Pixantrone for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma

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**Practice Points**

- Pixantrone is a novel aza-anthracenedione developed to address the need for effective, well-tolerated therapies in patients with multiply relapsed or refractory aggressive B-cell non-Hodgkin lymphoma.
- Promising efficacy and manageable toxicity has been demonstrated in Phase II and III clinical trials as a single agent and in combination.
- Neutropenia is the most commonly reported toxicity; significant clinical consequence is rare.
- In keeping with preclinical data and in contrast to anthracyclines and anthracenediones, cumulative cardiotoxicity is rarely seen; however, this requires evaluation within further prospective clinical trials.
- Pixantrone is currently approved for use as monotherapy in patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma in the EU; combination studies are ongoing.

**SUMMARY**

There is a clear need for efficacious, well-tolerated therapies in patients with multiply relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Pixantrone is a novel aza-anthracenedione manufactured by Cell Therapeutics Incorporated. Structurally related to anthracyclines and anthracenediones but engineered to minimize cardiotoxicity whilst maintaining efficacy, pixantrone has shown promise in Phase II and III clinical trials as a single agent and in combination. While further prospective studies are required to establish pixantrone as a standard salvage therapy, it has already received approval in the EU as monotherapy for adult patients with multiply relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Here we review the pharmacology, preclinical and clinical development of this novel agent and consider potential future utility.

Aggressive B-cell non-Hodgkin lymphoma (B-NHL) accounts for approximately one half of all cases of NHL in North America and western Europe [1]. Anthracycline-based combination regimens remain the cornerstone of first-line therapy [2]. Whilst highly efficacious, anthracyclines and anthracenediones are associated with irreversible, cumulative cardiotoxicity and have limited application in the salvage setting [3]. Patients with relapsed, aggressive B-NHL typically receive an intensive platinum-based second-line therapy such as R-ICE (rituximab, ifosfamide, cisplatin and etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin). Those who respond and remain fit proceed to autologous stem cell transplantation [4]. The outlook for nonresponders or individuals unfit for...
an intensive salvage regimen is poor with an expected survival of less than 1 year [5]. The outlook is similarly poor for those who relapse following high-dose therapy and autologous stem cell transplantation. In this setting there remains no approved combination or single-agent therapeutic regimen as standard of care. Progression is largely treated with palliative intent with single or experimental agents within a clinical trial setting [4,5].

Nearly one half of all patients with aggressive NHL ultimately die of recurrent disease with 50–60% becoming candidates for palliative systemic therapy during their disease course [1]. This population are often elderly with significant comorbidity and, whether secondary to previous cytotoxic therapy or the disease process itself, may have limited bone marrow reserve [6]. The identification of efficacious regimens with limited toxicity in the salvage setting is therefore imperative. The development of pixantrone aims to address this, demonstrating promise in both Phase II and III randomized trials [7–10]. Specifically, the compound was designed to minimize cardiac toxicity without compromising efficacy. Although yet to receive US FDA approval, pixantrone has been approved in the EU for treatment of adult patients with multiply relapsed or refractory aggressive B-NHL.

Indications & usage
Pixantrone is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive B-NHL.

Dosage & administration
The recommended dosage is 50 mg/m² of pixantrone base, intravenously on days 1, 8 and 15 of a 28-day cycle for up to six cycles. Dosage should be adjusted prior to each cycle according to nadir hematologic counts or maximum toxicity following the previous cycle. Dosage is based on body surface area, caution is therefore advised in obese patients and weight should be measured prior to day 1 of each cycle. Clinical trial experience is based on pixantrone dimaleate 85 mg/m², equivalent to 50 mg/m² of pixantrone base. Pixantrone is administered intravenously following reconstitution with 5 ml of sodium chloride 9 mg/ml (0.9%) and further dilution with sodium chloride 9 mg/ml (0.9%) to a final volume of 250 ml. Administration is as a slow intravenous infusion using an in-line filter over a minimum of 60 min [10,11].

Clinical pharmacology

■ Pharmacodynamics: mechanism of action
Pixantrone base (6,9-bis[(2-aminoethyl)amino]benzo[g]isoquinolone-5,10-dione-dimaleate) is a cytotoxic aza-anthracenedione. In contrast to anthracyclines and anthracenediones it is a relatively weak inhibitor of topoisomerase II. It acts to directly alkylate DNA forming stable DNA adducts and cross-strand breaks. The incorporation of a nitrogen heteroatom into the ring structure and lack of ketone groups reduces the potential for free radical generation, iron binding and formation of alcohol metabolites implicated in the cardiac toxicity associated with anthracyclines [11].

■ Pharmacokinetics
Absorption & distribution
Following intravenous administration, plasma concentrations of pixantrone base peak by the end of infusion, thereafter declining polynomially. Within the 3–105 mg/m² dose range, the pharmacokinetics of pixantrone are linear and dose independent with no significant difference observed when given as a single agent or in combination. At a dose of 50 mg/m² the median 28-day cycle exposure is 6320 ng/h/ml for three doses/4-week cycle. The volume of distribution is large at 25.8 l, with approximately 50% bound to plasma proteins [12–15].

Biotransformation & elimination
The major biotransformation products of pixantrone are acetylated metabolites. In human urine the compound is largely excreted unchanged, with small amounts of detected Phase I and II acetylated metabolites. Analyzed metabolites are pharmacologically inactive and metabolically stable. Metabolism is therefore not recognized as an important elimination pathway for pixantrone [5–9]. Total plasma clearance of pixantrone is high at 72.7 l/h; however, renal excretion is low, accounting for less than 10% of the administered dose in 0–24 h. The median terminal half-life is 21.2 h. Plasma clearance is therefore mainly nonrenal and, since metabolism is limited, biliary excretion is likely to represent the major elimination pathway [12–15].

In vitro inhibition studies
In vitro studies were conducted to evaluate the potential CYP450 inhibitory effects of pixantrone using the most common human CYP450 isoforms [5–9]. Mixed-type inhibition of CYP1A2
Pixantrone was found to have cytotoxic activity against a number of murine and human tumor cell lines with greatest activity in high-grade lymphoma, but also in advanced solid malignancies. Here, we discuss the preclinical studies followed by an overview of clinical trial data.

Preclinical studies

Pixantrone emerged as a promising compound in the search for second-generation analogues with a wider spectrum of action and improved side-effect profile compared with mitoxantrone and doxorubicin. A large number of new molecules bearing nitrogen atoms in the chromophore were synthesized and screened in vitro an in vivo [16]. Pixantrone was found to have cytotoxic activity against a number of murine and human tumor cell lines with greatest activity in leukemia and lymphoma cell lines [11]. In vivo, pixantrone was curative against L1210 murine leukemia and YC-8 murine lymphoma at the maximum tolerated dose with a number of long-term survivors, demonstrating higher activity and a broader therapeutic range than mitoxantrone and doxorubicin. Activity against solid tumors was comparable. No delayed cardiotoxic effect was observed with pixantrone compared with standards (mitoxantrone and doxorubicin). The cumulative cardiotoxic potential of pixantrone was further assessed via comparison with equiactive doses of mitoxantrone and doxorubicin in doxorubicin pretreated and doxorubicin naïve mice [17]. Doxorubicin pretreated mice developed a significant deterioration in existing degenerative cardiomyopathy following further exposure to doxorubicin or mitoxantrone. No such phenomenon was observed following exposure to pixantrone. Minimal cardiac change was seen in mice given repeated doses of pixantrone, while two cycles of doxorubicin resulted in marked degenerative cardiomyopathy. Such encouraging efficacy and safety data justified further evaluation of the compound within early clinical trials.

Overview of clinical trials

Single-agent therapy

In the first reported Phase I study conducted in patients with NHL [13], 26 patients with advanced or refractory NHL were enrolled and treated on seven individual dose levels. This was a heavily pretreated population with a median of two prior chemotherapies and additional radiation therapy in 15 of 26 patients. The most common histological subtype was diffuse large B cell lymphoma (DLBCL). Five responses were observed including three complete responses (CRs) and two partial responses (PRs). All CRs were observed at the seventh dose level. The dose-limiting toxicity (DLT) at this level was myelosuppression; particularly neutropenia. All other toxicities were manageable or of low clinical relevance. Importantly, no clinical signs of cardiotoxicity were observed. Although the maximum tolerated dose (MTD) was at the sixth dose level (56 mg/m²/week of pixantrone dimaleate), a dose of 84 mg/m²/week was recommended for Phase II studies given the efficacy seen at the seventh dose level and the probable overestimation of hematological toxicity in this heavily pretreated population. Two further Phase I trials were conducted in patients with advanced solid malignancies. These identified a higher MTD [12,14]; the DLT in both studies was neutropenia. Left ventricular ejection fraction (LVEF) was assessed serially via echocardiography; no significant cardiac toxicity was demonstrated. The recommended dose for Phase II studies was 112.5 mg/m² (once a week × 3 schedule) and 180 mg/m² (three-weekly schedule).
However, the MTD recommended by Borchmann and colleagues (84 mg/m²/week) was taken forward into the Phase II setting [13]. This was perhaps unsurprising, since this study consisted mainly of individuals with high-grade lymphoma and was highly applicable to the trial that followed.

An open-label, nonrandomized, non-comparative, multicenter Phase II trial of single-agent pixantrone in patients with relapsed, aggressive B-NHL followed at a dosage of 85 mg/m² pixantrone dimaleate in a once weekly schedule [7]. Thirty-three patients were recruited with a median age of 66 years. In contrast to many trials conducted in the salvage setting, there was less heterogeneity in histological diagnosis; 24 out of 33 patients with DLBCL. Grade III/IV neutropenia was seen in 19 out of 33 (58%) patients and led to a delay of treatment in 16 patients and dose reduction in five. No evidence of cumulative myelotoxicity was seen, however, and no patient was withdrawn from the study owing to prolonged neutropenia. A significant reduction in LVEF was seen in three elderly patients and may have related to therapy. All had received prior therapy with anthracyclines and two had a baseline LVEF of less than 50% at study entry (39 and 43%). Pixantrone was otherwise well tolerated with an overall response rate (ORR) of 27% and median progression-free survival (PFS) of 106(+ days at the time of reporting. This included five confirmed CRs and a PR in four patients. Duration of response was up to 17(+) months in those achieving a CR on therapy.

A Phase III, multicenter, open-label, randomized control trial followed in patients with relapsed/refractory aggressive or transformed NHL at 66 sites across Europe, India, Russia, South America, the UK and USA [9]. One hundred and forty patients were randomized on a one-to-one basis between pixantrone and investigator’s choice of single agent. Pixantrone dose and schedule was identical to that used in the Phase II setting. Baseline demographics were well matched apart from cardiac history; three patients in the pixantrone group had a history of congestive heart failure, two with ongoing cardiomyopathy. DLBCL was the most common histological subtype accounting for 76 and 73% of patients in the pixantrone and comparator groups, respectively. Since pixantrone cycle length was 28 days, median duration of therapy was longer for patients in the pixantrone group. In addition, blood count monitoring was more frequent in the pixantrone group with all patients scheduled to undergo full blood counts on days 1, 8 and 15. Finally, more patients underwent repeat LVEF assessments owing to a longer duration of therapy.

Similar proportions of patients experienced adverse events (AEs) in the pixantrone (66/68; 97.1%) and comparator (61/67; 91.0%) groups; however, more grade III/IV AEs were observed in the pixantrone arm (76.5 vs 52.2%) with neutropenia as the predominant event. Cardiac events were seen with increased frequency in the pixantrone group (24/68; 35.3%) than in the comparator (14/67; 20.9%), these largely represented asymptomatic declines in LVEF. No evidence of cumulative, dose-related decline in LVEF was observed in relation to pixantrone. The median change in baseline LVEF at the end of treatment was -4% in the pixantrone and 0% in the comparator group. The change in LVEF values in patients treated with pixantrone was not associated with clinical evidence of cardiac impairment.

Significantly more patients in the intention-to-treat (ITT) population of the pixantrone arm achieved a CR or unconfirmed complete response (CRu) at the end of treatment compared with those given a comparator drug (Table 1). Fourteen patients in the pixantrone arm achieved a CR or CRu compared with four in the comparator group by the end of treatment (p = 0.021). By the end of the study (18 month follow-up) 17 patients achieved a CR/CRu in the pixantrone arm compared with five in the comparator group (p = 0.009). ORRs were 37.1 versus 14.3% at the end of treatment and 40.0 versus 14.3% by the end of study in the pixantrone versus comparator groups, respectively. Median duration of CR/CRu in pixantrone treated patients was 9.6 months compared with 4.0 months for patients in the comparator group. Median PFS was significantly longer in the pixantrone group than the comparator (14/67; 20.9%) these largely represented asymptomatic declines in LVEF. However, more grade III/IV AEs were observed in the pixantrone group (24/68; 35.3%) than in the comparator (14/67; 20.9%), these largely represented asymptomatic declines in LVEF. No evidence of cumulative, dose-related decline in LVEF was observed in relation to pixantrone. The median change in baseline LVEF at the end of treatment was -4% in the pixantrone and 0% in the comparator group. The change in LVEF values in patients treated with pixantrone was not associated with clinical evidence of cardiac impairment.

Owing to slow enrollment, recruitment was terminated prior to accrual of the intended number of participants. The study was therefore underpowered to test the primary end point; proportion of patients achieving a CR or CRu in the ITT population at the end of
treatment. Despite this, the study provided convincing evidence that single-agent pixantrone salvage therapy in a high-risk population can achieve superior responses than comparator agents included within the trial with manageable toxicities.

**Combination studies**

The use of pixantrone in combination has also been evaluated for patients with relapsed/refractory aggressive B-NHL. A Phase I/II study investigated the use of pixantrone as a substitute for etoposide within the ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin) regimen [8]. Nineteen patients with histologically confirmed relapsed or refractory aggressive B-NHL were recruited, including 16 with DBLCL. DLT, consisting of bone marrow suppression, occurred at the first dose level (80 mg/m²) and this was subsequently defined as the recommended pixantrone dose. The treatment protocol consisted of pixantrone 80 mg/m² over 1 h on day 1, methylprednisolone 500 mg on days 1–5, cisplatin 25 mg/m² on days 1–4 and cytarabine 2000 mg/m² on day 5. Each cycle consisted of 21 days and was completed in an outpatient setting.

Grade III and IV toxicities were mainly hematological; only one patient developed febrile neutropenia. No clinically significant cardiotoxicity was observed. Seven patients (37%) had a decline in LVEF ≥10% from baseline and/or a decrease in LVEF to <50%. Three of these patients had an increase in ejection fraction when measured on subsequent cycles. No patient experienced a decline in LVEF greater than 19% from baseline. The ORR was 55%, including 37% CR and 21% PR. Six of 11 responders (55%) proceeded to stem cell transplantation. Median time to progression and overall median survival were 5.7 and 14.7 months, respectively. No significant interaction between pixantrone and the combination drugs was observed. PSHAP (pixantrone, methylprednisolone, cytarabine and cisplatin) was therefore deemed an active salvage regimen and further evaluation as a pretransplant cytoreductive regimen recommended.

A further Phase I/II, noncomparative study evaluated pixantrone in substitution for doxorubicin within the standard CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) regimen in patients with relapsed aggressive B-NHL who had previously received CHOP ± rituximab [15]. Thirty-five patients were enrolled in the Phase I and 30 patients in the Phase II component at multiple clinical sites across western Europe. DLBCL was the most common histological subtype accounting for 63 and 67% of patients in Phase I and II groups respectively. Pixantrone, cyclophosphamide 750 mg/m², vincristine 1.4 mg/m² and prednisolone 100 mg were administered on days 1 to 5 in up to six 21-day cycles.

The recommended dose was set at 150 mg/m² following the development of grade IV neutropenia in four out of 12 patients receiving pixantrone at 180 mg/m². Myelosuppression was the primary toxicity, with grade III/IV AEs observed in 74 and 70% of patients in Phase I and II respectively. Febrile neutropenia occurred in 11% of patients in Phase I and 20% of patients in Phase II. Cardiac events occurred in 13 patients in Phase I (37%) and eight patients in Phase II (27%). An LVEF decline of >10% was observed in 14 patients (ten in Phase I and four in Phase II). Two patients in Phase I developed grade III LVEF (<40%). At the end of the study, five patients in Phase I and three in Phase II developed cardiac failure; however, only the events in Phase I were attributed to therapy. The ORR in Phase II was 73% with notable CR and CRu rates of 47%. Median overall survival was 17.9 months and median

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**Table 1. Summary of efficacy in intention-to-treat population.**

<table>
<thead>
<tr>
<th></th>
<th>End of treatment</th>
<th>End of study</th>
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<tbody>
<tr>
<td></td>
<td>Pixantrone (n = 70)</td>
<td>Comparator (n = 70)</td>
</tr>
<tr>
<td>Complete/unconfirmed complete response</td>
<td>14 (20.0%, 11.4–31.3)</td>
<td>4 (5.7%, 1.6–14.0)</td>
</tr>
<tr>
<td>Complete response</td>
<td>8 (11.4%, 5.1–21.3)</td>
<td>0 (0%, 0.0–5.1)</td>
</tr>
<tr>
<td>Unconfirmed complete response</td>
<td>6 (8.6%, 3.2–17.7)</td>
<td>4 (5.7%, 1.6–14.0)</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>26 (37.1%, 25.9–49.5)</td>
<td>10 (14.3%, 7.1–24.7)</td>
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Data presented as n (%), 95% CI.

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PFS 8.2 months. Median duration of CR was 10.5 months and median disease-free survival for patients with a CR or CRu was 9.5 months. A total of 80% of patients in Phase I achieved an objective response. Study size precluded definitive conclusions with regard to the contribution of pixantrone to cardiotoxicity; however, reference to published data suggested clinically
significant cardiac events occurred less often in this study than would be expected if patients had received additional CHOP [2]. Response rates in the Phase II component of the trial compared favorably with those reported with other combination regimens used in this setting [18].

Such promising data led to the initiation of a Phase II, randomized, open-label, multicenter study of R-CPOP (cyclophosphamide, pixantrone, vincristine, prednisone and rituximab) versus R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) as first-line therapy for DLBCL [10]. Patients with untreated DLBCL (CD20⁺, stage II–IV disease) were randomized between R-CPOP and R-CHOP on a one-to-one basis. R-CHOP was administered at standard doses; within R-CPOP, pixantrone was administered at 150 mg/m² replaced doxorubicin. After four cycles, patients with a PR received four more cycles of therapy and those with a CR two. Follow-up after therapy was 36 months.

Overall AEs were similar between groups. Grade III/IV AEs occurred in approximately 85% of patients in both arms. Incidence of grade III/IV neutropenia (61.0 vs 60.3%), febrile neutropenia (15.3 vs 15.9%), thrombocytopenia (5.1 vs 6.3%) and infections (16.9 vs 17.5%) was similar between arms. LVEF was measured prospectively at intervals over 24 months; values were generally stable in R-CPOP arm but declined significantly from baseline in the R-CHOP group. One patient undergoing R-CPOP versus eight in the R-CHOP group had LVEF declines ≥20%. A total of 6.7% of patients in R-CPOP versus 35.2% in R-CHOP developed elevated troponin-T levels. No patients in R-CPOP versus four in R-CHOP developed congestive heart failure.

Of the 124 patients enrolled, 61 were randomized to R-CPOP and 63 to R-CHOP. Baseline characteristics were well matched. CR/CRu rate in the ITT population was 72.1% for R-CPOP and 79.4% for R-CHOP, and ORR was 82.0% versus 87.3%, respectively. PFS appeared similar as did time to progression. Median overall survival was not reached in either arm at the time of reporting. The 3-year survival rates were 66% in R-CPOP and 85% in R-CHOP. The 3-year survival rates for patients with an International Prognostic Index (IPI) score of ≤2 was 82% for R-CPOP and 86% for R-CHOP. The 3-year survival in patients with an IPI score ≥3 was 50 vs 84%. Within the R-CHOP arm, the observed improvement in survival at 3 years was greater in patients with the modal IPI score of 3 (n = 25) than those with an IPI score of ≤2. This was unusual and appeared responsible for the disparate survival rates between R-CPOP and R-CHOP in the IPI ≥3 cohort. Unfortunately, resource constraints led to premature closure of enrollment after 124 patients and the study was no longer powered to detect noninferiority. Despite this, R-CPOP demonstrated comparable efficacy and, critically, reduced cardiotoxicity compared with R-CHOP. Ongoing combination studies include a Phase III, multicenter comparison study of rituximab–gemcitabine versus rituximab–pixantrone in the salvage setting in those with relapsed/refractory DLBCL [101].

### Adverse reactions

The safety of pixantrone was evaluated in a total of 407 patients. Bone marrow suppression, particularly neutropenia, reduction in LVEF, skin discoloration and chromaturia were the most commonly observed toxicities.

### Hematological toxicity

The incidence of severe bone marrow suppression with clinical consequence is low. Grade III–IV neutropenia was observed with increased frequency in those treated with pixantrone however was uncomplicated in the majority of cases and noncumulative with a low incidence of febrile neutropenia or infection. Although rarely required, such toxicity was easily managed with growth factor support and transfusion of blood products as required.

### Nonhematological toxicity

- **Cardiac toxicity**

Although anthracyclines may be active in second-line therapy, their use is precluded by cumulative cardiotoxicity. Following first-line therapy for aggressive B-NHL most patients will have received near to their lifetime limit of doxorubicin [2]. Pixantrone was engineered specifically with the aim of achieving comparable efficacy to anthracyclines with minimal cardiotoxicity. Interpreting cardiotoxicity in small numbers of high-risk patients within early clinical trials is challenging. Whilst cardiotoxicity secondary to pixantrone may be overestimated in such a population, the median cumulative dose of pixantrone is often moderate owing to a high proportion of patients with progressive disease; potential for cumulative cardiotoxicity may therefore equally be underestimated. Cardiotoxicity was therefore
scrupulously investigated in the Phase III setting in individuals with relapsed/refractory aggressive B-NHL [9]. Cardiac events were seen more commonly in the pixantrone arm (35.3 vs 20.9%) but largely represented asymptomatic reductions in LVEF without clinical consequence. No cumulative dose-dependent cardiotoxicity was observed. Moreover, baseline cardiac characteristics were poorly matched between treatment arms for cardiac history. Three patients in the pixantrone group had a history of congestive heart failure; two with ongoing cardiomyopathy.

In the first-line setting, the efficacy and safety of R-CPOP versus R-CHOP was evaluated in a randomized Phase II study in patients with DLBCL [10]. Enrollment stopped early owing to resource constraints resulting in a loss of power to detect noninferiority; however, comparable efficacy and reduced cardiotoxicity was demonstrated. The cardiotoxic potential of pixantrone therefore requires further evaluation within prospective clinical trials. Current recommendations for individuals undergoing therapy with pixantrone include a baseline echocardiogram with a low threshold for repeat assessment in those with a high cumulative history of anthracycline exposure or significant pre-existing heart disease [9].

■ Skin discoloration, chromaturia & common toxicities
Skin discoloration and chromaturia occurs frequently secondary to the blue color of the compound, this is transient, with no recognized long-term sequelae. Toxicity commonly associated with cytotoxic agents including nausea, vomiting and diarrhea was infrequent, mild, reversible and easily managed. There was no recognized renal or hepatic toxicity and no significant drug interactions were observed.

Use in specific populations
■ Elderly patients (≥65 years)
No specific dose adjustment required.

■ Renal & hepatic impairment
The safety and efficacy of pixantrone in patients with renal and/or hepatic impairment is yet to be evaluated. Patients with serum creatinine levels >1.5-times the upper limit of normal range were excluded from randomized trials; pixantrone should therefore be used with caution in this population and dosed according to formally assessed body surface area. Similar caution should be exercised in those with mild or moderate hepatic impairment and is not recommended for use in those with severe excretory hepatic impairment.

■ Women of childbearing age, pregnancy & lactation
Animal studies have demonstrated reproductive toxicity; however, there is no data in human populations [102]. Pregnancy should therefore be avoided and effective contraception is advised during and up to six months following completion of therapy. It is unknown whether pixantrone or its metabolites are excreted in human breast milk, and therefore breastfeeding should be discontinued during therapy.

■ Fertility
Similar to other DNA-damaging agents, pixantrone may be associated with fertility impairment [102]. Although this has not been confirmed in human studies, male patients are advised to consider sperm banking prior to commencement of therapy and to use barrier contraception during and 6 months following completion of therapy.

Conclusion & future perspective
There are multiple novel cytotoxic, biological and immunomodulatory agents in development for relapsed or refractory aggressive B-NHL. Pixantrone has shown clear promise in this setting with predictable pharmacokinetics and manageable toxicity in heavily pretreated populations. Further safety data, with particular focus on long-term toxicity is required; this can be achieved through prospective trials earlier in therapy and postmarketing surveillance. Pixantrone is yet to receive approval from the FDA. The organization raised two major concerns with regard to the interpretability of the published Phase III data. Firstly the trial did not accrue the prespecified number of patients and secondly recruitment in the USA was poor, raising concerns of applicability to an American patient population. In order to address this further, a Phase III combination trial, R-pixantrone versus R-gemcitabine is in progress [101].

Future application is broad, with potential utilization beyond the salvage setting in first- and second-line combination regimens, possible substitution of anthracyclines and extension into therapy for solid malignancies. Optimal combinations and scheduling, particularly with novel agents, will need to be determined within clinical trials. Pixantrone brings hope to the salvage setting and has the potential to replace anthracyclines in first-line therapy thereby minimizing...
cardiotoxicity in a disease that continues to rise in incidence and frequently affects the elderly.

Financial & competing interests disclosure
R Pettengell has received honoraria from Cell Therapeutics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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Papers of special note have been highlighted as:
of interest
8 First Phase II study evaluating activity and safety of pixantrone in patients with relapsed, aggressive B-cell non-Hodgkin lymphoma.
10 First reported Phase I study evaluating safety of pixantrone in patients with advanced or refractory non-Hodgkin lymphoma.
11 Original scientific paper describing synthesis, preclinical activity and safety of BBR 2778.
18 Key animal studies comparing pixantrone to equiactive doses of doxorubicin and mitoxantrone demonstrating reduced cardiotoxic potential.

Websites
101 Comparison of Pixantrone + Rituximab With Gemcitabine + Rituximab In Patients With Aggressive B-cell Non-Hodgkin Lymphoma or Follicular Grade 3 Lymphoma Who Have Relapsed After Therapy and Are Not Eligible for Stem Cell Transplant (PIX-R).
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