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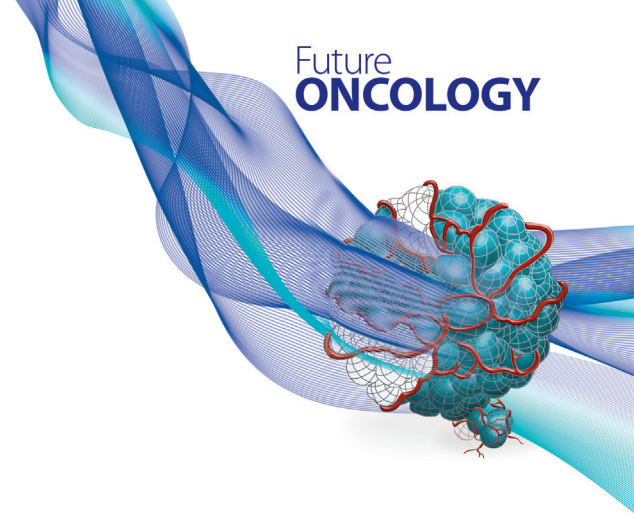

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Pixantrone–rituximab versus gemcitabine–rituximab in relapsed/refractory aggressive non-Hodgkin lymphoma

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We describe the rationale and design of the ongoing randomized, active-controlled, multicenter, Phase III study evaluating the efficacy of pixantrone and rituximab versus gemcitabine and rituximab in patients with diffuse large B-cell lymphoma or follicular grade 3 lymphoma, who are ineligible for high-dose chemotherapy and stem cell transplantation, and who failed front-line regimens containing rituximab. The administration schedule is pixantrone 50 mg/m^2 intravenously (iv.) or gemcitabine 1000 mg/m^2 iv. on days 1, 8 and 15, combined with rituximab 375 mg/m^2 iv. on day 1, up to six cycles. Pixantrone has a conditional European marketing approval for monotherapy in adults with multiple relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Our trial explores the efficacy of combining pixantrone with rituximab and completes postauthorization measures. Trial registration number: NCT01321541.

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KEYWORDS
• aggressive non-Hodgkin lymphoma • DLBCL • gemcitabine • pixantrone • relapse • rituximab

Pixantrone is a novel aza-anthracenedione compound with antitumor activity [1,2]. It received marketing approval in Europe for monotherapy in the treatment of adult patients with multiple relapsed or refractory aggressive non-Hodgkin lymphoma (NHL) [3], with a postauthorization marketing requirement. In this paper, we describe the rationale and design of the Phase III study PIX306, also known as PIX-R (pixantrone–rituximab vs gemcitabine–rituximab in treating relapsed/refractory transplant-ineligible aggressive NHL), which is intended to confirm the efficacy of pixantrone combined with rituximab and complete the postauthorization requirement.

Rationale

NHL is the fifth most common type of cancer with annual estimates of nearly 150,000 cases in the EU and the USA combined [4–6]. Aggressive NHL comprises 44% of all NHL [7], and diffuse large

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B-cell lymphoma (DLBCL) is the most common subtype, accounting for 75% of all aggressive lymphomas.

Anthracycline-based regimens are the standard of care for front-line therapy in aggressive NHL and DLBCL, notably with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) [8,9]. R-CHOP can produce good rates of durable response, but between 30 and 50% of patients relapse or prove to be refractory to initial therapy. A high-dose myeloablative regimen followed by stem cell transplant (SCT) is a potential curative option for those who can tolerate the procedure. However, a substantial proportion of relapsed patients do not receive SCT for a variety of reasons, such as comorbidities, advanced age, patient choice or failure to have a complete or partial response to second-line therapy [10]. Among patients who are not candidates for SCT, or who relapse following second-line regimens, response rates are low, complete remissions are rare and expected survival is <6 months. There is currently no standard treatment for patients with relapsed/refractory aggressive NHL beyond second-line treatment regimens [11]. Retreatment with anthracyclines is generally avoided because the risk of cardiac toxicity increases with the cumulative dose [12]. The lack of consensus regarding treatment of patients with relapsed or refractory aggressive NHL and the lack of robust data supporting current clinical practices clearly demonstrate the need for more controlled trials in this setting to define additional therapies for this patient population.

• Rationale for pixantrone & rituximab in aggressive relapsed or refractory NHL

Pixantrone is a novel aza-anthracenedione compound with a distinct chemical structure that confers a different toxicity profile and mechanism of action from anthracyclines [12]. Pixantrone was designed to improve efficacy and reduce the toxicity of anthracenediones, by increasing the stability of DNA adduct formation, while reducing the potential to form oxygen-free radicals and toxic drug–metal complexes. Pixantrone is a weak topoisomerase II inhibitor and forms stable DNA adducts through alkylation with specificity for DNA hypermethylated sites [13,14]. Moreover, pixantrone does not generate oxygen-free radicals since it cannot bind iron, which is the putative mechanism for the cardiac toxicity of anthracycline and anthracenediones. Recent findings suggest that pixantrone induces a latent type of DNA damage that impairs the fidelity of mitosis, without triggering DNA damage response or mitotic checkpoint activation, but is lethal after successive rounds of aberrant division [15]. This mechanism of cell killing appears to be by impairing chromosome segregation that generates severely aneuploid cells. The molecular mechanisms by which pixantrone impairs mitosis remain to be elucidated.

The efficacy of pixantrone has been evaluated in >400 patients with hematological and solid-tumor malignancies in single-agent or combination regimens. A randomized controlled Phase III trial with pixantrone [16] included 140 patients with stage III–IV aggressive NHL who had previously received two or more lines of systemic therapy (including SCT following high-dose myeloablative therapy). Eligible patients were aged 18 years or older and had adequate organ function (notably left ventricular ejection fraction [LVEF]: ≥50%). They were randomly allocated to pixantrone dimaleate 85 mg/m^2 by 1 h intravenous (iv.) infusion on days 1, 8 and 15 of each 28-day cycle for up to six cycles, or to physician's choice of the single-agent comparator drug most appropriate for that patient using prespecified standard doses and schedules. The pixantrone dimaleate dosage of 85 mg/m^2 used in the study is equivalent to 50 mg/m^2 in the currently approved base expression. The comparator was physician's choice of treatment, and vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone and gemcitabine were administered. As the trial took place before rituximab was standard of care, only 54% of patients had previously received rituximab. Treatment with pixantrone was associated with better rates of complete (or unconfirmed complete) response (24.3 vs 7.1% for comparator at the end of study; p = 0.009) [16]. Objective response rates (ORR) were also in favor of pixantrone (40.0 vs 14.3% for comparator; p = 0.001), as was median progression-free survival (PFS; 5.3 vs 2.6 months; hazard ratio [HR]: 0.60; p = 0.005) and median overall survival (OS; 10.2 vs 7.6 months; HR: 0.79; p = 0.25).

The Phase III study also confirmed the safety profile of pixantrone. The most common grade 3 or 4 adverse events were neutropenia (41.2 vs 19.4% with comparator), leukopenia (23.5 vs 7.5%) and thrombocytopenia (11.8 vs 10.4%), all of which were manageable [16]. Although the frequency of cardiac events was higher in the

pixantrone group, these were predominantly asymptomatic grade 1 and 2 declines in LVEF. This may have been related to the fact that more pixantrone patients had a history of cardiac disease at baseline (three patients with a history of congestive heart failure and two patients with cardiomyopathy, versus none in the comparator group). Other adverse events reported in the global safety analysis of pixantrone [17] include anemia (31%), asthenia (23%), pyrexia (23%), cough (22%), decreased LVEF (19%) and nausea (18%). Treatment with pixantrone is also associated with a reversible blue skin discoloration in about 10% of patients. The safety of pixantrone in NHL has also been explored in various combination therapies with no unexpected adverse events [17]. Pixantrone is indicated in the treatment of relapsed and refractory aggressive NHL with a postauthorization requirement for more evidence of the value of pixantrone in combination with rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody that binds to the transmembrane antigen CD20. Rituximab is the foundation of treatment regimens in CD20-positive NHL, and has been evaluated in the treatment of patients with relapsing or refractory aggressive lymphoma [18–20], with good results, including a median time to progression that exceeded 240 days. The dosing schedule in NHL is 375 mg/m^2 iv. on day 1 of a 28-day cycle. Treatment with rituximab is well-tolerated, and the most frequently reported adverse events are mild and related to infusion syndrome.

Combining pixantrone chemotherapy with the anti-CD20 agent rituximab is expected to produce synergistic effects with minimal overlapping toxicity and minimal drug interactions. Although single-agent rituximab has only modest activity in patients with aggressive NHL who have had prior rituximab therapy, it may have an additive or synergistic activity with an active agent such as pixantrone or gemcitabine in a combination setting [21]. Indeed, the potential benefit of added efficacy outweighs the risks of combining these agents in a setting for which there is no standard therapy. Pixantrone is excreted predominantly unchanged by the liver, whereas rituximab is a humanized monoclonal antibody with no known effects on hepatic excretory function. The likelihood of a pharmacokinetic interaction is therefore extremely low.

• Rationale for gemcitabine & rituximab in aggressive relapsed or refractory NHL

There is currently no established standard of care for the treatment of patients with relapsed or refractory DLBCL who are not candidates for SCT. Patients may be ineligible for transplant due to failure to respond to a standard salvage regimen, advanced age, toxicity from prior therapies or serious comorbidities.

Gemcitabine has activity as a single agent in lymphoma [22], and a synergy with rituximab has been reported in preclinical studies in lymphoma models. The choice of comparator was based on the National Comprehensive Cancer Network guidelines published at the time for patients with relapsed/refractory DLBCL who are not candidates for SCT [23], recommending entry to a clinical study, or single-agent, doublet, or multiagent regimens, some containing gemcitabine and/or rituximab. This is also supported in a study by Wenger *et al.* [24], which showed a 72% response rate for the combination of gemcitabine plus rituximab in a very limited number of patients. In relapsed or refractory DLBCL patients, the rate of complete response (CR) was 20%. This aligns with rates of 20–50% reported with other regimens.

Once they reach third-line treatment, nearly all patients will have been exposed to R-CHOP. There is no standard of care regimen beyond second-line therapy, and active drugs include pixantrone, gemcitabine, cisplatin, cytarabine and bendamustine. Gemcitabine is a nucleoside analog with broad antitumor activity in ovarian, breast, non-small-cell lung and pancreatic cancer [25,26], particularly in combination with chemotherapy. The most commonly used dosing schedules are 1000 mg/m^2 iv. infusion on days 1 and 8 of a 21-day cycle (ovarian cancer or breast cancer) and 1000 mg/m^2 on days 1, 8 and 15 of a 28-day cycle (lung and pancreatic cancer) [26]. The agent has a good safety profile, and the most common adverse effects are hematological toxicities. Other adverse effects are cutaneous rash, flu-like symptoms, edema and pulmonary toxicities, as well as nausea, vomiting and diarrhea.

Gemcitabine has been evaluated in patients with relapsed or refractory lymphoma [27–29], and has shown promising activity in heavily pretreated patients, even those who have progressed after SCT [30], with ORRs that are generally about 20% [22,24]. Its favorable toxicity profile implies that it can be safely combined with anti-CD20 therapies, and no cross-resistance with

other nucleoside analogs has been reported. Preclinical studies suggest that the use of a combination of gemcitabine with rituximab in lymphoma is associated with significant tumor growth inhibition [31]. The combination of gemcitabine and rituximab therefore appears as a reasonable therapeutic option in patients with relapsed NHL if they are ineligible for SCT. Both gemcitabine and rituximab have demonstrable activity against DLBCL in monotherapy, with approximately 20 and 30% ORRs, respectively. We therefore selected the combination of gemcitabine and rituximab for the comparator group of our study.

Study design

We designed a randomized, active-controlled, multicenter, Phase III study to evaluate the efficacy of pixantrone plus rituximab versus gemcitabine plus rituximab in patients with aggressive B-cell NHL. The study is being conducted in North America and Europe.

The target population is relapsed or refractory patients aged ≥18 years with either DLBCL or follicular grade 3 lymphoma (3a or 3b; tissue biopsy). Selected inclusion and exclusion criteria are presented in **Box 1**. All patients must have relapsed after at least one multiagent chemotherapy containing rituximab. *De novo* DLBCL patients and patients with follicular grade 3 lymphoma must have received one to three prior regimens, while those DLBCL transformed from indolent lymphoma must have received one to four prior regimens for NHL. Patients with primary refractory NHL were excluded. They should be currently ineligible for high-dose therapy or SCT, according to investigator's opinion. Patients not eligible for SCT could include those who relapsed after previous SCT, did not respond to a standard salvage regimen, did not mobilize an adequate number of stem cells for SCT or are unsuitable for SCT due to other medical conditions, age, patient choice, financial constraints or other reasons. Included patients also had to have performance status of Eastern Cooperative Oncology Group score ≤2, normal cardiac function (LVEF ≥45% and normal serum troponin T) and all acute toxicities to prior treatment recovered to at least grade 1 (with the exception of alopecia).

Treatment plan

The study design is presented in **Figure 1**. Patients are being randomly allocated (1:1) to one of two treatment groups with up to six cycles of 28 days each. In the investigational therapy arm, patients receive pixantrone 50 mg/m^2 iv. on days 1, 8 and 15 of each cycle plus rituximab 375 mg/m^2 iv. on day 1. Patients in the control arm receive gemcitabine 1000 mg/m^2 iv. on days 1, 8 and 15 of each cycle plus rituximab 375 mg/m^2 iv. on day 1. Investigators are requested to administer rituximab prior to the cytotoxic agent on day 1. Preparation of all study drugs and storage and handling follows the corresponding package inserts.

Randomization is performed using an electronic data capture system, and stratified by number of prior therapies for DLBCL or follicular grade 3 lymphoma (0–2 vs ≥3), International Prognostic Index (IPI; 0–2 vs ≥3), and length of time from initiation of first-line therapy for DLBCL or follicular grade 3 lymphoma until first relapse (<1 vs ≥1 year). Treatment assignment is known to investigators and patients, though the sponsor will remain blinded during the study.

Patients who discontinue pixantrone, gemcitabine or rituximab for toxicity may remain in the study on monotherapy with the other study treatment for up to six cycles. A single dose reduction in pixantrone (to 41 mg/m^2) is permitted due to toxicities during the study. Up to two dose reductions for gemcitabine are allowed, with the first reduction to 750 mg/m^2 and the second to 500 mg/m^2. Patients who complete six cycles of treatment or discontinue treatment for any reason enter a 6-month early follow-up period, followed by an 18-month intermediate follow-up for the purposes of evaluating disease response **(Figure 1)**. At the time patients experience progressive disease, begin subsequent anticancer therapy (except for rituximab given as maintenance therapy) or withdraw consent for study procedures, they enter the survival follow-up period.

Patients may receive all concomitant treatments deemed necessary to provide adequate support, including antiemetics, medications to prevent or treat rituximab hypersensitivity and medications to prevent tumor lysis syndrome. Colony-stimulating factors may be used at the investigator's discretion, but must be discontinued at least 2 days prior to study drug administration (and only after day 15 of each cycle in the case of pegfilgrastim). Photosensitivity is a potential clinical risk of pixantrone and so patients are advised to avoid sun exposure or use a sunscreen that absorbs UVA radiation.

Box 1. Selected inclusion and exclusion criteria.

Inclusion criteria

- Age ≥18 years old
- Documented *de novo* DLBCL, DLBCL transformed from indolent lymphoma or follicular grade 3 lymphoma on the basis of a tissue biopsy
- Previous therapies: one to three prior regimens for patients with *de novo* DLBCL or follicular grade 3 lymphoma; one to four prior regimens for patient with DLBCL transformed from indolent lymphoma
- Prior treatment with a rituximab-containing multiagent regimen
- For patients with DLBCL transformed from indolent lymphoma, previous complete or partial response to therapy for ≥12 weeks
- Not eligible for high-dose (myeloablative) chemotherapy and SCT (i.e., relapsed after SCT, no response to standard salvage regimen, inadequate number of cells for SCT or unsuitable for SCT due to other medical conditions, age, personal preference, financial constraints or other reasons)
- At least 28 days from completion of last therapy to randomization
- At least one bidimensionally measurable site of disease that has not been previously irradiated: nodal disease ≥1.5 cm in short axis or extranodal disease >1.0 cm in short axis
- ECOG performance status ≤2
- Life expectancy ≥12 weeks in investigator's judgment
- LVEF ≥45% and normal serum troponin T
- Hemoglobin ≥8 g/dl, platelet count ≥100 × 10^9/l (≥75 × 10^9/l if documented bone marrow involvement), ANC ≥1.5 × 10^9/l (≥1.0 × 10^9/l if documented bone marrow involvement), serum bilirubin ≤1.5 × ULN (≤5 × ULN in patients with Gilbert's syndrome), AST and ALT ≤2 × ULN (≤5 × ULN if elevation is due to hepatic involvement by lymphoma), serum creatinine ≤2 × ULN
- All acute toxicities related to prior treatment recovered to grade ≤1, except alopecia
- Written informed consent
- Effective birth control

Exclusion criteria

- Any of the following as the only site(s) of disease: palpable lymph nodes not visible on imaging studies, skin lesions or bone marrow involvement only
- Primary refractory *de novo* DLBCL or primary refractory follicular grade 3 lymphoma, defined as documented progression within 12 weeks of the last cycle of the first-line multiagent regimen
- Prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m^2
- Active grade 3/4 infection (National Cancer Institute Common Terminology Criteria for Adverse Events)
- Major surgery ≤28 days prior to randomization
- Known acute or chronic hepatitis B or hepatitis C virus infection or HIV
- Current CNS involvement by lymphoma
- Any experimental therapy ≤28 days prior to randomization
- Myocardial infarction in the past 6 months
- New York Heart Association class III or IV heart disease
- Other malignancy in the last 5 years (except curatively treated basal cell/squamous cell skin cancer, carcinoma *in situ* of the cervix, superficial transitional cell bladder carcinoma, *in situ* ductal carcinoma of the breast after complete resection, localized, resected and/or low-risk prostate cancer)
- Any contraindication, known allergy or hypersensitivity to any of the study drugs
- Pregnant or lactating
- Concomitant therapy with any anticancer agents, immunosuppressive agents or other investigational anticancer therapies

ALT: Alanine aminotransferase; ANC: Absolute neutrophil count; AST: Aspartate aminotransferase; DLBCL: Diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; LVEF: Left ventricular ejection fraction; SCT: Stem cell transplant; ULN: Upper limit of normal.

Patients receiving CYP1A2 substrates concomitant to pixantrone should be closely monitored, notably for theophylline levels, and coagulation should be monitored in those receiving warfarin. Blood counts should be closely monitored when pixantrone is coadministered with agents that inhibit membrane transport proteins Pgp/BRCP and OCT1, such as cyclosporine A or tacrolimus, and anti-HIV agents (e.g., ritonavir, saquinavir and nelfinavir). In addition, caution should be applied when pixantrone is continuously coadministered with efflux transport inducers (e.g., rifampicin, carbamazepine and glucocorticoids).

End points

The primary and secondary end points are listed in **Box 2**. PFS was selected as the primary end

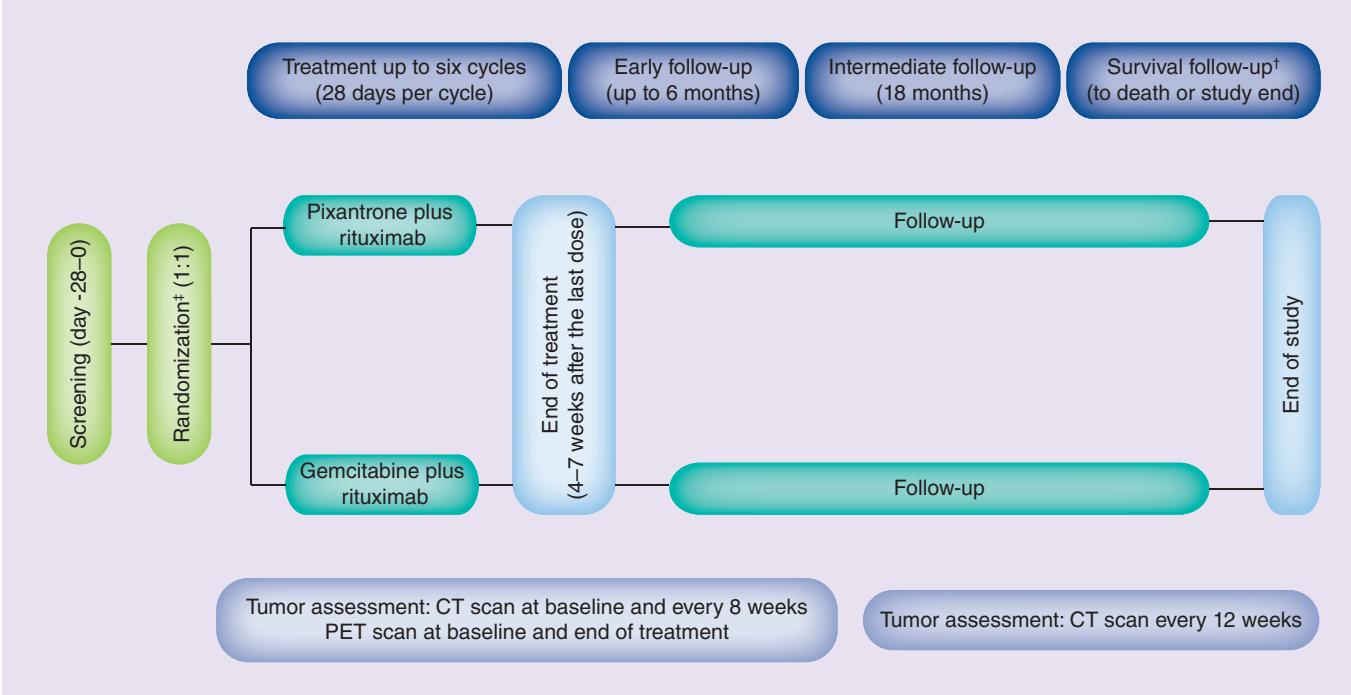

Figure 1. Study design.
†Any patient who develops progressive disease or relapses during treatment or in early or intermediate follow-up, begins nonprotocol-directed non-Hodgkin lymphoma therapy or withdraws consent for treatment and enters the survival follow-up period.
‡Stratification according to time to first relapse (<1 or ≥1 year), International Prognostic Index (0–2 vs ≥3), and number of prior regimens (0–2 or ≥3).

point since it reflects the effect of therapy on tumor growth and is not confounded by subsequent systemic anticancer therapy. PFS is defined as time from randomization to disease progression or death due to any cause (whichever occurs first). It is therefore considered as a surrogate for OS (i.e., time from randomization until death due to any cause), which is a secondary end point. Response is also recorded as a secondary end point according to international criteria [32] and reported as CR (the proportion of patients who achieve CR without subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy) and ORR (the proportion of patients who achieve CR or partial response without additional therapy). Safety is also assessed, including adverse events and laboratory values, with a particular focus on grade 3 and 4 adverse events, treatment-related adverse events, adverse events leading to treatment discontinuation or death, and cardiotoxicity as measured by echocardiography and troponin T. Exploratory end points include duration of complete and overall responses and proportion of patients receiving SCT after therapy.

Efficacy & safety evaluations

Demographics and baseline disease characteristics are collected at the screening visit, together with a physical examination, vital signs, bodyweight, medical and cardiac history and a detailed history of primary NHL diagnosis and all prior treatments for NHL. The sponsor or designated CRO reviews the pathology and immunohistochemistry reports documenting a current histological diagnosis to confirm patient eligibility. Prior tissue biopsy slides confirming follicular grade 3 lymphoma or DLBCL must be available at screening to be submitted for central pathology review. If a bone marrow biopsy has been performed at the investigator's initiative within 8 weeks of randomization, the results of the local review must be provided.

Disease assessment includes neck, chest, abdomen and pelvis via CT scan with iv. contrast, if possible, or else MRI of the neck, abdomen and pelvis with noncontrast chest CT scan. The imaging method used for each participant at baseline is used throughout the study. The assessment is carried out at baseline and performed at 8, 16, 24, 36, 48, 60, 72, 84 and

96 weeks. Baseline PET is not required except at the end of study visit. A bone marrow biopsy with core is required at end of treatment to confirm a CR, unless a bone marrow biopsy was obtained at baseline and was negative.

The safety assessment includes a complete chemistry panel (total bilirubin, alkaline phosphatase, ALT, AST, total protein, albumin, sodium, potassium, calcium, magnesium, phosphorous, glucose, creatinine, lactate dehydrogenase and uric acid); record of bodyweight, Eastern Cooperative Oncology Group performance status and complete blood count differential at baseline and at day 1 of each cycle. Urinalysis is performed only at baseline. A pregnancy test is performed on day 1 of each cycle for women with childbearing age during the treatment period. All laboratory test values are evaluated both locally and centrally, though local evaluations are used for decisions regarding study eligibility and clinical emergencies.

Cardiac assessment comprises LVEF by echocardiogram, ECG and serum troponin T at baseline and at end of treatment. LVEF and serum troponin T are performed at cycles 3 and 5, and at follow-up at 6 months.

An Independent Radiological Committee (IRC) assesses radiographic images based on a prespecified Image Charter, and response to treatment is evaluated using the Modified IWG Revised Response Criteria for Malignant Lymphoma [32]. Measurable sites of disease are defined as clearly bidimensionally measurable lymph nodes or nodal masses (≥1.5 cm in short axes) and extranodal sites (>1.0 cm in short axes) of lymphoma. One to six bidimensionally measurable nodal or extranodal sites of disease are selected at baseline as target lesions. Measurable lesions representative of all affected organs should be included; if measurable nodal disease is present in the mediastinum or retroperitoneum, at least one lesion from that region is included as a target lesion. Measurable lesions in a previously radiated site cannot be considered target lesions.

Statistical considerations

Sample size calculations indicate that 195 primary PFS events are required to detect ≥35% improvement in PFS with 85% power and a two-sided α of 0.05. The median PFS in the control group is assumed to be 2.8 months. On the basis of enrollment projections, it is estimated that 260 patients will need to be enrolled to reach the required 195 PFS events. For the secondary end point of OS, 220 deaths are planned to be sufficient to have 75% power to detect ≥30% improvement in OS allowing for 5% drop-offs, or 68% power to detect ≥28% improvement in OS. The median OS for the control group is assumed to be 7 months, according to a previous study [16].

The main efficacy analyses will be performed in the intention-to-treat population (i.e., all randomized patients). Analyses will also be performed in the histologically confirmed population (i.e., all randomized patients with DLBCL or follicular grade 3 lymphoma confirmed by central pathology review) and the per protocol population (all randomized patients who undergo at least one postbaseline disease assessment and have no major protocol violations). Sensitivity analyses will be performed to evaluate the robustness of the PFS result.

Treatment effect will be compared using a log-rank test stratified by IPI score, prior lines of therapy and length of time between first therapy and first relapse. The Kaplan–Meier product-limit method will be used to estimate the distribution of PFS. The primary end point analysis will be performed after 195 events have occurred. The final analysis for OS (end of study) will be performed after 220 OS events. All statistical analyses will be performed by CTI Biopharma Corp.

Other subgroup analyses will be performed as appropriate and will include the number of prior treatment regimens for DLBCL and follicular grade 3 lymphoma, length of time from initiation of therapy for DLBCL or follicular grade 3 lymphoma until first relapse, and IPI score. Safety will be assessed in all randomized patients who take at least one dose of study drug.

Box 2. Primary and secondary end points.

Primary end point

- Progression-free survival

Secondary end points

- Overall survival
- Overall response rate
- Complete response rate
- Safety

Exploratory end points

- Duration of overall response
- Duration of complete response
- Proportion of patients receiving stem cell transplant after study treatment

All end points will be compared between patients receiving pixantrone plus rituximab and those receiving gemcitabine plus rituximab.

Study organization

The study is being conducted in accordance with the International Conference on Harmonisation principles of Good Clinical Practice and the Declaration of Helsinki (1989), as well as all national, state and local laws of the applicable regulatory agencies. The trial is registered on ClinicalTrials.gov: NCT01321541.

A number of independent trial committees have been set up to oversee the conduct of the study. The Independent Data Monitoring Committee (IDMC) meets every 6 months or after 30 additional patients are randomized, whichever occurs first. The IDMC's responsibilities include: minimizing exposure of patients to unsafe therapies or doses; evaluating toxicity and appropriateness of doses and recommending design amendments if appropriate; and advising on the need for dose adjustments or assessments due to safety issues.

The IRC will determine the disease responses. The IRC will be blinded to site identifiers, patient treatment arm and investigator's designation of target lesions. All radiographic images will be read by two radiologists, and any disagreement will be adjudicated by a third radiologist. The final disease response assessment determined at each imaging evaluation will be determined by an independent oncologist and one of the radiologists who evaluate each patient's clinical, pathologic and radiologic data. Similarly, a Central Pathology Review Committee will evaluate biopsy specimens from all randomized patients to confirm the histological diagnosis. Pathology tissue and images will be read by two pathologists and any disagreement will be adjudicated by a third. Bone marrow biopsies (with cores) obtained during the study will undergo local pathology review to confirm a CR.

Conclusion

PIX-R is a randomized, active-controlled, multicenter, Phase III study evaluating the efficacy of pixantrone and rituximab versus gemcitabine and rituximab in patients with aggressive B-cell NHL. The trial has been designed to confirm the efficacy and safety of pixantrone in combination with rituximab. This is an important study insofar as there is currently no standard

EXECUTIVE SUMMARY

Background

- Pixantrone is a novel aza-anthracenedione compound with antitumor activity.
- Pixantrone currently has conditional marketing approval in Europe for monotherapy in the treatment of adult patients with multiple relapsed or refractory aggressive non-Hodgkin lymphoma.
- The PIX-R study has been set up to confirm the clinical efficacy observed in previous Phase III studies and complete the postauthorization measures.

Study rationale

- There is no standard of care in non-Hodgkin lymphoma patients who relapse or who are refractory of standard front-line therapy, or in those who are not eligible for stem cell transplantation.
- Monotherapy with pixantrone is known to be efficacious and safe in patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma compared with physician's choice of treatment.
- Combining pixantrone and rituximab is expected to be effective in such patients, with a likelihood of additive or synergistic effects, minimal overlapping toxicity and minimal drug interactions.

Study design

- PIX-R is a randomized, active-controlled, multicenter, Phase III study set up to evaluate the efficacy of pixantrone plus rituximab versus gemcitabine plus rituximab in patients with aggressive B-cell non-Hodgkin lymphoma.
- The target population is patients with either diffuse large B-cell lymphoma (*de novo* or transformed from indolent lymphoma) or follicular grade 3 lymphoma on the basis of a tissue biopsy, who are currently ineligible for high-dose (myeloablative) chemotherapy and stem cell transplantation, and who relapsed after at least one multiagent chemotherapy containing rituximab.
- The dosing schedule is pixantrone 50 mg/m^2 intravenously (iv.) or gemcitabine 1000 mg/m^2 iv. on days 1, 8 and 15, combined with rituximab 375 mg/m^2 iv. on day 1 in all patients for up to six cycles.
- Recruitment in PIX-R is ongoing.

of care in this population. Recruitment in the trial is ongoing.

Author contributions

All authors participated equally in the design of the study and the preparation of this manuscript report. They have all approved the final version and the participated in the decision to submit.

Financial & competing interests disclosure

D Belada, P Georgiev, S Dakhil, LF Inhorn, D Andorsky, JT Beck, D Quick, R Pettengell and K Hübel have received honoraria, research grants, or both from Servier or CTI Biopharma Corp. R Daly and JP Dean are employees of CTI Biopharma Corp. M Pavlyuk and N Failloux are employees of Servier. The trial is sponsored by CTI Biopharma Corp. The authors have no other relevant affiliations or financial involvement with any organization or entity in conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Open access

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