CMC-R-GEMOX

CLINICAL STUDY REPORT

Investigational Product:	CMC544
Protocol No./Study No.:	CMC-R-GEMOX
EudraCT No.:	2011-003849-18
Study Title:	A multi-center, phase Ib/II, open label, single arm study of inotuzumab ozogamicin plus rituximab (R-CMC544) alternating with gemcitabine-oxaliplatin plus rituximab (R-GEMOX) in patients aged from 18 to 80 years with CD20 and CD22 positive diffuse large B-cell lymphoma (DLBCL) in relapse after/refractory to 1st or 2nd line treatment, who are no candidates for autologous transplant.

Development Phase:	Ib/II
Indication:	Diffuse large B-cell Lymphoma in relapse after/refractory to 1st or 2nd line treatment

Date First Patient enrolled:	03-Dec-2012
Date Last Patient Last Visit:	02-Mar-2016
Report Date:	22-Mar-2017
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1. SYNOPSIS

Name of Sponsor/Company: LYSARC		
Name of Finished Product: CMC544, inotuzumab ozogamicin		
Name of Active Ingredient: CMC544, inotuzumab ozogamicin		

Title of Study:
A multi-center, phase Ib/II, open label, single arm study of inotuzumab ozogamicin plus rituximab (R-CMC544) alternating with gemcitabine-oxaliplatin plus rituximab (R-GEMOX) in patients aged from 18 to 80 years with CD20 and CD22 positive diffuse large B-cell lymphoma (DLBCL) in relapse after/refractory to 1st or 2nd line treatment, who are no candidates for autologous transplant

Coordinating Investigators:
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Study Centers:
Conducted in 10 centers in France and Belgieum.
Program coordinating center: LYSARC, Centre Hospitalier Lyon Sud, Secteur Sainte Eugénie – Pavillon 6D, F-69495 Pierre Bénite Cedex

Publications:
No publications based on this study are currently available (as of the date of this clinical study report).

Studied Period (years):		**Phase of Development:**
Date of first patient enrolled:	03-Dec-2012	Ib/II
Date of last patient last visit :	22-Mart-2016	

Primary Objective:
The primary objective of the phase Ib part of the study is to determine the tolerability, safety and MTD or recommended dose of R-CMC544 alternating with R-GEMOX in subjects aged from 18 to 80 years with CD20 and CD22 positive DLBCL in relapse after/refractory to 1st or 2nd line treatment, who are no candidates for autologous transplant.

The primary objective of the phase II part of the study is to assess the efficacy or R-CMC544 alternating with R-GEMOX as measured by the overall response rate (ORR) by IWG criteria (Cheson 1999) at the end of treatment (after complete treatment or at withdrawal).

Secondary Objectives:
The secondary objective is to obtain preliminary information on the anti-tumor activity of R-CMC544 alternating with R-GEMOX measured by the overall response rate (ORR) after induction according to Cheson 1999, the overall response rate (ORR) after induction and at the end of treatment according to Cheson 2007, complete response rate (CRR) at the end of treatment according to Cheson 2007, progression free survival (PFS), event free survival (EFS), overall survival (OS), duration of Response (DOR) and time to Progression (TTP)

Methodology:
Multicenter, phase Ib/II, open-label, single arm trial evaluating the efficacy and safety of R-CMC544 alternated with R-GEMOX in patients with CD20 and CD22 positive DLBCL in relapse after/refractory to 1st or 2nd line treatment, who are no candidates for autologous transplant.
All patients receive two 56 day induction cycles of alternating R-CMC544 (given on day 1) and R-GEMOX (given on day 29 and 43). Patients who obtain CR or PR, will go on a consolidation of another two 56 day cycles of alternating R-CMC544 (given on day 1) and R-GEMOX (given on day 29 and 43)

Number of Patients:
The number of dose levels examined and the emerging DLTs determined the exact sample size. It was anticipated that approximately 40 subjects would be enrolled in the total study: 10 up to 12 subjects to establish the maximum tolerated dose (MTD) in part 1 and up to 30 additional subjects to obtain preliminary

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efficacy data in part 2.

Finally, 11 patients were included in the study as part 2 was cancelled by Sponsor.

Inclusion criteria:

- Histologically documented CD20 and CD22 positive diffuse large B-cell lymphoma, according to WHO classification. Prior CD20 and CD22 immunophenotyping is acceptable. If such prior documentation is not available, then the immunophenotype of the current disease must be documented by fine-needle aspirate or biopsy or by circulating CD20 and CD22 positive non-Hodgkin lymphoma (NHL) cells from peripheral blood during screening. In case of relapse or partial response the disease must be histologically or cytologically proven.
- Upon registration the anapath report confirming the diagnosis, must be available.
- During the trial the tumor tissue biopsy must be made available for confirmation of the disease.
- In first or second relapse or refractory to first and/or second line treatment. Refractory is defined as less than PR to a prior rituximab containing regimen or relapse within 6 months of the last dose of a prior rituximab containing regimen.
- Not eligible for autologous transplantation.
- Previously treated with a chemotherapy regimen containing anthracyclines and rituximab.
- Aged 18 - 80 years.
- ECOG performance status 0 to 2.
- Minimum life expectancy of 3 months.
- Signed written informed consent.

Exclusion criteria:

- Burkitt, mantle cell and T-cell lymphomas.
- Central nervous system or meningeal involvement by the lymphoma.
- Contraindication to any drug contained in the R-GEMOX combination chemotherapy.
- Treatment with any investigational drug within 30 days before the first planned cycle of chemotherapy and during the study.
- Nitrosurea or mitomycin C administration within 6 weeks prior to study start.
- Major debulking surgery within 3 weeks of treatment start.
- Any of the following lab abnormalities (unless related to the lymphoma or bone marrow infiltration):
  - Absolute neutrophil count (ANC) < 1.500/µL (1,5.109/L).
  - Platelet count < 100.000/µL (100.109/L).
  - Creatinine level > 150 µmol/L (1,7 mg/dL) or 1,5 – 2,0x ULN.
  - Total bilirubin level > 30 µmol/L (1,8 mg/dL) or 1,5x ULN.
  - Serum AST/SGOT or ALT/SGPT >2,5x ULN.
  - Documented infection with HIV, active hepatitis B or C infection.
- Any serious active disease or co-morbid medical condition that, according to the investigator's decision, will substantially increase the risk associated with the subject's participation in the study. Prior history of malignancies other than lymphoma with the exception of non-melanoma skin tumors (basal cell or squamous cell carcinoma of the skin) or stage 0 (in situ) cervical carcinoma unless the subject has been disease-free for 5 or more years.
- LVEF less than 50% (measured by echocardiography or scintigraphy).
- Previous myocardial infarction or pulmonary hypertension within 6 months before the first dose of investigational product.
- Congestive heart failure NYHA stage III or IV
- Known chronic liver disease (e.g. Cirrhosis) or suspected alcohol abuse.
- Pregnant or lactating females
- Men and women who are biologically capable of having children not willing to use an adequate method of birth control during the study and up to 18 months after the last dose of investigational

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product.

- Adult patient unable to provide informed consent because of intellectual impairment, any serious medical condition, laboratory abnormality or psychiatric illness.

Investigational Product:

CMC544 (inotuzumab_ozogamicin): provided by Pfizer, SAS in 10 or 20 mL type I amber vials with rubber closure and aluminum flip-top cap.

Product	Mode of administration	Dose	Lot Numbers
CMC544	Intravenous	4 mg	2010B0009 349941 (not used) 12-000653 (F18454) – CLI7012 12-000653 (F18454) – CLI7265

Criteria for Evaluation:

For the part 1 of the study, the primary endpoint of the study is the determination of the Recommended Dose of R-CMC544 alternating with R-GEMOX. Therefore, primary analysis will be based on safety parameters and particularly on incidence of DLTs as defined as follows (NCI CTCAE vs. 4):

- Grade 4 neutropenia ≥ 7 days
- Grade 4 thrombocytopenia ≥ 7 days
- Grade 3 or 4 thrombocytopenia associated with bleeding requiring a transfusion
- Grade 3 non-hematologic toxicity (except alopecia) ≥ 7 days or determined to be investigational product-related
- Grade 4 non-hematologic toxicity (except alopecia)
- Grade 4 AST/ALT increase irrespective of duration
- Grade 2 hyperbilirubinemia (> 1.5 x ULN) > 7 days
- Grade 3 or greater QTc prolongation (average of three ECGs)
- Delayed recovery from an investigational product-related toxicity that prevents redosing by more than 21 days.

Frequency of patients with DLT will be reported by dose level. Toxicities related to study regimen and occurring during the assessment period will be reviewed to confirm if they were dose limiting according to protocol and initial patient condition (pre-existing signs and symptoms, medical history). A listing will provide the description of DLTs observed by dose level.

For the part 2 of the study, the primary endpoint is the Overall Response Rate according to Cheson 1999 at the end of treatment (after complete treatment or at withdrawal).

Secondary efficacy endpoints (for phase I and II parts of the study unless otherwise specified) will include ORR, CRR, PFS, EFS and OS. Analysis of safety will be performed by summarizing adverse events, laboratory data, vital signs and ECOG performance status.

Sample Size Determination:

For the part 1 of the study, the number of dose levels and the emerging dose limiting toxicities determined the sample size. It was anticipated that up to 18 patients will be required to establish the maximum tolerated dose (MTD) and the recommended dose of CMC544.

For the part 2 of the study, sample size calculation was based on efficacy criteria. Based on previous platin-

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cytarabine based studies ORR was estimated to 40% while on R-GEMOX study, the ORR is 60% (based on Cheson 99 criteria). We therefore estimated that an overall response rate was about 60% for an ineffective treatment (p0) and 82% for an effective one (p1). Sample size calculation was performed with NCSS-PASS 2008 using an exact single-stage phase II design (A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med. 2001.20(6):859-66). Assuming an alpha risk of 0.05 and beta of 0.10 with a one-tail formulation, 36 evaluable patients are needed with a cut-off number of 26 complete responses. As 6 patients will have already been included in Phase I of the study at the recommended dose, we planned to include 30 patients in the phase II study.

CONCLUSIONS:

Eleven patients were enrolled in the phase Ib part of CMC-R-GEMOX trial. Five of them did not have a DLT assessment during the DLT period (2 cycles of treatment) due to early progression or following investigator's decision. They were consequently excluded from the DLT evaluable set of patients. The toxicity review committee met at the end of each cohort of 3 evaluable patients, when the DLT observation period ended before starting cycle 3 (112 days).

Half of the patients progressed or withdrew the study during this period, so that the recruitment dynamic was difficult to keep. Two DLT were observed in the first cohort and 1 DLT were observed in the second cohort. On the 3 patients who had a DLT during first two cycles, one had gammaGT increased which was not considered as a clinically significant DLT by the toxicity review committee.

As written in the protocol and following the de-escalation rules, the recommended phase 2 study dose was found and confirmed by an IDMC. However, the long duration of the phase I slowed down the investigators motivation. In addition, the overall response rate was poor. Given these data, the study coordinators decided not to proceed the phase 2 part of CMC-R-GEMOX.

The results presented on this report come from the analysis performed at the end of the DLT period of the de-escalation phase for the determination of the RP2D by the IDMC.

Report Date:
22-Mar-2017