Randomized Phase 3 Trial of Pixantrone Versus Other Chemotherapeutic Agents for Third-Line Single-Agent Treatment of Relapsed Aggressive Non-Hodgkin's Lymphoma

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BACKGROUND

Anthracyclines

- Among the most active class of agents in 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)

Pixantrone

- Novel aza-anthracenedione
- Rationally designed to reduce reactive oxygen radical generation
- Significant reduction in cardiac damage in experimental animal models versus doxorubicin or mitoxantrone
- Promising Phase 1 and 2 studies produced encouraging rates of CR and ORR (single-agent or combination therapy) in aggressive or indolent NHL in 210 patients; low incidence of grade 3 and 4 cardiac disorders despite intensive doxorubicin exposure

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 ≥4 months, progression-free survival (PFS), overall survival (OS), safety

METHODS

Study Design

- Randomized, controlled, international, multi-center study
- ≥3 line treatment of relapsed aggressive (de novo or transformed) NHL
- ≥1 prior anthracycline-containing regimen (cumulative doxorubicin-equivalent dose limited to ≤450 mg/m^2)
- 140 patients randomized - 70 in pixantrone group, 70 in comparator group
- Up to six treatment cycles
  - Pixantrone 85 mg/m^2 q wk x 3, q 4 wk cycle
  - Comparators administered at standard doses and regimens
    - Choice of comparators included vinorelbine, oxaliplatin, ifosfomide, etopside, or mitoxantrone; gemicitabine or rituximab allowed if approved in region
- Follow up for 18 months after last study treatment
- Unless stated otherwise, data presented in this poster are for the intent-to-treat (ITT) patient population.

Key Inclusion/Exclusion Criteria

Inclusion

- Histologically confirmed aggressive NHL (REAL/WHO classification)
- Frontline therapy with CHOP or equivalent
- Relapse after 2 or more prior regimens
- Sensitive to the last anthracycline/anthracenedione containing regimen
- Age ≥18 years
- ECOG performance status of ≤2

Exclusion

- Prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m² or baseline LVEF by MUGA <50%
- Chemotherapy, radiotherapy, or other anticancer treatment within 2 weeks before randomization
- Clinically significant cardiovascular abnormalities
- Serious infection at randomization

RESULTS

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%)
ECOG Grade, n (%)		
0-1	56 (80.0%)	55 (78.6%)
2-3	14 (20.0%)	15 (21.4%)
Stage (Ann Arbor), n (%)		
I/II	19 (27.1%)	14 (20.0%)
III/IV	51 (72.9%)	56 (80.0%)
International Prognostic Index, 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 and Prior NHL Treatment

	Pixantrone (N=70)	Comparator (N=70)
Response to Most Recent Therapy		
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 Assessment		
Refractory *	40 (57.1%)	40 (57.1%)
Relapsed	28 (40.0%)	30 (42.9%)
Missing	2 (2.9%)	0
Prior SCT, n (%)	11 (15.7%)	10 (14.3%)
Chemotherapy regimens, median number	3.0	3.0
Doxorubicin dose equivalent, median mg/m^2	292.6	315.5

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

Patient Disposition

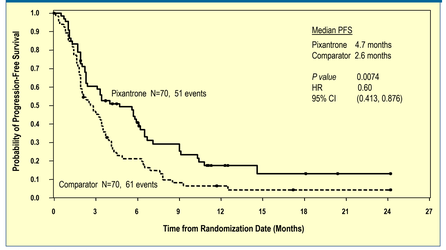
	Pixantrone	Comparator
Intent-to-treat population (ITT)	70 (100%)	70 (100%)
All treated patients	68 (97.1%)	67 (95.7%)
Discontinuation	49 (70.0%)	53 (75.7%)
Due to progression of disease	28 (40.0%)	39 (55.7%)
Due to adverse event	15 (21.4%)	9 (12.9%)
Deaths	41 (58.6%)	44 (62.9%)
Died within 30 days of last dose	10 (14.3%)	12 (15.7%)

Tumor Response Rates *

	Pixantrone (N=70)	Control (N=70)	P value
CR	8 (11.4%)	0	--
CRu	6 (8.6%)	4 (5.7%)	--
CR/CRu**	14 (20%)	4 (5.7%)	0.021
Overall response rate (ORR) (CR+CRu+PR)	26 (37.1%)	10 (14.3%)	0.003

*Response rates determined by independent review.
**Four additional patients, 3 in pixantrone group and 1 in control group, achieved CR/CRu during the follow-up phase (not reflected in the table above)..

Progression-Free Survival*

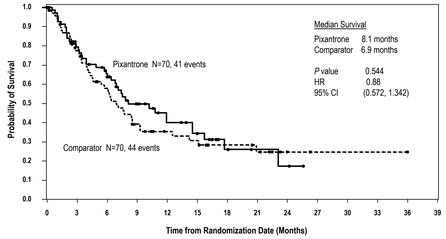


*Independent review

Percentage of All Patients With Responses Lasting ≥4 Months

	Pixantrone (N=70)	Comparator (N=70)	*P* Value
CR	7 (10.0%)	0	--
CRu	4 (5.7%)	3 (4.3%)	--
PR	7 (10.0%)	3 (4.3%)	--
Overall	18 (25.7%)	6(8.6%)	0.012

Overall Survival*

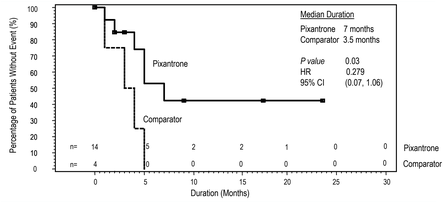


*These end-of-treatment results are to be updated after follow up.

Prior Anthracycline Dose and Rituximab Treatment in Responders

	Pixantrone (N=70)		Comparator (N=70)	
	CR/CRu	CR/CRu/PR	CR/CRu	CR/CRu/PR
Prior Anthracycline Dose				
≤300 mg/m^2	7/45(16%)	16/45(36%)	0/31 (0%)	3/31 (10%)
>300 mg/m^2	7/25(28%)	10/25(40%)	4/39 (10%)	7/39 (18%)
Prior Rituximab Treatment				
Yes	6/38 (16%)	12/38 (32%)	3/39 (8%)	7/39 (18%)
No	8/32 (25%)	14/32 (44%)	1/31 (3%)	3/31 (10%)

Time From Response to Progression of Disease/Death (CR/CRu Responder Analysis)



Drug Administration*

Drug	No. of Patients Administered Drug
Pixantrone	68
Comparator	
Oxaliplatin	30
Ifosfamide	12
Vinorelbine	11
Etoposide PO	5
Etoposide IV	4
Mitoxantrone	4
Gemcitabine	1
Rituximab	0

*Median number of cycles of drug received during the study - 4.0 in the pixantrone group (n=68), 3.0 in the comparator group (n=67)

Lifetime Anthracycline/Anthracenedione Exposure in Pixantrone Group (Doxorubicin Equivalent Dose)

Treatment Cycle	N	Pixantrone Treatment Cumulative Dose* Median mg/m^2	Lifetime Cumulative Dose** Median mg/m^2
1	68	74	365.2
2	54	148	430.2
3	43	209	498.1
4	36	275	571.8
5	25	356	631.5
6	22	427	695.0

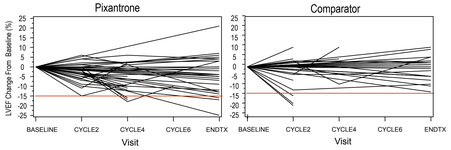
*Pixantrone dose converted to doxorubicin equivalent dose by factor 3.4
**Doxorubicin equivalent dose based on published calculations [3]

Grade 3/4 Adverse Events*

	Pixantrone (N=68)	Comparator (N=67)
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%)
Anaemia	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%)
Dyspnoea	4 (5.9%)	3 (4.5%)

*All treated patients and AE incidences ≥5% during any treatment

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

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
- A positive trend in OS

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 SAE for cumulative median doxorubicin equivalent doses of 513 mg/m^2

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

REFERENCES

[1] Sonnefeld, et al. J Clin Oncol. 1995; 13:2530-9
[2] Swain, et al. Cancer 2003; 97(1):2869-79,
[3] McLaughlin, et al. J Clin Oncol. 1996; 14(4):1262-8

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