Pixantrone: An Overview of Phase II and Phase III Studies in Non-Hodgkin's Lymphoma

R Van der Jagt,[1] R Pettengell,[2] D Rizzieri,[3] G Schiller,[4] P Cernohous,[5] L Wang,[5] and J Singer[5]

[1]Ottawa Hospital; Ottawa, Ontario, Canada; [2]St Georges Hospital; London, United Kingdom; [3]Duke University, Durham, North Carolina, USA; [4]UCLA School of Medicine, Los Angeles, California, USA; [5]Cell Therapeutics, Inc; Seattle, WA, USA

BACKGROUND

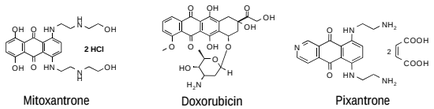
Anthracyclines

- Among the most active class of agents in non-Hodgkin's lymphoma (NHL)
- The standard of care for 1st line aggressive NHL is CHOP-R
- Infrequently used in relapsed NHL, even in sensitive patients, due to cumulative cardiac toxicity
  - ≤300 mg/m² doxorubicin (CHOPx6) [1]
    - 5.6% of patients develop CHF
    - 40% experience ≥15% reduction in LVEF
  - ≤550 mg/m² doxorubicin [2]
    - 26% of patients develop CHF
    - 50% experience ≥20% reduction in LVEF (grade 3/4 toxicity)

STRUCTURAL CHARACTERISTICS

Pixantrone Dimaleate (Pixantrone) [3,4,5]

- Novel aza-anthracenedione
- Structurally similar to anthracyclines (e.g. doxorubicin) and mitoxantrone
- Enhanced hydrogen bonding with greater DNA adduct formation
- Selectively binds to methylated CpG islands
- Reduction of free oxygen radical formation and subsequent cardiotoxicity



Mitoxantrone Doxorubicin Pixantrone

PRECLINICAL STUDIES

Comparative Activity of Pixantrone with Mitoxantrone and Doxorubicin

- Greater activity in hematologic tumor models
- Similar activity in solid tumor models
- Significantly reduced cardiotoxicity in animal models

CLINICAL STUDIES

Pixantrone in Non-Hodgkin's Lymphoma (NHL)

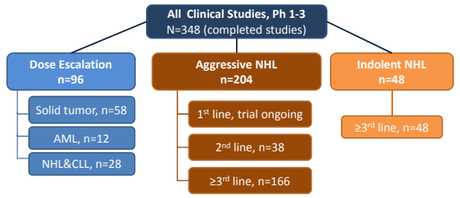
- Active as a single agent and in combination with other chemotherapeutic agents
- Active in the treatment of indolent and aggressive NHL

Overview of Clinical Studies With Pixantrone*

Study Type	Indication	# of Completed Studies	# of Patients Given Pixantrone
Single-agent, uncontrolled	NHL	2	59
Single-agent, uncontrolled	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



CLINICAL STUDIES IN INDOLENT NHL

Relapsed/Refractory Indolent NHL and Pixantrone-Rituximab, Phase 3 [6]

	Pixantrone + Rituximab (n=20)	Rituximab (n=20)	*P*-Value
Median age, years (range)	67 (52-77)	58.5 (45-74)	--
Male, n (%)	10 (50)	13 (72)	--
IPI score >2, n (%)	6 (30)	2 (11)	--
Line of therapy	3rd line, 2+ prior lines of therapy		
Median treatment cycles, n (range)	6 (2-6)	2 (2-2)	--
Treatment responses, n (%)			
Complete response (CR)	7 (35)	2 (11)	0.238
Overall response (ORR)	15 (75)	6 (33)	0.038
Time to progression, months	13.2	8.1	<0.001

Drug administration – 21 days/cycle, up to 6 cycles; rituximab at standard doses and regimens; pixantrone at 90 mg/m², Cycle 1 – Days 2,8; Cycle 2 – Days 1,8

Relapsed/Refractory Indolent NHL and FPD-R , Phase 2 [7]

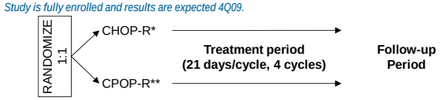
	FPD-R (n=29)
Median age, years (range)	63 (32-78)
Male, n (%)	15 (51.7)
REAL classification, n (%)	
Follicular center cell grade	18 (62.1)
Small lymphocytic	6 (20.7)
Lymphoplasmacytoid	1 (3.5)
Marginal zone	3 (10.3)
Diffuse large B-cell	1 (3.5)
Line of therapy	3rd line, 2+ prior therapies
Median treatment cycles, n (range)	5 (1-8)
Treatment responses*, n (%)	
CR	17 (63)
CR, 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/m²) replaced mitoxantrone.
*27 patients evaluable for efficacy

CLINICAL STUDIES IN AGGRESSIVE NHL

Diffuse Large B Cell Lymphoma/CHOP-R vs CPOP-R as 1st Line, Phase 2

Study is fully enrolled and results are expected 4Q09.



*CHOP-R: at standard dose and regimen
**CPOP-R: CHOP-R except doxorubicin replaced with pixantrone (150 mg/m²)

Baseline Characteristics	All
No. of patients	124
Median age, years (range)	68 (38-88)
Male, n (%)	63 (51)
Baseline ECOG ≥ 1, n (%)	80 (65)

Relapsed Aggressive NHL and CPOP, Phase 2 [8]

	ITT (n=30)	Evaluable (n=29)
Median age, years (range)	66 (26-76)	66 (26-76)
Male, n (%)	12 (40.0)	11 (37.9)
REAL classification, n (%)		
Diffuse large B-cell	20 (66.7)	19 (65.5)
Mantle cell	8 (26.7)	8 (27.6)
Follicular lymphoma, grade 3	2 (6.7)	2 (6.9)
Line of therapy	3rd line, 2+ prior lines of therapy	
Median treatment cycles, n (range)	6 (1-6)	6 (1-6)
Treatment responses, n (%)*		
CR	12 (40)	12 (41)
Cru	2 (7)	2 (7)
PR	8 (26)	5 (17)
ORR	22 (73)	19 (66)

Drug administration – 21 days/cycle, up to 6 cycles.
*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.

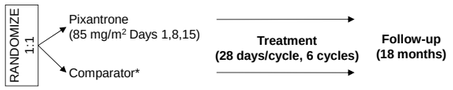
Relapsed Aggressive NHL and Pixantrone, Phase 2 [9]

	Pixantrone (n=33)
Median age, years (range)	66 (24-81)
Male, n (%)	18 (54.6)
REAL classification, n (%)	
Diffuse large B-cell	24 (73)
Mantle cell	7 (21)
Transformed high-grade follicular	1 (3)
High-grade variant of monocytoid B-cell	1 (3)
Line of therapy	3rd line, 2+ prior therapies
Median treatment cycles, n (range)	2 (1-6)
Treatment Responses, n (%)*	
CR	5 (15)
PR	4 (12)
PR, unconfirmed (PRu)	5 (15)
ORR	9 (27)

Drug administration – 28 days/cycle, up to 6 cycles. Pixantrone administered at 85 mg/m² on Days 1, 8, and 15.

PHASE 3 STUDY IN AGGRESSIVE NHL BEYOND 2ND RELAPSE

Study Design – Single Agent[10]



*Comparator drug was by investigator choice. These included vinorelbine, oxaliplatin, ifosfomide, etopside, or mitoxantrone; gemcitabine or rituximab allowed if approved in region.

Patient Characteristics

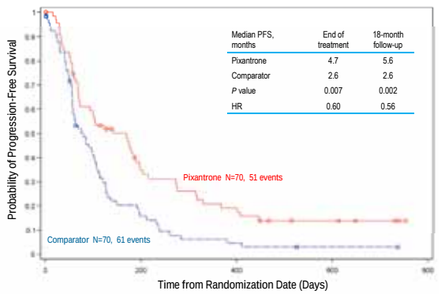
	Pixantrone (N=70)	Comparator (N=70)
Median age, years	60	58
>60 yrs, n (%)	32 (45.7)	29 (41.4)
Male, n (%)	46 (65.7)	40 (57.1)
IPI score, n (%)		
<2	20 (28.6)	18 (25.8)
≥2	50 (71.4)	52 (74.2)
Line of therapy	3rd line, 2+ prior lines of therapy	

Tumor Response: End of Treatment and at 18-Month Follow-Up Update*

Response (end of treatment), %	Pixantrone (n=70)	Comparator (n=70)	*P*-Value
CR/CRu	20.0	5.7	0.021
ORR (CR+CRu+PR)	37.1	14.3	0.003
Overall response lasting ≥4 months	25.7	8.6	0.012
Response (18-months post treatment), %			
CR/CRu	25.7	7.0	0.005
ORR (CR+CRu+PR)	40.0	14.3	0.001

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

Progression-Free Survival by Independent Review



Overall Survival : End of Treatment and at 18-Month Follow-Up Update

- At the end of treatment, the median OS was 8.1 months for the pixantrone group and 6.9 months for the comparator group (*P*=0.54; HR=0.88).
- At 18-months after end of treatment, the median OS was 10.2 months for the pixantrone group and 6.9 months for the comparator group (*P*=0.3; HR=0.82).

Tumor Response at End of Treatment by Subgroups *

	Pixantrone		Comparator	
	<65	≥65	<65	≥65
Age	(n=47)	(n=23)	(n=52)	(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	Relapsed
Refractory/Relapsed	(n=40)	(n=28)	(n=40)	(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%)
	≤1	≥2	≤1	≥2
IPI score	(n=20)	(n=50)	(n=19)	(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%)
	≤300 mg/m²	>300 mg/m²	≤300 mg/m²	>300 mg/m²
Prior doxorubicin**	(n=45)	(n=25)	(n=31)	(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%)
	Rituximab	No Rituximab	Rituximab	No Rituximab
Prior rituximab	(n=38)	(n=32)	(n=39)	(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 and assessments made by independent assessment panel (IAP)
**Anthracycline exposure (doxorubicin-equivalent)

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 included cardiac arrest, congestive heart failure, myocardial infarction, cyanosis, pericardial effusion, and tachycardia.

Summary and Conclusions for Phase 3 Study

The results of this study demonstrated that patients with relapsed/refractory NHL who were treated with pixantrone, achieved the following benefits when compared with other chemotherapy agents:

- A significantly greater ORR, including greater CR/CRu rate.
- A significantly greater PFS and percentage of patients with responses lasting ≥4 months.
- An impressive durability of response observed during the 18-month post treatment follow up.

An encouraging safety profile of pixantrone was observed in this heavily pretreated patient population:

- Neutropenia and leukopenia were the most commonly reported (≥10%) grade 3/4 adverse events
- A low incidence of febrile neutropenia (7.4%)
- Individual review of the cardiac failure events did not demonstrate a clear pattern of treatment-related causality.

OVERALL SUMMARY

- In preclinical studies, pixantrone had greater activity in hematologic tumor models, similar activity in solid tumor models, and significantly reduced cardiotoxicity in animal models when compared with doxorubicin and mitoxantrone.
- The results of clinical studies showed that pixantrone is active as a single agent and in combination with other chemotherapeutic agents 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.
- A randomized trial comparing CHOP-R to CPOP-R as first-line therapy in diffuse large B cell lymphoma has completed enrollment. Results will be reported in late 2009.

REFERENCES

[1] Sonnefeld, et al. J Clin Oncol 1995;13:2530-9
[2] Swain, et al. Cancer 2003;97:2869-79
[3] Beggiolin, et al. Tumori 2001; 87:407-416
[4] Krapcho, et al. J Med Chem 1994; 37:828-837
[5] Evison, et al. Mol Pharmacol 2008;74:184-94
[6] Santoro, et al. Presented at ASCO 2006
[7] Fayad, et al. Presented at ASH 2006
[8] Engert, et al. Presented at ASH 2006
[9] Borchmann, et al. Haematologica 2003;88:888-94
[10] Pettengell, et al. Presented at ASCO 2009