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Brentuximab vedotin as consolidation treatment in patients with stage I/II Hodgkin's lymphoma and FDG-PET positivity after 2 cycles of ABVD: final analysis of the BRAPP2 trial

Authors:
Loïc Renaud[1], Isabelle Chaillol[2], Jeau Galtier[3], Côme Bommier[4], Benoit Tessoulin[5], Jean Marc. Schiano de Colella[6], Thierry Lamy[7], Cécile Borel[8], Aapasia Stamatoullas[9], Anne Clair Gac[10], Franck Morschhauser[11], Marc Andre[12], Hervé Ghesquieres[13], Alexandra Traverse-Glehen[14], Olivier Casasnovas[15] and Thomas Gastine[5]

Affiliations:
1) Department of Hematology, Hopital Cochin, Paris, France
2) Department of biostatistics, LYSARC, LYON, France
3) Department of Hematology-Transplantation, CHU de Bordeaux, Pessac, France
4) Department of hemato-Oncology, Hôpital St Louis, Paris, France
5) Department of Hematology, CHU de Nantes, Nantes, France
6) Department of Onco-Hématology, Institut Paoli-Calmettes, Marseille, France
7) Department of Hematology, CHU Pontchaillou, Rennes, France
8) Department of Hematology, CHU Toulouse, Toulouse, France
9) Department of Hematology, Centre Henri Becquerel, Rouen, France
10) Department of Hematology, CHU CAEN, CAEN, France
11) Department of Hematology, CHU Lille, Lille, France
12) Department of Hematology, CHU UCL Namur – Site Godinne, Yvoir, Belgium
13) Department of Hematology, Hospices Civils de Lyon, Hopital Lyon Sud, Claude Bernard Lyon-1 University, Pierre-Bénite, France
14) Department of Pathology, Hospices Civils de Lyon, Hopital Lyon Sud, Claude Bernard Lyon-1 University, Pierre-Bénite, France
15) Department of Hematology, CHU Dijon, Dijon, France

Corresponding author: Loïc RENAUD
Adress: Hopital Cochin, service d'hématologie, 27 rue du Faubourg Saint-Jacques, 75014 Paris.
Phone : 01 58 41 50 32
Fax: + 01 58 41 40 97
Mail: loic.renaud@aphp.fr

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LR, TG and OC participated at data interpretation and wrote the manuscript.
IC performed statistical analysis.
TG designed the study, coordinated the work.
All authors but me and IC collected data
All authors but me and IC were involved in the care of the patients and interpreted data.
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Key Points:

- Of the 48 patients with localized cHL and positive PET after 2 cycles of ABVD included in this phase 2 study, 41 started Brentuximab vedotin consolidation after receiving 2 cycles of BEACOPPesc + 30 Gy IFRT and 35 patients completed the treatment.
- The 2-year PFS rate was 82.7% and 4 out of the 9 progression events occurred before the initiation of maintenance with BV.

Early-stage classical Hodgkin lymphoma (cHL) is highly curable following chemotherapy and radiotherapy (RT). However, patients with positive FDG-PET after 2 cycles (ePET), have poorer prognosis[1,2] and require treatment intensification. Indeed, The H10 trial showed that escalated BEACOPP (BEACOPPesc) plus RT improve 5-year PFS in PET-2 positive patients[3]. Brentuximab vedotin has shown efficacy in the treatment of Hodgkin's lymphoma as a monotherapy[4], to reduce the frequency of relapse after autologous stem cell transplantation[5], and has been successfully introduced in the first-line setting[6,7]. The main objective of the present study was to investigate the benefit of Brentuximab vedotin (BV) in newly diagnosed HL patients with insufficient response according to ePET.

This prospective, multicenter, phase 2 study (NCT02298283) was designed by the Lymphoma Study Association (LYSA) and conducted at 18 centers in Belgium and France. All inclusion and exclusion criteria are described in the protocol (supplementary 1). Inclusion for each patient was based on the local pathological diagnosis of cHL. A histopathology central review was then performed. Patients with early stage (Ann Arbor I-II) cHL were included in the trial if their PET/CT result after 2 courses of ABVD was positive (Deauville score (DS) 4 or 5)[8] but without progressive disease. Treatment consisted in 2 courses of BEACOPPesc every 3 weeks, followed by PET-CT. In case of progressive disease (PD), patients were excluded from the trial, while patients with complete response (CR), partial response (PR) or stable disease (SD) received IFRT 30 Gy 3 to 4 weeks after the last day of the 2nd course of BEACOPPesc and BV was initiated 4 to 6 weeks from the end of IFRT for a total of 8 cycles every 21 days.
Bv was administered at the dose of 1.8 mg/Kg with a maximum dose of 180mg. Intrapatient dose reduction to 1.2 mg/kg was allowed depending on the type and severity of toxicity (supplementary table 1). The primary endpoint of this phase 2 study was the progression free survival (PFS) rate according to the local review using the Lugano classification (PET-CT–based response)[8]. Secondary efficacy endpoints included overall survival (OS) and CR rate[9] at the end of study treatment; a safety profile, including immediate toxicities and nontumor events focusing on safety and tolerability of BV. An independent central review of PETs was performed.

An independent data monitoring committee composed of 3 independent members (2 experts in HL and 1 statistician) reviewed the safety data after 10 and 25 patients had been included and completed treatment.

The trial was designed to detect a 2-year PFS improvement from 70% (null hypothesis) to 85% (alternative hypothesis) assuming a 80% power at a 2-sided alpha (type I error) of 5%[10]. Based on these hypotheses, null hypothesis (H0: PFS of 70% at 2 years) will be rejected if the lower limit of 95%CI is >70%. With an estimated percentage of 5% Drop-out per year, a total of 40 evaluable patients treated with BV were required. The Kaplan–Meier method was used to estimate the

probability of survival (PFS, DFS, and OS) at any given point in time. The cut-off was July 9th, 2020; when the last patient completed 1.5 years of follow-up. All analyses were performed using SAS software version 9.3 and 9.4. The study was conducted in accordance with the declaration of Helsinki; institutional board approval was obtained. All patients received written information.

Between April 9, 2015 and April 4, 2018, a total of 48 patients were enrolled in the study ITT set, 41 patients received BV treatment (efficacy and safety sets). One patient withdrew consent, and six patients discontinued treatment during induction due to progression (n=4), insufficient response (n=1), or other reasons (CR after 2 ABVD, n=1) (figure 1). Baseline characteristics of the patients of the ITT are shown in Table 1. The administration of IFRT occurred within a median timeframe of 15 days (range 6–58) after the last day of BEACOPPesc. The median dose administered was 30 Gy (range 30-36), with a median of 24 days (range 19-34). The median time interval between the completion of radiotherapy and the initiation of Bv was 35 days (range 25-55).

Over a median follow-up of 3.1 years (95%CI = [2.6; 3.3]), the 2-year PFS of the efficacy and safety set (n=41) was 90.0% (95%CI [75.5%; 96.1%]) and the primary objective of the study was achieved (Figure 2). For the ITT set (n=48), the 2-year PFS and OS were respectively 82.7% (95%CI [68.4%; 91.0%]) and 97.8% (95%CI [85.3%; 99.7%]). One patient died during follow-up due to progression of lymphoma.The complete response rate at the end of treatment was 87.2%, 95%CI [72.6%; 95.7%] (n=34 patients) with 2 patients not evaluated for response.

Twenty-six patients (63.4%) had at least one grade ≥1 adverse event (AE), with 56 events reported by the investigators (Supplementary Table 2). The most common AEs are peripheral neuropathy in 29.3% of patients (n=12), including 4.9% (n=2) of grade 3, leading to discontinued consolidation therapy with BV for 9.8% (n=4). All peripheral neuropathy reported during the consolidation phase are related to BV. Four grade 4 AE concerning three patients were reported, all four febrile neutropenia following BEACOPPesc treatment. 15 patients (36.6%) experienced at least one SAE, the most common SAE being febrile neutropenia (12.2% of patients). No fatal AEs were reported. 2 patients (4.9%) developed a second primary malignancy, both papillary thyroid cancer, none of them was secondary to cervical irradiation. A total of 35 patients received the anticipated eight doses of BV. The primary rationale for Bv dose modification was the presence of peripheral neuropathy (n = 8) or neuropathy (n = 1). Four patients discontinued consolidation therapy with BV due to toxicity: grade 3 peripheral neuropathy in two patients (4.9%), grade 3 constipation in one patient, and grade 2 radiation pneumonitis in one patient. Two additional patients discontinued BV consolidation therapy due to disease progression (n=1) or withdrawal of consent.

This prospective trial met the primary endpoint, with beneficial results for the patients included in the consolidation phase (efficacy set). Unfortunately, five patients could not start the consolidation treatment due to progression (n=4) or insufficient response (n=1) after the induction treatment. These patients are in need of additional treatment options and were not addressed in the trial.

In the BRAPP2 trial we investigated the potential clinical benefit of adding Bv maintenance for early-stage HL with positive ePET, following BEACOPP escalation and consolidative radiotherapy as per EORTC/LYSA/FIL H10 experimental strategy. In the H10 trial, designed to evaluate an ePET response–based adaptation of treatment in patients with stage I and II HL, 18.8% of patients were ePET positive (cheson 2007[9]) after two cycles of ABVD. Patients were then randomized to receive two additional cycles of ABVD + Initial node (IN) radiotherapy (standard arm) or two cycles of BEACOPPesc + INRT (experimental arm). the 5-year PFS rates were 77.4% and 90.6% and the 5-year OS rates were 89.3% versus 96.0% in the ABVD + INRT and BEACOPPesc + INRT arms, respectively demonstrating a significant improvement of 5-year PFS and trend toward significant 5-year OS improvement[3]. With a 2-y-PFS of 82.7% for the ePET2 patients in the ITT set, we failed here to improve significantly the prognosis of these patients. It is interesting to note that 4 out of the 9 progression events occurs very early, before the initiation of BV maintenance, explaining in part the inability of this strategy to improve the prognosis of ePET+ patients. The use of the Cheson 2014 criteria and DS 4 or 5 for inclusion in this trial may explain the comparatively inferior outcomes observed in this study in comparison with the H10 trial using Mediastinal blood pool activity as the reference background activity to define PET positivity[11], resulting in the inclusion of a substantial proportion of false positive patients which would now be considered ePET negative due to their favorable prognosis. Furthermore, the inclusion of patients with positive results in the ePET imaging procedure might introduce a degree of bias.

It is important to acknowledge that since the BRAPP2 trial have been designed and completed, ABVD-based strategies have been outperformed by upfront escalated strategies (such as HD17) for patients with early unfavorable cHL while also restricting RT to PET+ patients[12,13]. In another hand, stage IIB/E bulky disease are now frequently allocated to advanced stage strategies[6,12,14]. As such, ABVD-based therapy with escalation following ePET+ may now be restricted to patient with early favorable disease at diagnosis.

In conclusion, the BRAPP2 trial demonstrates that Bv maintenance following BEACOPP escalation and IFRT for early-stage HL with eTEP+ after 2 cycles of ABVD is feasible yet associated with significant rate of neuropathy. The clinical benefit of this strategy remains unclear as excellent outcomes are already achieved following eBEACOPP treatment and consolidative radiotherapy. Furthermore, Bv maintenance strategy does not seem to prevent the remaining 10 - 20% rate of failure occurring early after ePET+. These results do not support the addition of Bv maintenance as part of first line of early-stage HL and rather suggest that upfront intensified or innovative regimen,

along with radiotherapy, are the key determinants of disease control in case of high-risk early stage cHL.

REFERENCES

1. Gallamini A, Hutchings M, Rigacci L, et al. Early Interim 2-[18F]Fluoro-2-Deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint italian-danish study. J Clin Oncol. 2007;25(24):3746-3752.
2. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood. 2006;107(1):52-59.
3. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response–adapted treatment in stage i and ii Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 Trial. J Clin Oncol. 2017;35(16):1786-1794.
4. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012;30(18):2183-2189.
5. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;385(9980):1853-1862.
6. Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024;404(10450):341-352.
7. Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. Lancet Haematol. 2021;8(6):e410-e421.
8. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014;32(27):3059-3067.
9. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J

Clin Oncol. 2007;25(5):579-586.

10. Cottereau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. Blood. 2018;131(13):1456-1463.
11. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25(5):571-578.
12. Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. Lancet Oncol. 2019;20(2):202-215.
13. Borchmann P, Plütschow A, Kobe C, et al. PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(2):223-234.
14. Rossi C, Manson G, Marouf A, et al. Classic Hodgkin lymphoma: the LYSA pragmatic guidelines. EurJ Cancer. 2024;213:115073.

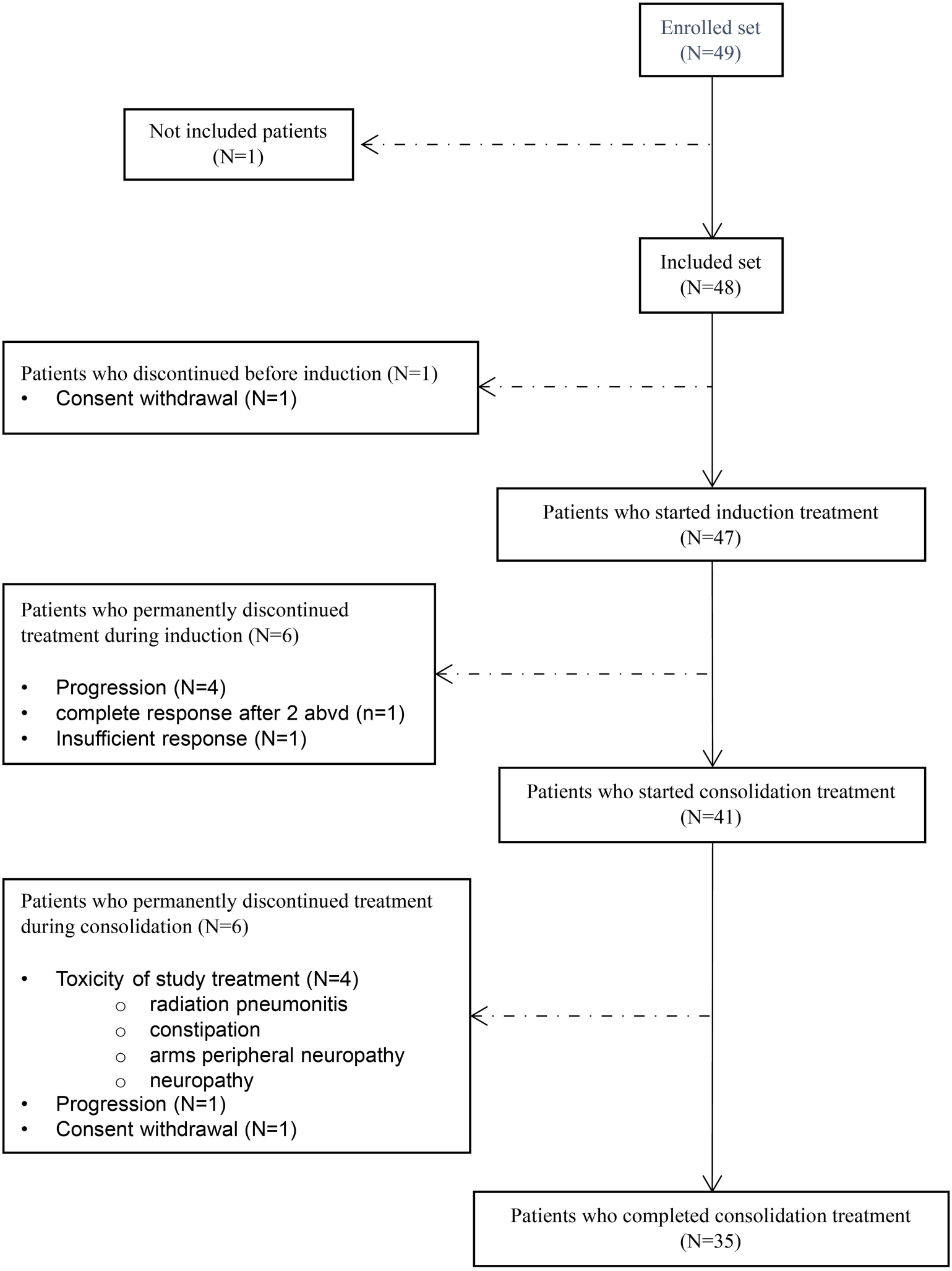
Table 1: baseline characteristics for the 48 included patients including the 41 patients of the efficacy set.

M/T, mediastino thoracic index; ESR, erythrocyte sedimentation rate. EORTC: european organisation for research and treatment of cancer ; LYSA: lymphoma study association. *Elevated ESR >=50 mm/h without B symptoms or >=30 mm/h with B symptoms

	ITT set (n=48)	%	Efficacy set (n= 41)	%
Sex				
Male	28	58.3	22	53.7
Female	20	41.7	19	46.3
Age at inclusion (years)				
Median (range)	31 (18-67)		32.0 (18-67)	
<50 years	41	85.4	36	87.8
>=50 years	7	14.6	5	12.2
B symptoms at baseline	20	41.7	16	39
Ann Arbor stage at baseline				
I	4	8.3	4	9.8
II	44	91.7	37	90.2
Number of involved nodal areas at baseline				
1	6	12.5	6	14.6
2	7	14.6	7	17.1
3	24	50	18	43.9
4	6	12.5	6	14.6
5	5	10.4	4	9.8
< 3	13	27.1	13	31.7
>=3	35	72.9	28	68.3
Elevated ESR*			13	31.7
Highest diameter of nodal involvement at baseline (mm)				
Median (range)	66.5 (23-190)		66.5 (23-190)	
Highest diameter of nodal involvement at inclusion (mm)				
Median (range)	35 (0-99)		35 (0-75)	
EORTC/LYSA clinical prognostic factors				
Unfavorable	33	86.8	28	87.5
Favorable	5	13.2	4	12.5
Missing	10		9	
Histological diagnosis (central review)				
Nodular sclerosis classical Hodgkin lymphoma	32	69.6	27	67.5
Classical hodgkin lymphoma	6	13	6	15
No sample	4	8.7	4	10
Hodgkin lymphocytes rich	1	2.2	1	2.5
Insufficient material	1	2.2	1	2.5
Mixed cellularity classical Hodgkin lymphoma	2	4.3	1	2.5
Missing	2	4.3	1	2.5

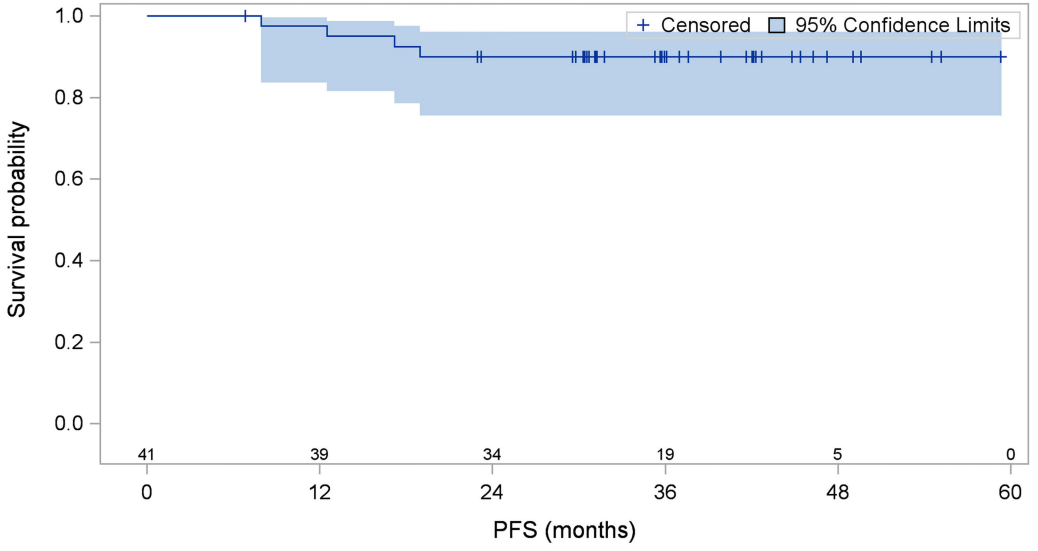
Figure 1. CONSORT diagram of patients in the BRAPP2 study.
CL, confidence limits.

Figure 2. Kaplan-Meier curves for outcome. (A) progression free survival (PFS); (B) overall survival (OS).


Enrolled set
(N=49)
Not included patients
(N=1)
Included set
(N=48)
Patients who discontinued before induction (N=1)
• Consent withdrawal (N=1)
Patients who started induction treatment
(N=47)
Patients who permanently discontinued
treatment during induction (N=6)
• Progression (N=4)
• complete response after 2 abvd (n=1)
• Insufficient response (N=1)
Patients who started consolidation treatment
(N=41)
Patients who permanently discontinued treatment
during consolidation (N=6)
• Toxicity of study treatment (N=4)
○ radiation pneumonitis
○ constipation
○ arms peripheral neuropathy
○ neuropathy
• Progression (N=1)
• Consent withdrawal (N=1)
Patients who completed consolidation treatment
(N=35)

A

PFS - Efficacy set
With number of subjects at risk

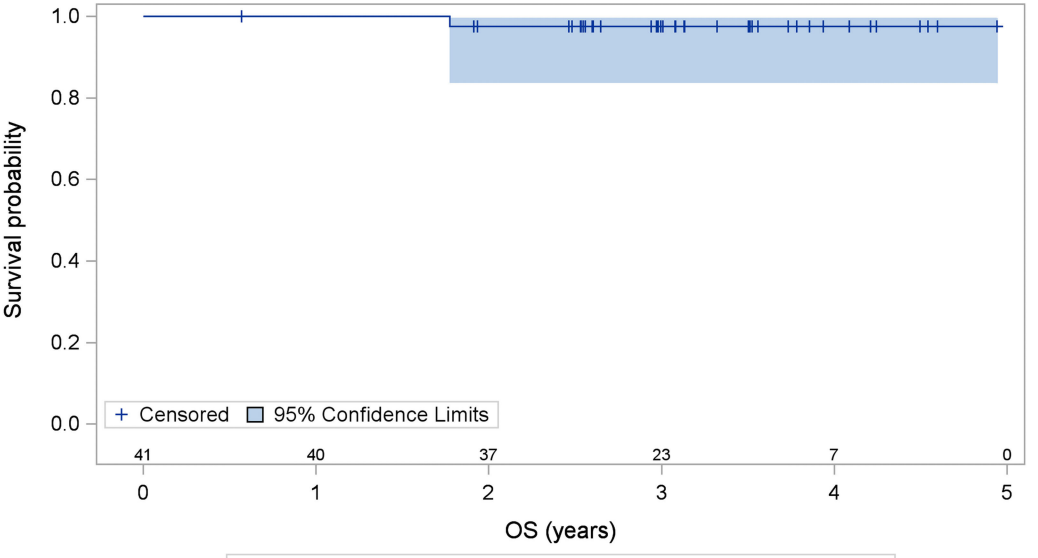


No. of subjects	Event	Censored	Median survival (95% CI)
41	9.8 % (4)	90.2 % (37)	Not reached

PFS is defined as the time between the date of the first cycle of ABVD to the first observation of disease progression or death. Patient with no event are censored at the time of last visit with adequate assessment.

B

OS - Efficacy set
With number of subjects at risk



No. of subjects	Event	Censored	Median survival (95% CI)
41	2.4 % (1)	97.6 % (40)	Not reached

OS is defined as the time between the date of the first cycle of ABVD to the first observation of disease progression or death. Patient with no event are censored at the time of last visit with adequate assessment.

Supplementary table 1: Brentuximab vedotin exposure – Efficacy set

Max, maximum; Min, minimum; Q, quartile; SD, standard deviation.

		Consolidation set N=41
Cycles performed		
Cycle 1		41
Cycle 2		40
Cycle 3		39
Cycle 4		37
Cycle 5		37
Cycle 6		36
Cycle 7		36
Cycle 8		35
Number of cycles performed		
Mean (SD)		7.3 (1.78)
Median		8.0
Q1 ; Q3		8 ; 8
Min ; Max		1 ; 8
Time between end of radiotherapy and 1st day of brentuximab vedotin (days)		
Mean (SD)		36.8 (7.69)
Median		35.0
Q1 ; Q3		32 ; 42
Min ; Max		25 ; 55
Duration of brentuximab vedotin treatment (months)		
Mean (SD)		4.56 (1.314)
Median		4.86
Q1 ; Q3		4.9 ; 4.9
Min ; Max		0.0 ; 6.2
Overall treatment duration (months)		
Mean (SD)		10.68 (1.384)
Median		11.04
Q1 ; Q3		10.4 ; 11.3
Min ; Max		6.2 ; 12.5

Supplementary table 2: Adverse events (AE) and Related serious adverse events (SAEs) classified by period and system organ classes (SOCs)

AEs									
System Organ Class Preferred Term	N = 41								
	Before treatment		Induction		Consolidation		Overall		
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	
Patients with at least one AE	**1 (2.4%)**	**1**	**12 (29.3%)**	**17**	**23 (56.1%)**	**38**	**26 (63.4%)**	**56**	
NERVOUS SYSTEM DISORDERS	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**12 (29.3%)**	**14**	**12 (29.3%)**	**14**	
NEUROPATHY PERIPHERAL	0 (0.0%)	0	0 (0.0%)	0	12 (29.3%)	14	12 (29.3%)	14	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**0 (0.0%)**	**0**	**8 (19.5%)**	**10**	**3 (7.3%)**	**4**	**11 (26.8%)**	**14**	
FEBRILE NEUTROPENIA	0 (0.0%)	0	5 (12.2%)	6	0 (0.0%)	0	5 (12.2%)	6	
FEBRILE BONE MARROW APLASIA	0 (0.0%)	0	3 (7.3%)	4	0 (0.0%)	0	3 (7.3%)	4	
NEUTROPENIA	0 (0.0%)	0	0 (0.0%)	0	2 (4.9%)	2	2 (4.9%)	2	
LEUKOPENIA	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
LYMPHOPENIA	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
INFECTIONS AND INFESTATIONS	**0 (0.0%)**	**0**	**2 (4.9%)**	**2**	**8 (19.5%)**	**10**	**9 (22.0%)**	**12**	
BRONCHITIS	0 (0.0%)	0	0 (0.0%)	0	2 (4.9%)	2	2 (4.9%)	2	
HERPES ZOSTER	0 (0.0%)	0	0 (0.0%)	0	2 (4.9%)	2	2 (4.9%)	2	
BARTHOLINITIS	0 (0.0%)	0	1 (2.4%)	1	0 (0.0%)	0	1 (2.4%)	1	
INFLUENZA	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
NASOPHARYNGITIS	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
PNEUMONIA	0 (0.0%)	0	1 (2.4%)	1	0 (0.0%)	0	1 (2.4%)	1	
SINUSITIS	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
URINARY TRACT INFECTION	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
VIRAL INFECTION	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
VULVOVAGINAL MYCOTIC INFECTION	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**0 (0.0%)**	**0**	**1 (2.4%)**	**1**	**3 (7.3%)**	**3**	**4 (9.8%)**	**4**	
PULMONARY EMBOLISM	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	2 (4.9%)	2	
LUNG DISORDER	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
RHINORRHOEA	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**3 (7.3%)**	**3**	**3 (7.3%)**	**3**	
ASTHENIA	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
CHEST DISCOMFORT	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
OEDEMA PERIPHERAL	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
GASTROINTESTINAL DISORDERS	**0 (0.0%)**	**0**	**1 (2.4%)**	**1**	**1 (2.4%)**	**1**	**2 (4.9%)**	**2**	
CONSTIPATION	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
VOMITING	0 (0.0%)	0	1 (2.4%)	1	0 (0.0%)	0	1 (2.4%)	1	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**1 (2.4%)**	**1**	**1 (2.4%)**	**1**	**0 (0.0%)**	**0**	**2 (4.9%)**	**2**	
PAPILLARY THYROID CANCER	1 (2.4%)	1	1 (2.4%)	1	0 (0.0%)	0	2 (4.9%)	2	
CARDIAC DISORDERS	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**1 (2.4%)**	**1**	**1 (2.4%)**	**1**	
TACHYCARDIA	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**1 (2.4%)**	**1**	**1 (2.4%)**	**1**	
RADIATION PNEUMONITIS	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
SURGICAL AND MEDICAL PROCEDURES	**0 (0.0%)**	**0**	**1 (2.4%)**	**2**	**0 (0.0%)**	**0**	**1 (2.4%)**	**2**	
HOSPITALISATION	0 (0.0%)	0	1 (2.4%)	2	0 (0.0%)	0	1 (2.4%)	2	
VASCULAR DISORDERS	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**1 (2.4%)**	**1**	**1 (2.4%)**	**1**	
VENOUS THROMBOSIS	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1	
Related SAEs									
System Organ Class Preferred Term	n= 41								
	Before treatment		Induction		Consolidation		Overall		
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	
Patients with at least one AESI	**0 (0.0%)**	**0**	**5 (12.2%)**	**6**	**14 (34.1%)**	**16**	**17 (41.5%)**	**22**	
NERVOUS SYSTEM DISORDERS	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**12 (29.3%)**	**14**	**12 (29.3%)**	**14**	
NEUROPATHY PERIPHERAL	0 (0.0%)	0	0 (0.0%)	0	12 (29.3%)	14	12 (29.3%)	14	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**0 (0.0%)**	**0**	**5 (12.2%)**	**6**	**2 (4.9%)**	**2**	**7 (17.1%)**	**8**	
FEBRILE NEUTROPENIA	0 (0.0%)	0	5 (12.2%)	6	0 (0.0%)	0	5 (12.2%)	6	
NEUTROPENIA	0 (0.0%)	0	0 (0.0%)	0	2 (4.9%)	2	2 (4.9%)	2	

BRAPP2

Brentuximab vedotin as consolidation treatment in patients with stage I/II Hodgkin's lymphoma and FDG-PET positivity after 2 cycles of ABVD

A STUDY SPONSORED BY:

LYSARC

LYSARC: **T**HE **L**YMPHOMA **A**CADEMIC **R**ESEARCH **O**RGANISATION

✉ : Centre Hospitalier Lyon Sud - Secteur Sainte Eugénie – Pavillon 6D

69495 Pierre Bénite Cedex– France

COORDINATING INVESTIGATORS	Dr Pauline BRICE, Dr Thomas GASTINNE
PROTOCOL WRITING COMMITTEE	Dr Pauline BRICE, Dr Marc ANDRE, Dr Thomas GASTINNE
IMAGING COORDINATOR	Pr Michel MEIGNAN, Romain RICCI
STATISTICAL COORDINATOR	Laurence GIRARD
PATHOLOGICAL COORDINATOR	Dr Alexandra TRAVERSE-GLEHEN Dr Diane DAMOTTE
COORDINATION CENTER	LYSARC

REGISTRATION (SEE SECTION 11.1)	http://study.lysarc.info
SAE REPORTING (SEE SECTION 13.3)	Fax to +33 (0) 3 59 11 01 86

Version and date of Protocol: 5.0 – 06/02/2017

EudraCT number: 2013-000734-35

CONFIDENTIALITY STATEMENT

PROTOCOL SIGNATURE PAGE

BRAPP2

Brentuximab vedotin as consolidation treatment in patients with stage I/II Hodgkin's lymphoma and FDG-PET positivity after 2 cycles of ABVD

LYSARC

Name: Pascal DESCHASEAUX
Title: General Manager

08 March 2017
Date

COORDINATING INVESTIGATORS

Name: Dr Pauline BRICE
Title: Coordinating Investigator

3 MAR 2017
Date

Name: Dr Thomas GASTINNE
Title: Coordinating Investigator

02/03/2017
Date

1 SYNOPSIS

Study ID **EudraCT N°**	BRAPP2 2013-000734-35
Title of the study	Brentuximab vedotin as consolidation treatment in patients with stage I/II Hodgkin's lymphoma and FDG-PET positivity after 2 cycles of ABVD
Development phase of the study	II
Investigational product	Brentuximab vedotin
Protocol version	5.0
Sponsor	LYSARC
Coordinating investigators	Dr Pauline BRICE, Dr Thomas GASTINNE
Centers	35 centers from the LYSA in France and Belgium
Study Objectives and endpoints	• **Primary objective**: Evaluation of PFS at 2 years • **Secondary objective:** - Safety and evaluation of toxicities (hematological, neurological, cardiac and pulmonary) of brentuximab vedotin given after radiotherapy - CR rate (Cheson 2007) at the end of treatment - Overall Survival
Study design	Single arm, open-label, multicentric
Duration of the study	The estimated duration of the study is ~ 6 years (3.5 years for recruitment, 35 weeks of treatment and at least 1.5 years of follow-up) Estimated recruitment period: 3.5 years (Q2 2015 – Q4 2018)
Number of patients	40 evaluable patients treated of brentuximab vedotin
Inclusion criteria	1. Patients must have histologically confirmed CD30+ classical Hodgkin lymphoma 2. Patients must have provided voluntary written informed consent before performance of any study-related procedures not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care 3. Supradiaphragmatic Ann Arbor clinical stage I or II (favourable and unfavourable according to the EORTC/GELA clinical prognostic factors) 4. Mandatory FDG-PET/ CT without IV contrast performed at diagnosis 5. Patients treated with first-line ABVD and FDG-PET positive after 2 cycles (Deauville score 4&5) and without progressive disease 6. Patients must have an ECOG performance status of 0-2 7. Life expectancy > 6 months 8. Patients must be 18-65 years of age 9. Patients must be available for periodic blood sampling, study-related assessments, and management of toxicity at the treating institution 10. Female patients who: • Are postmenopausal for at least 1 year before the screening visit, OR are surgically sterile, OR • If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse 11. Male patients, even if surgically sterilized (ie, status postvasectomy), who agree

	to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse. 12. Clinical laboratory values as specified below before the first dose of study drug: • Absolute neutrophil count ≥ 1,500/µL (1.5 x 10^9/L) unless is related to ABVD treatment • Platelet count ≥ 75,000/ µL (75 x 10^9/L) • Total bilirubin must be < 1.5 x the upper limit of the normal (ULN) unless the elevation is known to be due to Gilbert syndrome • ALT or AST must be < 3 x the upper limit of the normal range • Serum creatinine must be < 2.0 mg/dL (177 µmol/L) and/or creatinine clearance or calculated creatinine clearance > 40 mL/minute • Hemoglobin must be ≥ 8g/dL 13. Patient affiliated to social security system
Exclusion criteria	1. Patients with dementia or altered mental status that would preclude compliance with drug delivery 2. Women who are pregnant or breastfeeding 3. Patients with symptomatic pulmonary disease 4. Patients with known history of any of the following cardiovascular conditions: • Myocardial infarction within 2 years of inclusion • New York Heart Association (NYHA) Class III or IV heart failure • Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities • Recent evidence (within 6 months before first dose of study drug) of a left-ventricular ejection fraction <50% 5. Any history of cancer or cancer treatment during the last 3 years with the exception of non-melanoma skin cancer or stage 0 (in situ) carcinoma of any type if they have undergone complete resection 6. Uncontrolled infectious disease, including active HBV infection defined by either detection of HBs Antigen or presence of anti HBc antibody without detectable anti HBs antibody 7. Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics at the time of inclusion and planned to be still on going within 2 weeks prior to first study drug dose 8. Known HIV, known or suspected HCV serology positivity 9. Patients who have been treated previously with any anti-CD30 antibody 10. Known hypersensitivity to any excipients contained in the brentuximab vedotin formulation 11. Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of Progressive Multifocal Leukoencephalopathy (PML) 12. Any sensory or motor peripheral neuropathy greater than or equal to Grade 2 13. Patients that have not completed any prior treatment chemotherapy, except ABVD, and/or other investigational agents within at least 5 half-lives of last dose of that prior treatment

Study treatment

Induction treatment:

- 2 ABVD cycles **<u>received prior to inclusion</u>**
- 2 cycles of BEACOPP $_{escalated}$ every 3 weeks

Cyclophosphamide	1250 mg/m^2	i.v.	day 1
Doxorubicin	35 mg/m^2	i.v.	day 1
Vincristine	1.4 mg/m^2	i.v.(max.2mg)	day 8
Bleomycin	10 mg/m^2	i.v	day 8
Etoposide	200 mg/m^2/day	i.v.	day 1 to 3
Procarbazine	100 mg/m^2/day	p.o.	day 1 to 7
Prednisone	40 mg/m^2/day	p.o.	day 1 to 7
G-CSF	5 µg/kg/day	s.c.	day 9 to recovery leukocytes>1.0x10^9/L

Before radiotherapy, a FDG-PET / CT without IV contrast should be performed to exclude patients with progressive disease.

- Involved-field radiation therapy 30Gy (+boost 6Gy to residual lesions) starting 3 to 4 weeks after last day of second course of BEACOPP.

Consolidation treatment:

- **8 cycles of Brentuximab vedotin every 3 weeks**

Brentuximab vedotin 1.8 mg/kg starting 4 to 6 weeks after completion of RT.

A mandatory FDG-PET / CT without IV contrast must be performed at the end of treatment.

Assessment schedule

Baseline

Initial staging will be performed in current practice at diagnosis prior to first line ABVD: lymph node biopsy, clinical examinations (including vital signs, ECOG performance status) and laboratory tests (including complete blood counts, serum chemistries), FDG-PET / CT without IV contrast, tumor assessment and staging according to Ann Arbor classification and to the EORTC/GELA clinical prognostic factors.

All patients with supradiaphragmatic Ann Arbor clinical stage I or II and treated with ABVD can be identified and informed of the protocol.

Inclusion

Patients will be included in the trial if their FDG-PET / CT without IV contrast result after 2 courses of ABVD is positive (score 4 & 5) according to the 5 point-scale (Deauville criteria, Meignan et al 2012) but without progressive disease.

After their inclusion the patients will receive 2 courses of BEACOPP $_{escalated}$ (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) every 3 weeks followed by 30 Gy IFRT.

A FDG-PET / CT without IV contrast will be performed after the 2 BEACOPP $_{escalated}$ to eliminate the rare progressive patients.

Patients who discontinue from the trial during induction treatment (progressive patients or other reasons) will be replaced in order to reach the objective of 40 evaluable patients treated by brentuximab vedotin.

After radiotherapy treatment, patients will receive 8 cycles of brentuximab vedotin every 21 days. Immunotherapy will start 4 weeks after the last day of IFRT and up to 6 weeks.

Safety assessment

<u>During induction treatment with BEACOPP $_{escalated}$</u>

AE of any grade of toxicities related to SAE must be reported as AE in the e-CRF

<u>During consolidation treatment</u>, AE of grade 2-5 for infections and neurological toxicities and AE of grade 3-5 for other toxicities must also be reported as AE in the e-CRF. AEs/SAEs type, intensity, cycle, duration, seriousness, and relationship to study

	treatment will be assessed. Laboratory abnormalities and AEs/SAES intensity will be assessed according to the NCI-CTCAE v.4.03. **Tumor assessment** Tumor assessment will be performed at diagnosis (clinical examination, laboratory tests, mandatory FDG-PET / CT without IV contrast), after 2 cycles of ABVD (clinical examination, laboratory tests, mandatory FDG-PET / CTwithout IV contrast), after 2 cycles of BEACOPP $_{escalated}$ (clinical examination, laboratory tests, mandatory FDG-PET /CT without IV contrast), after IFRT (clinical examination, laboratory tests) and after 8 cycles of brentuximab vedotin (clinical examination, laboratory tests, mandatory FDG-PET/CT without IV contrast). Any patient who discontinues from the study treatment should be evaluated 4 ± 1 weeks after the last treatment dose. To ensure comparability, baseline and on-study methods for response assessment will be performed using identical techniques. Response criteria will be assessed using Cheson 2007 criteria at the end of treatment. **Follow-up** Follow-up visits (clinical examination, laboratory tests, neck and chest CT scan) will be performed every 3 months during the first year, then every 6 months until the end of the 1.5 years of follow-up of the last patient
Statistical consideration	**Sample Size Calculation** *Hypothesis:* - Alpha = 5% (two-sided), power = 80%, - Accrual rate: ~12 enrolled patients per year - Drop-out = 5% - HR = 2.2 (exponential distribution of events based on progression-free survival probability at 2 years of 85% vs. 70% in the reference population) - Accrual period: 3,5 years - Study duration: ~ 6 years - No interim analysis *Sample Size*:* N=40 evaluable patients (9 events required) **Sample size calculation was performed using a one arm sample size (Lawless, J. Statistical Models and Methods for Lifetime Data, John Wiley and Sons, 1982).* **Analysis Plan** The primary analysis will be presented as Kaplan-Meier plots of time to event (progression/relapse or death from any cause) and summary tables of Kaplan-Meier estimates for progression-free survival rates at 2 years, with 95% CIs. The median time to event (progression/relapse or death from any cause) will be calculated (if reached) with 95% confidence intervals. Secondary time to event endpoints will be analyzed as the primary criterion. Response rates will be described with 95% confidence limits according to Pearson-Clopper method. Secondary safety endpoints will also be displayed (AEs, laboratory results, vital signs). **Final Analysis** No interim analysis planned. The final analysis will be performed when the number of events (9 events) has been reached or at the latest when the last patient will finish follow-up. The approximate schedule of the final analysis will be ~ 6 years after the first patient enrolled.

	If necessary an update of time to event endpoints will be performed at the end of study follow-up.
Independent Data Monitoring Committee	This trial is designed to allow premature termination or modification of the protocol for safety concerns based on an Independent Data Monitoring Committee (IDMC). The IDMC will meet once when 10 patients will have completed 8 cycles of brentuximab vedotin or prematurely discontinued brentuximab vedotin treatment. During IDMC evaluation accrual will not be stopped. If any safety issues are pointed out, the IDMC might recommend changes in the conduct of the trial or ask the sponsor to stop the study.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
5PS	5 point-scale
ABVD	Adriamycin, Bleomycin, Vinblastine and DTIC/Dacarbazine
AE	Adverse Event
ALCL	Anaplasic Large Cell Lymphoma
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
AST (SGOT)	ASpartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
BEACOPP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine and Prednisone
BSA	Body Surface Area
CR	Complete Response
CRP	C Reactive Protein
CRF	Case Report Form
Cru	Complete Response unconfirmed
CS	Clinical stage
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	DeoxyriboNucleic Acid
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
EORTC	European Organisation for Research and Treatment of Cancer
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
ESR	Erythrocyte sedimentation rate
GELA	Groupe d'étude des Lymphomes de l'Adulte
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma
HTLV	Human T-lymphotropic virus
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IFRT	Involved Field Radiotherapy
IP	Investigational Product

IRB	Institutional Review Board
IRR	Infusion Related Reaction
IV	IntraVenous
JCV	John Cunningham Virus
LYSA	The Lymphoma Study Association
LYSA-IM	LYSA-Imagery
LYSA-P	LYSA-Pathology institute
LYSARC	The Lymphoma Academic Research Organisation
LVEF	Left-Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
MT ratio	Mediastinal-thoracic ratio
NCI	National Cancer Institute
NCIC CTG	National Cancer Institute of Canada - Clinical Trials Group
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
FDG-PET	^{18}F-FDG Positon Emission Tomography
PFS	Progression Free Survival
PML	Progressive Multifocal Leukoencephalopathy
PO	Per Os
PR	Partial Response
PS	Performance Status
RPPS	Répertoire Partagé des Professionnels de Santé
RR	Response Rate
SAE	Serious Adverse Event
SC	Sub-Cutaneous
SD	Stable Disease
SJS	Stevens-Johnson syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV max	Maximum Standardized Uptake Value
TEN	Toxic Epidermal Necrolysis
TLS	Tumor Lysis Syndrome
TMA	Tissue Micro Array
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infections
US	United States
WHO	World Health Organization

4 RESPONSIBILITIES

4.1 Sponsor and program coordination center

4.1.1 Sponsor

LYSARC (the Lymphoma Academic Research Organisation)

✉ : Centre Hospitalier Lyon Sud – Secteur Sainte Eugénie - Pavillon 6D
F-69495 Pierre Bénite Cedex

☎ : +33(4) 72 66 93 33 Fax : +33(4) 72 66 93 71

4.1.2 Coordinating investigators

Dr Pauline BRICE

✉ : Hôpital Saint Louis – Service d'hématologie - 1 avenue Claude Vellefaux - 75475 Paris cedex 10

☎ : +33(1) 42 49 98 40 Fax: +33(1) 42 38 50 27

Email: pauline.brice@sls.aphp.fr

Dr Thomas GASTINNE

✉ : CHU Hôtel Dieu - Service Hématologie - 1 place Alexis Ricordeau - 44093 Nantes cedex 1

☎ : +33(1) 2 40 08 32 53 Fax : +33(1) 2 40 08 32 50

Email: thomas.gastinne@chu-nantes.fr

4.1.3 Program coordination center

LYSARC (the Lymphoma Academic Research Organisation)

✉ : Centre Hospitalier Lyon Sud – Secteur Sainte Eugénie - Pavillon 6D
F-69495 Pierre Bénite Cedex

☎ : +33(4) 72 66 93 33 Fax : +33(4) 72 66 93 71

Project Manager:

Stéphanie DOYEN

Clinical Project Manager

✉ : Centre Hospitalier Lyon Sud - Secteur Sainte Eugénie - Pavillon 6D
69495 PIERRE-BENITE Cedex – France

☎ : +33(0) 4 27 01 27 36

Fax: +33(0) 4 26 07 40 55

Email: stephanie.doyen@lysarc.org

Data analysis, Statistical center, Pharmacovigilance (LYSARC):

Laurence GIRARD, Director of the biometry division (laurence.girard@lysarc.org)

Aude FIEVET, Head of Pharmacovigilance (aude.fievet@lysarc.org)

✉ : Centre Hospitalier Lyon Sud - Secteur Sainte Eugénie - Pavillon 6D
69495 PIERRE-BENITE Cedex – France

☎ : +33(0) 4 72 66 38 62 / +33(0) 4 72 66 93 33

Fax: +33(0) 4 72 66 93 71 Pharmacovigilance: Fax +33 (0) 3 59 11 01 86
Email : pharmacovigilance@lysarc.org

4.1.4 Imaging/Pathological coordinator

Nadine VAILHEN, Director of Biological and Histopathological Operations, LYSA-P (nadine.vailhen@lysarc.org)

Romain RICCI, Imaging Coordinator, LYSA-IM (romain.ricci@lysarc.org)

✉ : CHU Henri Mondor - 51, av. du Maréchal de Lattre de Tassigny
94010 CRETEIL – France

4.2 Investigators

Thirty five LYSA centers from France and Belgium may include patients in this study. Before any inclusion, each center must be declared to the Ethical Committee and national competent authority according to each country regulations and have had the initiation visit/call. To be declared as a participating center, the principal investigator must send to the LYSARC all administrative documents required for regulatory submission (e.g. Curriculum vitae, affiliation medical association number [CNOM] or RPPS number).

4.3 Laboratory sites

Laboratories of each study center must provide their normal values and an updated accreditation for quality control.

5 BACKGROUND AND STUDY RATIONALE

5.1 Background

Hodgkin's Lymphoma (HL) is a neoplasm of lymphoid tissue that is defined histopathologically by the presence of malignant Hodgkin Reed-Sternberg (RS) cells [1]. CD30 expression has been well established on RS cells in fresh tumor biopsies and on established in vitro cell lines and is constantly expressed in tumor cells [2]. Chemotherapy alone or combined with radiotherapy produces a durable remission rate of approximately 70-80 % in patients with newly-diagnosed HL [3].

Patients with limited stage disease do particularly well, and most of them with favorable prognostic factors can be cured [4]. The future challenge for this group of patients is to determine the minimum amount of treatment that is necessary to achieve cure. Good responders may need to receive less amount of treatment than poor responders. Alternatively, positron emission tomography (PET) using [^{18}F]-fluorodeoxyglucose (18F-FDG) may serve as a biomarker of response. FDG-PET is a functional imaging procedure in which the uptake of glucose is in turn related to tumor viability and has the advantage of functional tissue characterization that is largely independent of morphologic criteria. In HL, FDG uptake has been shown to reflect therapeutic efficacy more accurately than CT [5, 6].

The standard treatment for patients with clinical stage I/II Hodgkin's lymphoma (HL) consists of the combination of a fixed number of cycles (2-4) of chemotherapy (mostly ABVD: adriamycin, bleomycin, vinblastin and dacarbazin) followed by involved-field radiotherapy (IFRT) [7, 8].

In order to early evaluate the response, a FDG-PET / CT after 2 cycles of ABVD can delineate 2 categories with differences in progression free-survival (PFS) [5, 6]. Early recognition of the ineffectiveness of chemotherapy could result in a rapid change of therapy, which might improve clinical outcome and reduce long-term toxicity for these patients.

Since the first publications, the criteria defining interim FDG-PET has changed and now a five point scale (5PS Deauville criteria) is used to assess response after 2 cycles of ABVD [9].

5.2 CD30 expression

CD30, a member of the TNF-receptor (TNF-R) superfamily, is a transmembrane glycoprotein receptor and is normally found on the surface of activated T cells but has also been detected on a variety of cell types of hematopoietic origin. The CD30 antigen has a very low expression on normal cells but is found on the Hodgkin Reed-Sternberg (RS) cells of HL and on Anaplasic large cell lymphoma (ALCL) and other T cell lymphoproliferative disorders. While the function of CD30 has not been clearly defined, CD30 has been implicated both in cell death and proliferation [10]. The utility of CD30 as a diagnostic marker for HL and ALCL, its limited expression profile, and its apoptosis-inducing characteristics have led to the investigation of this antigen as a target for immunotherapy.

5.3 Switch from ABVD to BEACOPPesc regimen and side effects of BEACOPPesc regimen

In the retrospective study by Hutchings et al, FDG-PET was performed after 2-3 cycles of chemotherapy in 85 HL patients. The interim FDG-PET scans were negative in 63 patients, showed minimal residual uptake in 9 patients and were positive in 13 patients. The 5-year progression free survival was 92%, 88% and 42%, respectively [5].

These findings were confirmed in a prospective study in 77 HL patients. FDG-PET scans were performed after 2 cycles of chemotherapy. Two out of the 61 FDG-PET-negative patients experienced treatment failure, in comparison with 10 out of 16 FDG-PET-positive patients. With a median follow-up of 20 months highly significant associations were reported between early interim FDG-PET and progression free survival ($p<0.0001$) and overall survival ($p<0.01$) [6)].

Indeed the poor-risk group of patients with PET-positivity after two cycles of ABVD should be treated more intensively.

Despite a related increased toxicity, upfront use of BEACOPPesc appears to be critical to improve outcome as demonstrated by the german HD14 trial showing a significantly better PFS for patients with early unfavorable HL when treated by 2 cycles of BEACOPPesc followed by 2 cycles of ABVD, compared to 4 cycles of ABVD [11]. BEACOPPesc has been used for the intensification of chemotherapy in the investigational H10 (LYSA/EORTC) protocol.

BEACOPPesc is associated with an increase hematologic toxicity and is given together with G-CSF and a weekly blood test. An increased risk of infertility has been described but for patients receiving at least 4 courses [12], however in the present protocol only 2 courses of BEACOPPesc will be given. Some rare cases of myelodysplasia/secondary acute leukemia have been described with a rate below 2% when 6 cycles are given [13].

5.4 Antibody-Drug Conjugate Therapy and Brentuximab Vedotin

Antibody-drug conjugates (ADCs), which consist of cytotoxic agents or toxins chemically conjugated to a monoclonal antibody, potentially represent an advantage over treatment with chemotherapy because they are designed to deliver the cytotoxic agent specifically to tumor cells thereby resulting in an improved safety profile.

Brentuximab vedotin (cAC10-vcMMAE) is a novel ADC that binds to the cell-surface marker CD30. Brentuximab vedotin consists of the chimeric antibody cAC10 chemically conjugated to monomethylauristatin E (MMAE), a synthetic analog of the naturally occurring cytotoxic agent, dolastatin [10]. cAC10 binds to a number of CD30-positive cancer cell lines including HL, ALCL [10,14]. Binding of cAC10 has been detected on activated T cells. cAC10, also known as SGN-30, has been studied in Phase 2 clinical trials in both HL and ALCL and has demonstrated activity with a good tolerability profile as a single agent.

After binding to CD30-positive cells, brentuximab vedotin is internalized, releasing free MMAE that leads to cell death.

Brentuximab vedotin induces growth inhibition of HL cell lines in vitro and inhibits disease progression in both disseminated and subcutaneous HL xenograft models in immunodeficient mice. CD30 is also expressed on ALCL, certain types of non-Hodgkin lymphomas (NHL), as well as rare solid tumors such as embryonal carcinomas and seminomas. Thus, brentuximab vedotin has the potential to offer an immunotherapeutic option to patients with CD30-positive malignancies, particularly HL.

5.5 Preclinical Experience

Detailed information regarding the nonclinical pharmacology and toxicology of brentuximab vedotin may be found in the Investigators Brochure (IB).

5.5.1 Pharmacology and Drug Metabolism in Humans

Further detailed information regarding the pharmacology and drug metabolism may be found in the Investigator's Brochure (IB).

Pharmacokinetic properties

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients. In all clinical trials, brentuximab vedotin was administered as an intravenous infusion. Further detailed information regarding the pharmacokinetic properties of brentuximab vedotin may be found in the Investigator's Brochure (IB).

Distribution, Metabolism, and Elimination

In vitro, the binding of MMAE to human serum plasma proteins ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound medicines. The ADC is expected to be catabolized as a protein with component amino acids recycled or eliminated. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes. The ADC is eliminated by catabolism with a typical estimated CL and half life of 1.457 l/day and 4-6 days respectively. The elimination of MMAE was limited by its rate of release from ADC, typical apparent CL and half life of MMAE was 19.99 l/day and 3-4 days respectively.

Detailed information regarding distribution, metabolism and elimination may be found in the Investigator's Brochure (IB).

5.5.2 Pharmacokinetics in Special Populations

Detailed information regarding hepatic impairment, renal impairment, elderly patients and pediatric population may be found in the European Summary of Product Characteristics (SmPC).

5.5.3 Drug-Drug Interaction, Cardiac electrophysiology, Immunogenicity

Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73% and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; however, it reduced exposure to MMAE by approximately 31%. Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam.

Forty-six (46) patients with CD30-expressing hematologic malignancies were evaluable of the 52 patients who received 1.8 mg/kg of brentuximab vedotin every 3 weeks as part of a phase 1, single-arm, open-label, multicenter cardiac safety study. The upper 90% confidence interval (CI) around the mean effect on QTc was <10 msec at each of the Cycle 1 and Cycle 3 post-baseline time points. These data indicate the absence of clinically relevant QT prolongation due to brentuximab vedotin administered at a dose of 1.8 mg/kg every 3 weeks in patients with CD30-expressing malignancies.

Patients with relapsed or refractory HL or sALCL in two phase 2 studies were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Approximately 35% of patients in these studies developed antibodies to brentuximab vedotin. The presence of antibodies to brentuximab vedotin did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin.

Detailed information regarding drug-drug interaction, cardiac electrophysiology and immunogenicity may be found in the Investigators Brochure (IB). A non-exhaustive list of strong CYP3A 4 inhibitors and inducers medicinal products is provided in **Appendix 12**.

5.6 Completed and Ongoing Clinical Experience with Brentuximab vedotin in HL

5.6.1 Study SG035-0001: Phase 1 Brentuximab Vedotin Monotherapy

The primary objectives of the study were to define the safety profile and to determine the maximum tolerated dose (MTD) of brentuximab vedotin administered every 21 days in patients with relapsed/refractory CD30-positive hematologic malignancies. Secondary objectives included evaluation of the pharmacokinetics, immunogenicity, and antitumor activity of brentuximab vedotin. Brentuximab vedotin was administered on Day 1 of each 21-day cycle via a 2-hour intravenous (IV) infusion according to the dose level assigned to each cohort. The beginning dose of brentuximab vedotin was 0.1 mg/kg, which was escalated gradually until DLT was observed. Expansion of one or more cohorts at or below MTD was permitted. Tumor response assessments were performed on Days 15–21 of the second cycle according to International Working Group Revised Response Criteria for Malignant Lymphoma [15, 16]. Patients with complete remission (CR), partial remission (PR), or stable disease (SD) and clinical benefit as defined in the protocol were allowed to receive an additional 2 cycles of brentuximab vedotin. Additional treatment cycles were allowed on a case-by-case basis. Patients were monitored for a minimum of 4 weeks following administration of the final dose of brentuximab vedotin.

This trial was completed in August 2009 with 45 patients enrolled and the results were published [17]. The MTD of brentuximab vedotin administered on a q3week schedule was defined as 1.8 mg/kg.

Brentuximab vedotin was generally well tolerated in the study, and 17 objective responses were observed, including 11 complete remissions, were observed in 17 patients. Of 12 patients who received the 1.8 mg/kg dose, 6 (50%) had an objective response. The median duration of response was at least 9.7 months. Tumor regression was observed in 36 of 42 patients who could be evaluated (86%).

5.6.2 Study SG035-0003: Pivotal Study of Brentuximab Vedotin in Relapsed/Refractory HL

This pivotal study (single arm phase 2) has evaluated the antitumor activity of brentuximab vedotin administered every 3 weeks at a dose of 1.8 mg/kg given intravenously. The primary objective is overall objective response rate in patients with relapsed or refractory HL following autologous stem cell transplant. Tumour response assessments are performed at 4 and 7 cycles with CT and PET CT scans (visual evaluation) [16].

For patients who experience stable disease or better, the maximum number of cycles permitted was 16.

The study has completed enrollment with 102 patients enrolled. An Independent Data Monitoring Committee (IDMC) has oversight of the safety of the patients on a periodic basis. The data were recently published and confirmed the safety profile observed in the phase 1 [18].

Adverse Event N = 102	Any grade	Grade 3	Grade 4
Peripheral sensory neuropathy	42%	8%	0
Myalgia	11%	0	0
Peripheral motor neuropathy	11%	1%	0
Neutropenia	19 %	14%	6%
Diarrhea	18 %	1%	0
Pyrexia	14 %	2%	0

Therapeutic results were encouraging in these advanced HL patients and are summarized in the table below:

	Key response results	
Parameter	n = 102	%
Objective response	76	75
CR	35	34
Duration of response	6.7 months [3.6-14.8]	
Duration of response For CR patients n = 35	20.5 mo. [10.8 – not reached]	
PFS	5.6 mo. [5-9]	

After approximately 3 years of follow-up (median observation time from first dose = 32.7 months, range, 1.8 to 48.3 months), the median PFS was 5.6 months (95% CI: 5.0, 9.0 months [range, 1.2 to 44.4+ months]) and the median OS was 40.5 months (95% CI:28.7, – months [range, 1.8 to 48.3+ months]). The estimated 36-month survival rate was 54% (95% CI: 44%, 64%). Regarding these results we are encouraged to use Brentuximab vedotin earlier in the course of HL disease

Key efficacy endpoints in sALCL (SG035-0004) include ORR per IRF (86% [95% CI: 74.6-93.9%]), CR rate per IRF (59% (34 of 58 patients in ITT set),, and B symptom resolution rate (82%). Patients have been followed for approximately 3 years (median observation time from first dose = 33.4 months, range, 0.8 to 45.6 months). The estimated 36-month survival rate was 63% (95% CI: 51%, 76%) and the median PFS was 14.6 months (95% CI: 6.9, 20.6 months [range, 0.8 to 40.4+ months]). The median OS has not yet been reached (95% CI: 21.3, – months [range, 0.8 to 45.6+ months])

5.6.3 Study SG035-0005: Brentuximab vedotin in the post transplantation setting, AETHERA trial

After the promising results of phase I & II in HL a randomized study was launched in relapsing/refractory HL. Patients must have relapsed with at least one adverse prognostic factor (e.g. early relapse or relapse in an extranodal site) according to known adverse prognostic factors in this setting [19, 20]. These patients were randomized after high-dose therapy and autotransplantation to receive at Day 45 Brentuximab vedotin 1.8 mg/kg every 3 weeks for one year or a placebo with the same schedule. 300 patients have been included internationally but results are not expected before the end of 2013.

5.7 **H10 study in patient with PET positive after 2 ABVD**

We previously launched the H10 protocol where patients with positive PET after 2 cycles of ABVD received 2 cycles of BEACOPP escalated and IFRT in the experimental arm versus no change of treatment in the standard arm. In this protocol, 1137 patients with stage I/II supradiaphragmatic HL were randomized and with a visual evaluation (Juweid criteria) [16] the rate of PET2 positive after 2 cycles of ABVD was 14% in the favorable group and 25 % in the unfavorable [21]. Results for patients with positive PET at 2 cycles are not yet available but the strategy is well tolerated and we would like to continue to improve PFS in this setting.

5.8 **Rationale for Study**

Due to the good results observed in first line therapy for patients with stage I/II supradiaphragmatic HL, we decided to focus on the poor prognosis population which is best evaluated with PET [22, 9]. Patients with stage I/II supradiaphragmatic HL will be treated as usual with ABVD and an early interim PET after 2 cycles.

PET scans will be assessed visual and judged positive in case of detection of focal accented, increased uptake superior to liver activity as reference activity (score 4 and 5 of Deauville) [9]. Lesions with pathologically increased FDG uptake will be determined by the maximal standardized uptake value (SUVmax).

For these patients with PET 2 positive, the chemotherapy with ABVD will be stopped and they will receive 2 courses of BEACOPP escalated (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine and prednisone) every 3 weeks followed by 30Gys IFRT. Another PET scan will be performed before IFRT to exclude from the study progressive patients after 2 BEACOPP $_{\text{escalated}}$.

Brentuximab vedotin 1.8 mg/kg will be started at least 4 weeks after the end of IFRT and up to 6 weeks. It will be given every 3 weeks for 8 cycles.

6 STUDY OBJECTIVES

6.1 Primary Objective

Evaluation of the PFS at two years

6.2 Secondary objectives

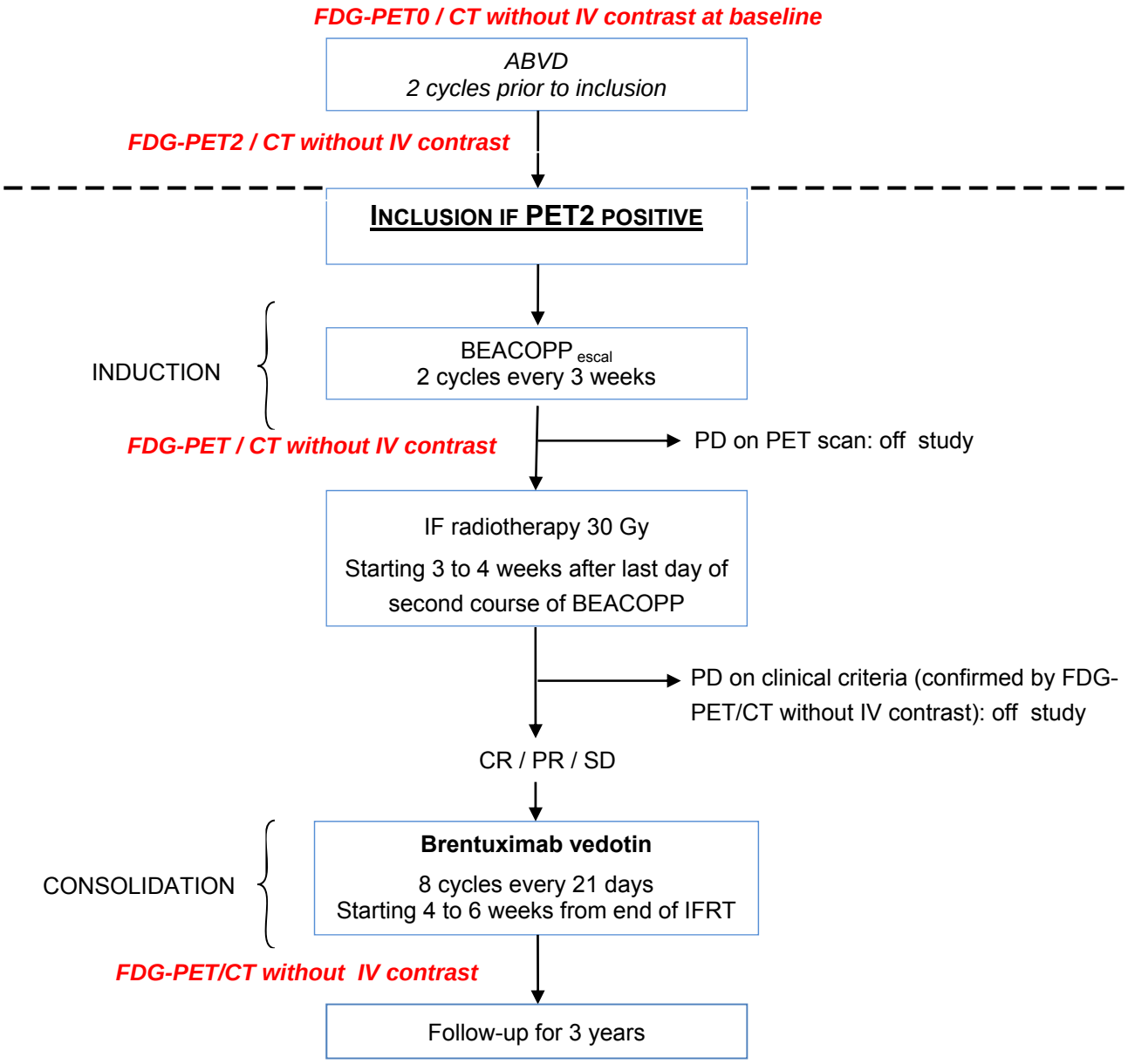
- To evaluate the safety and tolerability of brentuximab vedotin
- To analyze overall survival (OS) and CR rate (Cheson 2007) at the end of treatment (see **Appendix 8**)

6.3 Safety endpoint

- Type, incidence, severity, seriousness, and relatedness of adverse events
- Laboratory abnormalities

7 STUDY DESIGN

Figure 1: Overall study design



This study is a multicentric, open-label, single arm phase II trial.

Patients will be recruited over 3.5 years and followed until the end of the 1.5 years of follow-up of the last patient.

Study duration is approximately of ~ 6 years: 3.5 years for recruitment, 35 weeks of treatment and for at least 1.5 years of follow-up.

The anticipated study dates (start / end) are:

1st patient included (FPFV): Q2 2015

Last patient included (LPFV): Q4 2018

Last patient followed for final analysis: Q3 2020

It is expected that a total of 40 evaluable patients treated by brentuximab vedotin will be included in the study, any patient withdrawing before the brentuximab vedotin should be replaced.

The duration of the consolidation treatment is approximately 24 weeks for 8 cycles of Brentuximab vedotin.

End of study: is defined as the last visit of the last patient in follow-up planned in the protocol.

8 STUDY POPULATION

Patients aged from 18 to 65 years with an Ann Arbor clinical stage I or II classical Hodgkin lymphoma, FDG-PET positive score 4 & 5 according to Deauville criteria after 2 courses of ABVD and without progressive disease will be included in the trial.

Patient will receive 2 courses of $BEACOPP_{escalated}$ and in absence of progression, chemotherapy will be followed by 30 Gy IFRT before starting consolidation treatment.

8.1 Inclusion criteria

Subjects must meet all of the following criteria:

1. Patients must have histologically confirmed CD30+ classical Hodgkin lymphoma.
2. Patients must have provided voluntary written informed consent before performance of any study-related procedures not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Supradiaphragmatic Ann Arbor clinical stage I or II

   All eligible patients will be classified according to the classic EORTC/GELA clinical prognostic factors as favourable (F) or unfavourable (U) patients

   Unfavourable (U) subset includes patients with one or more of the following criteria: CSII ≥ 4 nodal areas or age ≥ 50 years or M/T ratio ≥ 0.35 or ESR ≥ 50 mm/hour (without B-symptoms) or ESR ≥ 30 mm/hour with B-symptoms.Favourable (F) subset has none of the above criteria.
4. Mandatory FDG-PET/ CT without IV contrast performed at diagnosis
5. Patients treated with first-line ABVD and FDG-PET/CT without IV contrast positive after 2 cycles (Deauville score 4 & 5) but without progressive disease
6. Patients must have an ECOG performance status of 0-2
7. Life expectancy > 6 months
8. Patients must be 18-65 years of age
9. Patients must be available for periodic blood sampling, study-related assessments, and management of toxicity at the treating institution
10. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR are surgically sterile,

OR

- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse

11. Male patients, even if surgically sterilized (ie, status postvasectomy), who agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse.
12. Clinical laboratory values as specified below before the first dose of study drug:
    - Absolute neutrophil count ≥ 1,500/µL (1.5 x 10^9/L) unless is related to ABVD treatment
    - Platelet count ≥ 75,000/ µL (75 x 10^9/L)
    - Total bilirubin must be < 1.5 x the upper limit of the normal (ULN) unless the elevation is known to be due to Gilbert syndrome
    - ALT or AST must be < 3 x the upper limit of the normal range
    - Serum creatinine must be < 2.0 mg/dL (177 µmol/L) and/or creatinine clearance or calculated creatinine clearance > 40 mL/minute
    - Hemoglobin must be ≥ 8g/dL
13. Patient affiliated to social security system

8.2 Exclusion criteria

Subjects must not meet all of the following criteria:

1. Patients with dementia or altered mental status that would preclude compliance with drug delivery
2. Women who are pregnant or breastfeeding
3. Patients with symptomatic pulmonary disease
4. Patients with known history of any of the following cardiovascular conditions:
    - Myocardial infarction within 2 years of inclusion
    - New York Heart Association (NYHA) Class III or IV heart failure (see **Appendix 11**)
    - Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities
    - Recent evidence (within 6 months before first dose of study drug) of a left-ventricular ejection fraction <50%
5. Any history of cancer or cancer treatment during the last 3 years with the exception of non-melanoma skin cancer or stage 0 (in situ) carcinoma of any type if they have undergone complete resection.
6. Uncontrolled infectious disease, including active HBV infection defined by either detection of HBs Antigen or presence of anti HBc antibody without detectable anti HBs antibody.
7. Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics at the time of inclusion and planned to be still on going within 2 weeks prior to first study drug dose
8. Known HIV, known or suspected HCV serology positivity
9. Patients who have been treated previously with any anti-CD30 antibody
10. Known hypersensitivity to any excipients contained in the brentuximab vedotin formulation
11. Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of Progressive Multifocal Leukoencephalopathy (PML)
12. Any sensory or motor peripheral neuropathy greater than or equal to Grade 2
13. Patients that have not completed any prior treatment chemotherapy and/or other investigational agents within at least 5 half-lives of last dose of that prior treatment

9 STUDY FLOW CHART (APPENDIX1) AND SCHEDULE OF ASSESSMENTS (APPENDIX2)

9.1 Study flow chart

See on **Appendix 1**.

9.2 Informed consent

To participate in this study and before any evaluation performed for inclusion in the protocol, a written informed consent must be signed by each patient.

This consent is signed after investigator gave all information required to the patient.

The patient and the investigator will date and sign the informed consent form.

An original copy of the signed consent will be provided to the patient; the original will be maintained in the investigator's study file. The investigator will attest on e-CRF that the patient has signed and dated informed consent.

9.3 Baseline examination and evaluation prior to inclusion

The subject's eligibility has to be evaluated after 2 courses of ABVD prior to inclusion in the protocol:

- Lymph node biopsy within 3 months before ABVD courses, for confirmation of a diagnosis HL
- Age, gender, weight, height, BSA (**see Appendix 4**: Body Surface Area calculation)
- Clinical examination (including tumor assessment) should be performed before and after the 2 ABVD courses
- ECOG Performance Status before and after the 2 ABVD courses (**see Appendix 6** "Performance Status Criteria")
- Vital signs (pulse, blood pressure and body temperature)
- Staging according to Ann Arbor classification (**see Appendix 3**) and to the EORTC/GELA clinical prognostic factors (**see Appendix 7**) prior to ABVD courses
- Relevant medical history, including menstrual status, method of contraception
- Concomitant medication
- History of the HL including B symptoms
- Hemoglobin, leukocyte count, neutrophils and lymphocytes, platelets
- Erythrocyte Sedimentation Rate (ESR) before ABVD (at diagnostic)
- Erythrocyte Sedimentation Rate (ESR) and/or C Reactive Protein (CRP) prior to inclusion (after 2 courses of ABVD)
- Biochemical tests: serum creatinin, bilirubin total, AST, ALT, alkaline phosphatase, Calcium, serum Albumin
- HIV, HBV and HCV serologies if not already done within 3 months before inclusion
- Pregnancy test in all premenopausal women of childbearing potential (Note: Females are defined as not of childbearing potential if there is documentation of "natural menopause for at least 12 consecutive months, a hysterectomy or bilateral oophorectomy")
- Mandatory FDG-PET/CT without IV contrast at diagnosis (before ABVD courses) and after 2 courses of ABVD
- Cervical, thoracic CT at diagnosis (before ABVD courses)
- ECG / Echocardiography or isotopic method to determine LVEF if not already done within 3 months before inclusion
- Chest X-Ray for M/T ratio evaluation (**see Appendix 5**: Mediastinum measurement)

9.4 Evaluation during induction treatment (BEACOPP + IFRT)

Evaluation during induction treatment consisting in 2 courses of BEACOPP $_{escalated}$ every 3 weeks will be done according to local practice.

A FDG-PET/CT without IV contrast will be performed after the 2 BEACOPP $_{escalated}$ to eliminate the rare progressive patients.

In the absence of progression, IFRT will be given after the 2 courses of BEACOPP $_{escalated}$ according to the schedule used in each center and the EORTC/GELA recommendations [4]. IFRT will start 3 to 4 weeks after the end of second BEACOPP $_{escalated}$.

During this induction treatment only Serious Adverse Events reporting (SAE form and the corresponding AE page in the e-CRF) will be performed.

9.5 Evaluation prior to consolidation treatment (brentuximab vedotin)

The following assessments are to be conducted **within 7 days** before administration of the study drug (brentuximab vedotin):

- Clinical examination (no sensory or motor peripheral neuropathy greater than or equal to Grade 2)
- ECOG Performance Status **(see Appendix 6** "Performance Status Criteria")
- Vital signs (heart rate, blood pressures and body temperature)
- ESR and/or CRP
- Hemoglobin, leukocyte count, neutrophils and lymphocytes, platelets
- Biochemical tests: serum creatinin, bilirubin total, AST, ALT, alkaline phosphatase,

In order to be able to receive brentuximab vedotin, for safety reason, the patient must fulfilled the following criteria:

- Absolute neutrophil count ≥ 1,500/µL (1.5 x 10^9/L)
- Platelet count ≥ 75,000/ µL (75 x 10^9/L)
- Hemoglobin must be ≥ 8g/dL
- Total bilirubin must be < 1.5 x the upper limit of the normal (ULN) unless the elevation is known to be due to Gilbert syndrome
- ALT or AST must be < 3 x the upper limit of the normal range
- Serum creatinine must be < 2.0 mg/dL (177µmol/L) and/or creatinine clearance or calculated creatinine clearance > 40 mL/minute
- No active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to first brentuximab vedotin dose

- Pregnancy test in all premenopausal women of childbearing potential
- Adverse events reporting / concomitant treatment (no systemic antibiotics are allowed within 2 weeks prior to first brentuximab vedotin dose)

9.6 Evaluation during consolidation treatment

The brentuximab vedotin treatment will start 4 weeks after the last day of IFRT and up to 6 weeks. Patients are scheduled to receive 8 cycles every 21 days.

	When
Weight and body surface area (see **Appendix 4** "Body surface area")	Day 1 prior to each brentuximab vedotin administration
Vital signs (Pulse, blood pressure, body temperature)	Day 1 prior to each brentuximab vedotin administration
Clinical examination	Day 1 prior to each brentuximab vedotin administration
ECOG PS	Day 1 prior to each brentuximab vedotin administration
Biochemical tests: serum creatinin, bilirubin total, AST, ALT, alkaline phosphatase	Day -1 or day 1 prior to each brentuximab vedotin administration
Hemoglobin, leukocyte count, neutrophils and lymphocytes, platelets	Day -1 or day 1 prior to each brentuximab vedotin administration
Adverse events / toxicities reporting	Continuous reporting of AEs up to 30 days after the last brentuximab vedotin administration

9.7 End of treatment and premature protocol treatment discontinuation's evaluations

Patients will be evaluated within 4 ± 1 weeks after end of cycle 8 of brentuximab vedotin or within 4 ± 1 weeks after last treatment dose in case of premature discontinuation of protocol treatment.

- Clinical examination
- Vital signs (Pulse, blood pressure, body temperature)
- ECOG Performance Status (**see Appendix 6** "Performance status criteria")
- Biochemical tests: serum creatinine, bilirubin total, AST, ALT, alkaline phosphatase, serum albumin
- ESR and/or CRP
- Hemoglobin, leukocyte count, neutrophils and lymphocytes, platelets
- Cervical, Chest CT scan with iodine contrast
- FDG-PET/CT without IV contrast (Deauville criteria, Meignan et al. 2012 [9])
- Evaluation of the disease response (Cheson 2007) (see **Appendix 8**)
- Any other evaluation or procedures performed at baseline for evaluation of the disease response
- Adverse events/List of toxicities

9.8 Follow-up assessments

Follow up visits will be performed every 3 months during the first year, then every 6 months until the end of the 1.5 years of follow-up of the last patient. Patients will be followed until death if possible up to the end of follow-up period. Thereafter, the long term follow-up of patients may be organized for further analysis.

- Clinical examination
- Hemoglobin, leukocyte count, neutrophils and lymphocytes, platelets
- ESR and/or CRP
- ECOG Performance Status (**see Appendix 6** "Performance status criteria")
- Cervical and chest CT scan with iodine contrast medium every 6 months for 3 years
- Any other evaluations or procedures for evaluation of the treatment response

Patients who withdraw from the study treatment or patients who progress / receive new treatment after study treatment period should be followed according the local requirements until death, up to the end of follow-up period. This will only be applicable for patients that have received at least one injection of brentuximab vedotin.

9.9 Progression/relapse

Progressive disease should be based on clinical criteria and confirmed by CT scan or FDG -PET scan according to Cheson 2007.

A pathological confirmation by biopsy of the lesion should be done if possible.

10 TREATMENTS

10.1 Drugs description, storage and handling

Drugs composing the BEACOPP $_{escalated}$ regimen are registered and are available at the hospital pharmacy. Chemotherapy products are to be used according to summary of product characteristics.

For consolidation treatment, brentuximab vedotin, will be supplied to clinical sites using designated distribution centers, and are to be used according to Investigator Brochure.

10.1.1 Brentuximab vedotin: Description

Brentuximab vedotin (ADCETRIS°) is an antibody-drug conjugate (ADC) directed to CD30-expressing cells and is being developed for the treatment of Hodgkin lymphoma and Systemic anaplastic large cell lymphoma. Brentuximab vedotin is manufactured by Millennium Pharmaceuticals, Inc. and is supplied free of charge for this clinical trial.

10.1.2 Brentuximab vedotin: Packaging and labeling

Brentuximab vedotin is a sterile, preservative-free, lyophilized cake for reconstitution for IV administration. Brentuximab vedotin for injection is supplied as a single-use, borosilicate glass vials. Each vial of the product contains 50 mg of useable brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. The lyophilized product, after reconstitution with 10.5 mL sterile Water for Injection, yields 11 mL of brentuximab vedotin solution (5 mg/mL concentration after reconstitution). Vials of study treatment will be packaged as one single-use vial per carton (kit). Vials and kits will be labeled to meet country-specific regulatory requirements.

Brentuximab vedotin will be labeled as IMP.

10.1.3 Brentuximab vedotin: Storage conditions

Investigational product will be distributed to clinical sites using a designated and authorized vendor that, on behalf of Principal Investigator and Sponsor of the study, will provide the investigators with adequate quantities of investigational product. All investigational products will be stored at 2°C to 8°C and must not be frozen.

10.1.4 Brentuximab vedotin: Handlings

If a drug shipment arrives damaged, or if there are any other drug complaints, the Sponsor should be immediatly informed (see Section 17.10).

Study treatment must not be administered as an IV push or bolus. Study treatment will be administered by outpatient IV infusion given over approximately 30 minutes on Day 1 of each 21-day cycle. In the absence of infusion toxicities (See Section 10.2.2.1) the infusion rate for all patients must be calculated in order to achieve a 30-minute infusion period. Study treatment will be administered through a dedicated IV line and cannot be mixed with other medications.

The dose of study treatment is 1.8 mg/kg.

Dosing is based on patient weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

Reconstitution

Brentuximab vedotin solutions should be prepared and transferred using aseptic technique in a biosafety hood. Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

Brentuximab vedotin vials are single-use containers and contain no preservative. Any partially used vials or diluted dosing solutions are to be discarded using appropriate institutional drug disposal procedures.

Brentuximab vedotin must be reconstituted with 10.5 mL of Sterile Water for Injection, gently swirling the vial until the contents are completely dissolved. The vial must not be shaken or vigorously swirled; excess agitation may cause aggregate formation. Visually inspect the reconstituted drug product for any particulate matter and discoloration.

Dilution

The appropriate amount of reconstituted brentuximab vedotin will be withdrawn from the vial(s) and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection.

There are no known incompatibilities between brentuximab vedotin and polypropylene (PP), ethyl vinyl acetate (EVA), polyolefin, or polyethylene (PE) bags. The bag should be gently inverted to mix the solution. The bag must not be shaken; excess agitation may cause aggregate formation. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

Following dilution, infuse the brentuximab vedotin solution immediately, or store the solution at 2-8˚C (36-46˚F) and use within 24 hours of reconstitution.

10.2 Treatment schedule and design

10.2.1 Induction treatment: BEACOPP$_{escalated}$ and IF-radiotherapy

Patients will be selected after the PET2 results and if positive, they will receive 2 courses of BEACOPP$_{escalated}$ every 3 weeks.

BEACOPP $_{escalated}$

	Dose	Route	Day
Cyclophosphamide	1250 mg/m²	i.v.	1
Doxorubicin	35 mg/m²	i.v.	1
Vincristine	1.4 mg/m²	i.v.(max. 2 mg)	8
Bleomycin	10 mg/m²	i.v	8
Etoposide	200 mg/m²	i.v.	1 to 3
Procarbazine	100 mg/m²/day	p.o.	1 to 7
Prednisone	40 mg/m²/day	p.o.	1 to 7
G-CSF	5 µg/kg/day	s.c.	From day 9 to recovery leukocytes>1.0x10^9/L

A mandatory FDG-PET/CT without IV contrast will be performed after the 2 courses of BEACOPP$_{escalated}$ to eliminate the rare progressive patients.

In the absence of progression, IFRT will be given 3 to 4 weeks after the last day of second BEACOPP at 30 Grays (+boost 6 Grays to area with residual lesion according to investigator's decision) in 3 weeks according the schedule used in each center and the EORTC/GELA recommendations [4].

10.2.2 Consolidation treatment: Brentuximab vedotin

10.2.2.1 Administration

The brentuximab vedotin treatment will start 4 weeks after the last day of IFRT and up to 6 weeks.

The dose of study treatment is 1.8 mg/kg. Brentuximab vedotin must not be administered as an IV push or bolus. Study treatment will be administered by IV infusion given over approximately 30 minutes. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute (approximate) infusion period.Brentuximab vedotin will be administered through a dedicated IV line and cannot be mixed with other medications.

Dosing is based on patient weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

Routine premedication should not be administered prior to the first dose of study treatment. However, patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment with premedication as described below.

Infusion-related reactions may occur during the infusion of study treatment. The infusion is to be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for at least 60 minutes following the first infusion of study treatment. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institutional standards. This includes adjusting the infusion time if necessary. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use. Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment infusions with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 10–25 mg IV) or according to institutional standards, administered 30–60 minutes prior to each 30-minute infusion.

If a Grade 3 or greater infusion-related reaction consistent with anaphylaxis occurs, immediately and permanently discontinue administration of brentuximab vedotin and administer appropriate medical therapy as per institutional guidelines and investigator discretion.

10.2.2.2 Dose adjustments

Intrapatient dose reduction to 1.2 mg/kg will be allowed depending on the type and severity of toxicity.

Table 1 describes the recommended dose modifications for study treatment-associated toxicity.

NCI CTCAE Toxicity Grade (v4.03)	Action Required
Neutropenia Grade 1 (< ULN – 1500/mm^3) or Grade 2 (< 1500/mm^3 – 1000/mm^3)	No treatment modification
Neutropenia Grade 3 (< 1000/mm^3 - 500/mm^3) or Grade 4 (< 500/mm^3)	Dosing should be held until resolution to baseline or Grade 2 or lower, then restart at same dose level. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. If Grade 4 neutropenia recurs despite growth factor support, discontinuation or dose reduction to 1.2 mg/kg should be considered
Peripheral motor or sensory Neuropathy Grade 1 (Asymptomatic; loss of deep tendon reflexes or paresthesia)	No treatment modification
Peripheral Neuropathy Grade 2 (limiting instrumental ADL) Grade 3 (limiting self-care ADL)	Dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg.
Peripheral Neuropathy Grade 4 (Life-threatening consequences; urgent intervention indicated)	Treatment discontinuation
Renal Impairment Creatinine > 2mg/dl and/or creatinine clearance < 40ml/minute	Reduce the dose to 1.2mg/kg and stop if persistence after reduction
Hepatic Impairment ALT or AST > 3 ULN	Reduce the dose to 1.2mg/kg and stop if persistence after reduction
Hepatic Impairment ALT or AST > 10 ULN	Treatment discontinuation

The start of the next cycle may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle. Delays greater than 3 weeks are prohibited without approval of the Sponsor and the patients will be off study.

Doses reduced for treatment-related toxicity should not be re-escalated.

10.2.2.3 Management of Clinical Events

Peripheral Neuropathy

Collectively, the data support that peripheral neuropathy is an effect of cumulative exposure to brentuximab vedotin. The first onset of any grade peripheral neuropathy increased incrementally with increasing numbers of cycles, and a trend toward increased incidence of first onset of Grade 3 peripheral neuropathy and peripheral motor neuropathy in later cycles was apparent. In line with these observations, the incidences of peripheral neuropathy (any Standard MedDRA Queries (SMQ) event, Grade 3 event, and/or motor event) were highest in later cycles.

Neuropathy associated with brentuximab vedotin was managed using a combination of dose delay and reduction to 1.2 mg/kg. Dose delay and reduction appeared to mitigate worsening of neuropathy. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at the 1.2 mg/kg dose level (or as specified in individual protocols). For Grade 4 peripheral neuropathy, brentuximab vedotin should be discontinued.

Hematological Toxicities

The hematological AEs of thrombocytopenia, anemia, and neutropenia were reported in the pivotal studies. Neutropenia was the most common hematological AE (21%) and was not unexpected based on the toxicology results from the sponsor's nonclinical program and phase 1 safety and clinical pharmacology studies. Although neutropenia was a common treatment-emergent AE in the pivotal studies, it appeared to be well managed with the protocol-specified recommendations for hematologic toxicity (i.e., dose delay, growth factor support). The median duration of Grade 3 or Grade 4 neutropenia was limited (1 week); 3 patients had Grade 4 neutropenia that lasted ≥7 days. Less than half of the patients with Grade 3 or 4 neutropenia had temporally associated infections, and the majority of temporally associated infections were Grade 1 or 2. Although not reported in the pivotal studies, febrile neutropenia has been reported in additional completed studies with brentuximab vedotin. Patients should be monitored for cytopenias.

For new or worsening Grade 3 or 4 neutropenia, dosing should be held until neutropenia improves to ≤ Grade 2 or baseline and then restarted at the same dose level (or as specified in individual protocols). Growth factor support (G-CSF or GM-CSF) should be considered for subsequent cycles (refer to Sections 10.2.2.2 and 10.5).

Infusion-Related Reactions

Brentuximab vedotin is administered via IV infusion. Infusion of proteins can result in hypersensitivity reactions that may be fatal if not rapidly and appropriately managed. Infusion interruption for IRR treatment generally led to the successful completion of the dose and continued treatment with brentuximab vedotin with or without IRR prophylaxis, according to the clinical judgment of the investigator.

Although the experience with IRRs related to brentuximab vedotin is limited, in part due to the low incidence observed to date, data support brentuximab vedotin administration by appropriately trained personnel without the need for routine prophylaxis. If IRR symptoms develop, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Premedication

should be administered for subsequent infusions in patients who have experienced a prior IRR. If anaphylaxis occurs, brentuximab vedotin should be immediately and permanently discontinued and appropriate medical management instituted.

Infections

Serious and opportunistic infections have been reported for patients treated with brentuximab vedotin. Monitor patients for the emergence of possible bacterial, fungal, or viral infections.

Although infections were observed in 61% of patients in the completed phase 2 studies (Studies SG035-0003 and SG035-0004), the majority of infections were Grade 1 to 2 and occurred with an incidence comparable to that reported in similar populations. While serious infections were reported in 10% of patients, the majority of infections were not considered by the investigator to be related to brentuximab vedotin. Infection led to dose delay in 14% of HL patients and 7% of ALCL patients. No patient discontinued treatment because of infection. The infection with the highest incidence was Grade 1 or 2 URTI, which occurred in more HL than ALCL patients. Grade 3 or 4 infections occurred in 7% of HL patients and 12% of ALCL patients. No Grade 5 infections were reported. HL patients had a higher incidence of infections, largely reflective of the higher incidence of Grade 1 to 2 URTI (37%). Several factors may have contributed to this higher incidence, including the high frequency of respiratory tract infections in HL patients post-transplant, the lower median age of the HL patients compared with systemic ALCL patients, and differences in exposure to respiratory viruses. These URTIs, while frequent, led to dose delay in only 3 patients. Importantly, the rate of pneumonia was low, which is indicative of a low rate of progression from URTI to pneumonia, and the incidence was lower than that reported in the literature for comparable populations.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with brentuximab vedotin. Fatal outcomes have been reported. If SJS or TEN occurs, discontinue brentuximab vedotin and administer appropriate medical therapy.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is typically reported in patients with acute leukemias and high-grade non-Hodgkin lymphomas after the initiation of cytotoxic therapy.

TLS has been reported with brentuximab vedotin. Patients with rapidly proliferating tumor and high tumor burden are at risk of TLS. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

Progressive Multifocal Leukoencephalopathy

PML can occur in patients receiving brentuximab vedotin. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). The onset of neurological deficits may occur over weeks to months [23].

Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML.

If PML is suspected, a diagnostic work-up should be performed. The work-up may include, but is not limited to:

- Neurologic examinations, as warranted
- Brain MRI: features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically non-enhancing and do not have mass effect.
- PCR analysis: JCV DNA detectable in CSF or there is evidence of JCV in a brain biopsy
- Neurology consultation

Brentuximab vedotin dosing should be held if PML is suspected. If PML is confirmed, brentuximab vedotin should be permanently discontinued.

Pulmonary Toxicity in Combination with Bleomycin

Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial that studied brentuximab vedotin with bleomycin as part of a combination regimen (ABVD), the rate of noninfectious pulmonary toxicity was higher than the historical incidence reported with ABVD. Monotherapy with brentuximab vedotin has not been associated with a clinically meaningful risk of pulmonary toxicity. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately.

Acute Pancreatitis

Acute pancreatitis has been reported for patients treated with brentuximab vedotin. Patients should be monitored for signs of new or worsening acute abdominal pain and, if observed, a diagnostic workup for pancreatitis should be considered. A diagnostic workup may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Brentuximab vedotin should be held for any suspected case of acute pancreatitis. Brentuximab vedotin should be discontinued if a diagnosis of acute pancreatitis is confirmed.

Hepatotoxicity

Hepatotoxicity, predominately in the form of asymptomatic mild to moderate transient elevations in AST and/or ALT, has been reported for patients treated with brentuximab vedotin. Patients should be monitored for elevated liver enzymes.

Embryogenesis, Reproduction, and Spermatogenesis

The effects of brentuximab vedotin on embryogenesis, reproduction, and spermatogenesis in humans are unknown. In addition, data about the effects of brentuximab vedotin in pregnant women are unavailable. Therefore, women of childbearing potential and fertile men should be advised to use adequate and effective contraception during and 6 months after treatment with brentuximab vedotin.

10.3 Drug Dispensation and accountability

10.3.1 Responsibilities

All drug packages are to be inspected upon receipt at the study site prior to being drawn up. If any particulate matter is detected, the packaging is not to be used. Damaged packaging is to be reported to the sponsor and stored until instructions have been given.

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product (Brentuximab vedotin) are responsible for ensuring that the Investigational Products used in the clinical trial are securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements. All

Investigational Medical Products are stored in accordance with labeling and shall be dispensed in accordance with the Investigator's prescription. The Investigator is in charge of ensuring that an accurate record of Investigational Product issued and returned is maintained. Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure (see Section 17.10). Under no circumstances will the Investigator supply Investigational Product to a third party, allow the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

10.3.2 Retrieval or destruction

All partially used or unused treatments will be verified by the Sponsor. A detailed treatment log of the returned Investigational Product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator (or the Pharmacist) and the Sponsor representative. The Investigator (or the pharmacist) will not destroy the unused Investigational Product unless the Sponsor provides written authorization. In case of a potential defect in the quality of Investigational Product, the Sponsor may initiate a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

10.3.3 Accountability and compliance

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational product. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments dispensed and used for each patient, to assess the patient treatment compliance. The sponsor representative will periodically check the supplies of investigational products held by the investigator or pharmacist to verify accountability of all investigational products used. All unused investigational products and all medication containers will be destroyed by the study sites. The Sponsor will verify that a final report of drug accountability at the unit dose level is maintained and archived in the investigator study file. Administration of the study treatment will be supervised by the investigator or sub-investigator.

10.4 **Concomitant treatment restrictions**

During the administration of investigational drug, no other anticancer drugs are allowed.

The use of steroids is not allowed during the study treatment with the exception of hydrocortisone or other steroids in a dose not higher than 1 mg/kg of prednisone or equivalent when used for prophylaxis of infusion reactions.

Systemic antibiotics required for treatment of any active viral, bacterial or fungal infection are not allowed within 2 weeks prior to first study drug dose.

10.5 **Prophylactic measures**

No prophylaxy is mandatory, we only can suggest Valacyclovir 500 mg daily for patients with a lymphocyte count below 1000/mm^3 for zona prophylaxis.

Antibacterial, antifungal, or antiviral prophylaxis is permitted as per local policy.

Prophylaxis use of G-CSF is based on physician assessment of risk of febrile neutropenia.

Therapeutic use of G-CSF is allowed according to treating physician.

Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 10–25 mg IV) or according to institutional standards, administered 30–60 minutes prior to each 30-minute infusion.

10.6 Therapeutic option after brentuximab vedotin

For patients who fail to obtain a complete response after brentuximab vedotin treatment (stable disease (SD) or partial response (PR)), high-dose chemotherapy (i.e. chemotherapy intensification) followed by an autologous stem cell transplant will be evaluated, and, within the realms of possibility, favored by the investigator as a therapeutic option that will be offered for a potential cure (according to the Lymphoma Study Association (LYSA) guidelines) [24]. These information will be collected during the study.

11 STUDY PROCEDURES

11.1 Inclusion procedure

A patient will be included after verification of eligibility directly on the data capture system by the investigators through the internet network with the address below. To access the interactive registration program, the investigator needs to record the study name (BRAPP2), a username and a password.

Internet: http://study.lysarc.info

Inclusion should be done before the start of the protocol treatment. The study site will receive back the inclusion number.

The investigator should fax (**+33 (0)4 26 07 40 13**) at the same time the following documents: copy of the pathology reports (tumor and if available bone marrow report), copy of PET0 and PET2 reports or enough information for organizing PET review (see concerned chapters).

11.2 Pathological diagnosis

The pathological diagnosis of Hodgkin lymphoma should have been performed locally before the inclusion for each patient.

Histopathology central review process has become in the last years a common and prerequisite procedure for clinical trials in the field of lymphomas. A mandatory pathological review will therefore be organized for all patients included in the trial at diagnosis. The goal of this central review will be to confirm the diagnosis and to precise its classification according to the WHO classification 2008.

The pathological review will be centralized at the LYSA-Pathology institute (LYSA-P), Hôpital Henri Mondor, Créteil. For each patient, the investigator will be requested to join with the form of inclusion a copy of the anonymised histopathological report (tumor and bone marrow report) where the name and address of the pathologist having diagnosed the lymphoma will be easily identified.

All requested tumor paraffin embedded blocks from the formalin fixed sample (that have been used for diagnosis), or 10 unstained slides will be sent to the LYSA-P according to the process described in **Appendix 10**. At reception, routinely stained sections will be performed and an appropriate panel of antibodies will be applied according to the morphological aspects. A pathological review, performed by at least 2 experts hematopathologists will be organized at the LYSA-P and a consensus diagnosis will be established. A LYSA-P pathological report will then be sent to the clinical coordinator and to the initial pathologist.

Initial tumor block will also be used to make tissue microarray (TMA), from which will be study the expression of markers known to influence the prognosis of Hodgkin lymphoma.

At the end of the inclusions, frozen tumor tissue will be requested for all included patients. The collection of the frozen tumor specimen will be organized and centralized at the LYSA-P. On frozen tissue, gene and protein expression will be analysed to assess their influence the outcome of Hodgkin lymphoma patients.

For the need of the ancillary study, paraffin blocks will be kept temporarily at the LYSA-P, to avoid a second request. Meanwhile, the block will be at the entire disposition of the initial anatomopathology laboratory under request if they need it.

11.3 FDG-PET / CT Review

A central review of the FDG-PET / CT is organized for this study and mandatory.

For each patient when applicable, the following data and images will be reviewed by a panel of PET experts:

- FDG-PET/CT without IV contrast at diagnosis
- FDG-PET/CT without IV contrast after 2 courses of ABVD, mandatory for the inclusion
- FDG-PET/CT without IV contrast after 2 courses of $BEACOPP_{escalated}$
- FDG-PET/CT without IV contrast at end of treatment by brentuximab vedotin

The review processing is described on the **Appendix 9** “PET-scans”.

11.4 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC), including at least three independent members (2 experts in HL and one statistician) will be established.

The IDMC will meet once when 10 patients will have completed 8 cycles of brentuximab vedotin or prematurely discontinued brentuximab vedotin treatment. During IDMC evaluation accrual will not be stopped.

The IDMC will review the overall safety of the trial. All data presented at the meeting will be considered confidential.

Following the meeting, the IDMC will prepare a report and may recommend changes in the conduct of the trial or stop the study.

Details of the IDMC operation will be provided in the IDMC Charter which will be developed prior to the first patient being enrolled.

12 CRITERIA FOR PREMATURE DISCONTINUATION

12.1 Premature protocol treatment discontinuation

Circumstances that lead to premature protocol treatment discontinuation of a patient must be reported by the investigator on the appropriate CRF page.

Criteria for subject permanent treatment discontinuation include (but are not limited to):

- death,
- toxicity (unacceptable according to investigator discretion, that does not allow to give the study drug),
- lymphoma progression,
- concomitant disease,
- noncompliance (including loss of subject to follow-up),
- consent withdrawal,
- and major protocol violation, including initiation of alternate anti-neoplasic therapy.

All alive patients, even withdrawn (except consent wtihdrawal) should however remain in the trial for the purposes of follow-up and data analysis.

Any patient who discontinues before completing the study will be encouraged to return to the study centre within 4 ± 1 weeks for an evaluation.

12.2 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states his/her wish not to contribute further data to the study, the relevant LYSARC contact should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. However, data up to the time of consent withdrawal will be included in the data reported for the study, unless the patient objects to any use of his personal data.

12.3 Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time site investigator must document attempts to contact the patient either by phone or letter.

12.4 Premature discontinuation of the study

The sponsor reserves the right to stop the trial at any time based on the following criteria:

- One of the stopping rules has been reached;
- There is evidence of an unacceptable risk for study patients (i.e. safety issue);
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrolment of more patients; for example insufficient enrolment that cannot be improved.

The investigators will be informed of this decision in writing.

The same applies to any investigator wanting to discontinue his/her participation to the trial. The investigator must immediately inform the sponsor in writing of this decision.

13 SAFETY PARAMETERS

13.1 Definitions

13.1.1 Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

Abnormal laboratory values reporting rules:

An abnormal laboratory value is considered to be an AE (from grade 3-5) if the abnormality:

- results in permanent investigational treatment discontinuation or
- requires treatment modification/ interruption of IP dose, or any other therapeutic intervention (e.g. G-CSF, blood transfusion) or
- is judged to be of significant clinical importance by the investigator. The investigator has to notify in the patient's medical file all the abnormal laboratory values considered as clinically significant (write next to each abnormal laboratory value assessed as clinically significant "CS" or precise in the medical report).

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the e-CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

13.1.2 Serious Adverse Events

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (t*he term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event ; it does not refer to an event which hypothetically might have caused death if it were more severe)*
- Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs, they are reported according to AEs reporting rules (see Section 13.2). If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious, they are reported according to SAEs reporting rules (see Section 13.3). When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Results in persistent or significant disability/incapacity. This means a substantial disruption of a person's ability to conduct normal life functions. It does not include experiences of relatively minor medical significance or accidental trauma (e.g. sprained ankle), which do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is a medically significant event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Any new primary cancer must be reported as an SAE (see 13.3). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), whether pathogenic or non-pathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

The term "severe" is a measure of intensity, thus a severe AE is not necessarily serious. For example, "nausea of several hours" duration may be severe but may not be clinically serious.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriated in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.

13.1.3 Intensity

The **intensity of the AE or SAE** will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) grading system v4.0 in the toxicity categories that have recommended grading (see Investigator's file or online at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

AEs not listed on this grading system will be graded according to the five-point system below:

- Mild (grade 1) Discomfort noticed but no disruption of normal daily activity
- Moderate (grade 2) Discomfort sufficient to reduce or affect normal daily activity
- Severe (grade 3) Incapacitating with inability to work or perform normal daily activity
- Life-threatening (grade 4) Substantial risk of dying at time of event
- Death (grade 5)

13.2 **Adverse Events reporting rules**

During induction:

Any episode of any grade of toxicities, related to a Serious Adverse Event (SAE) will be recorded by the Investigator as Adverse Event (AE) from the time the subject signs informed consent up to start brentuximab vedotin.

SAE and the corresponding AE are not to be reported after premature protocol treatment discontinuation, if premature protocol treatment discontinuation occurred during induction treatment (i.e. in case of progression).

Non-serious AE are not to be reported if occurred during the induction phase.

During Consolidation:

Any episode of any grade of toxicities, related to a Serious Adverse Event (SAE) will be recorded by the Investigator as Adverse Event (AE) from the start of first Brentuximab vedotin infusion to 30 days after the last dose of consolidation treatment.

AE of grade 2-5 for infections and neurological toxicities and AE of grade 3-5 for other toxicities (CTCAE – version 4.03) must be reported as "AE".

At baseline and prior to consolidation, any abnormal medical condition which is not reported in laboratory tests (biochemistry, hematology) should be declared on medical history page, whether due to lymphoma or not.

This medical condition should be followed at each clinical examination: if it worsens in consolidation phase (transition to grade ≥ 3 or ≥ 2 for infections and neurological toxicities), it should be declared as an AE.

AEs and serious adverse events will be recorded on the AE page of the e-CRF and in the subject's source documents.

General AE/SAE reporting rules during the trial:

When associated to a SAE and regardless the time of occurrence and the grade, the AE must be reported as "Adverse Event" in the appropriate e-CRF pages and in the subject's source documents.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all AEs and his opinion as to whether the AE can be related to the study drug.

All events that meet one or more criteria of seriousness (see Section 13.1.2.) will be reported as SAE (see Section 13.3). All SAEs must be reported to LYSARC Pharmacovigilance Department, within 24 hours of the Investigator's knowledge of the event by facsimile using the BRAPP LYSARC SAE Report Form.

Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as "Adverse Event".

"Alopecia" toxicity (any grade) will never be reported as "Adverse event".

13.3 **Serious Adverse Events reporting rules**

All events that meet one or more criteria of seriousness (see Section 13.1.2.) and occurred **after the informed consent signature to end of treatment evaluation (30 days after the last study drug administration),** regardless the relationship to the study treatment, will be reported as SAE.

A SAE that occurs after this time, including during the follow-up period, **if considered related to the study medication**, will be reported.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all SAEs and his opinion as to whether the SAE can be related to the study drug.

General SAE reporting rules:

- Any episode of any grade of toxicities, which meets one of the seriousness criteria must be reported as "Serious Adverse Event" in the appropriate SAE form
- Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as "Serious Adverse Event"
- "Alopecia" toxicity (any grade) will never be reported as "Serious Adverse Event"
- Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the study or before study drug was given are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the study (e.g. surgery was performed earlier than planned)
- Any new primary cancer must be reported as an SAE (according to SAE reporting rules)

13.3.1 Obligations of the Investigator

In a case of SAE the Investigator must immediately (within 24 hours):

- **SEND (preferably by fax) the SAE pages to**

  LYSARC Pharmacovigilance department:

  FAX: +33 (0) 3 59 11 01 86

  All SAE forms must be dated and signed by the responsible Investigator or one of his/her authorized staff Members.
- May attach the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical study are properly mentioned on any copy of source document. For laboratory results, include the laboratory normal ranges.
- Follow up of any SAE Event that is fatal or life-threatening should be provided within one calendar week.

For SAEs, the following must be assessed: relationship to each study drug, action taken, and outcome to date. The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the investigator, it can be one of two possibilities:

- Unrelated
- Related

13.3.2 Obligations of the Sponsor

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to study drugs, to the EMA, Health Authorities, Ethics Committees in each country in accordance with international and local regulations, and to the Investigators. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

The expectedness of a serious adverse reaction will be determined by the Sponsor according to the reference safety information (Investigator's Brochure) of brentuximab vedotin.

The LYSARC Pharmacovigilance department will report all safety information from the trial in the Development Safety Update Reports and will notify the reports to the Health Authorities and Ethics Committees in accordance with international and local regulations.

The Sponsor will send all SAE reports to Millennium/Takeda Pharmacovigilance (or designee) within 24 hours of receipt as per any agreements.

13.4 **Pregnancy**

13.4.1 Females of Childbearing Potential

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered events to be reported immediately to LYSARC Pharmacovigilance on the appropriate Pregnancy Form.

LYSARC fax number +33 (3) 59 11 01 86.

If the subject is on study drug, the study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the Investigator.

The exposure of any pregnant female (e.g. caregiver or pharmacist) to study drug is also an immediately reportable event.

The female should be referred to an obstetrician/gynecologist preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify LYSARC immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (i.e., spontaneous or therapeutic abortion) the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to LYSARC within 24 hours of the Investigator's knowledge of the event using Pregnancy form.

13.4.2 Male patients

If a female partner of a male patient taking study drug becomes pregnant, the male patient taking study drug should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

If a pregnancy related event is reported in a female partner of a male subject, the investigator should determine whether the female partner is willing to release her medical information to LYSARC Pharmacovigilance and allow the pregnancy related event to be followed-up to completion.

The Sponsor will report all pregnancies according to protocol reporting rules to Millennium Pharmacovigilance (or designee) as per any agreements.

13.5 **Follow up of AEs and SAEs**

Any SAE should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported should be sent to the LYSARC as soon as information becomes available.

All AEs must be documented and the outcome must be followed-up until the return to normal or consolidation of the patient's condition.

Subjects withdrawn from the study due to any AE will be followed at least until the outcome is determined even if it implies that the follow-up continues after the patient has left the trial.

The Sponsor will send all follow-up SAE reports to Millennium Pharmacovigilance (or designee) within 24 hours of receipt as per any agreements.

14 STATISTICAL CONSIDERATIONS

14.1 Study design

This is an open label, multi-center phase II study, to evaluate the efficacy brentuximab vedotin as consolidation treatment in patients with stage I/II Hodgkin's lymphoma and FDG-PET positivity after 2 cycles of ABVD.

14.2 Primary endpoint

The primary efficacy endpoint is progression-free survival (PFS) according to investigator assessment.

PFS is defined as the time from the date of the first cycle of ABVD to the first observation of documented disease progression or death due to any cause. If a subject has not progressed or died, PFS will be censored at the time of last visit with adequate assessment.

14.3 Secondary endpoints

14.3.1 Efficacy endpoints

Secondary efficacy endpoints will include:

- **RESPONSE RATE ACCORDING TO THE RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA 2007**

Response rate (Complete Response) will be evaluated after 8 cycles of brentuximab vedotin. Assessment of response will be based on the International Workshop to Standardize Response criteria for NHL (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson, 2007)). Patient without response assessment (due to whatever reason) will be considered as non-responder.

- **OVERALL SURVIVAL (OS)**

Overall survival will be measured from the date of the first cycle of ABVD to the date of death from any cause. Alive patients will be censored at their last follow-up date.

14.3.2 Safety endpoints

Summary of study drug administration including treatment duration, average dose, dose reduction will be displayed.

Number, frequency and reasons for treatment discontinuation, study discontinuation will be summarized.

Adverse events, vital sign measurements, clinical laboratory measurements, and concomitant medications will be described.

AEs will be classified using the latest version of Medical Dictionary for Drug Regulatory Activities (MedDRA) coding system at the time of database lock. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) whenever possible. Subsets of AEs to be summarized include serious, NCI CTCAE grade severities, suspected treatment-related, and events that resulted in withdrawal of investigational product. The most severe grade of each preferred term for a patient will be utilized for summaries of adverse events by NCI CTCAE grade.

All AEs will be described by system organ class, preferred term (a patient having the same event more than once will be counted only once)and serious adverse events) will also be displayed in a separate table. Specific AEs (i.e. sensory or motor peripheral neuropathies, adverse events leading to death or to discontinuation from treatment and serious adverse events), will also be displayed in a separate table.

All AEs of special interest will be displayed in a by-patient listing.

All deaths will be listed and also summarized by cause of death.

Clinical laboratory tests will be normalized and their change from baseline will be described. The frequencies of the worst severity grade observed during the treatment will be displayed in cross-tabulations by baseline status for each study arm.

Graphical displays may be provided where useful to assist in the interpretation of results.

14.4 Analysis Sets

14.4.1 Full Analysis Sets (following an intent-to-treat principle)

The full analysis set (FAS) includes all patients enrolled in the study and having signed the informed consent, regardless of whether they have received study treatment or not.

This set will be used for demographic data, medical history, concomitant medication, baseline diagnosis and patient disposition summaries, unless otherwise noted.

14.4.2 Evaluable Set

The evaluable set includes all patients included in the FAS and with at least one administration of brentuximab vedotin treatment.

The evaluable set will be used to analyze all efficacy parameters.

14.4.3 Safety Set

The safety set includes all patients who receive at least one dose of treatment regimen (brentuximab vedotin).

This set will be used for safety analyses, including extent of exposure to trial medication, adverse events, laboratory data and vital signs summaries

14.5 Statistical methods

14.5.1 Descriptive variables

Quantitative variables will be summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles will also be presented when considered relevant.

Qualitative variables will be described in terms of frequencies of each response category and frequencies converted into percentages of the number of patients examined (of non-missing).

14.5.2 Efficacy variables

Time to event variables will be 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% confidence intervals (CIs). The median time to event will be calculated (if reached) with 95% CIs.

Response rates will be expressed as percentages with their 95% exact Clopper Pearson CI limits.

14.6 Hypothesis testing

The hypothesis are:

H_0: PFS = exponential distribution of events (progression or death) based on probability at 2 years of 70% (based on our experience in the H10 protocol)

Versus

H_1: PFS = exponential distribution of events (progression or death) based on probability of 85% at 2 years

Where PFS denotes the progression free survival distribution.

The overall significance level for the final analysis will be 5%, so 95% confidence intervals of progression free survival at 2 years will be assessed.

For secondary endpoints, confidence intervals and tests will be two-sided and performed using a 5% level of significance. Given to the exploratory nature of the analyses, no adjustment for multiple comparisons will be made.

14.7 Sample size calculation

Sample size determination is based on progression-free survival (PFS) which serves as the primary efficacy endpoint in this study.

To provide 80% power to detect an improvement of the PFS at 2 years from 70% to 85%) (corresponding to a Hazard Ratio (HR) of 2.2) with 2-sided alpha (type I error) of 0.05 a total of 9 events would be required.

The calculation takes account the following assumptions:

- Sample size calculation was performed using a one arm sample size [25]
- an exponentially distributed PFS time with a constant hazard rate over the course of the study
- Accrual rate : 12 patients/year
- 5% drop-out rate per year
- a total of 3.5 years enrollment period

This results in the enrollment of a total of 40 evaluable patients treated by brentuximab vedotin. The entire duration of the study is projected to be about 6 years to have a cumulative 9 events (3.5 years of enrollment + 8 months of treatment and 1.5 years of Follow Up for the last patient).

14.8 Interim analysis

No interim analysis will be performed.

To ensure patients' safety, an Independent Data Monitoring Committee will be established to assess early safety data when 10 patients will have completed 8 cycles of brentuximab vedotin or prematurely discontinued brentuximab vedotin treatment (see section 11.4).

14.9 Final analysis

The final analysis will be performed when the number of events (9 events) has been reached or at the latest when the last patient will finish follow-up. The approximate schedule of the final analysis will be 6 years after the first patient enrolled.

If necessary an update of time to event endpoints will be performed at the end of study follow-up.

15 STUDY MONITORING

15.1 Responsibilities of investigators

The investigator(s) undertake(s) to perform the study in accordance with Good Clinical Practice and specifically either good clinical practice for trials on medicinal products in the European Community (ISBN 92 - 825-9563-3) and guidelines for the monitoring of clinical investigations.

The investigators ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the study. The investigators agree to provide all information requested in the case report form in an accurate and legible manner according to instructions provided.

15.2 Responsibilities of the sponsor

The sponsor (LYSARC) of this study has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, study adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the sponsor project leader and of the Sponsor clinical research support team (LYSARC) is to help the investigator maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, by a representative of the monitoring team (LYSARC) to review study progress, investigator and subject adherence to study requirements and any emergent problems.

During monitoring visits, the following points will be assessed with the investigator for each patient selected and included: subject informed consent signature, patient eligibility (inclusion and exclusion criteria), subject recruitment and follow-up, subject compliance to the study treatment, study treatment accountability (if applicable), concomitant therapy use, evaluations of response, serious/non serious adverse event documentation and reporting, and quality of data. Sections of Case Report Forms may be collected/entered (in case of e-CRF) on a visit per visit basis.

15.3 Source document requirements

According to the guidelines on Good Clinical Practice, the sponsor representative will check some data (specifically eligibility, safety items and items answering the main objective) from the case report form entries against the source documents. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

15.4 Use and completion of electronic case report form (e-CRF)

An electronic Case Report Form (e-CRF) will be completed for each study subject. It is the investigator's responsibility to ensure the accuracy, completeness, legibility and timeliness of the data reported in the subject's e-CRF.

Source documentation supporting the e-CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events and subject status.

The investigator, or designated representative, should complete the e-CRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure and within a maximum of 10 working days. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

All data entry and corrections are recorded in the audit trail (date of data entry/correction, name of person, type of action).

16 ETHICAL AND REGULATORY STANDARDS

16.1 Ethical principles

This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and subsequent amendments and will be conducted according to ICH/GCP guidelines.

16.2 Laws and regulations

This study is performed also in accordance with applicable laws and regulations of each country involved in the trial, as well as any applicable guidelines.

All data of the patients collected by the sponsor will be anonymized.

16.3 Informed consent

It is the responsibility of the investigator to obtain informed consent in compliance with national requirements from each subject prior to entering the trial or, where relevant, prior to evaluating the patient's suitability for the study.

The informed consent document used by the investigator for obtaining subject's informed consent must be reviewed and approved by LYSARC prior to Ethics Review Committee submission.

The investigator must explain to potential patient the aims, methods, reasonable anticipated benefits and potential hazards of the trial and any discomfort it may entail. Patients will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.

The consent form will include a statement by which the patients allow the sponsor's duly authorized personnel (trial monitoring team) to have direct access to source data which supports data on the case report forms (e.g. patient's medical file, appointment books, original laboratory records, etc.).

The patient should receive a signed and dated copy of the informed consent form and patient information leaflet. The inclusion process will be documented in each patient's medical records.

16.4 Ethics Review Committee and competent authorities submission

The sponsor must submit this study to country central ethics review committee, and to competent authorities and it is required to forward a copy of written approvals / advices signed to the investigators.

17 ADMINISTRATIVE PROCEDURES

17.1 Curriculum vitae

An updated copy of the *curriculum vitae* of each investigator and sub-investigator will be provided the LYSARC prior to the beginning of the study.

17.2 Confidentiality agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this study, the patient case report forms are the exclusive property of LYSARC.

They may not be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of LYSARC.

It is specified that the submission of this study and other necessary documentation to the Ethics Review Committee or a like body is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

17.3 Record retention in investigating center(s)

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.

However national regulations should be taken into account, the longest time having to be considered.

For trials performed in the European Community, the investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

Any center will notify the sponsor before destroying any data or records.

17.4 Ownership of data and use of the study results

The sponsor has the ownership of all data and results collected during this study. In consequence the Sponsor, or any third Party either appointed by the Sponsor or having concluded a specific agreement with the Sponsor, reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

The Investigator is committed to give his support to any requests for a patent or any property title based on, or illustrated with the results of the present Study for any country.

17.5 Publication

The results of the trial will be published after complete data collection and evaluation. Partial or preliminary results can be published beforehand. Publication is to be initiated by the two chairmen in charge of the study with approval of coordinators.

Any publication in the form of a lecture, poster or article must be basically approved by the Scientific Committee of the LYSA.

The authors will be proposed (according to the updated LYSARC publication rules) by the chairmen in charge of the study, approved by coordinators and finally decided by the Steering Committee of the LYSA.

All study data and publications are the property of the LYSARC.

17.6 Insurance compensation

The sponsor certifies having taken out appropriate liability insurance policy which covers the Sponsor, the investigator and his co-workers and which is in accordance with the local laws and requirements. Specific statements will be contained in appendix where needed.

A certificate of insurance will be provided to the investigator in countries in which this document is required.

The Investigator(s) will remain responsible towards the Sponsor of any fault or misconduct regarding the performance of the Study.

17.7 Company audits and inspections by regulatory agencies

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines it may be necessary to conduct a site audit or an inspection.

By signing this study, the investigator agrees to allow LYSARC and its representative, and drug regulatory agencies to have direct access to his study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in CRF, review of documentation required to be maintained, and checks on drug accountability.

LYSARC will in all cases help the investigator prepare for an inspection by any regulatory agency.

17.8 Clinical study report

The sponsor will inform of the end of the trial the Competent Authorities and Ethics Committees during the 3 months following the end of the study. A publication, as a study report will be prepared under the responsibility of the sponsor, less than one year after the end of the study and forwarded to the Competent Authorities and Ethics Committees.

17.9 Protocol amendments

It is specified that the appendices attached to this study and referred to in the main text of this study, form an integral part of the study.

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the investigator and the LYSARC.

Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be appended to this study.

Approval / advice of amendments by Ethics Review Committee and Competent Authorities are required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.

In some instances, an amendment may require a change to a consent form. The investigator must receive approval / advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

Prior to initiating the changes, study amendment must be submitted to regulatory agencies, where applicable, except under emergency conditions.

17.10 **Product Complaints**

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Millennium (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

All product complaints with the receipt or use of the Investigational Product must be promptly notified by the study-site personnel to the Sponsor, who will initiate a complaint procedure.

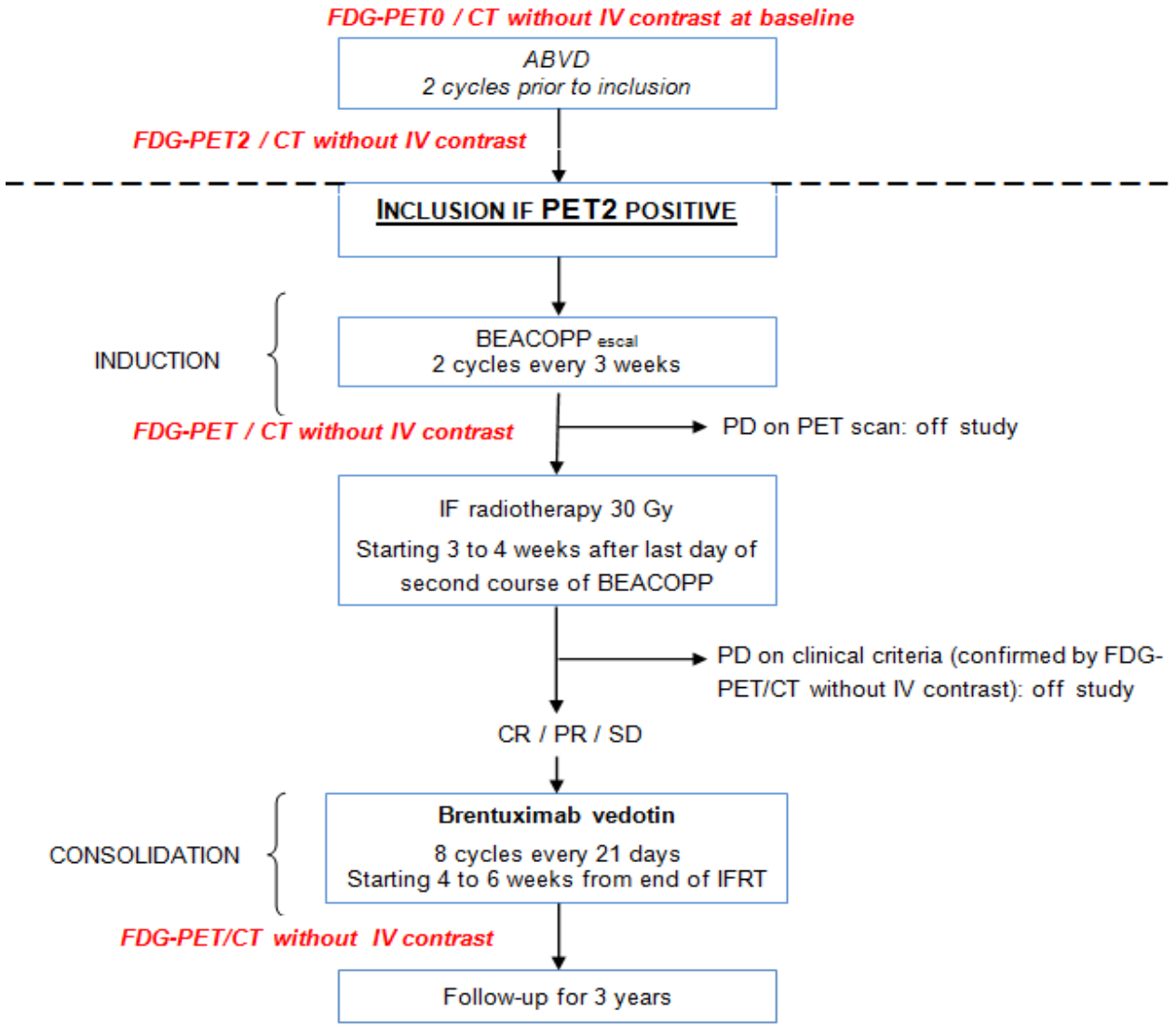
For Product Complaints call:
Phone: + 1-866-835-2233
E-mail: medical@mlnm.com
FAX: ++ 1-800-881-6092
Hours: Mon – Fri, 9a.m. – 7 p.m. ET
(US and International)

18 REFERENCES

1. Swerdlow SH, Campo E, Harris NL, *et al*. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2008.
2. Küppers R. The biology of Hodgkin's lymphoma. Nat Rev Cancer. 2009; 9:15-27.
3. Connors, J.M., State-of-the-art therapeutics: Hodgkin's lymphoma. J Clin Oncol. 2005; 23(26): 6400-8.
4. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early stage Hodgkin's disease. New Engl J Med. 2007; 357: 1916-27.
5. Hutchings M, Loft A, Hansen M et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 2006; 107: 52-59.
6. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol. 2007 Aug 20; 25(24): 3746-52.
7. Engert A, Plütschow A, Eich HT et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med. 2010; 363(7): 640-52.
8. Meyer RM, Gospodarowicz MK, Connors JM et al. ABVD alone versus radiation-based therapy in limited-stage HL. N Engl J Med. 2011; 366: 399-408.
9. Meignan M, Gallamini A, Itti E, Barrington S, Haioun C and Polliack A. Report on the third international workshop on interim-PET scan in lymphoma held in Menton. Leuk Lymphoma. 2012; Oct; 53(10): 1876-81.
10. Wahl, A.F., et al., The anti-CD30 monoclonal antibody SGN-30 promotes growth arrest and DNA fragmentation in vitro and affects antitumor activity in models of Hodgkin's disease. Cancer Res. 2002; 62(13): 3736-42.
11. Von Tresckow B, Plütschow A, Fuchs M et al. .Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial. J Clin Oncol. 2012; 30(9): 907-13.
12. Behringer K, Mueller H, Goergen H, et al. Gonadal Function and Fertility in Survivors After Hodgkin Lymphoma Treatment Within the German Hodgkin Study Group HD13 to HD15 Trials. J Clin Oncol. 2013; 31(2): 231-239.
13. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial Lancet 2012; 379(9828): 1791–99.
14. Francisco, J.A., et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003; 102(4): 1458-65.
15. Cheson, B.D., et al., Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25(5): 579-86.
16. Juweid ME, Stroobants S, Hoekstra OS et al. Use of positron emission tomography for response assessment in lymphomas. J clin Oncol. 2007; 25: 571-78.
17. Younes, A., et al., Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010; 363(19): 1812-21.
18. Younes A, Gopal AK, Smith Se et al Results of a pivotal phase II study of Brentuximab vedotin for relapsed or refractory Hodgkin's Lymphoma. J Clin Oncol. 2012; 30(18):2183-89.
19. Brice P, Bastion Y, Diviné M et al.: analysis of prognostic factors after the first relapse of Hodgkin's disease in 187 patients. Cancer. 1996; 78: 1293-1299.
20. Josting A, Franklin J, May M et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J Clin Oncol. 2002; 20: 221-30.
21. Andre MPE, Reman O, Federico M et al. First Report On the H10 EORTC/GELA/IIL Randomized Intergroup Trial On Early FDG-PET Scan Guided Treatment Adaptation Versus Standard Combined Modality Treatment in Patients with Supra-Diaphragmatic Stage I/II Hodgkin's Lymphoma, for the Groupe d'Etude Des Lymphomes De l'Adulte (GELA), European Organisation for the Research and Treatment of Cancer (EORTC) Lymphoma Group and the Intergruppo Italiano Linfomi (IIL). Blood (ASH Annual Meeting Abstracts) 2009; 114: Abstract 97.
22. Le Roux PY, Gastinne T, Le Gouill S et al. Prognostic value of interim FDG PET/CT in Hodgkin's lymphoma patients treated with interim response-adapted strategy: comparison of international harmonization project, Gallamin and London criteria. Eur J Med Mol Imaging 2011; 38: 1064-71.
23. Brew BJ, Davies NW, Cinque P, Clifford DB, Nath A. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. Nat Rev Neurol. 2010;6(12):667-79.
24. Van den neste E, Casanovas RO, André MA et al.Classical Hodgkin's lymphoma : the Lymphoma Study Association (LYSA) guidelines for relapsed and refractory adult patients eligible for transplant Haematologica 2013; 98:8.
25. Lawless, J. Statistical Models and Methods for Lifetime Data, John Wiley and Sons, 1982

19 APPENDIXES

19.1 Appendix 1: Study Flow Chart



19.2 **Appendix 2: Schedule of Evaluations**

	Inclusion	**Treatment**				**Follow-up**
		Induction treatment : BEACOPPx2 And RT	Evaluation prior to start of consolidation treatment	Consolidation treatment: D-1 or D1 of Cycle 1 to 8	Evaluation at the end of treatment	FUx
Date (weeks or months)			Within 7 days before D1 Cycle 1	Every 21 days	Within 4 ± 1 weeks after last cycle Or within 4 ± 1 weeks after last cycle for premature discontinuation	Every 3 months during 1st year then every 6 month
Written informed consent	X					
Patient characteristics (a)	X					
Clinical examination (b)	X	X (h)	X	X	X	X
Vital sign (c)	X	X (h)	X	X	X	
Lymph node biopsy (d)	X					
ECG / Echocardiography or Isotopic method	X(j)					
HIV, HBV and HCV serologies	X(j)					
ESR and/or CRP	X		X		X	X
Blood cell counts (e)	X	X(h)	X	X	X	X
Pregnancy test	X		X			
Biochemical tests (f)	X	X(h)	X	X	X	
Chest X Ray	X					
Cervical, thoracic, CT (g)	X				X	X (every 6 months)
PET Scan (i)	X	X	X (optional)		X	
Adverse events / toxicities	Safety reporting according to protocol section 13					

(a) : Age, gender, relevant medical history (including menstrual status and method of contraception), concomitant medication, history of the HL (including B symptoms), Ann Arbor Stage.
(b) : weight, BSA, height, ECOG PS at inclusion, weight, BSA, ECOG PS during consolidation treatment; ECOG PS at and at end of consolidation treatment and during follow-up.
(c): vital signs (pulse, blood pressure, temperature).
(d) : within 3 months prior to first ABVD course.
(e) : Hemoglobin, leukocytes, neutrophils, lymphocytes count, platelets at inclusion, at evaluation prior consolidation treatment, during Brentuximab vedotin cycles, at end of consolidation treatment and during follow up.
(f) : Serum creatinin, bilirubin total, AST, ALT, alkaline phosphatase, calcium and serum albumin **at inclusion**; Serum creatinin, bilirubin total, AST, ALT, alkaline phosphatase **at evaluation prior to and during consolidation treatment**. Serum creatinin, bilirubin total, AST, ALT, alkaline phosphatase, serum albumin **at end of treatment**.
(g) : Performed at baseline (before ABVD courses) and at end of consolidation treatment ; during follow-up every 6 months during 3 years.
(h) : Evaluation should be done according to local practice.
(i) : Mandatory at diagnosis (before ABVD courses), after 2 cycles of ABVD, after the 2 BEACOPP and at end of consolidation treatment.
(j) : If not already done within 3 months before inclusion

19.3 Appendix 3: Ann Arbor staging * - Cotswolds recommendations **

ANATOMICAL STAGING CRITERIA

Lymph node involvement. (a) Clinical enlargement of a node when alternative pathology may reasonably be ruled out (suspicious nodes should always be biopsied if treatment decisions are based on their involvement); and (b) enlargement on plain radiograph, CT scan, or lymphography.

Spleen involvement. Unequivocal palpable splenomegaly alone, or equivocal palpable splenomegaly with radiological confirmation of either enlargement or multiple focal defects which are neither cystic nor vascular (radiological enlargement alone is inadequate).

Liver involvement. Multiple focal defects which are neither cystic nor vascular noted with at least two imaging techniques. Clinical enlargement alone with or without abnormalities of liver function tests is not adequate.

Lung involvement. Radiological evidence of parenchymal involvement in the absence of other likely causes especially infection.

Bone involvement. History of pain or elevation of serum alkaline phosphatase, supported by plain X-ray changes or evidence from other imaging studies (isotope, CT scan or MRI).

CNS involvement. (a) A spinal extradural deposit may be diagnosed on the basis of the clinical history and findings supported by plain X-ray, myelography, CT scan and/or MRI ; and (b) intracranial involvement will rarely be diagnosed clinically at presentation. It should be considered on the basis of a space occupying lesion in the face of disease in additional extranodal sites.

CRITERIA FOR "B" SYMPTOMS

(a) Unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation;

(b) Unexplained, persistent, or recurrent fever with temperatures above 38°C during the previous month;

and (c) Recurrent drenching night sweats during the previous months.

CRITERIA FOR BULK DISEASE

The bulk of palpable lymph nodes will be defined by the largest dimension (cm) of the single largest lymph node or conglomerate node mass in each region of involvement. A node or nodal mass must be 10 cm or greater to be recorded as "bulky".

A mediastinal mass will be defined as "bulky" on a postero-anterior chest radiograph, when the maximum width is equal or greater than one-third of the internal transverse diameter of the thorax at the T5-T6 level. The chest radiography should be taken with maximal inspiration in the upright position at a source-skin distance of 2 m. (see also Appendix 5 for detailed description)

CRITERIA FOR EXTRANODAL SPREAD (E)

Involvement of extra lymphatic tissue on one side of the diaphragm by limited direct extension from an adjacent nodal site will be classified as extranodal extension (E) with the implicit expectation of a prognosis equivalent to that for treatment of nodal disease of the same anatomical extent.

The E category may also include an apparently discrete single extranodal deposit consistent with extension from a regionally involved node. Multiple extranodal deposits will not be included. A single extralymphatic site as the only site of disease should be classified as IE.

STAGING NOTATION

Nodal disease (I-III)

Stage I

Involvement of a single lymph node region (e.g. cervical, axillary, inguinal, mediastinal) or lymphoid structure as spleen, thymus and Waldeyer's ring.

Stage II

Involvement of two or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be "lateralized" and when involved on both sides, constitute stage II disease. The number of anatomical regions involved should be indicated by a subscript (e.g. II3). For the purpose of defining the number of anatomical regions, all nodal disease within the mediastinum is considered to be a single lymph node region. Hilar involvement constitutes an additional site of involvement.

Stage III

Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. This may be subdivided stage III1 or III2, stage III1 being described for patients with spleen or splenic, hilar, coeliac or portal node involvement and stage III2 for those with paraaortic, iliac or mesenteric node involvement.

Bulky disease

The subscript "X" will be used if bulky disease is present. No subscripts will be used in the absence of bulk.

Extranodal disease

"E" subscript if limited extranodal extension as described above, is documented. More extensive extranodal disease will be designated stage IV.

Example

Asymptomatic clinically staged patient with bilateral neck and axillary nodes, bulky mediastinum, enlarged left hilar node and extension into chest wall: $CSII_{6XE}A$.

Source:

*Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer. Res. 31:1860-1861, 1971.

**Lister TA, Crowther D, Sutcliffe SB, et al. Staging for Hodgkin's disease. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J. Clin. Oncol. 7:1630-1636, 1989 (Erratum J. Clin. Oncol. 8:1602, 1990).

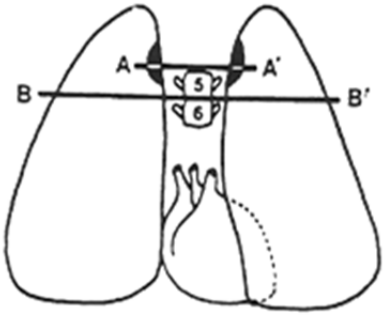
19.4 Appendix 4: Body Surface Area calculation

The algorithm to be used in this study to calculate BSA is must be performed according to Mosteller formula:

BSA (m^2) = √ [(Height (cm) x Weight (kg))/3600]

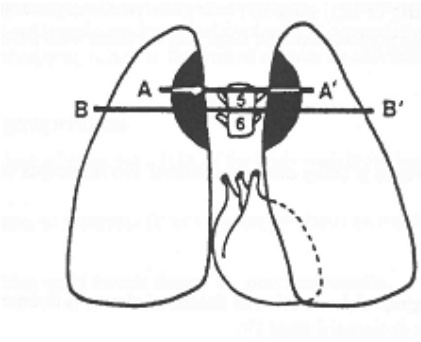
19.5 Appendix 5: Mediastinum measurement

M/T ratio evaluation: largest diameter of the mediastinum/thoracic diameter at the T5-T6 level, in standing position



A-A'/B-B' < 0.35

Non Bulky



A-A'/B-B' ≥ 0.35

Bulky

19.6 **Appendix 6: Performance Status Criteria**

The following table presents the ECOG performance status scale:

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

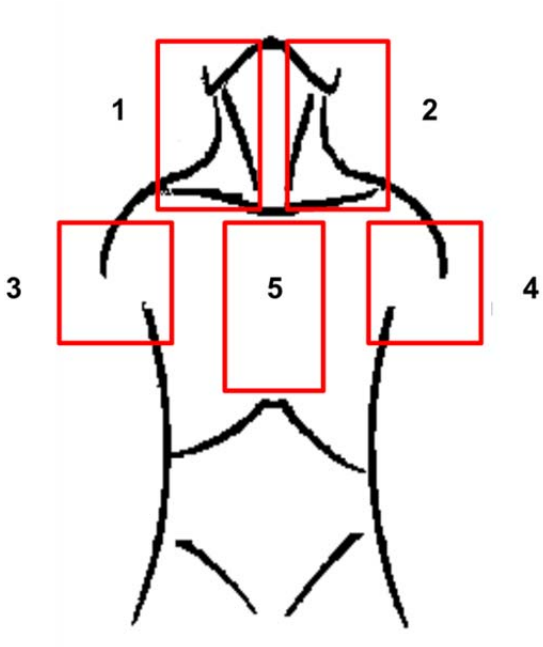
Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

19.7 Appendix 7: EORTC/GELA clinical prognostic factors

Favorable *All of the following factors is required for classify patient as Favorable (F) group* according	*Unfavorable* *At least one of the following factors is required for classify patient as Unfavorable (U) group*
Age < 50 years	Age ≥ 50 years
CSII with < 4 nodal areas	CSII with ≥ 4 nodal areas
M/T ratio < 0.35	M/T ratio ≥ 0.35
ESR < 50 mm/hour without B-symptoms	ESR ≥ 50 mm/hour without B-symptoms
ESR < 30 mm/hour with B-symptoms	ESR ≥ 30 mm/hour with B-symptoms

Source: Tubiana M, Henry-Amar M, van der Werf-Messing B, et al. (1985) *A multivariate analysis of prognostic factors in early stage Hodgkin's disease.* Int J Radiat Oncol Biol Phys 11(1): 23-30

Scheme to calculate the number of affected nodal areas:



1 : cervical, supra/infra-clavicular right
2 : cervical, supra/infra-clavicular left
3 : axillary, pectoral right
4 : axillary, pectoral left
5 : mediastinal, hilar

Source*:* Ferme, C., et al., *Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease.* N Engl J Med, 2007. **357**(19): p. 1916-27.

19.8 Appendix 8: Response criteria for lymphoma – Cheson 2007

Cheson BD et al. J Clin Oncol. 2007; 25: 579-586

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Complete response = CR

The designation of CR requires the following (Table 2):

- 1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- 2a- Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- 2b- Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to < 1.0 cm in their short axis after treatment.
- 3- The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not al-ways reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma
- 4- If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small

population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Complete Response Unconfirmed = CRu

The use of the above definition for CR and that below for PR eliminates the category of CRu.

Partial response = PR

The designation of PR requires all of the following:

- 1- At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- 2- No increase should be observed in the size of other nodes, liver, or spleen.
- 3- Splenic and hepatic nodules must regress by > 50% in their SPD or, for single nodules, in the greatest transverse diameter.
- 4- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- 5- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

  When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- 6- No new sites of disease should be observed.
- 7- Typically FDG-avid lymphoma: for patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
- 8- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

  In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease = SD

Stable disease (SD) is defined as the following:

- 1- A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
- 2- Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
- 3- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes < 1.0X< 1.0cmwillnotbe considered as abnormal for relapse or progressive disease.

- 1- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- 2- At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by > 50% and to a size of 1.5 X 1.5 cm or more than 1.5 cm in the long axis.
- 3- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
- 4- Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

19.9 Appendix 9: PET SCAN guidelines

FDG PET/CT imaging should follow the standardized protocol elaborated by EANM organization (*).

In particular, careful attention should be paid to the scheduled protocol (1 hour between FDG administration and PET acquisition), the glycemic status and, for each patient, unchanged technical parameters of acquisition.

*FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0, Ronald Boellaard & Mike J. O'Doherty &Wolfgang A. Weber & Felix M. Mottaghy., November 2009 Eur J Nucl Med Mol Imaging DOI 10.1007/s00259-009-1297-4 (available on http://www.eanm.org/publications/guidelines/index.php?navId=37)

19.9.1 Timing of FDG PET scans

- A FDG-PET/CT without IV contrast at diagnostic (PET0)
- A FDG-PET/CT without IV contrast at registration **(PET2)** performed after 2 courses of ABVD is mandatory, and the result form indicating at least one hypermetabolic lesion has to be faxed for allowing patient /inclusion
- Carrying out an interim FDG-PET/CT without IV contrast after 2 courses of BEACOPP is mandatory
- A mandatory FDG-PET/ CT without IV contrast has to be performed 3 ± 1 weeks after the completion of treatment

19.9.2 Patient preparation

- Patients are not allowed to consume any food or sugar for at least 6 h prior to the start of the PET study (i.e. with respect to time of injection of FDG)
- Adequate pre-hydration is important to ensure a sufficiently low FDG concentration of FDG in urine (fewer artifacts) and for radiation safety reasons (for example, 1 l of water in the 2 h prior to injection)
- Parental nutrition and intravenous fluids containing glucose should be discontinued at least 4 h before the PET/CT examination. In addition, the infusion used to administer intravenous pre-hydration must not contain any glucose
- During the injection of FDG and the subsequent uptake phase the patient should remain seated or recumbent and silent to minimize FDG uptake in muscles
- Blood glucose level must be measured prior to administering FDG:
  - If plasma glucose level is <7 mmol/l (or <120 mg/dl) the FDG PET study can be performed
  - If plasma glucose level is ≥7 mmol/l (or >120 mg/dl) the FDG PET study must be rescheduled or the patient excluded depending on the patient circumstances.
- The following recommendations apply to patients with diabetes mellitus:
  - type II diabetes mellitus (controlled by oral medication)
    - the PET study should preferably be performed in the late morning
    - patients must comply with the fasting rules indicated above
    - patients continue to take oral medication to control their blood sugar
  - type I diabetes mellitus and insulin-dependent type II diabetes mellitus
    - ideally, an attempt should be made to achieve normal glycemic values prior to the PET study, in consultation with the patient and his/her attending medical doctor
    - the PET study should be scheduled for late morning
    - the patient should eat a normal breakfast at 7.00 a.m. and inject the normal amount of insulin
- Height and body weight must be determined at first scan and weight must be measured directly prior to each PET study because body weight often changes during course of disease

19.9.3 PET scanner technical requirements

- FDG-PET scanning must be performed with a modern full-ring dedicated PET camera. Coincidence PET cameras are not allowed, because of lower sensitivity. Combined PET / CT without IV contrast in which the images are fused, are recommended for an improved data interpretation.
- Each patient is preferably scanned on the same camera for baseline, intermediate and final study

19.9.4 PET acquisition and reconstruction

- 18-FDG injected activity will be defined according to on site rules and type of machine used, thereby keeping ALARA principles in mind as well. A maximum FDG activity of 529 MBq for patients above 90 kg is recommended.
- The recommended interval between FDG administration and the start of acquisition is 60 min.

It is especially important to ensure that the time between tracer administration and starting of PET acquisition will be the same (± 5 min) at each of the 4 PET scans

- The patient should be positioned with the arm elevated over the head and PET acquisition should cover at least from the mid-femora to the external auditory meatus.
- FDG PET/CT imaging should follow the standardized protocol elaborated by EANM organization. In particular, a careful attention should be paid to maintain unchanged technical parameters of reconstruction within patient.
- A standard diagnostic CT scan with (i.v.) contrast agent may, if appropriate, be carried out according to standard radiological methods **after** the low-dose CT(i.e. without IV contrast) and PET acquisition.

19.9.5 PET review logistics

19.9.5.1 Local FDG-PET reports

As soon as the inclusion of the patient is effective, the local nuclear medicine physician will be asked to upload PET reports on the Imagys platform: https://lysarc.imagys.com

19.9.5.2 PET review board

Local and the central analysis of the PETs should be done according to Deauville criteria for PET2 (after 2 courses of ABVD) and for final PET CT (at end of treatment).

The reviewer panel is composed by 3 nuclear physicians for review the PETs according to the following rules:

- 2 reviewers will analyze the PET scans independently
- In case of disagreement between the 2 first reviewers, the third reviewer analyze the PET scan independently

19.9.6 PET analysis: Deauville criteria

The whole body scans will be displayed in both projection and volume views, the latter using coronal, sagittal and transaxial views. Non attenuation corrected and attenuation corrected scan must be analyzed.

Scoring system used to define metabolic response on interim F18FDG PET/CT (after 2 courses of ABVD chemotherapy).

We will use a 5 points scale (adapted from the Deauville workshop in: Leukemia & Lymphoma, Oct 2012; 53(10): 1876–1881), with new modifications (mainly 4 and 5 scores).

It includes visual and quantitative analysis:

1. No uptake.
2. Uptake < mediastinum.
3. Uptake > mediastinum but < liver.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and/or new sites of disease. A markedly uptake more than liver uptake is define as an uptake more or equal than 200% of SUV max liver (assessed on 3 slides on the liver middle region)

Using these Deauville criteria:

- PET positive is defined by scale level 4 and 5 (as described above)
- PET negative is defined by scale level 1, 2 and 3.

19.10 Appendix 10: Central Pathological Samples Review

General principles and organization of the pathological review:

The BRAPP2 study requires a central pathological review of all cases included in the trial at diagnosis. The aims of this centralized histopathological review will be to **confirm the diagnosis of Hodgkin lymphoma**, according to the criteria of the updated WHO classification 2008 (S. Swerdlow et al.) for each patient in the BRAPP2 study. Histological criteria of inclusion and exclusion have been detailed in the current protocol.

The review process will be organized by the LYSA-Pathology institute, Hôpital Henri Mondor, Créteil (LYSA-P).

Practical aspects of the LYSA-P central review:

1. Information on patient inclusion

At patient inclusion, the investigator will be requested to fax to LYSARC registration centre with the inclusion form a copy of the histopathological reports (tumor and when possible bone marrow reports) on which the name and address of the pathologist having diagnosed the Hodgkin lymphoma will be easily identified. The LYSARC registration centre will then fax/mail these documents to the LYSA-P.

2. Sample request

At reception of the pathological reports and inclusion form, the LYSA-P will send to the initial pathologist a letter requesting:

- The paraffin block from the formalin fixed sample that was used to set the diagnosis and/ or 10 unstained Superfrost+ slides
- A copy of the bone marrow pathological report if not sent previously
- To notify the LYSA-P of the presence of a frozen tissue

3. Sample centralisation at LYSA-P

All these requirements (excluding frozen tissue) will be sent in prepaid envelope and centralized by the LYSA-P at the following address:

LYSA-P, LYSA – BRAPP2 Study,
Hôpital Henri Mondor
51, avenue de Lattre de Tassigny, 94010 Créteil France

4. Sample review

At sample reception, routinely stained sections will be performed and an appropriate panel of antibodies will be applied according to morphological aspects. When sufficient slides are available, a pathological review will be organized at the LYSA-P with the designated panel of pathologists for this study. All the cases will be reviewed by at least 2 experts hematopathologists and a consensus diagnosis will be set and registered in the LYSA-P data base. This consensus diagnosis will then be sent to the clinical investigator and to the initial pathologist. For the need of the ancillary study, blocks will be kept temporarily to avoid a second request. Meanwhile, the block will be at the entire disposition of the initial anatomopathology laboratory under request if they need it.

Tissue microarray realisation:

Tissue microarray (TMA) will be made from initial tumor block, from which will be studied the expression of biomarkers known to influence the prognosis of Hodgkin lymphoma.

***Request for frozen tissue*:**

At the end of the inclusion, frozen tumor tissue will be requested for all included patients. The collection of the frozen tumor specimen will be organized and centralized at the LYSA-P. On frozen tissue, gene and protein expression will be analyzed to assess the level of expression of genes/proteins known to influence the outcome of Hodgkin lymphoma patients.

It is therefore highly important to consider at diagnosis all the possibilities to freeze the tumor sample.

The LYSA-P Institute will make a commitment to stock the frozen samples in a tumor library or a biological center insuring the respect of a convention which declines commitments of LYSARC relating to collection, conservation and use of frozen biological samples

All the samples will be stored in:

Hôpital Henri Mondor
Département de Pathologie
Plateforme de Ressources Biologiques: Tissuthèque
51 av du Mal de Lattre de Tassigny
94010 CRETEIL – France

19.11 **Appendix 11: New York Heart Association (NYHA) Classification of Stages of Heart Failure**

Class	Functional Capacity
Class I (Mild)	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

19.12 **Appendix 12: Example List of Strong Cytochrome P450 3A (CYP3A) Inhibitors and Inducers**

The following are considered to be strong inhibitors of CYP3A:

- boceprevir
- clarithromycin
- conivaptan
- grapefruit juice
- indinavir
- itraconazole
- ketoconazole,
- lopinavir/ritonavir
- mibefradil
- nefazodone
- nelfinavir
- posaconazole
- ritonavir
- saquinavir
- telaprevir
- telithromycin
- voriconazole

The following are considered to be strong inducers of CYP3A:

- avasimibe
- carbamazepine
- phenytoin
- rifampicin (permitted only on Arm B as study drug)
- St. John’s wort