mitoxantrone and instead contains a nitrogen heteroatom. As shown below, the quinone-hydroquinone site responsible for oxygen-free radical generation and iron binding in mitoxantrone and doxorubicin is not present in pixantrone.



Doxorubicin



Mitoxantrone
Scientists removed the OH groups in mitoxantrone that are thought to be the cause of free-radical production.



Pixantrone
Unlike other anthracycline-like agents, pixantrone cannot bind iron and so does not perpetuate the generation of toxic oxygen-free radicals. In addition, pixantrone does not form alcohol metabolites.

Non-Hodgkin Lymphoma NHL is caused by the abnormal proliferation of lymphocytes, cells key to the functioning of the immune system. It usually originates in lymph nodes and spreads through the lymphatic system.

NHL can be broadly classified into two main forms — aggressive NHL is a rapidly growing form of the disease that moves into advanced stages much faster than indolent NHL, which progresses more slowly.

According to the National Cancer Institute's SEER database, on Jan. 1, 2006 there were approximately 419,533 people in the U.S. living with a history of NHL. The American Cancer Society estimated that 65,980 people would be diagnosed with NHL in 2009 with 19,500 estimated to die.

Since the early 1970s, incidence rates for NHL have nearly doubled. It is the fifth most common cancer in the United States.

CLINICAL RESEARCH

Aggressive NHL

Initial therapy for aggressive NHL with anthracycline-based combination therapy cures up to 50 percent of patients.⁴ Of the remaining patients, approximately half will respond to second-line treatment⁵, but few are cured and there is no effective therapy for patients relapsing after or refractory to second-line treatment.

PIX-R TRIAL (PIX306) - Now enrolling

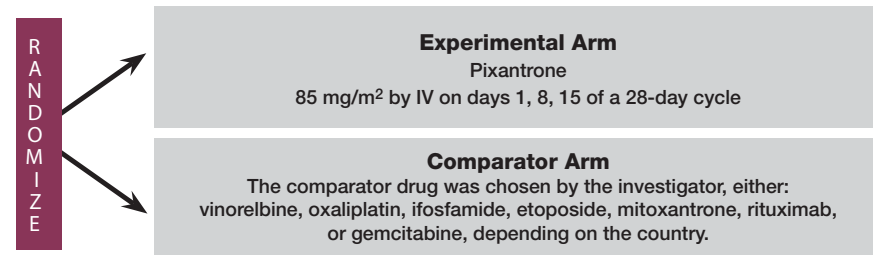
The PIX-R TRIAL (PIXantrone-Rituximab vs Gemcitabine-Rituximab in Treating Relapsed/Refractory transplant Ineligible Aggressive non-Hodgkin Lymphoma) is a phase III randomized multicenter study comparing pixantrone + rituximab with gemcitabine + rituximab in patients with Diffuse Large B-Cell Lymphoma (DLBCL) who have relapsed after therapy with CHOP-R or an equivalent regimen and are ineligible for stem cell transplant.

Study Objectives

Primary: The primary objective of this study is to evaluate the efficacy (as measured by progression-free survival and overall survival) of pixantrone plus rituximab compared to gemcitabine plus rituximab in patients with relapsed or refractory DLBCL or DLBCL transformed from follicular lymphoma who have received 1-3 prior lines of therapy for aggressive NHL, including CHOP-R or an equivalent regimen, and are not currently eligible for high-dose (myeloablative) chemotherapy and stem cell transplant.

Secondary: To compare the two treatment arms with regard to the following secondary endpoints: Overall response rate, complete response rate and safety.

EXTEND (PIX301) Study Schema



Patients were to be treated for up to 6 cycles, with the exception of patients treated with rituximab, who were to receive it on day 1, 8, and 15 of cycle 1 and day 1 of cycle 2 only. Patients were to be withdrawn for disease progression, withdrawal of consent, or unacceptable toxicity.

EXTEND (PIX301)

The pivotal EXTEND clinical trial (Expanding the reach of anthracyclines with piXanTronE in relapsed or refractory aggressive NHL Disease) was a phase III single-agent trial of pixantrone for patients with relapsed or refractory aggressive NHL who received two or more prior therapies and who were sensitive to treatment with anthracyclines. The multicenter, international, controlled trial enrolled a total of 140 patients with aggressive NHL. Patients were randomized to receive either pixantrone or another single-agent drug of physician's choice currently used for the treatment of this patient population.

Study Objectives

Primary: Compare efficacy (CR/CRu rate by independent review on an ITT basis) of pixantrone to other commonly used single agents in treatment of relapsed aggressive NHL.

Secondary: Overall response rate (CR+CRu+PR), response lasting four months or more, progression-free survival (PFS), overall survival (OS), safety.

Study Results⁶

The EXTEND trial achieved the primary efficacy endpoint based on an intent-to-treat efficacy analysis. This study demonstrated that patients with relapsed/refractory aggressive NHL who were treated with pixantrone, compared with other chemotherapy agents achieved:

- Significantly higher rate of confirmed and unconfirmed complete remission (CR/CRu)
- Significant increase in overall response rate (ORR)
- Significantly greater progression-free survival (PFS)
- Positive trend in overall survival (OS)

At end of treatment, 14 out of 70 patients (20.0%) for the pixantrone arm achieved CR/CRu compared to four out of 70 patients (5.7%) for the standard chemotherapy arm ($P=0.021$). No patient in the standard chemotherapy arm achieved a confirmed complete remission compared to eight out of 70 (11.0%) of pixantrone recipients. At minimum 9-month follow-up, 25.7% of patients for the pixantrone arm achieved CR/CRu compared to 7.0% for the standard chemotherapy arm ($P=0.005$).

ORR also increased significantly in patients who received

pixantrone, 40.0% for the pixantrone arm compared to 14.3% for the control arm ($P=0.001$).

Subgroup analyses examining the effect of age, IPI score, disease status or prior anthracycline doses on PFS demonstrate that pixantrone consistently improved PFS across subgroups compared with other chemotherapy agents. At minimum 9-month follow-up, the pixantrone arm achieved a statistically significant 115% increase in median overall PFS compared to the standard chemotherapy arm (5.6 months versus 2.6 months, $P=0.002$).

Additionally, a positive trend was seen in OS, with a 48% increase in median overall survival for the pixantrone arm (10.2 months) versus the comparator arm (6.9 months).

PFS, CR/CRu, and ORR were determined by an independent assessment panel that was blinded to the treatment assignments.

End of treatment results were presented at the American Society of Clinical Oncology (ASCO) 2009 Annual Meeting. Update results with a minimum 9-month follow-up were presented at the American Society of Hematology (ASH) 2009 Annual Meeting. Additional follow-up is ongoing. More data is available at: www.CellTherapeutics.com/investor_updates

Safety Assessment

EXTEND trial: most common adverse reactions ($\geq 20\%$)⁷

Pixantrone (n = 68)	All grades	Grade 3/4
Neutropenia	50%	41%
Infection	43%	18%
Anemia	29%	6%
Leukopenia	25%	24%
Thrombocytopenia	21%	12%
Asthenia	22%	4%
Pyrexia	22%	4%
Cough	22%	0%

Active control (n = 67)	All grades	Grade 3/4
Neutropenia	24%	19%
Infection	27%	13%
Anemia	33%	13%
Leukopenia	8%	5%
Thrombocytopenia	20%	10%
Asthenia	13%	5%
Pyrexia	24%	9%
Cough	5%	0%

EXTEND (PIX301) Phase III Trial in Relapsed NHL

Tumor Response End of Treatment and Minimum 9-Month Update*

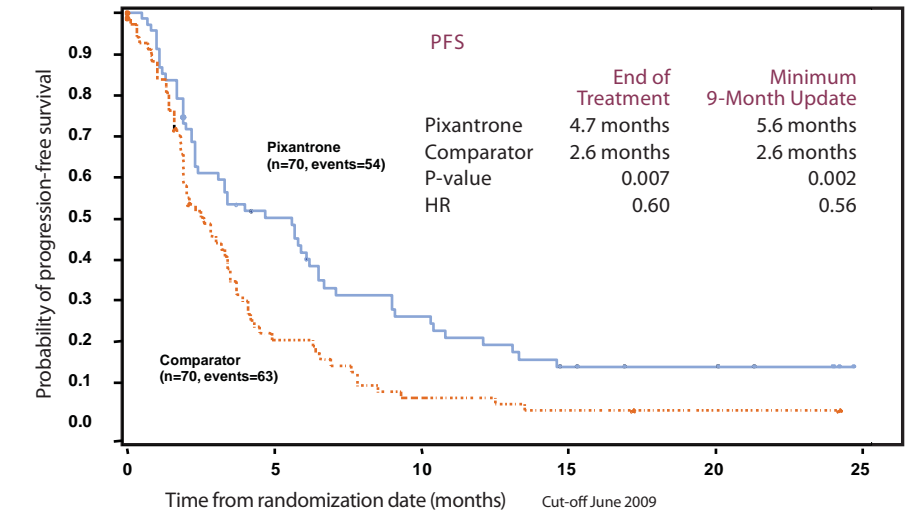
CR/CRu	End of Treatment	Minimum 9-Month Update
Pixantrone	20.0%	25.7%
Comparator	5.7%	7.0%
P-Value	0.021	0.005

ORR (CR+CRu+PR)	End of Treatment	Minimum 9-Month Update
Pixantrone	37.1%	40.0%
Comparator	14.3%	14.3%
P-Value	0.003	0.001

Overall response lasting ≥ 4 months	End of Treatment	Minimum 9-Month Update
Pixantrone	25.7%	8.6%
Comparator	8.6%	

* Responses for ITT population determined by independent review; follow-up analysis is ongoing.

Increase in Progression-Free Survival



Overall Survival

