Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial

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Summary

Background Pixantrone dimaleate (pixantrone)—a novel aza-anthracenedione—was synthesised to reduce anthracycline-related cardiotoxicity without compromising antitumour efficacy. We aimed to assess the efficacy and safety of pixantrone versus an investigator's choice of a single-agent therapy in heavily pretreated patients with relapsed or refractory aggressive non-Hodgkin lymphoma.

Methods In this phase 3, multicentre, open-label, randomised trial at 66 hospitals in Europe, India, Russia, South America, the UK, and the USA, patients with histologically confirmed aggressive non-Hodgkin lymphoma who had relapsed after two or more previous chemotherapy regimens were randomly assigned (1:1) by an interactive voice response system to treatment with pixantrone dimaleate (85 mg/m² intravenously on days 1, 8, and 15 of a 28-day cycle, for up to six cycles) or to a comparator (vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, or gemcitabine) given at prespecified standard doses and schedules. Patients were stratified by region, International Prognostic Index score, and previous stem-cell transplantation. Patients and investigators were not masked to treatment assignment; however, an independent assessment panel was masked. The primary endpoint was the proportion of patients with a complete or unconfirmed complete response in the intention-to-treat (ITT) population at the end of treatment. Primary analyses of efficacy were based on the independent assessment panel's data review. The study is registered at ClinicalTrials.gov, number NCT00088530.

Findings The ITT population comprised 70 patients randomly assigned to the pixantrone group and 70 to the comparator. Five patients (two in the pixantrone group and three in the comparator group) dropped out before receiving their study drug. 14 patients (20·0% [95% CI 11·4–31·3]) who received pixantrone achieved a complete or unconfirmed complete response at end of treatment compared with four patients (5·7% [1·6–14·0]) in the comparator group (p=0·021). The most common grade 3 or 4 adverse events in patients given pixantrone were uncomplicated, non-cumulative neutropenia (28 [41·2%] of 68 patients *vs* 13 [19·4%] of 67 patients in the comparator group), leucopenia (16 [23·5%] *vs* five [7·5%]), and thrombocytopenia (eight [11·8%] *vs* seven [10·4%]).

Interpretation Pixantrone, given as a single-agent salvage therapy in heavily pretreated patients with relapsed or refractory aggressive non-Hodgkin lymphoma, is efficacious and tolerable. It could be a treatment option for patients whose aggressive non-Hodgkin lymphoma has failed to respond to at least two previous chemotherapy regimens.

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Introduction

An anthracycline-containing regimen, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), is the cornerstone of first-line therapy for diffuse large B-cell lymphoma.[1] Anthracyclines, however, have limited use in salvage regimens because they cause cumulative, dose-related progressive myocardial damage, leading to an unacceptable incidence of congestive heart failure.[2] Patients with relapsed non-Hodgkin lymphoma typically receive intensive regimens such as R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), with stem-cell transplantation for those who respond to chemotherapy.[3] For patients who have an inadequate response to, or who are not candidates for, intensive salvage regimens, prognosis is poor, with expected survival of less than 1 year.[4] For these patients, no combination or single-agent therapy is regarded as the standard of care.

Pixantrone dimaleate (pixantrone) is a novel aza-anthracenedione that is structurally related to anthracyclines and anthracenediones. It was synthesised to reduce anthracycline-related cardiotoxicity,[5] which is associated with free-radical formation[6] linked to iron binding and reduction to cardiotoxic alcohols (eg, doxorubicinol), neither of which occur with pixantrone because of structural modifications.[7,8] Results of preclinical studies showed substantially less cardiotoxicity with

pixantrone than with doxorubicin or mitoxantrone, and pixantrone had enhanced efficacy in haematological neoplasia models.[9] A single-agent, phase 2 study in patients with multiply relapsed aggressive non-Hodgkin lymphoma[10] showed encouraging efficacy with an adequate safety profile that justified our decision to proceed to a phase 3 trial with an identical dose and schedule. The objective of this study was to assess the efficacy and safety of pixantrone when used as a single agent in patients who had received two or more previous regimens of chemotherapy for relapsed or refractory aggressive non-Hodgkin lymphoma, compared with an investigator's choice of an alternative single chemotherapeutic agent.

Methods

Study design and patients

The study was a phase 3, multicentre, open-label, randomised trial in patients aged 18 years or older with aggressive de novo or transformed non-Hodgkin lymphoma (according to the Revised European–American Lymphoma and WHO classification) who had relapsed after two or more previous regimens of chemotherapy, including at least one standard anthracycline-containing regimen with a response that had lasted at least 24 weeks. The trial was done at academic and community-based hospitals across Europe, India, Russia, South America, the UK, and the USA. Patients living in a country where rituximab was available were only eligible if they had received rituximab therapy (when their neoplastic cells expressed CD20). Patients with non-Hodgkin lymphoma that had relapsed after stem-cell transplantation were eligible. Other inclusion criteria included life expectancy of at least 3 months, Eastern Cooperative Oncology Group performance status of 2 or less, measurable disease, left ventricular ejection fraction (LVEF) of at least 50% (measured by a multiple-gated acquisition scan), no persistent toxicities from previous therapy, and adequate bone marrow and organ function. Patients were not eligible if they had received a cumulative dose of doxorubicin or equivalent of 450 mg/m², or if they were classified as having New York Heart Association grade 3 or 4 cardiovascular abnormalities. Patients with histological diagnosis of Burkitt's lymphoma, lymphoblastic lymphoma, or mantle-cell lymphoma, or with active CNS lymphoma or HIV-related lymphoma, did not enter the study.

All patients provided written informed consent before inclusion in the study. The protocol, amendments, and patient-informed consent documents were reviewed and approved by institutional review boards or ethics committees at participating study sites. The study was performed in compliance with good clinical practices and the principles of the Declaration of Helsinki.

Randomisation and masking

Patients were randomly assigned (1:1) to the pixantrone or comparator group by an interactive voice response system (IVRS). The randomisation schedule was created by the IVRS vendor. Stratified blocked randomisation was used with a block size of two within each of the 18 unique stratification combinations. Stratification factors were region (North America *vs* western Europe *vs* rest of world), International Prognosis Index score (0 or 1 *vs* ≥2), and previous stem-cell transplantation (yes *vs* no). The study was open label—ie, treatment assignments were known to the patients and investigators—but the independent assessment panel was masked to the treatment assignment and to the tumour response assessments made by the investigators (ie, the panel did not have access to the randomisation code or the investigators' assessment of efficacy). The sponsor, including authors of this Article who are employees of the sponsor, was masked to the treatment assignment until the end of treatment, when the database was locked for analysis. The success of masking was confirmed by external audit of the independent assessment panel.

Procedures

Pixantrone dimaleate was supplied in 50 mg vials (equivalent to 29 mg of pixantrone in its base form). Patients randomly assigned to the pixantrone group were given pixantrone dimaleate, intravenously infused over 1 h at a dose of 85 mg/m² (equivalent to 50 mg/m² of pixantrone in its base form) on days 1, 8, and 15 of a 28-day cycle, for up to six cycles. One reduction in dose was allowed for patients who had neutropenia during treatment. Patients randomly assigned to the comparator group received their physician's choice of a comparator agent at prespecified standard doses and schedules (table 1). Patients were followed up for 18 months after last treatment for disease progression and survival.

We monitored cardiac function by assessment of LVEF with echocardiography or a multiple-gated acquisition

	Dose	Days of cycle*	Length of cycle
Study drug			
Pixantrone dimaleate	85 mg/m²	1, 8, and 15	28 days
Comparator drugs†			
Vinorelbine[11]	30 mg/m²	1, 8, 15, and 22	4 weeks
Oxaliplatin[11]	100 mg/m²	1	3 weeks
Ifosfamide[11,12]	3000 mg/m²	1 and 2	4 weeks
Etoposide[11,12]	100 mg/m²	1, 2, 3, 4, and 5	4 weeks
Etoposide[11,12]‡	50 mg/m²	Daily for 21 days	4 weeks
Mitoxantrone[11,12]	14 mg/m²	1	3 weeks
Gemcitabine[11,13]	1250 mg/m²	1, 8, and 15	4 weeks
Rituximab[14]	375 mg/m²	1, 8, and 15 of cycle 1 and day 1 of cycle 2	3 weeks

*Days of cycle on which dose was given; up to a maximum of six cycles, except for rituximab (two cycles only). †Published studies of dose and responses were used to determine which comparator drugs to test. ‡Administered orally; all other regimens were administered intravenously.

Table 1: **Treatment regimens for study and comparator drugs**

scan. We reported serious adverse events from time of patient consent to 30 days after last study treatment. During the follow-up period, we reported only new adverse events that were thought to be related to the study drug.

The primary endpoint was the proportion of patients who achieved a complete response or an unconfirmed complete response in the intention-to-treat (ITT) population at end of treatment, and was assessed by an independent assessment panel of three experts (a radiologist, an oncologist, and a pathologist). At the request of the US Food and Drug Administration (FDA), the CT imaging of tumour response was also reviewed by an independent radiological review panel. Secondary endpoints included the proportion of people who achieved an overall response (complete, unconfirmed complete, and partial response), and length of progression-free and overall survival. We analysed the effect of previous rituximab therapy on the efficacy of pixantrone (for those patients for whom rituximab was commercially available). We also did subgroup analyses of complete response or unconfirmed complete response, overall response, progression-free survival, and overall survival for potentially important demographic and disease characteristics and for number of previous chemotherapy regimens.

The study was initiated in 2004, before the adoption of the 2007 International Working Group (IWG) response criteria for non-Hodgkin lymphoma; therefore, we based our assessment on the 1999 IWG criteria.[15] In 2007, the IWG criteria introduced the use of PET and removed the outcome of unconfirmed complete response. We made minor modifications to our study to provide clarification to the radiology reviewers, which was routine for lymphoma trials before 2007, because criteria for target and non-target nodal disease were not clearly defined in the 1999 IWG document. In our study, we needed target lesions to be 1·5 cm or larger in both perpendicular directions. The 1999 IWG criteria regarded lesions of 1·1–1·5 cm to be non-target lesions, as did we. To identify a new lesion as a sign of progressive disease, we needed the new lesion to be 1·5 cm or larger, whereas no clear minimum requirement was stated in the 1999 IWG criteria (although it inferred a size of 1·5 cm or larger). This minimum requirement is consistent with the 2007 IWG criteria.

Eligibility for the study in terms of histology was assessed at each site's pathology laboratory. In view of the unstable nature of these patients and their urgent need for therapy, coupled with the many geographical study sites, we did not regard an additional central histological review before study entry to be feasible. However, a retrospective review of histology took place at a central laboratory, where a consensus from two of three pathologists was needed to verify aggressive non-Hodgkin lymphoma.

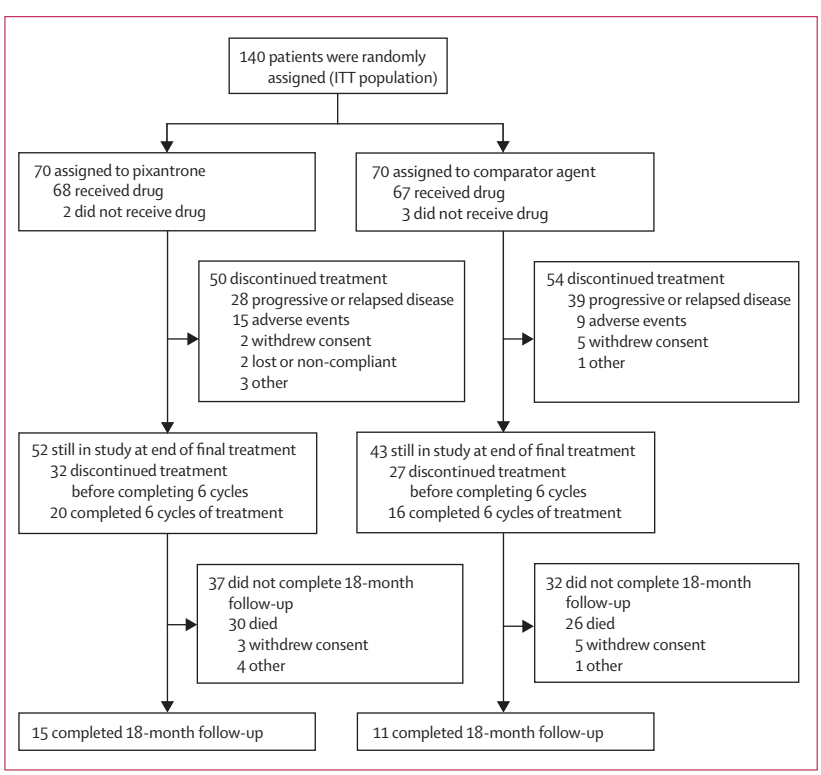

Figure 1: **Trial profile**

Statistical analysis

Our efficacy analyses were based on assessments, by the independent assessment panel, of the ITT population, which included all patients randomly assigned to either the pixantrone or comparator group. The safety analyses consist of data from patients who received any amount of protocol therapy. We used SAS version 9.2 for statistical analyses.

We analysed the primary outcome with Fisher's exact test, comparing the proportion of patients with a complete or unconfirmed complete response in the two treatment groups at end of treatment. Analysis took place when the last patient finished their last treatment visit. We also did an additional analysis at the end of the study when patients had finished 18-month follow-up. We also used Fisher's exact test to compare overall responses between groups. In the analysis of progression-free survival—ie, the time between randomisation and documentation of progressive or relapsed disease or death by any cause—patients starting follow-up therapy were thought to have progressed, irrespective of whether progression had been confirmed radiologically. We censored patients at their last tumour assessment. We assessed progression-free survival and overall survival with Kaplan-Meier methods and the unstratified log-rank test. We used a Cox proportional hazards model to assess the significance of subgroups for the efficacy variables and to establish the hazard ratio (HR) and 95% CI for each subgroup.

We also did secondary analyses of response and survival endpoints that included prespecified analyses of the histologically confirmed ITT population—ie, those whose lymphoma had been retrospectively assessed by independent, central histological review.

We designed the study to have at least 80% power to test the primary endpoint in the ITT population with a sample size in each group of 160, assuming complete and unconfirmed complete response rates of 15% for the pixantrone group and 5% for the comparator group. Despite expansion of the study to 189 sites in 24 countries, enrolment was slow. We decided in September, 2007, while the sponsor and the independent assessment panel were masked to the data, to close the study once 100 patients with confirmed pathology (by central review) had been randomly assigned. We did not change the statistical analysis methods after this point.

This study is registered at ClinicalTrials.gov, number NCT00088530.

Role of the funding source

The sponsor of the study contributed to the study design, analysis and interpretation of the data, and the writing of this report. All authors had full access to the raw data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

This phase 3, multicentre, open-label, randomised controlled trial took place at 66 sites in Europe, India, Russia, South America, the UK, and the USA. Between Oct 12, 2004, and March 17, 2008, 140 patients were randomly assigned to either the pixantrone group or the comparator group (ITT; n=70 in both groups; figure 1). 36 patients completed six cycles of protocol treatment and 104 patients discontinued early, five before the drug was given. 68 patients received pixantrone and 67 received a comparator agent. The last patient completed protocol-defined therapy on Aug 28, 2008. The data cutoff for the end of treatment analyses was Sept 30, 2008. The most common reason for early discontinuation in both groups was disease progression or relapse. 95 patients entered the follow-up period after completing study treatment and 26 completed 18 months of follow-up. The last follow-up assessment took place on Feb 16, 2010.

Demographic characteristics of patients at baseline were well balanced (table 2) except for cardiac history. Three patients in the pixantrone group had a history of congestive heart failure and two had continuing cardiomyopathy, compared with no patients with either disorder in the comparator group. Diffuse large B-cell lymphoma was the most common histological subtype (table 2). At baseline, 46 (66%) of 70 patients in the pixantrone group and 44 (63%) of 70 in the comparator group had an International Prognostic Index score of 2 or lower. Both groups received the same median number of previous chemotherapy regimens, and the median dose of doxorubicin

	Pixantrone (n=70)	Comparator (n=70)
Median age, years	60 (18–80)	58 (26–82)
>60 years	36 (51%)	31 (44%)
Sex		
Female	24 (34%)	30 (43%)
Male	46 (66%)	40 (57%)
ECOG grade 1 and 2	44 (63%)	46 (66%)
Median NHL duration, months	32·0 (7–160)	31·6 (0–333)
Baseline tumour assessment*		
Refractory†	40 (57%)	40 (57%)
Relapsed‡	28 (40%)	30 (43%)
Ann Arbor stage III–IV	51 (73%)	56 (80%)
International Prognostic Index score§		
0–1	21 (30%)	17 (24%)
2	25 (36%)	27 (39%)
≥3	24 (34%)	25 (36%)
≥1 extranodal sites	34 (49%)	33 (47%)
Subtypes (histologically confirmed on-site)		
DLBCL	53 (76%)	51 (73%)
Transformed indolent lymphoma	10 (14%)	9 (13%)
Peripheral T-cell lymphoma, NOC	3 (4%)	7 (10%)
Primary anaplastic large-cell lymphoma, null cell type	3 (4%)	1 (1%)
Follicular lymphoma, grade 3	1 (1%)	2 (3%)
Response to most recent chemotherapy		
CR/CRu	17 (24%)	18 (26%)
Partial response	19 (27%)	25 (36%)
Stable disease	9 (13%)	6 (9%)
Progressive disease	22 (31%)	21 (30%)
Median time from last chemotherapy to randomisation, months	9·0 (1–86)	8·0 (1–190)
Median number of previous chemotherapy regimens	3·0 (2·0–9·0)	3·0 (2·0–9·0)
Median previous doxorubicin dose equivalent	292·9 mg/m² (51–472)	315·5 mg/m² (15–681)
Previously received rituximab	38 (54%)	39 (56%)
Previously received stem-cell transplantation	11 (16%)	10 (14%)
Patients per regimen		
Pixantrone	68/68 (100%)	..
Vinorelbine	..	11/67 (16%)
Oxaliplatin	..	30/67 (45%)
Ifosfamide	..	12/67 (18%)
Etoposide (intravenous)	..	4/67 (6%)
Etoposide (oral)	..	5/67 (7%)
Mitoxantrone	..	4/67 (6%)
Gemcitabine	..	1/67 (1%)
Rituximab	..	0

Data are number (%) or median (range). ECOG=Eastern Cooperative Oncology Group. NHL=non-Hodgkin lymphoma. DLBCL=diffuse large B-cell lymphoma. NOC=not otherwise classified. CR/CRu=complete response or unconfirmed complete response. *Values from two patients in pixantrone group are missing. †Refractory patients are those with less than 8 months from the start of their most recent previous chemotherapy regimen to randomisation (irrespective of response) or those with stable or progressive disease since their most recent previous chemotherapy regimen. ‡Relapsed patients were defined as those for whom 8 months or longer had passed from the start of their most recent previous chemotherapy regimen to randomisation with a complete or partial response. §Data missing for one patient in the comparator group.

Table 2: **Baseline demographics and response to previous therapy in intention-to-treat population and number of patients who received each regimen**

	End of treatment			End of study*		
	Pixantrone (n=70)	Comparator (n=70)	p value	Pixantrone (n=70)	Comparator (n=70)	p value
Complete/unconfirmed complete response	14 (20·0%, 11·4–31·3)	4 (5·7%, 1·6–14·0)	0·021	17 (24·3%, 14·8–36·0)	5 (7·1%, 2·4–15·9)	0·009
Complete response	8 (11·4%, 5·1–21·3)	0 (0%, 0·0–5·1)	0·006	11 (15·7%, 8·1–26·4)	0 (0%, 0·0–5·1)	0·001
Unconfirmed complete response	6 (8·6%, 3·2–17·7)	4 (5·7%,1·6–14·0)	0·075	6 (8·6%, 3·2–17·7)	5 (7·1%, 2·4–15·9)	1·000
Overall response rate†	26 (37·1%, 25·9–49·5)	10 (14·3%, 7·1–24·7)	0·003	28 (40·0%, 28·5–52·4)	10 (14·3%, 7·1–24·7)	0·001

Data are n (%, 95% CI) unless specified otherwise. Efficacy was determined by an independent assessment panel. *Analyses of treatment and 18-month follow-up. †Responses included patients with complete, unconfirmed complete, or partial responses.

Table 3: **Summary of efficacy in the intention-to-treat population**

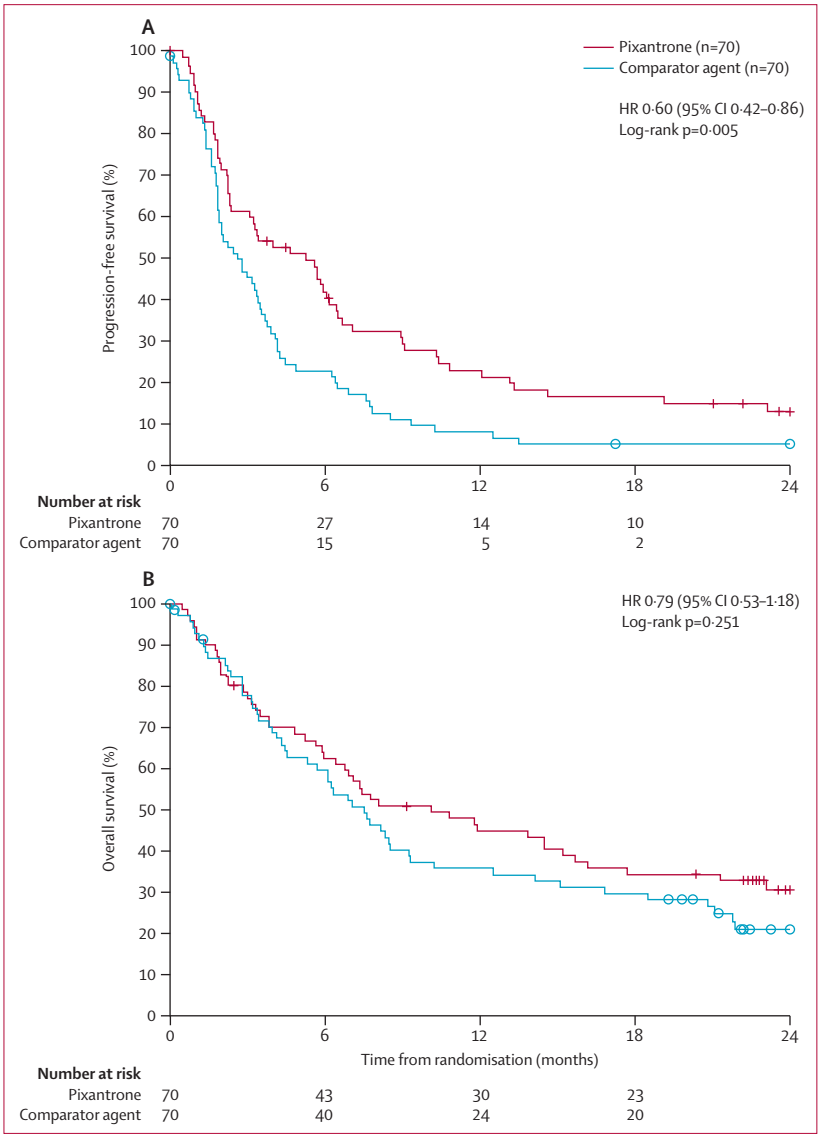

Figure 2: **Kaplan-Meier curves for progression-free survival and overall survival in the intention-to-treat population at end of study**

(A) Progression-free survival and (B) overall survival. 58 patients (82·3%) who received pixantrone had progressive disease (33 patients), died (13 patients), or received additional treatment for non-Hodgkin lymphoma (12 patients) during follow-up *vs* 64 (91·4%) of those in the comparator group (40 had progressive disease, 14 died, and 10 received additional treatment during follow-up).

dose-equivalent exposure was slightly lower in the pixantrone group than in the comparator group (table 2). A similar number of patients in each group had previously received rutuximab, and the same number of patients in each group were refractory to their previous therapy (table 2).

Aggressive histological features were identified on site in all patients before treatment was given, and the central independent pathological review histologically confirmed aggressive non-Hodgkin lymphoma in 54 (77%) of 70 patients in the pixantrone group and 50 (71%) of 70 patients in the comparator group, retrospectively. Of the remaining 36 patients, reference pathologists did not achieve consensus for ten patients, but agreed that 13 had low-grade histological features and five had a non-aggressive subtype other than non-Hodgkin lymphoma. Two patients were reviewed by only one pathologist, and six did not have a review because of shortage of specimen.

Significantly more patients in the ITT population who received pixantrone had a complete or unconfirmed complete response at end of treatment compared with those given a comparator drug (table 3). Three patients in the pixantrone group, two with stable disease at end of treatment, and one patient in the comparator group with a partial response at end of treatment, achieved a complete or unconfirmed complete response during the follow-up period without additional treatment. Median duration of complete or unconfirmed complete response in patients given pixantrone was 9·6 months (95% CI 4·0–20·8) compared with 4·0 months (1·0–5·1) for patients in the comparator group (HR 0·32 [95% CI 0·09–1·23]; log-rank p=0·081). At the end of the study, three of the 17 patients who received pixantrone who had a complete or unconfirmed complete response at end of treatment had been in continuous remission for more than 1 year (range of 448–679 days) without additional non-Hodgkin lymphoma therapy, whereas the maximum duration of response in the comparator group was 154 days for one patient with an unconfirmed complete response at end of treatment. Significantly more overall responses were noted for patients in the pixantrone group than in the comparator group at end of treatment (table 3). Median progression-free survival in the ITT population was significantly longer for patients in the pixantrone group

compared with survival in those in the comparator group (5·3 months [95% CI 2·3–6·2] *vs* 2·6 months [1·9–3·5]; HR 0·60 [95% CI 0·42–0·86]; log-rank p=0·005; figure 2). Patients in the pixantrone group had longer median overall survival than those in the comparator group, but not significantly so (10·2 months [95% CI 6·4–15·7] *vs* 7·6 months [5·4–9·3]; HR 0·79 [95% CI 0·53–1·18]; log-rank p=0·251; figure 2).

Twice as many patients in the pixantrone group (12 patients [17·1%]) as in the comparator (six patients [8·6%]) had an overall response lasting at least 4 months (from first documented response until disease progression, follow-up treatment, or death), a measurement of both frequency and durability of response. Time to initial overall response was similar, with a median of 1·9 months for both groups (95% CI 1·8–2·3 for pixantrone *vs* 1·6–2·3 for comparator; HR 0·68 [95% CI 0·32–1·43]; p=0·304), including 28 patients in the pixantrone group and ten in the comparator. 17 patients in the pixantrone group and five in the comparator had complete or unconfirmed complete responses at the end of the study, and the median time to complete response was 2·0 months (95% CI 1·7–3·7) for the pixantrone group and 3·6 months (2·3–19·0) for the comparator (HR 1·92 [95% CI 0·64–5·77]; p=0·237).

The proportion of patients with a complete or unconfirmed complete response, or an overall response, in the histologically confirmed ITT population at the end of study was higher for patients in the pixantrone group than for those in the comparator group (table 4), and progression-free survival was significantly longer in the pixantrone group (table 4). Overall survival was longer in the pixantrone group than in the comparator group, but not significantly so.

64 (91·4%) of 70 patients in the pixantrone group and 62 (88·6%) of 70 in the comparator group had aggressive B-cell lymphoma (diffuse large B-cell lymphoma, transformed indolent lymphoma, or follicular lymphoma, grade 3; table 2). In post-hoc analyses, the proportion of these patients with a complete or unconfirmed complete response was significantly higher for those who received pixantrone than for those given a comparator agent (table 4). The proportion of patients with aggressive B-cell lymphoma who achieved an overall response was higher in the pixantrone group than in the comparator group and median progression-free survival was significantly longer in the pixantrone group (table 4). In all histological subtypes, median overall survival in the pixantrone group was longer than in the comparator group, although the difference was not significant (10·2 months [95% CI 6·4–15·7] *vs* 7·6 months [5·4–9·3]; HR 0·79 [95% CI 0·53–1·18]; log-rank p=0·251).

38 (54·3%) of 70 patients in the pixantrone group and 39 (55·7%) of 70 patients in the comparator group received rituximab before study entry. Table 5 summarises the post-hoc analysis of the response rates and length of

	Histologically confirmed ITT population				Aggressive B-cell lymphoma*			
	Pixantrone (n=54)	Comparator (n=50)	p value	HR (95% CI)	Pixantrone (n=64)	Comparator (n=62)	p value	HR (95% CI)
Complete/unconfirmed complete response	10 (18·5%, 9·3–31·4)	4 (8·0%, 2·2–19·2)	0·154	..	15 (23·4%, 13·8–35·7)	5 (8·1%, 2·7–17·8)	0·027	..
Overall response†	19 (35·2%, 22·7–49·4)	8 (16·0%, 7·2–29·1)	0·043	..	26 (40·6%, 28·5–53·6)	10 (16·1%, 8·0–27·7)	0·003	..
Median progression-free survival, months‡	5·0 (2·3–6·1)	2·6 (1·9–3·4)	0·003§	0·54 (0·36–0·82)	5·7 (2·4–6·5)	2·5 (1·9–3·5)	0·002§	0·56 (0·38–0·81)
Median overall survival, months‡¶	7·5 (5·7–14·5)	6·2 (4·1–8·2)	0·166§	0·74 (0·48–1·14)	..	..	..	..

Data are n (%, 95% CI) or median (95% CI) unless specified otherwise. Efficacy was determined by an independent assessment panel after 18-month follow-up. ITT=intention-to-treat. HR=hazard ratio. *Patients with diffuse large B-cell lymphoma, transformed indolent lymphoma, and follicular lymphoma, grade 3, determined by on-site pathology. †Responses included patients with complete, unconfirmed complete, or partial response. ‡Kaplan-Meier analysis. §Log-rank p value. ¶Aggressive B-cell lymphoma analyses were exploratory and did not include median overall survival.

Table 4: **Summary of efficacy in the histologically confirmed intention-to-treat population and in patients with aggressive B-cell lymphoma**

	Previous rituximab						No previous rituximab					
	Pixantrone (N=38) by number of previous chemotherapy regimens			Comparator (N=39) by number of previous chemotherapy regimens			Pixantrone (N=32) by number of previous chemotherapy regimens			Comparator (N=31) by number of previous chemotherapy regimens		
	2 (n=10)	3 (n=15)	≥4 (n=13)	2 (n=9)	3 (n=16)	≥4 (n=14)	2 (n=22)	3 (n=9)	≥4 (n=1)	2 (n=15)	3 (n=16)	≥4 (n=0)
Complete/unconfirmed complete response	3 (30·0%)	3 (20·0%)	1 (7·7%)	0 (0·0%)	1 (6·3%)	3 (21·4%)	8 (36·4%)	2 (22·2%)	0 (0·0%)	1 (6·7%)	0 (0·0%)	..
Overall response rate	5 (50·0%)	6 (40·0%)	1 (7·7%)	0 (0·0%)	3 (18·8%)	4 (28·6%)	11 (50·0%)	4 (44·4%)	1 (100·0%)	2 (13·3%)	1 (6·3%)	..
Median progression-free survival, months*	5·7 (1·1–14·6)	3·3 (1·1–6·7)	..	2·8 (0·7–4·3)	2·8 (1·4–7·8)	..	5·7 (2·0–9·0)	6·5 (1·9–NA)	..	1·9 (0·8–4·9)	3·4 (1·3–4·1)	..

Data are number (%) or median (95% CI). Analysis done at the end of the study. Rituximab therapy is included in the number of previous chemotherapy regimens (for those patients who had previously received rituximab). *No analysis for four or more previous chemotherapy regimens because of an insufficient number of patients in the group that had not received rituximab previously. Hazard ratio between pixantrone group and comparator group for patients who had previously received: two chemotherapy regimens (at least one including rituximab), HR 0·28 (95% CI 0·08–0·94); three chemotherapy regimens (at least one including rituximab), HR 1·44 (0·66–3·15); two chemotherapy regimens (but no rituximab), HR 0·49 (0·24–0·99); three chemotherapy regimens (but no rituximab), HR 0·29 (0·10–0·82).

Table 5: **Effect of previous rituximab therapy and number of previous chemotherapy regimens on efficacy of pixantrone and comparator agents**

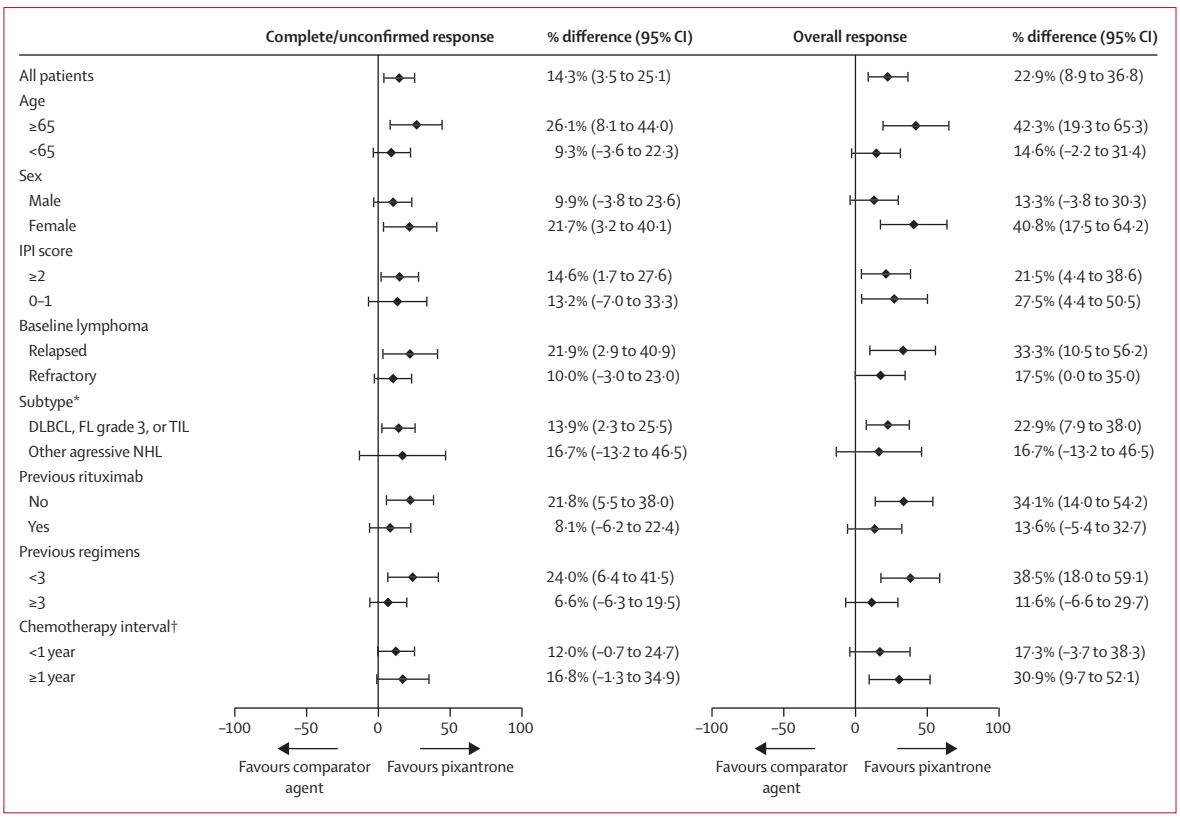

Figure 3: **Subgroup analyses of response in the intention-to-treat population**
IPI=International Prognostic Index. DLBCL=diffuse large B-cell lymphoma. FL grade 3=follicular lymphoma, grade 3. TIL=transformed indolent lymphoma. NHL=non-Hodgkin lymphoma. *Confirmed histologically. †Time between first and second previous chemotherapy regimens.

survival of patients with or without previous rituximab therapy and by number of previous chemotherapy regimens. Response rates were consistent for patients in the pixantrone group, and appeared to be more affected by number of previous chemotherapy regimens than by whether the patient had previously received rituximab.

Additional subgroup analyses showed that overall, the effect of pixantrone on the proportion of patients who achieved a complete or unconfirmed complete response or an overall response (figure 3), and on the length of progression-free survival and overall survival (figure 4), was consistent across subgroups.

The median number of drug cycles received was four (range of two to six) in the pixantrone group and three (range of two to six) in the comparator group. More patients began a sixth cycle of study treatment in the pixantrone group (22 of 68 [32·4%]) than in the comparator (19 of 67 [28·4%]). Median dose intensity for the pixantrone group was 55 mg/m² per week (range 24–64) with a median relative dose intensity of 90·6% (range 20–102). Median relative dose intensity was greater than 93% for all patients in the comparator group, except for those who received vinorelbine. Because the pixantrone treatment cycle was 28 days, compared with 21 or 28 days for comparator regimens, median duration of therapy (time from randomisation to last treatment visit) was longer for patients in the pixantrone group (3·8 months [range 0·5–8·1] *vs* 2·6 months [0·0–6·1]). Additionally, blood count monitoring was more frequent in the pixantrone group, with all patients scheduled to receive weekly complete blood counts (on days 1, 8, and 15 of the 28 day cycle) compared with only once per cycle for 29 (43·3%) of 67 patients in the comparator group. More patients in the pixantrone group than in the comparator group had repeat LVEF assessments because they had a longer duration of therapy.

The most common adverse events (seen in ≥10% of patients) and grade 3 or 4 events reported in the two groups are summarised in table 6. Irrespective of the relation to treatment, similar proportions of patients had adverse events in the pixantrone (66 of 68 [97·1%]) and comparator (61 of 67 [91·0%]) groups, whereas more patients had a grade 3 or 4 event in the pixantrone group than in the comparator group (52 of 68 [76·5%] *vs* 35 of 67 [52·2%]), with neutropenia as the predominant event. More patients in the pixantrone group than in the comparator group reported treatment-related adverse events (55 of 68 [80·9%] *vs* 38 of 67 [56·7%]), consistent with the higher incidence of neutropenia, and possibly related to more frequent blood counts.

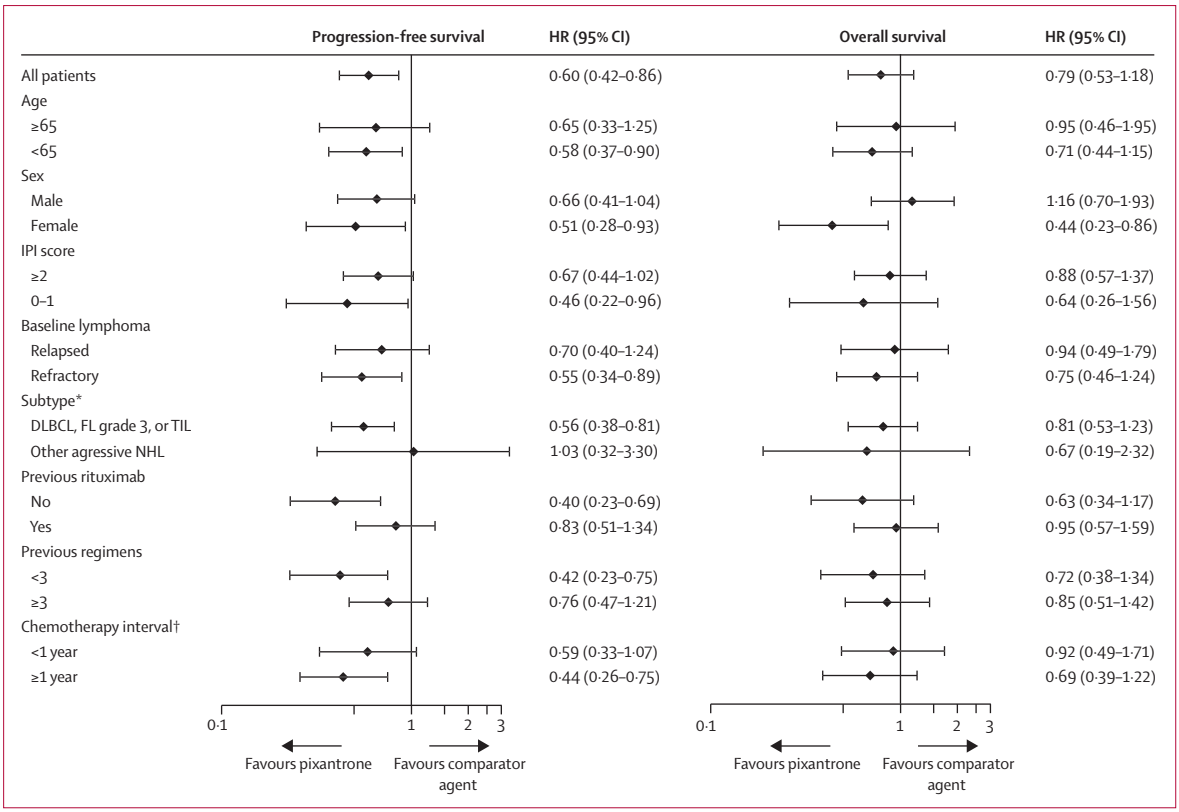

Figure 4: **Subgroup analyses of progression-free and overall survival in the intention-to-treat population**
HR=hazard ratio. IPI=International Prognostic Index. DLBCL=diffuse large B-cell lymphoma. FL grade 3=follicular lymphoma, grade 3. TIL=transformed indolent lymphoma. NHL=non-Hodgkin lymphoma. *Confirmed histologically. †Time between first and second prior chemotherapy regimens.

Patients in the pixantrone group had higher rates of the common adverse events neutropenia, leucopenia, cough, and skin discolouration, whereas patients in the comparator group had higher rates of diarrhoea and renal failure. The severity of neutropenia did not increase with increasing cycle number. In the pixantrone group, the highest incidence of grade 4 neutropenia occurred in cycle 2 (eight of 54 [14·8%]). More patients who received pixantrone were given an immunostimulant than were those who received a comparator agent (35 of 68 [51·5%] *vs* 18 of 67 [26·9%]); however, a substantial proportion of patients who were given an immunostimulant received only one dose of it. Febrile neutropenia occurred in more patients given pixantrone than in those given a comparator agent; however, more patients in the comparator group had grade 3 or 4 pyrexia (table 6). The overall rates of grade 3 and 4 infections were similar between the study groups. Serious adverse events were reported in 35 (51·5%) of 68 patients in the pixantrone group and 30 (44·8%) of 67 in the comparator group. Malignant neoplasm progression was reported as a serious adverse event more frequently in the comparator group. Overall for both groups, the most common serious adverse events (in ≥5% of patients) were neutropenia (nine [13·2%] of 68 patients in the pixantrone group *vs* six [9·0%] of 67 patients in the comparator group), pyrexia (seven [10·3%] *vs* seven [10·4%]), malignant neoplasm progression (one [1·5%] *vs* nine [13·4%]), pneumonia (five [7·4%] *vs* four [6·0%]), anaemia (two [2·9%] *vs* five [7·5%]), and thrombocytopenia (one [1·5%] *vs* six [9·0%]).

More cardiac adverse events occurred in the pixantrone treatment group (24 of 68 [35·3%]) than in the comparator (14 of 67 [20·9%]). Most were asymptomatic decreases in LVEF (table 6). One patient's LVEF in the pixantrone group reversibly reduced to less than 40%. We saw no evidence of cumulative, dose-related declines in LVEF with pixantrone: the median change in LVEF values from baseline to end of treatment was –4% (ranging from –25 to 21) in the pixantrone group and 0% (–13 to 10) in the comparator group. The change in LVEF values in patients who received pixantrone was not associated with clinical evidence of cardiac impairment.

Ten (14·7%) of 68 patients in the pixantrone group and 12 (17·9%) of 67 in the comparator died within 30 days of receiving their last dose of treatment. The deaths of five patients in the pixantrone group and 11 in the comparator group were thought to be caused by progressive disease; the remaining deaths were due to a range of other causes, but nearly all were from uncontrolled lymphoma.

	Common any-grade AE		Grade 3 or 4 AE	
	Pixantrone (n=68)	Comparator agent (n=67)	Pixantrone (n=68)	Comparator agent (n=67)
Blood and lymphatic system disorders				
Anaemia	21 (30·9%)	22 (32·8%)	4 (5·9%)	9 (13·4%)
Febrile neutropenia	6 (8·8%)	2 (3·0%)	5 (7·4%)	2 (3·0%)
Leucopenia	17 (25·0%)	7 (10·4%)	16 (23·5%)	5 (7·5%)
Lymphopenia	3 (4·4%)	0 (0%)	2 (2·9%)	0 (0%)
Neutropenia	34 (50·0%)	16 (23·9%)	28 (41·2%)	13 (19·4%)
Thrombocytopenia	14 (20·6%)	13 (19·4%)	8 (11·8%)	7 (10·4%)
Gastrointestinal disorders				
Abdominal pain	11 (16·2%)	7 (10·4%)	5 (7·4%)	3 (4·5%)
Constipation	8 (11·8%)	3 (4·5%)	0 (0%)	0 (0%)
Diarrhoea	3 (4·4%)	12 (17·9%)	0 (0%)	0 (0%)
Nausea	12 (17·6%)	11 (16·4%)	0 (0%)	1 (1·5%)
Vomiting	5 (7·4%)	10 (14·9%)	0 (0%)	2 (3·0%)
General and administration-site disorders				
Asthenia	16 (23·5%)	9 (13·4%)	3 (4·4%)	3 (4·5%)
Fatigue	9 (13·2%)	9 (13·4%)	2 (2·9%)	0 (0%)
Mucosal inflammation	8 (11·8%)	2 (3·0%)	0 (0%)	1 (1·5%)
Pain	2 (2·9%)	3 (4·5%)	1 (1·5%)	2 (3·0%)
Peripheral oedema	10 (14·7%)	4 (6·0%)	0 (0%)	0 (0%)
Pyrexia	16 (23·5%)	16 (23·9%)	3 (4·4%)	6 (9·0%)
Infections and infestations				
Pneumonia	5 (7·4%)	4 (6·0%)	4 (5·9%)	3 (4·5%)
Cellulitis	4 (5·9%)	2 (3·0%)	2 (2·9%)	2 (3·0%)
Investigations				
Ejection fraction decreased	13 (19·1%)	7 (10·4%)	2 (2·9%)	0 (0%)
Neutrophil count decreased	3 (4·4%)	0 (0%)	3 (4·4%)	0 (0%)
Platelet count decreased	4 (5·9%)	2 (3·0%)	2 (2·9%)	2 (3·0%)
Weight decreased	5 (7·4%)	5 (7·5%)	1 (1·5%)	2 (3·0%)
Metabolism and nutrition disorders				
Anorexia	8 (11·8%)	4 (6·0%)	2 (2·9%)	1 (1·5%)
Dehydration	5 (7·4%)	2 (3·0%)	3 (4·4%)	0 (0%)
Hypokalaemia	3 (4·4%)	1 (1·5%)	2 (2·9%)	1 (1·5%)
Hyponatraemia	2 (2·9%)	3 (4·5%)	1 (1·5%)	2 (3·0%)
Metabolic acidosis	2 (2·9%)	0 (0%)	2 (2·9%)	0 (0%)
Neoplasms (benign, malignant, and unspecified)				
Malignant neoplasm progression	1 (1·5%)	9 (13·4%)	0 (0%)	1 (1·5%)
Psychiatric disorders				
Depression	2 (2·9%)	3 (4·5%)	2 (2·9%)	1 (1·5%)
Renal and urinary disorders				
Renal failure	0 (0%)	5 (7·5%)	0 (0%)	3 (4·5%)
Respiratory, thoracic, and mediastinal disorders				
Cough	15 (22·1%)	3 (4·5%)	0 (0%)	0 (0%)
Dyspnoea	9 (13·2%)	9 (13·4%)	4 (5·9%)	3 (4·5%)
Skin and subcutaneous tissue disorders				
Alopecia	9 (13·2%)	3 (4·5%)	0 (0%)	0 (0%)
Skin discolouration	7 (10·3%)	0 (0%)	0 (0%)	0 (0%)
Vascular disorders				
Hypotension	5 (7·4%)	3 (4·5%)	2 (2·9%)	1 (1·5%)

Data presented for any-grade events reported in 10% or more of patients in either group or that occurred at grade 3 or 4 in more than 2% of patients in either group. AE=adverse event.

Table 6: **Summary of adverse events**

Discussion

More patients who received pixantrone achieved a complete or unconfirmed complete response or an overall response at the end of treatment than did those who received a comparator drug, and had longer progression-free survival at the end of the study. These primary efficacy findings were confirmed by a second independent radiological review requested by the FDA (data not shown). Although the central histological review was retrospective, analysis of those patients with histologically confirmed aggressive non-Hodgkin lymphoma was consistent with the overall study results. The proportion of patients with a complete or unconfirmed complete response in the comparator group was consistent with data published in reports of existing salvage therapies.[16–20]

When we designed this study, rituximab was not available in all regions. As the study progressed, rituximab became the standard of care for aggressive non-Hodgkin lymphoma; therefore, we amended the study protocol so that patients had to have received rituximab before randomisation, if it was commercially available in their region. In post-hoc analyses, pixantrone was more effective than were comparator agents in patients who received previous rituximab and as many as three other previous treatment regimens. As with other trials in patients with relapsed disease,[3] previous therapy with rituximab was associated with diminished response rates, particularly in patients who had received three or more previous regimens.

Results from this study were internally consistent across additional subgroup analyses. Particularly noteworthy was the potential benefit of pixantrone for older patients (≥65 years), women, and patients with fewer than three previous regimens. In subgroup analyses of response by region, a higher proportion of patients in western Europe and North America had undergone four or more previous chemotherapy regimens than had those from the rest of the world (19 of 46 [41·3%] *vs* nine of 94 [9·7%]), which confounded interpretation of response by region.

Toxicities were readily manageable in both study groups. Although the longer duration of therapy with pixantrone led to a longer time at risk for on-study adverse events, the proportions of patients with adverse events were similar between the two groups and the type of events reported were consistent with what is expected in heavily pretreated patients receiving a cytotoxic agent. Neutropenia was the most common event in the pixantrone group, febrile neutropenia of all intensities was low in both groups, and myelosuppression did not increase with increasing cycle number in both groups.

Because no standard single-agent salvage therapy exists for patients with aggressive non-Hodgkin lymphoma, we relied on published reports and the advice of clinical experts to establish the doses and treatment schedules for the agents tested in the

comparator group. Of all the agents in this group, we only needed to substantially adjust and delay the dose of one (vinorelbine) during the study. The greater incidence of cytopenia in the pixantrone group may have been a result of more frequent assessment, since patients in the pixantrone group had weekly blood count monitoring, compared with a less frequent schedule for many patients in the comparator group.

In 2008, Wiernik and colleagues' study[17] on lenalidomide as a monotherapy in relapsed or refractory aggressive non-Hodgkin lymphoma was published. However, when we began our study in 2004, lenalidomide was not available and could not be included as an agent in the comparator group. The response rates for the comparator group in our study were lower than the rate reported by Wiernik and colleagues[17] for single-agent lenalidomide tested in a similar population (overall response rate was 35%). When we look at the lenalidomide study's analysis of only the patients who met the same histological eligibility criteria used in our study (ie, diffuse large B-cell lymphoma; follicular lymphoma, grade 3; and transformed indolent lymphoma), 26·5% of patients achieved an overall response, 11·8% achieved a complete or unconfirmed complete response, with only one patient (2·9%) reported as having a complete response. Of the 26 patients with diffuse large B-cell lymphoma, 19·2% had an overall response and 11·5% achieved a complete or unconfirmed complete response. The proportions of patients with an overall response, complete or unconfirmed complete response, and complete response in our pixantrone group were higher than or similar to those reported in patients given lenalidomide monotherapy. These initial results by Wiernik and colleagues were supported by a larger study that also tested single-agent lenalidomide in a similar patient population.[20]

Unlike anthracyclines, pixantrone is less likely to generate reactive oxygen species because of its inability to bind iron or form longlasting alcohol metabolites.[7,8] These characteristics should reduce cardiac toxicity when compared with commonly used anthracyclines, and our analysis of cardiac adverse events supports this premise. Although the frequency of cardiac adverse events was higher in the pixantrone group than in the comparator group, the cardiac events did not increase with increasing pixantrone exposure, and were predominantly asymptomatic grade 1 and 2 declines in LVEF. Additionally, the higher frequency of cardiac adverse events in the pixantrone group might have been because five patients in this group (compared with none in the comparator group) had histories of congestive heart failure or cardiomyopathy at the time of study enrolment.

Because of slow enrolment, recruitment was terminated before we achieved the intended number of participants, and was thus underpowered according to the original sample size assumptions. The study was originally powered to detect a difference of 10% in the proportion of patients who achieved a complete or unconfirmed complete response. According to the original sample size assumptions, a sample size of 70 in each group would have about 40% power. To achieve 81% power with 70 patients per group, the true proportion of patients with a complete or unconfirmed complete response would have to have been 22% in the pixantrone group and 5% in the comparator group.

The limitations of this study are its small number of patients and the potential confounding effect that a small population size has on the extrapolation of results to patients with previous stem-cell transplantation and those who have received rituximab (a now standard component of first-line therapy). Additional trials are needed to provide definitive evidence for the efficacy of pixantrone in these patients.

Results from our study show that when pixantrone is given as a single-agent salvage therapy to patients with relapsed or refractory aggressive non-Hodgkin lymphoma, patients can achieve a better response than if given a comparator agent, with manageable toxicities (panel). Additional studies with pixantrone are warranted to establish it as a standard salvage therapy for patients with relapsed or refractory aggressive non-Hodgkin lymphoma. Future research with pixantrone includes a phase 3, multicentre study to assess the efficacy of

***Panel:* Research in context**

Systematic review

In 2004, we searched PubMed for all studies, written in English, of relapsed or refractory diffuse large B-cell lymphoma and aggressive non-Hodgkin lymphoma, with the search terms "NHL", "DLBCL", "relapse DLBCL", "refractory DLBCL", "vinorelbine and DLBCL", "oxaliplatin and DLBCL", "ifosfamide and DLBCL", "etoposide and DLBCL", "mitoxantrone and DLBCL", "gemcitabine and DLBCL", and "rituximab and DLBCL". We also searched ClinialTrials.gov for continuing studies in the same specialty. Results from in-vitro and in-vivo preclinical studies with pixantrone led to early clinical studies of pixantrone as a single agent or in combination therapies in patients with non-Hodgkin lymphoma or other malignancies.[21] On the basis of the results from these studies, in which pixantrone showed a high level of activity and an acceptable level of clinical toxicity, we designed and did the first phase 3 study to compare the efficacy and safety of pixantrone with investigator's choice of a single-agent chemotherapeutic in patients with relapsed or refractory aggressive non-Hodgkin lymphoma.

Interpretation

A significantly higher proportion of patients with relapsed or refractory non-Hodgkin lymphoma who received single-agent pixantrone achieved a complete or unconfirmed complete response or overall response than did those who received an investigator's choice of a single-agent comparator drug. This improvement in response translated to a prolongation of progression-free survival. Because no combination or single-agent therapy is considered the standard of care for patients with relapsed or refractory non-Hodgkin lymphoma, and palliative care or clinical trials are often the only remaining treatment options, an effective salvage therapy is needed for these patients. The results from our study suggest that pixantrone is an effective single-agent treatment for patients with aggressive non-Hodgkin lymphoma and that it could fill the need for a standard salvage therapy that leads to improved outcomes with manageable toxicities.

pixantrone plus rituximab compared with gemcitabine plus rituximab on overall survival of patients with relapsed or refractory diffuse large B-cell lymphoma or diffuse large B-cell lymphoma transformed from follicular lymphoma (NCT01321541). Eligible patients will have received one to three previous lines of therapy (including R-CHOP or equivalent) for aggressive non-Hodgkin lymphoma but no high-dose (myeloablative) chemotherapy or stem-cell transplantation.

Contributors

RP, BC, and JWS were responsible for the design of the study. IG, the study monitor, oversaw the conduct of the study. GN, FHdM, RD, HG, PLZ, GS, and DR recruited patients and obtained study data. PC and LW collected and assembled data for statistical analyses. RP, BC, GS, DR, GB, PC, LW, CK, IG, and JWS analysed and interpreted the data. RP, PC, CK, and JS wrote the manuscript. CK is a medical writing consultant. All authors reviewed and approved the final manuscript.

Conflicts of interest

PC, LW, IG, and JWS are employees of Cell Therapeutics, Inc. BC, RD, DR, GB, and CK have had a consulting role with the company. PC, LW, CK, IG, and JWS own stock in Cell Therapeutics. Cell Therapeutics has provided RP with an honorarium, RD with travel funding, and GS with research funding. All other authors declare that they have no conflicts of interest.

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