BRIEF

CLINICAL STUDY REPORT

Investigational Product:	Bendamustine, LEVACT™ (Mundipharma) Rituximab, MABTHERA™ (Roche)
Protocol No./Study No.:	BRIEF
EudraCT No.:	2010-020757-14
Study Title:	Bendamustine and Rituximab In Elderly Follicular: a multicentric phase II study evaluating the benefit of a short induction treatment by Bendamustine and Rituximab followed by maintenance therapy with Rituximab In Elderly (≥ 60 years old) patients with untreated Follicular lymphoma patients, with an intermediate or high FLIPI score

Development Phase:	II
Indication:	Untreated Follicular Lymphoma

Date First Patient enrolled:	22/02/2011
Date Last Patient Last Visit:	01/07/2016
Report Date:	30/07/2018
Report Written by:	Florence Broussais MD and Marine Crouzille LYSARC, Pierre-Bénite, France
Sponsor:	LYSARC - The Lymphoma Academic Research Association Centre Hospitalier Lyon Sud, Secteur Sainte Eugénie (Bâtiment 6D) Chemin du Grand Revoyet, 69310 Pierre Bénite, France ☎: +33(0)4.72.66.93.33 Fax : +33(0)4.72.66.93.71
Project Managers:	Marine Crouzille (marine.crouzille@lysarc.org) LYSARC ☎: +33(0)4.72.66.93.33 Fax : +33(0)4.72.66.93.71
Coordinating Investigators:	Pr Pierre FEUGIER (Coordinating Investigator) Dr Emmanuel GYAN (Co-coordinating Investigator) Dr Anne SONET (Co-coordinating Investigator)

1 SYNOPSIS

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Module x.x.x	*(For National Authority Use only)*
Name of Finished Product: LEVACT™ (Mundipharma) MABTHERA™ (Roche)	Volume:	
Name of Active Ingredient: Bendamustine Rituximab	Page:	

Title of Study:
Bendamustine and Rituximab In Elderly Follicular: a multicentric phase II study evaluating the benefit of a short induction treatment by Bendamustine and Rituximab followed by maintenance therapy with Rituximab In Elderly (≥ 60 years old) patients with untreated Follicular lymphoma patients, with an intermediate or high FLIPI score

Coordinating Investigators:
Pr Pierre FEUGIER (Coordinating Investigator)
Dr Emmanuel GYAN (Co-coordinating Investigator)
Dr Anne SONET (Co-coordinating Investigator)

Study Centers:
Conducted in 29 centers in France, 2 in Belgium
Program coordinating center: LYSARC, Centre Hospitalier Lyon Sud, Secteur Sainte Eugénie (Bâtiment 6D), Chemin du Grand Revoyet, 69310 Pierre Bénite, France

Publications:
One publication based on this study is currently available (as of the date of this clinical study report).

Studied Period (years):		**Phase of Development:**
Date of first patient enrolled:	Feb 22, 2011	II
Date of last patient last visit :	Aug 1, 2016	

Primary Objective:
The primary endpoint was the Complete Response Rate at the end of induction phase. Assessment of response was based on the International Workshop to Standardize Response criteria for NHL (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson, 1999). Response was assessed at the end of induction phase if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) was considered as non-responder.

Secondary Objectives:
• The secondary objectives of the study were to evaluate:

- Complete response rate at the end of induction phase according to Cheson 2007
- Overall response rates at the end of induction phase according to Cheson 1999
- Overall response rate at the end of induction phase according to Cheson 2007
- Response rates at the end of maintenance phase according to Cheson 1999
- Response rates at the end of maintenance phase according to Cheson 2007
- Response duration (RD)
- Progression-free survival (PFS)
- Overall survival (OS)

Methodology:
This study was a multicentric single-arm phase II trial evaluating the benefit of a short induction treatment by Bendamustine and Rituximab followed by maintenance therapy with Rituximab In Elderly (≥ 60 years old) patients with untreated Follicular lymphoma patients, with an intermediate or high FLIPI score

The induction phase included 4 weekly doses of rituximab at 375 mg/m² intravenously (IV), combined with 2 courses of bendamustine (90 mg/m² D1-D2 and D29-D30). Patients achieving a partial remission (PR) or

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Module x.x.x	*(For National Authority Use only)*
Name of Finished Product: LEVACT™ (Mundipharma) MABTHERA™ (Roche)	Volume:	
Name of Active Ingredient: Bendamustine Rituximab	Page:	

CR/CRu at week 12 received rituximab as a maintenance therapy at 375 mg/m² IV every 2 months for 2 years (Figure 1). Patients with stable or progressive disease (PD) at week 12 were withdrawn from the study.

Number of Patients:
Sixty-three patients were included in the study between Feb 22, 2011 and June 20, 2012.

Inclusion criteria:

- Histologically confirmed follicular lymphoma CD20+, all grades except the grade 3b with a lymph node biopsy performed within 6 months before study entry and with material available for central review
- A minimal initial immunology is required, including : CD20, bcl-2, CD10 and CD5
- Age must be ≥ 60 years
- Patients not previously treated
- Patients with an intermediate or high risk **FLIPI** score requiring **2 or more** of the following adverse prognostic factors:
  1. Age >60 ans
  2. Ann Arbor Stage (I-II vs. III-IV)
  3. Hemoglobin level (< 12g/dL vs. ≥ 12 g/dL)
  4. Number of nodal areas (< 5 vs. ≥ 5)

(Note: LDH should not be considered as an adverse prognostic factor in this study since it is considered as high tumor burden in the GELF criteria)

- Low burden disease at study entry according to the GELF criteria
- Patients with at least one measurable site of disease: patients with only blood or marrow or splenic infiltration are excluded
- Performance status ≤ 2 on the ECOG scale
- Adequate hematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) including:
  - o Hemoglobin ≥ 8.0 g/dL (5.0 mmol/L)
  - o Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
  - o Platelet count ≥ 100 x 109/L
- Adequate renal function: calculated creatinine clearance > 50 ml/min (according to MDRD method) unless these abnormalities are related to lymphoma
- Adequate hepatic function: Total bilirubin < 2.0 mg/dl (34 µmol/L), AST (SGOT) and ALT (SGPT) ≤ 2.5 x the upper limit of normal unless these abnormalities are related to lymphoma
- Adequate cardiac function: LEVF ≥ 50% calculated by echocardiography or scintigraphy
- Having previously signed a written informed consent

Exclusion criteria:

- Other histological types of lymphoma than follicular lymphoma
- Grade 3b follicular lymphoma
- Patients previously on watch and wait since more than 6 months from diagnosis
- Patients previously treated for lymphoma, except splenectomy
- Patients with low FLIPI score (0 or 1 adverse prognostic factors not considering elevated LDH)
- Bulky disease at study entry according to the GELF criteria
- Presence or history of CNS disease (either CNS lymphoma or lymphomatous meningitis)

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Module x.x.x	*(For National Authority Use only)*
Name of Finished Product: LEVACT™ (Mundipharma) MABTHERA™ (Roche)	Volume:	
Name of Active Ingredient: Bendamustine Rituximab	Page:	

- Patients with prior or concomitant malignancies except non-melanoma skin cancer or adequately treated in situ cervical cancer or previous cancer in CR without any treatment in the last 5 years
- Positive HIV, HBV (anti-HBc positivity) and HCV serologies before inclusion
- Poor Performance status > 2 on the ECOG scale
- Known contra-indication to study product
- Serious underlying medical conditions, which could impair the ability of the patient to participate in the trial (e.g. ongoing infection, uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease).
- Any other co-existing medical or psychological condition that will preclude participation in the study or compromise ability to give informed consent.

Investigational Product:

Bendamustine (LEVACT®) at the dose of 90 mg/m² intravenously - provided by Mundipharma as a lyophilized powder.

Rituximab (MABTHERA®) 375 mg/m² intravenously - supplied by Roche only for the induction phase

Criteria for Evaluation:

Primary efficacy endpoints: Complete response Rate

The primary endpoint of the study was the Complete Response (CR+CRu) rate at the end of induction. Assessment of response was based on the International Workshop to Standardize Response criteria for NHL 1999 (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson 1999). Response was assessed at the end of induction if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) was considered as non-responder.

A descriptive analysis has also been performed considering as non-responders all patients who relapsed or died during treatment phase even if they were prematurely withdrawn as responder.

Secondary efficacy endpoints

1. Complete response rate at the end of induction phase according to Cheson 2007:

The Complete Response (CR+CRu) rate at the end of induction was evaluated and based on the International Workshop to Standardize Response criteria for NHL 2007 (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson 2007). Response was assessed at the end of induction if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) was considered as non-responder.

2. Overall response rates at the end of induction phase according to Cheson 1999

The Overall Response (CR+Cru+PR) rate at the end of induction was evaluated. Assessment of response was based on the International Workshop to Standardize Response criteria for NHL 1999 (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson 1999). Response was assessed at the end of induction if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) was considered as non-responder.

3. Overall response rate at the end of induction phase according to Cheson 2007

The Overall Response (CR+Cru+PR) rate at the end of induction was evaluated and based on the International Workshop to Standardize Response criteria for NHL 2007 (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson 2007). Response was assessed at the end of induction if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason)

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Module x.x.x	*(For National Authority Use only)*
Name of Finished Product: LEVACT™ (Mundipharma) MABTHERA™ (Roche)	Volume:	
Name of Active Ingredient: Bendamustine Rituximab	Page:	

was considered as non-responder.

4. Response rates at the end of maintenance phase according to Cheson 1999

The Complete Response (CR+Cru) and Overall Response (CR+Cru+PR) rate at the end of maintenance were evaluated. Assessment of response was based on the International Workshop to Standardize Response criteria for NHL 1999 (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson 1999). Response was assessed at the end of maintenace if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) was considered as non-responder.

5. Response rates at the end of maintenance phase according to Cheson 2007

The Complete Response (CR+Cru) and Overall Response (CR+Cru+PR) rate at the end of maintenance were evaluated. Assessment of response was based on the International Workshop to Standardize Response criteria for NHL 2007 (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson 2007). Response was assessed at the end of maintenance if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) was considered as non-responder.

6. Response duration (RD)

Response duration was measured from the time of attainment a CR or PR (according to Cheson 1999) to the date of progression, relapse or death from any cause. For patients achieving a response but who have not progressed or relapsed or died at the time of analysis, RD was censored on the date of last tumor assessment.

7. Progression-free survival (PFS)

Progression-Free Survival was defined as the period from the date of inclusion to the date of first documented disease progression, relapse, or death from any cause. For patients who have not progressed, relapsed, or died at the time of analysis, PFS was censored on the date of last tumor assessment. If no tumor assessments were performed after the baseline visit, PFS was censored at the time of inclusion.

8. Overall survival (OS)

Overall survival was defined as the period from the date of inclusion to the date of death from any cause. Alive patient were censored at the last date of contact.

<u>Safety endpoints</u>

The following safety endpoints were summarized:

- All adverse events were tabulated and graded for highest intensity level according to the NCI-CTCAE (Version 4.0) for each patient. Verbatim descriptions of SAEs reported during the study period were mapped to MedDRA-Preferred Term and System Organ Class.
- All SAEs, grade 3 and higher, study drug related events, AEs leading to death were listed and summarized in frequency tables.
- All deaths were listed and also summarized by cause of death.
- laboratory data
- Vital signs and ECOG performance status.

When applicable, summary of safety data have also been performed by cycle. Clinical laboratory tests were summarized in terms of mean, median, minimum and maximum values and standard deviation by visit. Vital signs were summarized in terms of mean, median, minimum and maximum values and standard deviation by visit.

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Module x.x.x	*(For National Authority Use only)*
Name of Finished Product: LEVACT™ (Mundipharma) MABTHERA™ (Roche)	Volume:	
Name of Active Ingredient: Bendamustine Rituximab	Page:	

Statistical Methodology:
Continuous variables was summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles have also been presented when considered relevant. Categorical data was described in counts and percentages (of non-missing data). Censored data was presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% CIs. The median time to event was calculated (if reached) with 95% confidence intervals.
The number and percent of subjects falling into each category of response according to Cheson criteria 1999 and 2007 have been provided. Deaths have also been included as a category, if patients died during the corresponding period. Response rates was expressed with 95% confidence limits according to Pearson Clopper method. The effects of prognostic factors on response rates was assessed in an exploratory analysis using logistic regression. The results was presented in terms of odds ratios including 95% confidence limits and associated pvalues.

For exploratory purpose, impact of individual important baseline prognostic factors on PFS/OS was assessed by a two-sided log-rank test and estimates was expressed as risk ratios based on the Cox regression analysis with 95% confidence intervals. A multivariate Cox regression analysis have then been performed with these factors.

Sample Size Determination:
Based on previous studies in this population of follicular lymphoma patients, we estimated that the complete response rate was about 40% for an ineffective treatment (p0) and 60% for an effective one (p1).
Sample size calculation was performed with NCSS-PASS 2002 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, 56 evaluable patients were needed with a cut-off number of 28 complete responses.
If the number of responses was 29 or more, the hypothesis that P <= 0.400 was rejected with a target error rate of 0.050 and an actual error rate of 0.049. If the number of responses was 28 or less, the hypothesis that P >= 0.600 was rejected with a target error rate of 0.100 and an actual error rate of 0.083.

CONCLUSIONS:
Two cycles of bendamustine administered concomitantly with 4 weekly cycles of rituximab may result in a high response rate and PFS. Due to the observed toxicity-related deaths, this scheme may not be recommended in LTBFL. Further research aiming at proposing short-term treatments with low toxicity and prolonged PFS should be encouraged for these patients.

Because of 3 deaths evaluated to be related to the experimental treatment, the Scientific Board of the LYSA met on November 13, 2012, and decision was made to definitively stop rituximab treatment during maintenance phase, according to DSMC recommendations

Report Date:
30/07/2018