Overview of Pixantrone Dimaleate Activity in Non-Hodgkin's Lymphoma

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BACKGROUND

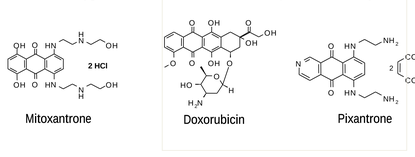
Anthracyclines

- Among the most active class of agents in non-Hodgkin's lymphoma (NHL)
- Standard of care CHOP-R for 1st line aggressive NHL
- Infrequently used in relapse, even in sensitive patients, due to cumulative cardiac toxicity
  - ≤300 mg/m^2 doxorubicin (CHOPx6) [1]
    - 5.6% patients develop CHF
    - 40% experience ≥15% reduction in LVEF
  - 500 mg/m^2 to 550 mg/m^2 doxorubicin [2]
    - 26% patients develop CHF
    - 50% experience ≥20% reduction in LVEF (grade 3/4 toxicity)

STRUCTURE AND CYTOTOXICITY

Pixantrone Dimaleate (Pixantrone) [1,2,3]

- Novel aza-anthracenedione
- Structurally similar to mitoxantrone and anthracyclines (eg, doxorubicin)
- Enhanced hydrogen bonding with greater DNA adduct formation
- Higher affinity and avidity for topoisomerase II than doxorubicin
- Reduction of oxygen free radical formation and subsequent cardiotoxicity



Mitoxantrone

Doxorubicin

Pixantrone

These characteristics led to preclinical and clinical studies with pixantrone as a single agent or in combination therapies. The goal of these studies was to investigate the use of pixantrone as a potential second-generation compound with antitumor activity that is comparable or superior to existing therapies, but without cardiotoxicity.

PRECLINICAL STUDIES

Pixantrone Activity With Mitoxantrone and Doxorubicin

- Greater activity than mitoxantrone and doxorubicin in hematologic tumor models
- Similar activity in solid tumor models
- Significantly reduced cardiotoxicity in animal models

CLINICAL STUDIES

Clinical Studies With Pixantrone in Non-Hodgkin's Lymphoma (NHL)

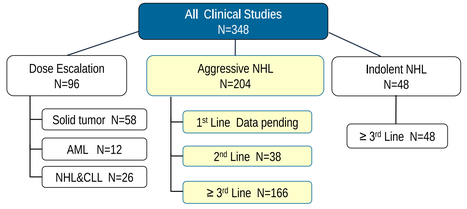
- Active as a single agent and in combination with other chemotherapeutic agents
- Active in the treatment of indolent and aggressive NHL

Overview of Clinical Studies With Pixantrone

Study Type	Indication	No. of completed Studies	No. of Patients Administered Pixantrone
Single-agent, uncontrolled	NHL	2	59
	Other malignancies	4	70
Single-agent , controlled	NHL	1	68
Combination, controlled	NHL	5	151
Total			348

* Includes eight phase 1, two phase 2, and three phase 3 studies.

Cancer Patients Treated With Pixantrone - By Indication



INDOLENT NHL IN CLINICAL STUDIES

Relapsed/Refractory Indolent NHL and Pixantrone-Rituximab, Phase 3 [4]

	Pixantrone + Rituximab	Rituximab	*P* Value
No. of patients	20	18	—
Male, n (%)	10 (50)	13 (72)	—
Age, median years (min-max)	67 (52-77)	58.5 (45-74)	—
IPI >2, n (%)	6 (30)	2 (11)	—
Line of therapy	3rd line, 2+ prior lines of therapy		
No. treatment cycles, median (min-max)	6 (2-6)	2 (2-2)	—
Treatment Responses, n (%)			
Complete response (CR)	7 (35)	2 (11)	0.238
Overall response (ORR) (CR+CRu+PR)	15 (75)	6 (33)	0.038
Time to progression	13.2 months	8.1 months	<0.001

Drug administration – 21 days/cycle, up to 6 cycles; rituximab at standard doses and regimens; pixantrone at 90 mg/m^2, Cycle 1 – Days 2,8; Cycle 2 – Days 1,8

Relapsed/Refractory Indolent NHL and FPD-R , Phase 2 [5]

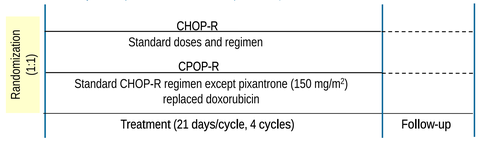
No. patients enrolled/evaluable for efficacy	29/27
Male, n (%)	15 (52)
Age, median years (min-max)	63 (32-78)
REAL Classification, n (%)	
Follicular center cell grade	18 (62)
Small lymphocytic	6 (21)
Lymphoplasmacytoid	1 (4)
Marginal zone	3 (10)
Diffuse large B cell	1 (4)
Line of therapy	3rd line, 2+ prior therapies
No. treatment cycles, median (min-max)	5 (1-8)
Treatment Responses, n (%)	
CR	17 (63)
Complete response unconfirmed (CRu)	2 (7)
Partial response (PR)	5 (19)
ORR	24 (89)

Drug administration – 28 days/cycle, up to 8 cycles. Followed standard FND-R regimen except pixantrone (80-120 mg/m^2) replaced mitoxantrone.

AGGRESSIVE NHL IN PHASE 2 CLINICAL STUDIES

Diffuse Large B Cell Lymphoma/CHOP-R vs CPOP-R as 1st Line Therapy

Enrollment for study is complete and results are expected 4Q09.



Baseline Characteristics	All
No. of patients	124
Male, n (%)	63 (51%)
Age, median years (min-max)	68 (38-88)
ECOG ≥1, n (%)	80 (65%)

Relapsed Aggressive NHL and CPOP

	ITT	Evaluable
No. of patients	30	29
Male, n (%)	12 (40)	11 (38)
Age, median years (min-max)	66 (26-76)	66 (26-76)
REAL Classification, n (%)		
Diffuse large B cell lymphoma	20 (67)	19 (66)
Mantle cell	8 (27)	8 (28)
Follicular lymphoma grade 3	2 (7)	2 (7)
Line of therapy	3rd line, 2+ prior therapies	
No. treatment cycles, median (min-max)	6 (1-6)	6 (1-6)
Treatment Responses, n (%)*		
CR	12 (40)	12 (41)
CRu	2 (7)	2 (7)
PR	5 (17)	5 (17)
ORR	19 (63)	19 (66)

Drug administration – 21 days/cycle, up to 6 cycles. Followed standard doses and regimens for CHOP-R except pixantrone (150 mg/m^2) replaced doxorubicin.
*Response data for evaluable group based on 27 patients. One of the 29 evaluable patients did not receive treatment and a second patient had a protocol violation.

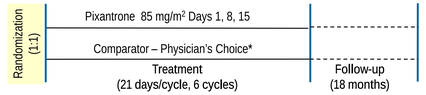
Relapsed Aggressive NHL and Pixantrone [6]

No. of patients (ITT)	33
Male, n (%)	18 (54.6)
Age, median years (min-max)	66 (24-81)
REAL Classification, n (%)	
Diffuse large B cell lymphoma	24
Mantle cell	7
Transformed high grade follicular	1
High-grade variant of monocytoid B cell	1
Line of therapy	3rd line, 2+ prior lines of therapy
No. treatment cycles, median (min-max)	2 (1-6)
Treatment Responses, n (%)	
CR	5 (15)
PR	4 (12)
PR unconfirmed	5 (15)
ORR	9 (27)

Drug administration – 28 days/cycle, up to 6 cycles. Pixantrone administered at 85 mg/m^2 on Days 1, 8, and 15.

AGGRESSIVE NHL IN PHASE 3 CLINICAL STUDY

Study Design [7]



* Comparators included vinorelbine (n=11), oxaliplatin (n=30), ifosfomide (n=12), etoposide (n=9), mitoxantrone (n=4), gemicitabine (n=1) or rituximab (n=0).

Patient Characteristics

	Pixantrone (N=70)	Comparator (N=70)
Age, median yrs	60	58
>60 yrs, n (%)	32 (45.7)	29 (41.4)
Male, n (%)	46 (65.7)	40 (57.1)
IPI, n (%)		
<2	20 (28.6)	18 (25.8)
≥2	50 (71.4)	52 (74.2)
Line of therapy	3rd line, 2+ prior lines of therapy	

Tumor Response During Treatment *

Response, n (%)	Pixantrone (N=70)	Comparator (N=70)	*P* Value
CR	8 (11.4)	0	—
CRu	6 (8.6)	4 (5.7)	—
CR/CRu	14 (20.0)	4 (5.7)	0.021
ORR	26 (37.1)	10 (14.3)	0.003
Overall responses lasting ≥4 months	18 (25.7)	6(8.6)	0.012

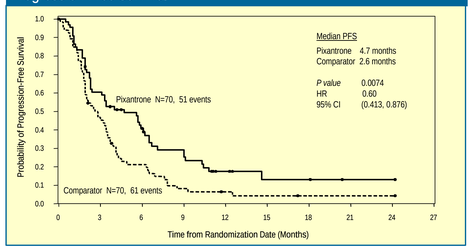
* Responses for ITT population as determined by independent review.

Tumor Response During Treatment and Follow-Up Periods *

Response, n (%)**	Pixantrone (N=70)	Comparator (N=70)	*P* Value
CR	11 (15.7)	0	—
CRu	6 (8.6)	5 (7.0)	—
CR/CRu	17 (24.0)	5 (7.0)	0.009
ORR	28 (40.0)	10 (14.3)	0.001

* Responses for ITT population; follow-up is ongoing.
** Responses determined by independent review with data from September 2008 database cutoff.

Progression-Free Survival *



* Independent review

Tumor Response by Subgroup *

	Pixantrone		Comparator	
Age	<65 (n=47)	≥65 (n=23)	<65 (n=52)	≥65 (n=18)
CR/CRu	8 (17.0%)	6 (26.1%)	4 (7.7%)	0
ORR	15 (31.9%)	11 (47.8%)	9 (17.3%)	1 (5.6%)
Refractory/Relapsed	Refractory (n=40)	Relapsed (n=28)	Refractory (n=40)	Relapsed (n=30)
CR/CRu	6 (15.0%)	8 (28.6%)	2 (5.0%)	2 (6.7%)
ORR	12 (30.0%)	14 (50.0%)	5 (12.5%)	5 (16.7%)
IPI Score	≤1 (n=20)	≥2 (n=50)	≤1 (n=19)	≥2 (n=51)
CR/CRu	5 (25.0%)	9 (18.0%)	1 (5.3%)	3 (5.9%)
ORR	10 (50.0%)	16 (32.0%)	2 (10.5%)	8 (15.7%)
Prior Anthracyclines**	≤300 mg/m^2 (n=45)	>300 mg/m^2 (n=25)	≤300 mg/m^2 (n=31)	>300 mg/m^2 (n=39)
CR/CRu	7 (15.6%)	7 (28.0%)	0	4 (10.3%)
ORR	16 (35.6%)	10 (40.0%)	3 (9.7%)	7 (17.9%)
Prior Rituximab	Rituximab (n=38)	No Rituximab (n=32)	Rituximab (n=39)	No Rituximab (n=31)
CR/CRu	6 (15.8%)	8 (25.0%)	3 (7.7%)	1 (3.2%)
ORR	12 (31.6%)	14 (43.8%)	7 (17.9%)	3 (9.7%)

* ITT population; assessments made by independent assessment panel (IAP)
** Prior anthracycline (doxorubicin-equivalent) dose

Cardiac Safety Assessment

	Pixantrone		Comparator	
LVEF Assessment	N	Median %	N	Median %
Baseline	64	58	64	57
End of Treatment	28	59	23	58
Change from Baseline	28	-5	23	1
Patients with cardiac disorder SAEs*, n/N (%)	6/68 (8.8)		3/67 (4.5)	

* Events considered cardiac disorders in the pixantrone group included cardiac arrest, congestive heart failure, myocardial infarction, cyanosis, pericardial effusion, and tachycardia.

Summary and Conclusions for Phase 3 Study

This study demonstrated that relapsed/refractory aggressive NHL patients treated with pixantrone, compared with other chemotherapy agents, achieved:

- Significant increase in CR/CRu rate
- Significant increase in ORR
- Significant improvement in PFS and percentage of all patients with responses lasting ≥4 months

An encouraging safety profile in this heavily pretreated patient population was reported:

- Neutropenia and leukopenia most common (≥10%) grade 3/4 adverse events
- Low incidence of febrile neutropenia (7.4%)
- Lower than expected incidence of cardiac AE: 65% with cumulative doxorubicin dose of 550 mg/m^2 and 21% for pixantrone treatment group with a median cumulative doxorubicin-equivalent dose of 535 mg/m^2

OVERALL SUMMARY

- In preclinical studies, when compared with mitoxantrone and doxorubicin, pixantrone activity is greater in hematologic tumor models and similar in solid tumor models with significantly reduced cardiotoxicity in animal models.
- Clinical studies (phase 1-3) showed that pixantrone is active in combination with other chemotherapeutic agents and as a single agent in the treatment of indolent and aggressive NHL.
- Pixantrone is efficacious and has a tolerable safety profile in heavily pretreated patients with relapsed aggressive NHL.
- Enrollment complete for randomized trial comparing CHOP-R and CPOP-R as the first line therapy in patients with diffuse large B cell lymphoma. Trial is in progress and will be reported in late 2009.

REFERENCES

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Pan Pacific Lymphoma 2009