

## PVAB STUDY

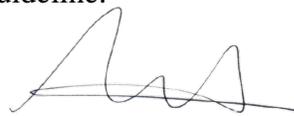
### **A prospective phase II study of bendamustine in patients aged over 60 years with classical Hodgkin lymphoma treated by prednisone, vinblastine and doxorubicin**

Indication studied: *Hodgkin lymphoma*  
Developmental phase of study: *Phase 2*  
EudraCT No. *2014-001002-17*  
First subject enrolled: *17 July 2015*  
Last subject completed: *10 November 2020*  
Data cutoff date: *10 November 2020*  
Overall survival update *10 November 2020*  
Release date of report: *16 May 2021*

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This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Sponsor's Responsible Medical Officer:



Pascale Cony-Makhoul, MD

8-JUN-2022

Date

## 2. SYNOPSIS

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: PVAB		
Name of Active Ingredient: PVAB		
<b>Title of Study:</b> A prospective phase II study of bendamustine in patients aged over 60 years with classical Hodgkin lymphoma treated by prednisone, vinblastine and doxorubicin.		
<b>Coordinating Investigators :</b> Pr Hervé GHESQUIÈRES - Centre Hospitalier Lyon-Sud – Service Hématologie – Chemin du Grand Revoyet, F-69310 Pierre-Bénite, France  Dr Pauline BRICE - Hôpital Saint Louis – Service Hématologie– Coquelicot 6 1 avenue Claude Vellefaux - F-75475 Paris 10, France		
<b>Study site(s) and countries:</b> 34 study centers in France and Belgium.		
<b>Publications (reference):</b>		
<b>Studied period (years):</b> Date first subject first visit: 20/07/2015 Date last subject completed: 10/11/2020 Data cutoff date: 10/11/2020	<b>Phase of development:</b> Phase II	
<b>Trial registry number(s):</b> ClinicalTrials.gov identifier: NCT02414568 EudraCT number: 2014-001002-17		
<b>Objectives:</b> <u>Primary:</u> to assess the Complete Metabolic Response (CMR) rate at the final evaluation after completion of study treatment (after 6 cycles of study treatment or at premature treatment discontinuation) defined according to Lugano Classification (PET-CT-Based response).  <u>Secondary:</u> to evaluate: <ul style="list-style-type: none"> <li>• The feasibility of the protocol, with adequate protocol adherence (adequate dose without excessive delay)</li> <li>• The safety profile including immediate toxicities and non-tumor events</li> <li>• Progression-free survival (PFS), disease-free survival (DFS) and overall survival (OS)</li> <li>• The geriatric assessment program (G8, reduced IADL, ADL, CIRS-G, MNA, QLQ-C30 and QLQ-ELD14).</li> </ul> <u>Exploratory:</u> <ul style="list-style-type: none"> <li>• EBV assessment in plasma (at baseline, after the 4th cycle of induction, at the end of treatment and at progression/relapse)</li> <li>• EBER evaluation in tumor</li> <li>• Plasma samples before any treatment for proteomic assessment</li> <li>• Serum samples for cytokine profile before any treatment and at progression/relapse</li> </ul>		

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<ul style="list-style-type: none"> <li>• Blood samples for genomic DNA</li> <li>• Lymphocytes T typing CD3/CD4/CD8</li> <li>• Evaluation of tumor response rate by centralized PET scan review</li> <li>• Evaluation of initial metabolic tumor volume and correlation with CMR.</li> </ul>		
<p><b>Methodology:</b></p> <p>This study was a multicentric, open-label phase 2 trial. Treatment consisted of an induction with four courses of PVAB every three weeks, followed by a CT scan. For patients in CR and partial response (PR) according to CT-based response Lugano classification criteria, patients received two additional cycles of PVAB delivered every 3 weeks. Patients in stable disease (SD) and progressive disease (PD) were considered as treatment failure. The evaluation at the end of treatment after six cycles of PVAB was done according to Lugano Classification criteria (PET-CT-Based response). Concomitant administration of any other chemotherapy regimen or radiotherapy during study treatment was not allowed. PVAB regimen consisted of prednisone (40mg/m<sup>2</sup> day 1 to 5), vinblastine (6mg/m<sup>2</sup>, day 1), doxorubicin (40mg/m<sup>2</sup>, day 1) and bendamustine (120mg/m<sup>2</sup>, day 1). Sub-cutaneous G-CSF was recommended from day 6 to day 13 or until neutrophils <math>\geq 1.0</math> G/L. Anti-infective prophylaxis including anti-viral for preventing herpesviruses and Pneumocystis jiroveci pneumonia with valaciclovir and trimethoprim/sulfamethoxazole or equivalent was recommended. In case of acute toxicities, a dose reduction scheme was provided in the full version of the protocol.</p>		
<p><b>Number of subjects (planned, enrolled, and analyzed):</b></p> <p>Planned: 90 patients Enrolled: 90 patients Analyzed: 89 patients</p>		
<p><b>Diagnosis and main criteria for inclusion:</b></p> <p>Eligible patients were first diagnosis of cHL according to WHO criteria excluding nodular lymphocyte predominant subtype; age of 61 years or older; no previous treatment for Hodgkin lymphoma; advanced Ann Arbor stages corresponding to stage 2 with ratio mediastinum/thorax <math>\geq 0.33</math> or extranodal localization with B symptoms, stage 3 and 4; Baseline 18-FDG PET scan performed before any treatment with at least one hypermetabolic lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2; adequate cardio-pulmonary function with left ventricular ejection fraction (LVEF) <math>\geq 50\%</math>; adequate renal function with creatinine clearance <math>\geq 40</math> mL/mn (MDRD formula); patients were required to have normal liver and hematological functions unless abnormalities were related to cHL; for patients aged 70 years old and more, a MNA <math>\geq 17</math> was mandatory.</p>		
<p><b>Test product, dose, and mode of administration:</b></p> <p>All drugs composing the regimens of the study were registered and were available at the hospital pharmacy. PVAB was administered according to the standard preparation and infusion procedures of each investigational site.</p>		
<p><b>Duration of treatment:</b></p> <p>Patients were recruited for 3 years and followed until the last patient had 2 years of follow-up, which occurred 5 years after the first included patient. The duration of the treatment period was approximately 18 weeks for 6 cycles of chemotherapy.</p>		
<p><b>Reference therapy, dose, and mode of administration:</b></p> <p>PVAB as reference therapy was used in this study.</p>		

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<b>Criteria for evaluation:</b>		
<u>Efficacy:</u>		
Response was assessed after complete study treatment if patient received all planned cycles or at premature treatment discontinuation according to Lugano Classification (PET-CT-Based response).		
The categorization of the patients according to response results at the end of study treatment or at premature treatment discontinuation was performed as follows:		
<ul style="list-style-type: none"> <li>• CMR → responder</li> <li>• PMR → non responder</li> <li>• NMR → non responder</li> <li>• PMD → non responder</li> <li>• Not Evaluated / Missing (for any reason) → non responder</li> </ul>		
<u>Safety:</u>		
This trial was designed to allow early termination or modification of the protocol for safety concerns (serious adverse event, adverse event leading to treatment discontinuation or dose modifications, death) based on the advice of an independent IDMC.		
<b>Statistical methods:</b>		
<u>Full Analysis Set (following an intent to treat principle)</u>		
The Full Analysis Set (FAS) included all patients enrolled in the study and having signed the informed consent form, and who received at least one dose of bendamustine.		
This set was used for demographic data, disease characteristics at inclusion, medical history, patient reported outcome questionnaires, patient disposition summaries and efficacy parameters. This set was also used for safety analyses, including extent of exposure to trial medication, adverse events and laboratory data summaries.		
<u>Efficacy Set</u>		
The Efficacy Set included all patients included in the FAS with an available response evaluation at end of study treatment and with no major protocol violation. Major protocol violations are described below:		
<ul style="list-style-type: none"> <li>• Non respect of inclusion/exclusion criteria</li> <li>• Diagnosis not confirmed by central review</li> <li>• No treatment received</li> </ul>		
The Efficacy Set was used to ensure the robustness of the results obtained with the Full Analysis Set. It was therefore used to support the primary efficacy analysis.		
<u>Efficacy analyses</u>		
The efficacy analyses, including the primary efficacy analysis, was based on the Full Analysis Set (FAS). Response rates were expressed with 90% confidence limits (to be consistent with one sided 5% level of significance) according to Pearson-Clopper method. The number and percent of patients falling into each category of response (CMR/CR, PMR/PR, NMR/SD, PMD/PD, Not evaluated, Missing) were provided.		
Deaths were included as a category if patients died during the corresponding period.		

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### SUMMARY – CONCLUSION

Between July 20, 2015, and July 31, 2018, 90 patients were enrolled in the study but one patient did not receive chemotherapy. The median age was 68 years (range, 61-88) with 35 (39%) aged of 70 years or older. The ECOG PS was 0-1 for 74 patients (73%) and 57% of patients had B-symptoms at diagnosis. A majority of patients had advanced stage (III, n=30, 34%; IV, n=56, 63%). Nodular sclerosis was the most frequent cHL subtype according to local diagnosis (n=61, 69%) or after central histological review (n=56, 63%). Tumors was associated to EBV using LMP1 or EBER staining in 26 of 82 available cases (32%) and 33/70 (47%) cases, respectively. For geriatric assessments, the median cumulative illness rating scale for geriatrics (CIRS-G) at baseline was 3 (range, 0-12) with 8 patients with at least one grade 3-4 comorbidities. Of

Among the 89 included patients, 83 (93%) and 78 (88%) patients completed 4 and 6 cycles, respectively with a median of 6 cycles received (range, one to 6). As expected, patients <70 years completed the 6 cycles (94%) more frequently as older patients (77%). The administrated dose of prednisone, vinblastine, adriamycin and bendamustine per cycle was closed to the expected dose. Pre-defined dose adjustments according to hematological toxicities or infections were applied for 10 patients. Among the 83 patients who completed the first four cycles, 28 patients were in CR (34%), 53 patients were in PR (65%) and one patient had a stable disease (SD) based on CT scan evaluation.

CMR at the end of the 6 cycles of PVAB (n=78) or at discontinuation (n=11) was obtained for 69 patients (77.5%, 95%CI, 67% to 86%). Partial metabolic response, no metabolic response and progression metabolic response were obtained for 8 (9%), 2 (2%), 5 (6%) patients, respectively and 5 patients (6%) were not evaluable.

Eighty-four patients (94%) presented at least one AE with a grade $\geq$ 3 corresponding to 346 events declared by investigators. Twenty-eight patients (31.5%) presented at least one serious adverse events (SAEs), for a total of 57 events. Among these SAEs, 41 were considered as related SAEs presented by 18 patients. As expected, the number of SAEs and related SAEs were influenced by age and ECOG PS. For patients <70 and  $\geq$ 70 years old, 18.5% and 51.4% of patients presented at least one SAEs, respectively (9.3% and 37.1% for related SAEs). Similarly, 25.7% and 60% of patients with ECOG PS 0-1 and >1 presented at least one SAEs, respectively (14.9% and 46.7% for related SAEs). Interestingly, for the 34 older patients who had a MNA evaluation, 33% of patients with a normal MNA score had related SAEs as compared to 44% for patients with an abnormal MNA score. Four patients presented toxic death (4.5%). Three patients presented fatal toxicities after cycle 1 with one cardiogenic shock (71 years old), one septic shock (70 years old) and one brain stem hematoma in a context of grade 4 thrombocytopenia (76 years old). Last patient presented a fungal infection after cycle 4 (86 years old).

With a median follow-up of 42 months (95%CI, 40-47), the median PFS was 55.2 months (95%CI, 27-not reached). The 4-year PFS rate was 50% (95%CI, 39-61). Events for PFS were progression or relapses for 31 patients (35%) and death from any cause for 12 patients (28%). The 4-year DFS rate was 63% (95% CI, 49-74) for the 69 patients who obtained a CMR at the end of treatment with 18 relapses. Among the 89 patients, 24 patients (27%) died: 11 from HL (46%), 4 from toxicity during treatment (17%) and 6 from for second cancers (25%). Five patients who died of second cancers (colic adenocarcinoma, esophagus adenocarcinoma, biliary tract adenocarcinoma, lung adenocarcinoma) were in CR after PVAB regimen at last follow-up. The last patient who died of an acute myeloid leukemia presented a relapse treated by BV in combination with cytarabine and oxaliplatin followed by radiotherapy that allowed a new CR for HL. The remaining three patients (12%) died from other causes after PVAB: one pulmonary infection in CR at last follow-up, one cardiac insufficiency in CR at last follow-up, one pulmonary embolism in PD at the end of treatment who did not receive salvage therapy.

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<p>The median OS was not reached with a 4-year OS rate of 69% (95%CI, 57-79).</p> <p>As PFS is influenced by related and non-related lymphoma events, we estimated cumulative incidence of each event for PFS. At 4 years, the cumulative risk of progression/relapse, death from lymphoma and death from other cancer were 35% (95%CI, 25-45), 9% (95%CI, 4-16) and 6% (95%CI, 2-13), respectively. Cumulative incidence of death at 4 years of lymphoma, toxicity and unrelated cancer were 13.5% (95%CI, 7-22), 8.7% (95%CI, 4-16), 8.8% (95%CI, 3-18), respectively.</p> <p>In conclusion, PVAB regimen provided high CMR in first-line therapy for older classical HL patients with acceptable toxicity. Patients who obtained CMR after PVAB regimen had a favorable outcome. For these patients, the 4-year cumulative risk of events is 6.5% of progression and relapse, 3.9% of death from lymphoma and 7.8% of non-lymphoma events. Our trial also brings important information about challenges for older cHL patients. It confirms the feasibility of geriatric assessments to select patients unable to tolerate frontline chemotherapy and the usefulness of MNA scale; the higher rate of SAEs during first cycle and at the end of the planned therapy. These informations are in favor of tailored therapies for older HL patients. The sequential approach with frontline immunotherapy (BV or checkpoint inhibitors and in combination) followed by shortened courses of chemotherapy depending on early response should be confirmed in clinical trial setting. The choice of “standard” chemotherapy remains important, as “alternative” therapies or the use of non-anthracycline regimens seem to alter PFS and OS. As demonstrated by large epidemiological series, we observed an increased risk of second cancers that inclines specific follow-up. Finally, it was observed in recent prospective trials of collaborative groups, a high inclusion rate for this rarer subgroup of cHL patients. This could be great opportunity for international collaborations to design largest prospective trials to evaluate innovative therapeutic strategies for older cHL patients.</p> <p><b>Date of the report:</b> 16 May 2022</p>		