Phase III Trial of Pixantrone Dimaleate Compared With Other Agents As Third-Line, Single-Agent Treatment of Relapsed Aggressive Non-Hodgkin's Lymphoma (EXTEND): Results from the Treatment and Follow-Up Periods

R Pettengell[1], B Coiffier[2], G Narayanan[3], FH Mendoza[4], R Digumarti[5], H Gomez[6], P Zinzani[7], G Schiller[8], D Rizzieri[9], P Cernohous, L Wang, J Singer[10],

[1]St Georges Hospital, London, United Kingdom; [2]Centre Hospitalier Lyon SudPierre-Benite, France; [3]Regional Cancer Center, Thiruvananthapuram, India; [4]Hospital Edgardo Rebagliati, Marin, Lima, Peru; [5]Nizam's Institute of Medical Science, Hyderabad, India; [6]Oncocenter, Lima, Peru; [7]Institute of Hematology "L. e A. Seràgnoli", University of Bologna; [8]UCLA, Los Angeles, California, USA; [9]Duke University, Durham, North Carolina, USA; [10]Cell Therapeutics, Inc., Seattle, Washington, USA

BACKGROUND

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

- Novel aza-anthracenedione
- Structurally similar to mitoxantrone and anthracyclines
- Designed to reduce the generation of reactive oxygen species
- Significantly reduced cardiotoxicity in animal models compared to mitoxantrone and doxorubicin
- Phase I and II results of pixantrone as both single-agent and in combination showed:
  - substantial response rates in patients with aggressive or indolent NHL
  - a low incidence of grade 3/4 cardiac disorders despite prior doxorubicin exposure of up to 450 mg/m^2

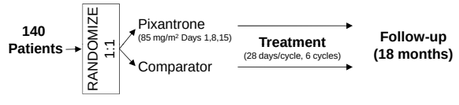
METHODS

Eligibility Criteria

- Histologically confirmed aggressive NHL
- Relapse after ≥2 prior chemotherapy regimens
- Sensitivity to last anthracycline/anthracenedione-containing regimen
- Age ≥18 years
- ECOG PS 0-2
- No prior cumulative dose of doxorubicin or equivalent >450 mg/m^2 or baseline LVEF <50%
- No clinically significant cardiovascular abnormalities
- No serious intercurrent infection

*Study Design**

- Randomized, controlled, international, multicenter study
- ≥3rd-line treatment of relapsed aggressive (de novo or transformed) NHL
- Comparators administered at standard doses and regimens. Choice of comparators included vinorelbine, oxaliplatin, ifosfomide, etoposide, or mitoxantrone; gemicitabine or rituximab were allowed if approved in region
- Follow-up at 18 months



- Follow-up is ongoing. Data presented in this poster include treatment period and minimum 9-month follow-up period.

Study Objectives

- The primary study endpoint was complete response (CR/CRu) rate, which was evaluated by an independent assessment panel.
- Secondary endpoints included:
  - Overall response rate (ORR [CR/CRu + PR])
  - Response lasting ≥4 months
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Safety

RESULTS

Patient Characteristics

	Pixantrone (n=70)	Comparator (n=70)
Median age, years	60	58
>60 years, n (%)	32 (45.7)	29 (41.4)
Male gender, n (%)	46 (65.7)	40 (57.1)
ECOG PS, n (%)		
0-1	56 (80.0)	55 (78.6)
2-3	14 (20.0)	15 (21.4)
Median NHL duration, months	32.0	31.6
Ann Arbor stage, n (%)		
I/II	19 (27.1)	14 (20.0)
III/IV	51 (72.9)	56 (80.0)
IPI score, n (%)		
<2	20 (28.6)	18 (25.8)
≥2	50 (71.4)	52 (74.2)
Extranodal sites, n (%)		
0	35 (50.0)	35 (50.0)
≥1	34 (48.6)	33 (47.1)
Missing	1 (1.4)	2 (2.9)

Patient Response to Prior Therapy

	Pixantrone (n=70)	Comparator (n=70)
Response to most recent therapy, n (%)		
CR/CRu	17 (24.3)	18 (25.7)
PR	19 (27.1)	26 (37.1)
SD	9 (12.9)	6 (8.6)
PD	22 (31.4)	20 (28.6)
Baseline tumor assessment, n (%)		
Refractory*	40 (57.1)	40 (57.1)
Relapsed	28 (40.0)	30 (42.9)
Missing	2 (2.9)	0
Median time from last chemotherapy to randomization, months	8.8	8.5
Prior SCT, n (%)	11 (15.7)	10 (14.3)
Prior chemotherapy regimens, n (%)		
2	32 (45.7)	24 (34.3)
3	24 (34.3)	33 (47.1)
4	7 (10.0)	6 (8.6)
5	4 (5.7)	3 (4.3)
≥6	3 (4.3)	4 (5.7)
Median doxorubicin dose equivalent, mg/m^2	292.6	315.5

*Patients <8 months from initiation of most recent prior chemotherapy to randomization (any response) or patients with a response of PD/SD to most recent prior chemotherapy.

Patient Disposition

	Pixantrone	Comparator
Intent -to-treat patients, n (%)	70 (100)	70 (100)
Treated patients, n (%)	68 (97.1)	67 (95.7)
Median number of cycles, n	4.0	3.0
Treatment discontinuation, n (%)	49 (70.0)	53 (75.7)
Disease progression, n (%)	28 (40.0)	39 (55.7)
Adverse event, n (%)	15 (21.4)	9 (12.9)
Deaths, n (%)	41 (58.6)	44 (62.9)
Within 30 days of last dose, n (%)	10 (14.3)	12 (15.7)

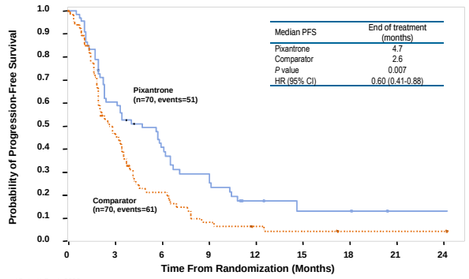
Tumor Response: *

Response (end of treatment), n (%)	Pixantrone (n=70)	Comparator (n=70)	*P* Value
CR/CRu	14 (20.0)	4 (5.7)	0.021
ORR	26 (37.1)	10 (14.3)	0.003
Response (min. 9-month follow-up), n (%)			
CR/CRu	18† (25.7)	5 (7.0)	0.005
ORR	28 (40.0)	10 (14.3)	0.001

*Analysis is based on the 120-day update. Minimum 9-month follow-up; follow-up period is ongoing.

† One patient received CVP after 1 month and had CR at month2

Progression-Free Survival: End of Treatment*



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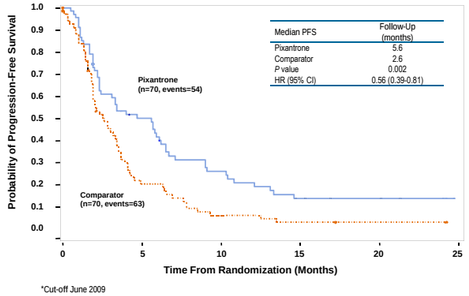
Progression-Free Survival: Minimum 9-Month Follow-Up*



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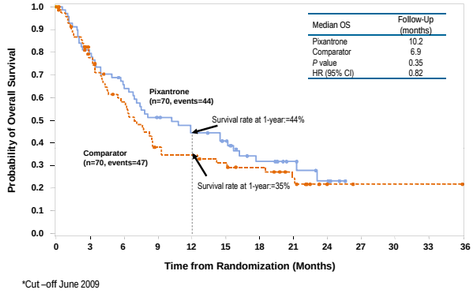
Overall Survival: Minimum 9-Month Follow-Up*



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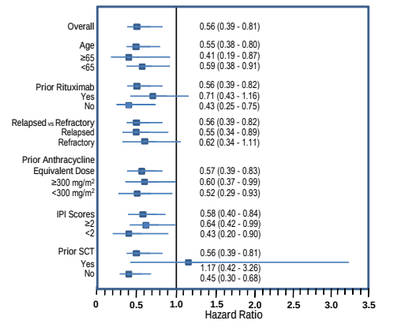
Subgroup Analysis of PFS*



*Plot and values shown are HR (95% CI) and *P* value for patient subgroups. On-study and follow-up data were used in this analysis. *P* value is for the Cox proportional hazards model with treatment and subgroup as independent variables.

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%)
	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)

Subsequent Therapy

	Pixantrone (n=24)*	Comparator (n=25)**
Corticosteroids only	3	0
Single-agent chemotherapy	9	6
Low- to moderate-intensity combination therapy	5	13
High-intensity combination therapy	7	6

*14/21 patients initiated subsequent therapy at 2-month follow-up; 7/21 at ≥6-month follow-up
**22/25 patients initiated subsequent therapy at 2-month follow-up; 3/25 at ≥6-month follow-up

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
Serious cardiac events n/N (%)	6/68 (8.8)		3/67 (4.5)	

*Events included cardiac arrest, congestive heart failure, myocardiac infarction, cyanosis, pericardial effusion, and tachycardia.

Lifetime Anthracycline Exposure As Doxorubicin Equivalents and Cardiac Events of Interest in Pixantrone-Treated Patients

Lifetime cumulative dose (mg/m^2)*	Patients n (%)	Decrease in LVEF (>10% to <50%) (n)	CHF** (n)
<400	17 (25)	1	1
401-500	17 (25)	4	1
501-600	12 (18)	2	0
601-700	12 (18)	3	0
701-800	4 (6)	1	0
801-900	5 (7)	0	0
>900	1 (1)	0	0

*Pixantrone dose converted to dox-equivalent dose by factor 3.4. Dox-equivalent dose based on published calculations.[4]
**Assessed by independent cardiology review.

Thirty-two percent of pixantrone-treated patients reached lifetime doxorubicin-equivalent doses of >600 mg/m^2; there was 1 asymptomatic decrease in LVEF and no cases of CHF. A greater majority of cardiac events of interest were observed in patients who received a lifetime doxorubicin-equivalent dose of <500 mg/m^2 where the proportion of pixantrone received was lesser than in patients who received greater lifetime dose levels.

In accordance with study protocol, pixantrone was discontinued in patients with a significant decline in LVEF at scheduled assessments. Discontinuation occurred in 1 patient after cycle 1, 3 patients after cycle 2, 6 patients after cycle 4, and 1 patient completed 6 cycles.

Grade 3/4 Adverse Events*

	Pixantrone (n=68)	Comparator (n=67)
All Grade 3/4 Adverse Event	51 (75.0%)	34 (50.7%)
Neutropenia	28 (41.2%)	13 (19.4%)
Leukopenia	16 (23.5%)	3 (4.5%)
Anemia	4 (5.9%)	9 (13.4%)
Pyrexia	3 (4.4%)	6 (9.0%)
Febrile neutropenia	5 (7.4%)	2 (3.0%)
Abdominal pain	5 (7.4%)	3 (4.5%)
Pneumonia	4 (5.9%)	3 (4.5%)
Dyspnea	4 (5.9%)	3 (4.5%)

*AEs included those with ≥5% incidence

SUMMARY AND CONCLUSIONS

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

- Significant increase in CR/CRu rate
- Significant increase in ORR
- A positive trend in OS

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

- Lower than expected incidence of serious cardiac events for cumulative median doxorubicin-equivalent doses of 535 mg/m^2
- Neutropenia and leukopenia were the most frequent (≥10%) grade 3/4 adverse events
- Low incidence of febrile neutropenia (7.4%)

An anthracycline with reduced cardiotoxicity that can be used for salvage therapy of aggressive NHL meets a significant unmet medical need.

REFERENCES

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