Pixantrone monotherapy in histologically confirmed, relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: *post-hoc* analyses from a phase III trial

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BACKGROUND

Pixantrone is conditionally approved by the European Medicines Agency for the treatment of multiply relapsed or refractory (3rd or 4th line) aggressive B-cell NHL. The benefit of pixantrone has not been established in patients when used as 5th-line or greater chemotherapy. The phase III EXTEND trial compared pixantrone with physicians' choice of monotherapy in patients with aggressive *de novo* or transformed NHL who had previously received ≥ 2 regimens (Figure 1). In the intent-to-treat (ITT) population, pixantrone was associated with a higher rate of complete response (CR) or unconfirmed CR (CRu) compared with comparator (20.0% vs 5.7%, p = 0.021) and longer PFS (5.3 vs 2.6 months, log-rank p = 0.005) (Pettengell R et al. Lancet Oncol 2012).

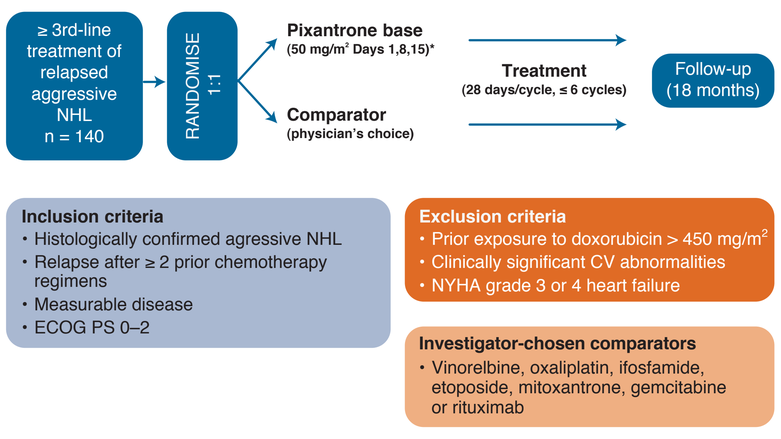
AIMS

These *post-hoc* analyses of EXTEND aimed to evaluate the efficacy of pixantrone in the subset of patients who had aggressive B-cell lymphoma, as confirmed by central independent pathological review. In this subgroup and in patients with aggressive B-cell NHL determined by site, we also investigated efficacy in the approved indication: those with 2–3 previous regimens (i.e. excluding patients with ≥ 4 previous regimens). The effect of previous rituximab in these subgroups was also evaluated.

METHODS

EXTEND was a multicentre, open-label, randomised phase III trial of pixantrone vs physicians' choice of monotherapy (vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine or rituximab) (Figure 1). The primary endpoint was CR or CRu. Secondary endpoints were ORR, PFS and OS.

Figure 1. Study design



*Clinical trials were based on pixantrone dimaleate 85 mg/m², equivalent to 50 mg/m² pixantrone base, the EU approved dose.

For these *post-hoc* subgroup analyses, patients with the following were retrospectively identified:

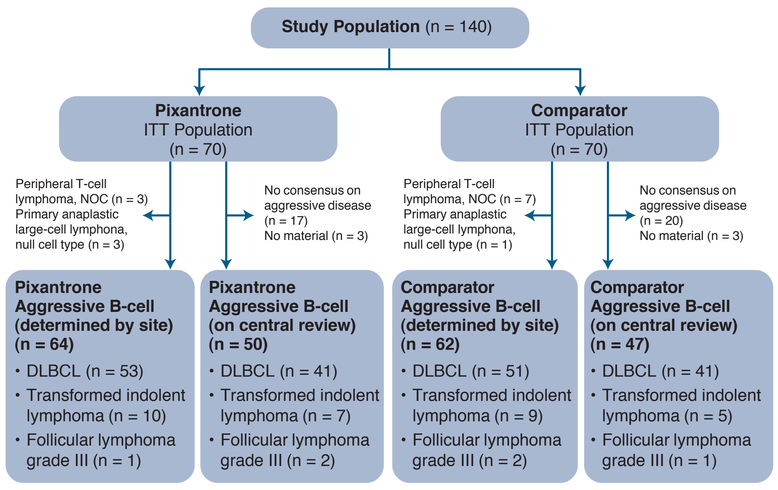
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma grade III
- Transformed indolent lymphoma (confirmation that current disease was high-grade DLBCL or FG3-like in patients with a history of indolent disease).

Decisions regarding pathology were reached through consensus of two (three in case of disagreement) independent pathologists.

RESULTS

- A total of 140 patients (pixantrone/comparator; n = 70/70) were randomised into the EXTEND study, of whom 126 had aggressive B-cell histology as determined by on-site pathologists.
- The numbers of patients determined to have aggressive B-cell NHL according to on-site histology was 64 and 62 in the pixantrone and comparator groups, respectively. On retrospective, independent pathological review, 50 and 47 patients in the pixantrone and comparator groups, respectively were determined to have aggressive B-cell NHL (concordance rate of 76% between site and independent review).
- In the subpopulation with aggressive B-cell NHL (on central review), the panel diagnoses in pixantrone/comparator groups were DLBCL in 82.0%/87.2%, transformed indolent lymphoma in 14.0%/10.6%, and follicular lymphoma grade III in 4.0%/2.1%.

Figure 2. Histology results in EXTEND



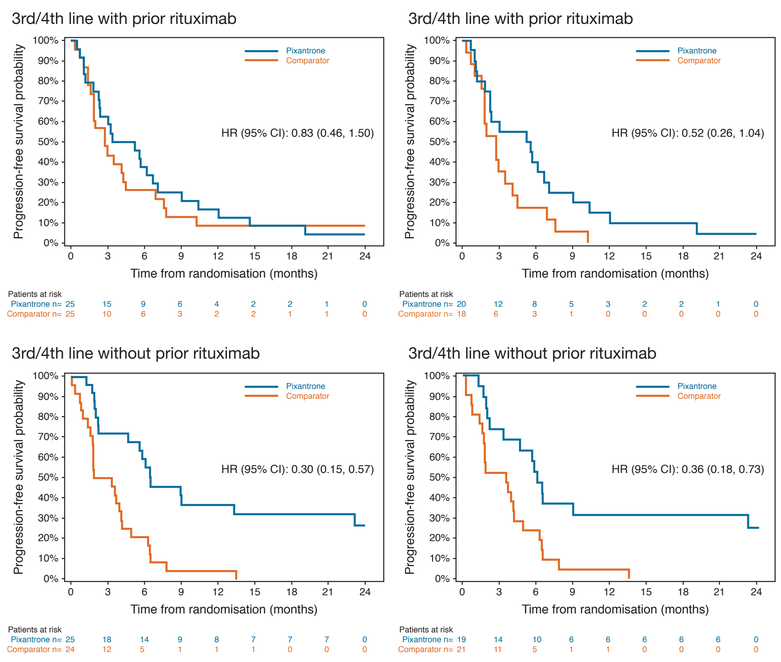
NOC, not otherwise classified

Table 1. Baseline characteristics

	Aggressive B-cell (determined by site) (all lines)		Aggressive B-cell (on central review) (all lines)	
	PIX	Comp	PIX	Comp
n	64	62	50	47
Median age, years (range)	60.0 (18–80)	58.0 (26–77)	60.0 (28–80)	58.0 (26–77)
Sex, % female	37.5	45.2	38.0	48.9
International Prognostic Index, % 0,1 ≥ 2	26.6 73.4	24.6 75.4	24.0 76.0	27.7 72.3
Ann Arbor stage, % I/II III/IV	26.6 73.4	19.4 80.6	26.0 74.0	25.5 74.5
≥ 1 extranodal site, %	48.4	45.2	48.0	46.8
Median chemotherapy regimens (range)	3.0 (2–9)	3.0 (2–8)	3.0 (2–9)	3.0 (2–8)
Previous rituximab, %	59.4	61.3	60.0	55.3

PIX, pixantrone; comp, comparator

Progression-free survival



SAFETY

- Full safety and tolerability data have been previously published (Pettengell R et al. Lancet Oncol 2012).
- Uncomplicated neutropenia was more common in the pixantrone vs comparator arm (all grades, 50.0% vs 23.9%; grade 3/4, 41.2% vs 19.4%).
  - Non-cumulative and generally < 3 days
  - Grade 4 approximately 10%/cycle with no increase in late cycles
  - Routine G-CSF not required.
- Other grade 3/4 haematological AEs with total incidence > 10% (pixantrone vs comparator):
  - Leukopenia: 23.5% vs 7.5%
  - Thrombocytopenia: 11.8% vs 10.4%.
- Non-haematological AEs (pixantrone vs comparator):
  - All-grade diarrhoea: 4.4% vs 17.9%
  - All-grade cough: 22.1% vs 4.5%.

DISCUSSION

- Pixantrone is conditionally approved by the European Medicines Agency for the treatment of multiply relapsed or refractory (3rd or 4th line) aggressive B-cell NHL. The benefit of pixantrone has not been established in patients when used as 5th-line or greater chemotherapy.
- In this unplanned analysis, single agent pixantrone appears to be more efficacious than physicians' choice of monotherapy in the 3rd or 4th line setting whether or not previously exposed to rituximab.
- When patients with aggressive B-cell NHL were identified by central review, the resulting HR for PFS was lower than when disease was determined by site (0.52 versus 0.85). This suggests that the superior efficacy of pixantrone in the patients with prior rituximab was not due to inclusion of more patients with indolent disease based on site pathology.
- In all subgroups, there was a positive trend towards improved OS in patients treated with pixantrone.
- The concordance between on-site histology and retrospective central review was 76%. This was consistent with rates of concordance reported in the literature, which range from 58% to 84% (Jones SE et al. Cancer 1977; Stel HV et al. Pathol Res Pract 1989; Matasar MJ et al. Ann Oncol 2012).

REFERENCES

Pettengell R et al. Lancet Oncol. 2012;13:696–706
Jones SE et al. Cancer 1977;39:1071–1076
Stel HV et al. Pathol Res Pract 1989;184:242–247
Matasar MJ et al. Ann Oncol 2012;23:159–166

CONFLICTS OF INTEREST

This study was funded by CTI.
RP has acted as a consultant for CTI and received honoraria for speaker engagements. PT is an employee of CTI Life Sciences and owns stock in CTI. PC, LW, JS and HM are employees of CTI and own stock in CTI .

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Table 2. Outcomes in patients with aggressive B-cell NHL, determined by site or by central review

End of Study	3rd/4th line								All lines							
	Aggressive B-cell (determined by site)				Aggressive B-cell (on central review)				Aggressive B-cell (determined by site)				Aggressive B-cell (on central review)			
	+ ritux		- ritux		+ ritux		- ritux		+ ritux		- ritux		+ ritux		- ritux	
	PIX	Comp	PIX	Comp	PIX	Comp	PIX	Comp	PIX	Comp	PIX	Comp	PIX	Comp	PIX	Comp
n	25	25	25	24	20	18	19	21	38	38	26	24	30	26	20	21
CR/CRu, n (%)	6 (24.0)	1 (4.0)	8 (32.0)*	1 (4.2)	6 (30.0)	1 (5.6)	3 (15.8)	1 (4.8)	7 (18.4)	4 (10.5)	8 (30.8)*	1 (4.2)	6 (20.0)	3 (11.5)	3 (15.0)	1 (4.8)
ORR, n (%)	11 (44.0)*	3 (12.0)	13 (52.0)*	3 (12.5)	9 (45.0)*	2 (11.1)	8 (42.1)	3 (14.3)	12 (31.6)	7 (18.4)	14 (53.8)*	3 (12.5)	9 (30.0)	5 (19.2)	9 (45.0)*	3 (14.3)
Median PFS, months	4.3	2.8	6.5	2.6	5.4	2.8	6.1	3.5	3.3	2.4	6.5	2.6	3.5	2.3	6.3	3.5
HR (95% CI)	0.83 (0.46, 1.50)		0.30 (0.15, 0.57)		0.52 (0.26, 1.04)		0.36 (0.18, 0.73)		0.83 (0.51, 1.34)		0.29 (0.15, 0.55)		0.66 (0.38, 1.14)		0.35 (0.17, 0.70)	
Median OS, months	10.2	6.1	23.1	8.3	7.5	5.4	14.5	7.8	6.4	5.7	23.1	8.3	6.0	4.6	16.1	7.8
HR (95% CI)	0.90 (0.47, 1.75)		0.62 (0.30, 1.28)		0.76 (0.38, 1.55)		0.56 (0.26, 1.20)		0.97 (0.57, 1.62)		0.59 (0.28, 1.21)		0.85 (0.48, 1.50)		0.52 (0.24, 1.11)	

PIX, pixantrone; comp, comparator; ritux, rituximab. *pixantrone vs comparator: p < 0.05