Phase III Trial of Pixantrone Dimaleate Compared with Other Agents as Third-Line, Single-Agent Treatment of Relapsed Aggressive Non-Hodgkin's Lymphoma (EXTEND): End of Study Results

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BACKGROUND

Treatment Landscape

- There is currently no treatment with reliable, durable efficacy for patients with aggressive non-Hodgkin's lymphoma who relapse following ≥2 lines of therapy.

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

- Novel aza-anthracenedione
- Structurally similar to mitoxantrone and anthracyclines
- Minimally promotes formation 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

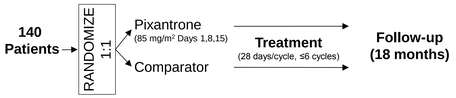
METHODS

Eligibility Criteria

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

Study Design

- Randomized, controlled, international, multicenter open-label study
- ≥3rd-line treatment of relapsed aggressive (de novo or transformed) NHL with ≥1 prior anthracycline-containing regimen and ≥2 relapses
- Comparators administered at standard doses and regimens. Choice of comparators included vinorelbine, oxaliplatin, ifosfamide, etoposide, or mitoxantrone; gemcitabine or rituximab were allowed if approved in region (US only)
- Both groups were followed for 18 months after last treatment



- Data presented in this poster include both treatment and 18-month follow-up periods (end of study results).
- Exploratory subgroup analyses of CR/CRu rates, ORR, PFS, and OS for potentially significant patient demographics, disease characteristics, and prior treatment history were conducted to further assess the effect of pixantrone.

Study Objectives

- The primary study endpoint was complete response (CR/CRu) rate in the intent-to-treat (ITT) population, which was evaluated by an independent assessment panel.
- Secondary endpoints included:
  - Overall response rate (ORR [CR/CRu + PR])
  - Response duration
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Safety

RESULTS

Table 1. 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	21 (30.0)	17 (24.3)
≥2	49 (70.0)	53 (75.7)
Extranodal sites, n (%)		
0	35 (50.0)	35 (50.0)
≥1	34 (48.6)	33 (47.1)
Missing	1 (1.4)	2 (2.9)

Table 2. 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)	25 (35.7)
SD	9 (12.9)	6 (8.6)
PD	22 (31.4)	21 (30.0)
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	9.0	8.0
Prior SCT, n (%)	11 (15.7)	10 (14.3)
Prior chemotherapy regimens, n (%)		
2	32 (45.7)	24 (34.3)
3	24 (34.3)	32 (45.7)
4	7 (10.0)	6 (8.6)
5	4 (5.7)	4 (5.7)
≥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.

Table 3. 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
Median treatment duration, months	3.8	2.6
Treatment discontinuation, n (%)	50 (71.4)	54 (77.1)
Disease progression, n (%)	28 (40.0)	39 (55.7)
Adverse event, n (%)	15 (21.4)	9 (12.9)
Deaths (treated patients), n (%)	49 (72.1)	52 (77.6)
Within 30 days of last dose, n (%)	10 (14.7)	12 (17.9)

- The median number of treatment cycles was greater for patients in the pixantrone group versus the comparator group.
- The median duration of treatment for patients in the pixantrone group was approximately 1 month longer than in the comparator group.

Response

Table 4. Tumor Response Rates

	Pixantrone (N = 70)	Comparator (N = 70)	P-value
End of Treatment, n (%)			
CR/CRu	14 (20.0)	4 (5.7)	0.021
ORR	26 (37.1)	10 (14.3)	0.003
End of Study, n (%)			
CR/CRu	17 (24.3)	5 (7.1)	0.009
ORR	28 (40.0)	10 (14.3)	0.001

- The primary endpoint of CR/CRu rate at the end of treatment was 20% (n = 14) in the pixantrone group compared to 5.7% (n = 4) in the comparator group.
- At the end of study, 3 additional patients in the pixantrone group achieved CR despite no subsequent therapy. The CR/CRu rate at the end of study was 24.3% (n = 17) in the pixantrone group versus 7.1% (n = 5) in the comparator group.
- The median duration of CR/CRu was 9.6 months for the pixantrone group and 4.0 months for the comparator group (P = 0.081).

Survival

Figure 1. Progression-Free Survival: End of Study

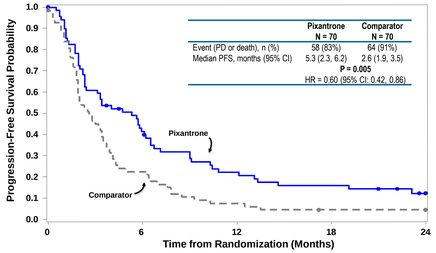
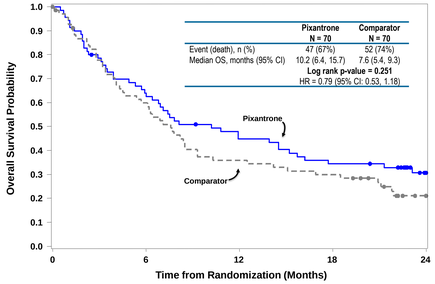


Figure 2. Overall Survival: End of Study



- Patients in the pixantrone group had a 40% improvement in PFS and 21% improvement in OS versus patients in the comparator group.

Exploratory Subgroup Analyses

Table 5. Subgroup Analyses of Response Rate

	CR/CRu, %		ORR, %	
	Pix	Comp	Pix	Comp
All patients*	24	7	40	14
Age				
≥65 years	26	0	48	6
<65 years	17	8	32	17
Gender				
Male	17	8	28	15
Female	25	3	54	13
IPI score				
≥2	20	6	39	17
0-1	19	6	33	6
Prior rituximab				
No	25	3	44	10
Yes	16	8	32	18
Relapsed	29	7	50	17
Refractory	15	5	30	13
Prior regimens				
≥3	13	7	29	17
<3	28	4	47	8
Time from 1st to 2nd prior chemo				
≥1 year	27	10	47	16
<1 year	12	0	28	11

*Responses for all patients were calculated with end of study data. Responses for subgroups were calculated with end of treatment data.

Table 6. Subgroup Analyses of Survival

	PFS, HR (95% CI)	OS, HR (95% CI)
All patients*	0.60 (0.42 - 0.86)	0.79 (0.53 – 1.18)
Age		
≥65 years	0.65 (0.33 – 1.25)	0.95 (0.46 – 1.95)
<65 years	0.58 (0.37 – 0.90)	0.71 (0.44 – 1.15)
Gender		
Male	0.66 (0.41 – 1.04)	1.16 (0.70 – 1.93)
Female	0.51 (0.28 – 0.93)	0.44 (0.23 – 0.86)
IPI score		
≥2	0.67 (0.44 – 1.02)	0.88 (0.57 – 1.37)
0-1	0.46 (0.22 – 0.96)	0.64 (0.26 – 1.56)
Prior rituximab		
No	0.40 (0.23 – 0.69)	0.63 (0.34 – 1.17)
Yes	0.83 (0.51 – 1.34)	0.95 (0.57 – 1.59)
Relapsed	0.70 (0.40 – 1.24)	0.94 (0.49 – 1.79)
Refractory	0.55 (0.34 – 0.89)	0.75 (0.46 – 1.24)
Prior regimens		
≥3	0.76 (0.47 – 1.21)	0.85 (0.51 – 1.42)
<3	0.42 (0.23 – 0.75)	0.72 (0.38 – 1.34)
Time from 1st to 2nd prior chemo		
≥1 year	0.44 (0.26 – 0.75)	0.69 (0.39 – 1.22)
<1 year	0.59 (0.33 – 1.07)	0.92 (0.49 – 1.71)

*Responses for all patients were calculated with end of study data. Responses for subgroups were calculated with end of treatment data.

- The results of the analyses showed a benefit with pixantrone versus comparators across subgroups.
- Pixantrone appeared particularly beneficial in the following subgroups: female gender, <3 prior regimens, rituximab-naïve, and ≥1 year from 1st- to 2nd- line prior therapy.

Safety

Table 7. Grade 3/4 Adverse Events

	Pixantrone (N = 68)	Comparator (N = 67)
All Grade 3/4 Adverse Event	52 (76.5%)	35 (52.2%)
Neutropenia	28 (41.2%)	13 (19.4%)
Leukopenia	16 (23.5%)	5 (7.5%)
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%)

- During treatment, neutropenia and leucopenia were the most commonly reported grade 3/4 adverse events.
- The incidence of grade 3/4 febrile neutropenia was 7.4% for the pixantrone group and 3.0% for the comparators group.

Cardiac Adverse Events

- Six patients (8.8%) in the pixantrone group and 3 patients (4.5%) in the comparator group experienced a serious cardiac adverse event.
- Thirteen patients (19.1%) in the pixantrone group had decreased LVEF (defined as >10% decrease regardless of absolute value): 11 (16.2%) of these were grade 1/2 and 2 (2.9%) were grade 3. Seven patients (10.4%) in the comparator group had decreased LVEF, all grade 1/2.

SUMMARY AND CONCLUSIONS

- This phase III study demonstrated that patients with relapsed/refractory aggressive NHL who were treated with pixantrone compared with other chemotherapy agents achieved:
  - Superior CR/CRu rate
  - Superior ORR
  - Superior PFS
  - A positive trend in OS
- Pixantrone had a tolerable safety profile.
- An anthracycline with reduced cardiotoxicity that can be used for salvage therapy of aggressive NHL meets a significant unmet medical need.

REFERENCES

[1] Beggiolin, et al. Tumori 2001;87:407-16
[2] Kraphco, et al. J Med Chem 1994;37:828-37
[3] Evison, et al. Mol Pharmacol 2008;74:184-94

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