2. SYNOPSIS

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: BEACOPPesc		
Name of Active Ingredient: BEACOPP		

Title of Study:
Randomized phase III study of a treatment driven by early PET response compared to a treatment not monitored by early PET in patients with Ann Arbor Stage III-IV or high risk IIB Hodgkin lymphoma.

Coordinating Investigator: Dr R-O Casasnovas, Service d'hématologie, CHU Dijon, Dijon, France

Study site(s) and countries:
88 study centers in France and Belgium.

Publications (reference):
THELANCETONCOLOGY-D-18-01387R2 S1470-2045(18)30784-8

Studied period (years): Date first subject first visit: 19 May 2011 Date last subject completed: 29 April 2019 Data cutoff date: 29 April 2019	**Phase of development:** 3

Trial registry number(s):
ClinicalTrials.gov identifier: NCT01358747
EudraCT number: 2010-022844-19

Objectives:
Primary: To demonstrate the non-inferiority in term of progression free survival (PFS) of a therapeutic strategy driven by PET with an ABVD conventional dose chemotherapy for patients reaching a negative PET after 2 cycles of BEACOPPesc, compared to a treatment not monitored by early PET delivering 6 cycles of BEACOPPesc.

Secondary:

- To compare the efficacy of patients included in both arms based on the following efficacy parameters:
  - the response rate (after 4 cycles of chemotherapy and at end of treatment)
  - the event free survival (EFS)
  - the disease-free survival (DFS)
  - the overall survival (OS)
- To compare the safety data in both arms including immediate toxicities, and secondary tumor and non-tumor events
- To assess the SUVmax reduction between baseline PET and PET2 or PET4 and analysis of its impact on response rate, EFS, DFS, PFS and overall survival in both arms.

Exploratory:

- To assess the prognostic impact of Ann Arbor stage and IPS at baseline (stratification factors) on time-

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: BEACOPPesc	Volume:	
Name of Active Ingredient: BEACOPP	Page:	

to-event endpoints and response rates

- To assess the prognostic impact of PET2 and PET4 results according to the central review on PFS and OS
- To compare the fertility parameters of patients under 45-year-old before and after treatment in both arms
- To identify the biological parameters related to the Hodgkin lymphoma cells and the tumor micro-environment, influencing the early response to treatment assessed by PET and PFS
- To assess the influence of the genetic polymorphisms of cytokine and cytokine receptor involved in the lymphoma process, and enzyme genes involved in the drug metabolism, on the early response to treatment assessed by PET and PFS.

Methodology:

This study was an international multicentric, randomized phase III trial. Patients were recruited over 3 years and followed until 5 years after the last patient was randomized. A total of 823 patients with first diagnosis of classical Hodgkin lymphoma, aged of 16 to 60 years, were randomized in the study.

The duration of the treatment period was approximately 18 weeks for 6 cycles of BEACOPPesc or 22 weeks for 2 cycles of BEACOPPesc followed by 4 cycles of ABVD.
The study consisted in 3 phases: Screening Phase, Treatment Phase, and Follow-up Phase.

Subjects were to be eligible for screening once the subject had approved and signed the informed consent form. In the Screening Phase, the subject was to undergo baseline assessments of their disease and other assessments up to 30 days before first dose of study drug. Subject eligibility was based on local pathology diagnosis.

Upon completion of the required assessments in the Screening Phase and fulfillment of the eligibility criteria, subjects were included.

Treatment should start as soon as possible after randomization. A pathological review for diagnosis was mandatory to confirm the HL histology. Outcome of the central pathology confirmation was not required for entry into the study. Response assessment included review of computed tomography (CT) and [^{18}F]-Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, bone marrow (BM) examination, laboratory tests, and clinical examination according to International Working Group (IWG) response criteria for non-Hodgkin lymphoma (NHL).

All subjects were to be followed in the Follow-up Phase for PFS and OS with clinic visits every 3 months for the first 2 years, every 6 months for the next 3 years, and then once a year thereafter. Once the subjects had been discontinued from study drug, they were to be followed for progression of disease or relapse, lymphoma treatments, and death.

One interim analysis for futility (rejection of alternative hypothesis) was performed during the conduct of the study. The statistical evaluation was done on the primary parameter. The interim analysis for progression-free survival followed a Lan-De Mets sequential design according to Pocock like boundaries with overall 80% power and a one-sided $\alpha = 0.025$. The timing of the interim analysis was after 50% (49 events) of the total number of planned events (n=97). Analysis of other efficacy endpoints were

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: BEACOPPesc	Volume:	
Name of Active Ingredient: BEACOPP	Page:	

performed as supportive analyses.

The final analysis was realized when the number of 97 events has been reached.

Number of subjects (planned, enrolled, and analyzed):

Planned: 810 subjects
Enrolled: 823 subjects
Analyzed: 823 subjects

Diagnosis and main criteria for inclusion:

Male or female adult (aged 16 to 60 years old) subjects with histologically proven HL not previously treated, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, or 2, and life expectancy ≥ 90 days were eligible for participation in the study. Subjects with other categories of lymphoma were excluded from the study. Other exclusion criteria included: severe cardio-pulmonary or metabolic disease interfering with normal application of protocol treatment, impossibility to perform a baseline PET (PET0) before randomization and treatment beginning.

Test product, dose, and mode of administration:

Drugs composing the BEACOPPesc and the ABVD regimen were registered and were available at the hospital pharmacy. Chemotherapy products were to be used according to summary of product characteristics.

Duration of treatment:

Subjects were to receive study drugs for up to 6 cycles, or until unacceptable toxicity developed, or progression, or voluntary withdrawal.

Reference therapy, dose, and mode of administration:

BEACOPPesc as reference therapy was used in this study.

Criteria for evaluation:

Efficacy: Response to treatment, assessed after 4 cycles of induction treatment and at the end of protocol therapy (6 cycles if patient received all planned cycles otherwise at withdrawal) were classified as CR, PR, SD and PD (not evaluable patients were considered as an additional category) according to Cheson 2007 criteria.

SUVmax reduction was assessed between SUVmax at baseline (PET0) and SUVmax at PET C2 (PET2) and between SUVmax at baseline (PET0) and SUVmax at PET C4 (PET4).

Safety: Safety assessments included recording of adverse events, clinical laboratory measurements (hematology and serum chemistry, pregnancy), and vital signs. Adverse events included severity graded according to the Common Terminology Criteria for Adverse Events (CTCAE; Version 4.03), causality; dose interruption, dose adaptation, study treatment discontinuation, and death.

Statistical methods:

Analysis Sets

Intent to Treat (ITT) set

The ITT set included all patients who were formally randomized regardless of whether they have received treatment or not (following an intent-to-treat principle). Patients were analyzed according to the treatment arm they were randomized to receive. The ITT set was used for the efficacy analysis.

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: BEACOPPesc		
Name of Active Ingredient: BEACOPP		

Per Protocol (PP) set

The Per Protocol set included all randomized patients without major protocol violations. Major protocol violations were defined at the time of previous statistical analyses.

Safety set

The safety set included all randomized patients and have received at least one dose of treatment regimen. Patients were analyzed according to the treatment they received: BEACOPPesc vs BEACOPP + ABVD. Patients randomized in experimental arm and who did not receive cycle 3 of treatment were included in BEACOPP + ABVD group. The safety set was used for all safety analyses.

Efficacy analyses

The median follow-up throughout the study was calculated using a reverse Kaplan Meier plot of time to death with 95% CIs. Time to event variables were 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% CIs. Difference in survival rates were calculated at fixed time points, with 95% CIs. Cox proportional hazard regression models were used to estimate the hazard ratios (HR) and associated 95% CIs. Non-inferiority was established based on the upper limit of the hazard ratio (HR). Non inferiority of PFS and OS was tested in a post-hoc analysis using the Com-Nougue test.

Response rates were expressed as percentages with their 95% Exact Clopper Pearson Confidence Interval limits and compared using a chi-square test.

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: BEACOPPesc		
Name of Active Ingredient: BEACOPP		

SUMMARY – CONCLUSION

Study Disposition

In total, 823 subjects (ITT set) were enrolled between May 19th, 2011, to April 29th, 2019, in 88 centers in France and two in Belgium. Among the 823 enrolled patients, 819 patients received at least one cycle of treatment (412 patients in the standard arm and 407 in the experimental arm), constituting the safety population.

Study Population

352 patients out of 413 (85%) and 361 out of 410 (88%) completed induction treatment in the BEACOPPesc and BEACOPPesc + ABVD arms, respectively.

PET2 and 4 were performed in 401 (100%) and 387 (99.7%) out of 413 patients in the standard arm and 398 (100%) and 379 (100%) out of 410 patients in the experimental arm.

Efficacy Results

Primary Endpoint:

The primary endpoint was progression-free survival. PFS was measured from the date of randomization to the date of first documented progression of the lymphoma in non-responding patients, relapse for CR patients or death from any cause without progression, whichever occurs first. Patients alive and free of progression or who are lost to follow-up are censored at their last tumor assessment date.

The 5-year progression-free survival estimates among PET4 positive patients were similar in the two treatment groups. 20 (47%) of the 43 patients had progressive disease at the time of the positive PET4 examination and received salvage chemotherapy. Of the remaining 23 patients, 21 continued BEACOPPescalated, one received radiotherapy on a residual mediastinal mass, and one proceeded to salvage therapy.

Progression-free survival was also significantly different among PET4-negative patients according to PET2 results (HR 3·588, 95% 2·01–6·40, p<0·0001).

Secondary Efficacy Endpoints

Analysis of the full PET driven strategy by response assessment after two cycles of chemotherapy (PET2) and at end of induction (PET4) identified three prognostic subgroups. PET4 positive patients had a lower 5-year progression-free survival than those with negative PET4 scans, irrespective of PET2 results: 75.4% (95% CI 62.5–84.4) in PET2 positive and PET4 negative patients, and 90.9% (95% CI 87.7–93.3) in PET2 negative and PET4 negative patients versus 46.5% (95% CI 31.2–60.4) in PET4 positive patients; both p<0.0001).

Safety Results

The most common treatment-emergent adverse events of any cause or grade were hematological toxicity, gastrointestinal disorders, and general disorders such as fatigue, fever, and infections.

Serious adverse events related to treatment were reported in 47% of patients in the standard treatment group and 28% in the PET-driven treatment group and were mainly infections and febrile neutropenia.

Five (1.2%) patients in the standard treatment group died from serious adverse events deemed related to

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: BEACOPPesc		
Name of Active Ingredient: BEACOPP		

study treatment, as did two (0.5%) in the PET-driven treatment group.

15 secondary primary malignancies have been reported, including ten (2%) among patients in the standard treatment group and five (1%) among patients in the PET-driven treatment group.

73 pregnancies were declared by 63 patients since the start of treatment including 28 in the standard treatment group and 45 in the PET-driven treatment group. Assisted reproduction was required in six (21%) and three (7%) pregnancies, respectively.

Conclusions

AHL2011 was the first large phase 3 randomized study that has compared standard treatment with PET-driven treatment head-to-head in patients with advanced Hodgkin lymphoma. Interim PET monitoring of chemotherapy response led to similar outcomes as standard treatment.

Reducing treatment intensity in patients who achieved early metabolic response was safe and does not compromise disease control in these patients. Indeed, the primary endpoint of the study was met, with patients in the standard treatment group having a 5-year progression-free survival of 86.2% (95% CI 81.6–89.8) and those in the PET-driven treatment group 85.7% (81.4–89.1). PET2 was negative in 84% of patients in the ITT population (88% in patients assessable for PET2) and, therefore, our findings suggest that high-dose-intensity chemotherapy beyond the first two cycles of BEACOPPescalated is not needed in most patients. Indeed, 97% of PET2 negative patients were assigned ABVD and received ABVD in this study.

Furthermore, the frequency of early treatment-related toxicity and the risk of treatment discontinuation due to toxicity were lower among patients who received ABVD than among those who continued taking BEACOPPescalated. Long-term toxicity might also be reduced although follow-up so far is too short to draw firm conclusions.

In this analysis, we observed lower incidence of secondary primary malignancies in patients who received ABVD than in those who continued BEACOPPescalated, as has been found in previous studies. Additionally, there were significantly more pregnancies reported in the PET driven treatment group than in the standard treatment group.

We recommend this modification to the definition of PET2 positivity and to make decisions about PET-driven BEACOPPescalated dose de-escalation in routine practice. Choosing the Deauville score cutoff for positive PET results is important to minimize the risk of false-positive results.

Therefore, the full PET-driven strategy including PET2 and PET4 has a strong independent prognostic value for progression-free survival and improved risk stratification for death and disease progression of patients with advanced Hodgkin lymphoma independently of IPS.

Our results also suggest that PET4 at end of induction therapy (after 4 cycles of chemotherapy) is probably more suitable for management of patients than PET at the end of treatment. First, negative results on PET2 and PET4 are associated with improved outcomes. Second, the 62 patients with positive PET2 scans who had negative PET4 scans maintained a high probability of a favorable progression-free survival without treatment modification. Third, PET4 permitted early identification of patients with progressive disease who needed salvage therapy.

Although doxorubicin, vinblastine, and dacarbazine plus brentuximab vedotin showed significant

Name of Sponsor/Company: LYSARC	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: BEACOPPesc		
Name of Active Ingredient: BEACOPP		

improvement in modified progression-free survival compared with the ABVD group (82.1% vs 77.2%), the survival achieved was disappointing. Additionally, doxorubicin, vinblastine, and dacarbazine plus brentuximab vedotin was associated with more toxicity related serious adverse events (43%), infections worse than grade 3 (18%), and treatment discontinuations related to toxicity (4%) than were seen in the PET-driven treatment group of our study (28%, 10%, and 1%, respectively). PET-driven strategies were also developed for use after upfront ABVD. PET2 negativity after ABVD ranges from 80% to 84%, compared with 88% after two cycles of BEACOPPescalated in the present study.

In addition, the 89.4% 5-year progression-free survival reached in PET2-negative patients after upfront BEACOPPescalated compares favorably to that in patients with negative PET2 scans after ABVD (3-year progression free survival ranges from 79% to 87%), resulting in more patients with better outcomes when using upfront BEACOPPescalated.

This study has several limitations. We used a progression-free survival non-inferiority design with a predefined wide margin of 10% between the two treatment groups. At the time the study was launched, this margin seemed relevant because in the worst-case non-inferiority of the PET-driven treatment group would be declared with a 5-year progression-free survival greater than 75% compared with standard treatment (i.e., higher than the 70% 5-year progression-free survival reported with standard ABVD) and with a balance of effectiveness to toxicity that was probably better than is seen with six cycles of BEACOPPescalated.

In summary, PET used after two cycles of BEACOPPescalated can safely guide subsequent treatment and supports the use of a response-adapted strategy to deliver four cycles of ABVD in patients who achieve early response to treatment without impairing the disease control (treatment was non-inferior compared with six cycles of BEACOPPescalated). The full PET-driven strategy allowed de-escalation of BEACOPP-based chemotherapy, consequently improving its tolerability in most patients with advanced stage Hodgkin lymphoma. PET4 provided additional prognostic information to PET2 and could identify patients with particularly poor prognosis. Full interim PET staging with the modified Deauville score allowed accurate monitoring of treatment and thus could be considered as a strategy for the routine management of patients with advanced Hodgkin lymphoma.

Date of the report: 10 September 2021