CLINICAL STUDY REPORT

R-CPOP as first line therapy for elderly patients with DLBCL and for patients with limited cardiac function with DLBCL

Name of test drug:	Pixantrone (Pixuvri®)
Indication studied:	Diffuse large B-cell lymphoma (DLBCL)
Protocol identification/Study number:	Pix-P000798
Drug development phase:	II
Study initiation date (first patient in):	03 Feb 2016
Date of early study termination:	15 Sep 2019
Study completion date (last patient out):	29 Oct 2019
Co-ordinating investigator:	**PD Dr. med. Reinhard Marks** Department of Medicine I: Hematology, Oncology, and Stem-Cell Transplantation Medical Center – University of Freiburg Hugstetter Str. 55 79106 Freiburg, Germany
Sponsor:	**Medical Center - University of Freiburg** - represented by the Chief Medical Officer (CMO) and the Chief Financial Officer (CFO) Breisacher Str. 153, 79110 Freiburg, Germany
Report ID:	Pixantrone_CSR
Report version:	1.0
Report date:	12 April 2022

Quality Assurance Statement:

This trial has been performed in compliance with Good Clinical Practises (GCP), including the archiving of essential documents.

Confidentiality Statement:

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1. SYNOPSIS

Title of Study: R-CPOP as first line therapy for elderly patients with DLBCL and for patients with limited cardiac function with DLBCL

Protocol no. Pix-P000798 and EudraCT no. 2014-005069-60

Investigators:

Coordinating Investigator was PD Dr. med. Reinhard Marks.

The list of principal investigators of participated centres is provided in Appendix 16.1.4.

Study centre(s):

A total of 5 centres in Germany participated in this study and enrolled patients (13, 10, 4, 3, and 3, respectively). One further centre in Austria was initiated but did not enrol any patients.

Germany
Universitätsklinikum Freiburg
Klinik für Innere Medizin I
Hugstetter Str. 55
79106 Freiburg

Vivantes Klinikum Am Urban
Klinik für Innere Medizin – Hämatologie und Onkologie
Dieffenbachstraße 1
10967 Berlin

Klinikum Stuttgart
Cancer Center, Tumorzentrum Eva Mayr-Stihl
Interdisziplinäre internistische Onkologie und
Hämatologie
Kriegsbergstr. 60
70174 Stuttgart

Pi.Tri Studien GmbH
Ebertplatz 12 (Ärztehaus 4. OG)
77654 Offenburg

Klinikum Augsburg
II. Medizinische Klinik
Hämatologie-Onkologie-Nephrologie-Angiologie
Interdisziplinäres Cancer Center
Stenglinstraße 2
86156 Augsburg

Austria
08 Universitätsklinik für Innere Medizin V
Hämatologie & Onkologie
Anichstr. 35
6020 Innsbruck

Publication (reference):

None.

Study period (years):	**Phase of development**:
First patient in: 03 Feb 2016	Phase II
Last patient out: 29 Oct 2019	

Objectives:

The primary objective of the trial was a first evaluation of the efficiency of R-CPOP as first line therapy in patients with diffuse large B-cell lymphoma (DLBCL), measured as treatment response (CR) after induction. Two populations characterized as follows were investigated:

I.) by age (≥ 75 years) (without limited cardiac function) or

II.) by limited cardiac function

In addition to complete remission (CR) rates, overall survival (OS) und progression-free survival (PFS) and cardiac toxicity of this regimen were monitored and compared to historical controls

Methodology:

Non-randomized, multicentre, prospective phase II clinical trial conducted at a total of 5 investigational sites in Germany.

Number of patients (planned and analysed):

Planned: 100 to be assessed of eligibility, 60 to be allocated to the trial, 54 to be analysed

Enrolled: 34 (23 in population I, 11 in population II)

Analysed: 33 (23 in population I, 10 in population II)

Completed: 21 (63.6%)

Discontinued: 12 (36.4%)

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Written informed consent obtained according to international guidelines and local laws
2. Male or female patients aged ≥ 18 years without upper age limit
3. Previously untreated and histologically confirmed diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma grade 3B according to REAL/WHO classification (Harris et al. 1994, Swerdlow et al. 2008)
4. At least one objectively bi-dimensionally measurable lesion as demonstrated by CT, spiral CT, or MRI that can be followed for response as target lesion; patients with the following sites of disease were NOT eligible:
   - Patients with only skin lesions or only palpable lymph nodes
   - Patients with spleen or bone marrow as only site of disease
5. Life expectancy ≥ 3 months according to investigator's opinion
6. Ann Arbor stage: II-IV
7. Ability to understand the nature of the trial and the trial-related procedures and to comply with them
8. Criteria for stratification:

Population I:

Age ≥ 75 years (without limited cardiac function)
Not eligible for standard R-CHOP 21 treatment

or

Population II:

Impaired cardiac function:

<u>First 10 patients:</u>
Ejection fraction: ≥ 40% and ≤ 50%

<u>additional patients:</u>
Ejection fraction: > 30% and ≤ 50%

Note: Patients ≥ 75 years of age with impaired cardiac function were eligible for population II.

Exclusion criteria:

1. Severe pulmonary, hepatic or renal comorbidities which make the patient ineligible for cytotoxic drug treatment
2. Severe cardiac impairment, e.g. NYHA class IV, (with the exception of inclusion criterion 8) which makes the patient ineligible for cytotoxic drug treatment, or resting cardiac troponin T levels >0.05 ng/ml (according to > grade 1 CTCAE 3.0)
3. Prior treatment for lymphoma other than pre-treatment with steroids
4. History of indolent lymphoma
5. Manifestation of DLBCL disease in central nervous system (CNS)

6. Active hepatitis B or C, serologic positivity for HIV infection
7. HIV-related lymphoma
8. Immunisation with live virus vaccines within the last 14 days
9. Major thoracic and/or abdominal surgery within the 4 weeks before trial registration from which the patient had not fully recovered except for diagnosis of non-Hodgkin lymphoma (NHL); patients who had minor surgery may be enrolled after a ≥ 1 week recovery period except for diagnosis of NHL
10. Serious (NCI CTCAE grade 3-4) intercurrent infection at the time of trial registration or deep-seated or systemic mycotic infection
11. Active or history of another malignancy except cured basal cell carcinoma of skin or carcinoma in situ of uterine cervix; patients who had been in remission from another previous malignancy for >5 years were considered eligible
12. Known hypersensitivity to pixantrone, or any drugs or excipients of the associated chemotherapy R-CPOP that the patient will receive
13. - 18. Refer to section **Fehler! Verweisquelle konnte nicht gefunden werden.**

Investigational Product, dose and mode of administration, batch number:

Population I:

Rituximab 375 mg/m² i.v. day 0 or day 1
Cyclophosphamide 750 mg/m² i.v. day 1
Pixantrone* 88 mg/m² i.v. day 1 (= 150 mg/m² pixantrone dimaleate)
Vincristine 1.0mg absolute i.v. day 1
Prednisone 100 mg orally day 1-5

Population II:

Rituximab 375 mg/m² i.v. day 0 or day 1
Cyclophosphamide 750 mg/m² i.v. day 1
Pixantrone* 88 mg/m² i.v. day 1 (= 150 mg/m² pixantrone dimaleate)
Vincristine 1.4 mg/m² (maximum dose 2 mg) i.v. day 1
Prednisone 100 mg orally day 1-5

* = investigational medicinal product

Treatment schedule:
6 cycles R-CPOP every 21 days
additional 2 cycles of rituximab (R) every 21 days
Follow-up per patient: 2 years

A listing of used batch numbers is provided in Appendix 16.1.6.

Duration of Treatment (planned):

Recruitment period: 12 months

First patient in to last patient out: 42 months

Duration of the entire trial: 48 months

Treatment duration per patient: 6 months + 24 months follow-up

Criteria for evaluation:

Efficacy:

Primary endpoint: Rate of complete remission (CR) after induction therapy (6 x R-CPOP + 2 x R) as assessed by PET-CT at end of treatment

Secondary endpoints: Overall survival (OS) and progression-free survival (PFS)

Safety:

- Cardiac toxicity (echocardiography, ECG, NT-proBNP, Troponin T, NYHA classification)
- Adverse events (AEs) and serious adverse events (SAEs)

Statistical methods:

The statistical methods used are described in detail in the final version of the Statistical Analysis Plan (SAP), dated 21 October 2021 (see Appendix 16.1.9). All analyses were done using the Statistical Analysis System (SAS), Version 9.2.

Efficacy:

Efficacy was determined by CR rates after first line treatment. The trial was analysed according to Simon's two stage minimax design with a one sided exact binomial test (level 10%) of the null hypothesis that the CR rate is below 60%.

Secondary endpoints:

OS and PFS rates were estimated and displayed using the Kaplan Meier method.

Safety:

Documentation of cardiac toxicity and adverse events according to clinical standards of care. Descriptive analysis and comparison with published results.

Changes in the Conduct of the Study:

The study was conducted according to the final version V1.1 of the trial protocol, dated 24 April 2015, that was approved by the leading ethics committee (Freiburg) on 26 May 2015.

Afterwards, there were no changes in the conduct of the study.

SUMMARY - CONCLUSIONS:

EFFICACY RESULTS:

The primary objective of the study was to assess the rate of complete remission (CR) after induction therapy. For this goal, the rate of CR after induction therapy as determined by PET-CT 6 weeks after last treatment (EOT visit) was evaluated.

As result, this rate was higher in population II (patients with limited cardiac function) than in population I (patients aged ≥75 years), i.e. 4 patients (40.0%, 95%-CI: 12.2% to 73.8%) in population II vs. 5 patients (21.7%, 95%-CI: 7.5% to 43.7%) in population I showed CR or unconfirmed CR (uCR) at the end of treatment.

Overall response was also distinctly better in patients of population II (50% CR and 50% PR) as compared to the patients in population I (25% CR and 31% PR).

At cycle 3 (day 42), the overall response assessment yielded no differences between the two study populations, i.e. only 1 patient, each, showed CR or uCR at this time point. Also for the other tumor ratings PR, SD and PD no relevant differences between populations I and II were observed.

As result of the analysis of overall survival, OS rates were distinctly higher in the patients with limited cardiac function (population II) as compared to the patients ≥75 years (population I). This applied to all time points during the study.

A similar picture was observed for progression-free survival with higher PFS rates at all time points in the patients with limited cardiac function as compared to the older patients.

SAFETY RESULTS:

Overall, all patients experienced at least one AE during the study.

On a MedDRA SOC basis, the most frequently reported AEs regardless of relationship to trial medication were 'General disorders and administration site conditions' (mainly PTs fatigue and oedema), 'Gastrointestinal disorders' (mainly nausea and constipation), 'Cardiac disorders' (mainly chronic cardiac failure), 'Investigations' (mainly ejection fraction decreased and weight decreased), and 'Metabolism and nutrition disorders' (mainly hypokalaemia and decreased appetite). Comparison of the two study populations revealed slightly higher incidences of most events in population II.

In about 80% of patients in both study populations AEs were assessed by the investigator as possibly related to the trial medication pixantrone. On a MedDRA SOC and PT basis, a similar picture was observed as for the incidence of all AEs. In both study populations a similar percentage of patients experienced at least one AE related to IMP pixantrone and being CTCAE grade ≥3, i.e.

56.5% in population I and 60.0% in population II. The evaluation of toxicities and AEs related to the IMP did not show any new safety issues.

A total of 14 patients (60.9%) in population I and 6 patients (60.0%) in population II had at least 1 SAE. In half of these patients, i.e. 7 and 3 patients in populations I and II, respectively, the SAEs were assessed by the investigator as possibly related to pixantrone. The most frequently reported diagnoses were from MedDRA SOC 'Infections and infestations' (mainly PT pneumonia).

AEs of special interest were equally reported for both populations, i.e. in 14 patients (60.9%) in population I and 6 patients (60.0%) in population II. Accordingly, the incidence of the event "increase in NYHA class since last visit" was 47.8% in population I and 50.0% in population II and the event "reduction in ejection fraction of ≥15% as compared to baseline" was documented in 26.1% and 20.0% of patients, respectively.

In 1 patient an SAE with fatal outcome was documented. The patient died due to atypical pneumonia. This event was judged to be unrelated to the study medication. Besides this, a total of 13 patients, 10 in population I and 3 in population II, died in the course of the present study, mostly due to progression or relapse of primary disease.

Regarding the assessment of laboratory data, there were very few clinically relevant changes observed only for single parameters. Concerning the cardiac parameters NT-ProBNP and Troponin T, comparison of the number of patients with clinically relevant values at screening and end of treatment (EOT) at day 189 revealed no great changes.

For the vital signs only minor changes in classification were observed in the course of the study. NYHA assessment at screening revealed 2 patients in each population with NYHA class III. None of the patients had NYHA class IV. At the end of treatment this changed to 1 patient, each, in populations I and II. Regarding the ECG, only 1 patient in population I had an abnormal and clinically significant ECG at screening and EOT. An abnormal and clinically significant echocardiogram at screening was documented for 3 patients (13.0%) in population I and 4 patients (40.0%) in population II. This ratio decreased constantly during the study to 1 patient (7.1%) in population I and 2 patients (33.3%) in population II at the end of treatment.

CONCLUSIONS:

Treatment of elderly or cardiac frail patients R-CPOP regimen resulted in a moderate rate of complete remissions after induction therapy. This emphasizes the general frailty of especially elderly patients with aggressive lymphoma, resulting in only slow recruitment in both cohorts.

Nevertheless, the exploratory treatment of DLBCL patients with strict contraindication of anthracycline medication due to reduced cardiac function (population II) revealed encouraging efficacy with side effects as expected for this population. In particular, monitoring of cardiac parameters did not reveal substantial problems in this cohort compared to the cardiac healthy group in population I.

In conclusion, these data are helpful in treatment decisions for DLBCL patients with cardiac impairment and invites further studies in this group with a R-CPOP platform.

Date of the Report: 12 April 2022