"Phase II randomized study with R-DHAP +/- Bortezomib as induction therapy in relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) patients eligible to transplantation. BR-DHAP versus R-DHAP."

STUDY DRUG Bortezomib

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1 INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

_____

Investigator's Signature Date

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Name of Investigator (Typed or Printed)

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Institution, Address*

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Investigator-Sponsor Signature* Date (where required)

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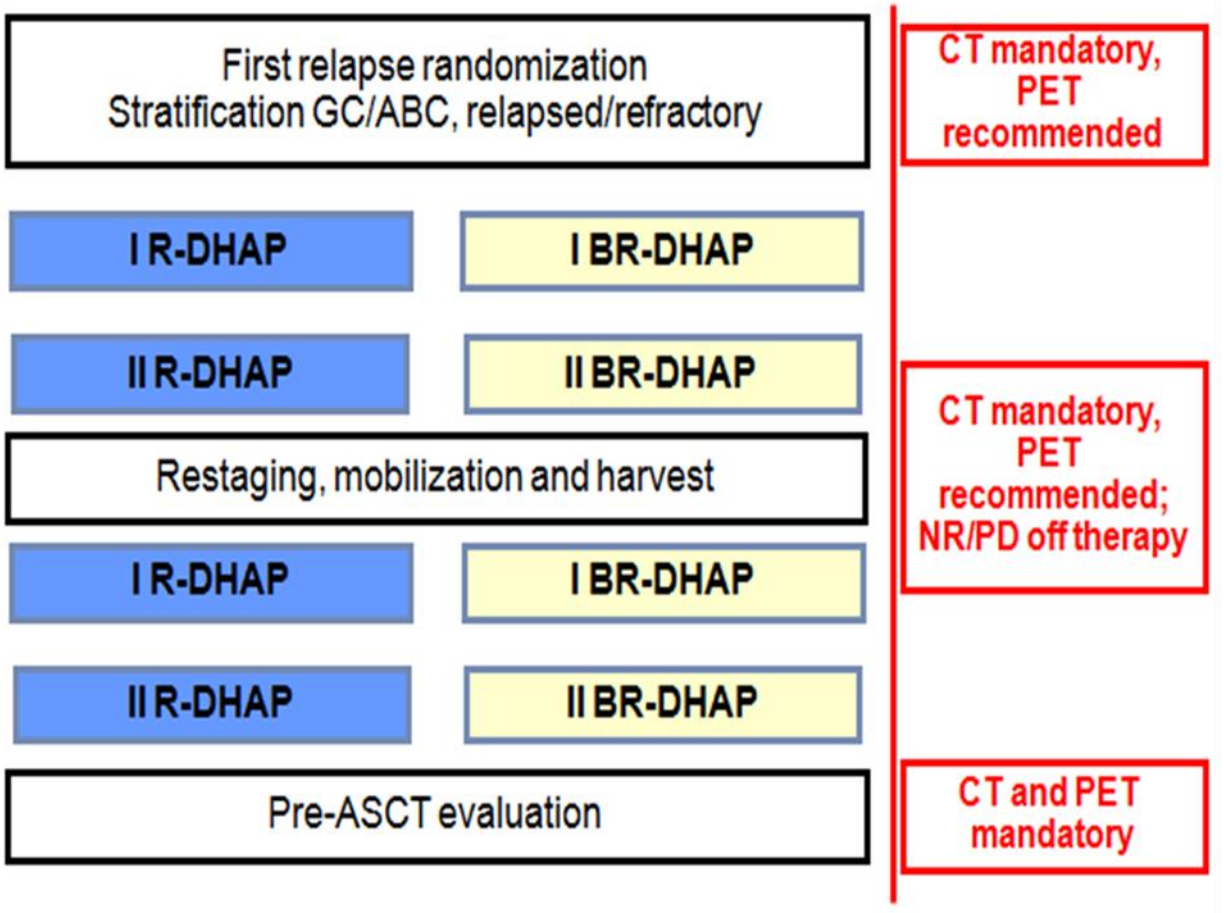
2 * If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s)INDEX

Sommario

3 FLOW CHART



4 BACKGROUND AND INTRODUCTION

4.1 Diffuse large B cell Lymphoma

Diffuse Large B-cell Lymphoma (DLBCL) is the most common lymphoma subtype, accounting for roughly 30-40% of all non-Hodgkin Lymphoma (NHL) in adults, and its incidence is increasing. Median age at diagnosis is 55-60 years.[1,2]

The addition of rituximab to first line anthracycline-containing chemotherapy has significantly improved the prognosis of DLBCL patients at any stage and age , and data of original trials have been recently been confirmed after longer follow up.[3,4,5] Furthermore, dose-dense and dose –intense chemoimmunotherapy is supposed to have added further improvement in DLBCL outcome[6] and results of ongoing prospective trials are soon expected.

4.2 Relapsed /refractory DLBCL

Despite the improvement with first line treatment in the rituximab era, a proportion of DLBCL patients still relapse and need further treatment.

In younger patients, induction chemotherapy followed by high dose consolidation and autologous stem cell support (ASCT) represents the gold standard since the publication of the PARMA trial.[7] Approximately 50% of all relapsed patients can be cured by this strategy, with main prognostic factors being represented by duration of first response,[8-9] International Prognostic Index at relapse (secondary IPI, sIPI),[10-11] and chemosensitivity to 2nd line induction therapy before transplantation.

More recently, the achievement of complete remission /CR) defined by PET negativity as per Cheson 2007 criteria[12] has emerged as a strong discriminant at transplantation.[13-15] Thus, further efforts to increase PET negative rate at transplantation are highly needed.

The addition of rituximab to second line chemotherapy significantly improves the outcome of patients non-pretreated with rituximab during first line treatment.[16] Otherwise, recent retrospective[17] as well as a randomized prospective (CORAL)[18] trials have pointed out the lower likelihood of obtaining an objective response with second-line chemotherapy in patients failing first line rituximab-containing regimens. The CORAL[18] trial randomly compared R-DHAP and R-ICE as induction regimens before transplantation overall response rate (ORR) was 83% in patients without as compared to 51% in those with prior exposure to rituximab, and CR rate was as low as 30% in cases previously treated with rituximab (C. Gisselbrecht, personal communication). Both 3-year event-free survival (EFS, 47 vs 21%) and overall survival (OS, 66% vs 40%) were also significantly affected by previous treatment with rituximab. As virtually all patients with relapsed DLBCL are actually pretreated with rituximab, strategies to improve ORR through the addition of other active compound to R-chemotherapy in the induction phase are warranted.

Molecular classification of DLBCL has allowed the description of two main subgroups with different prognosis: the germinal center B cell like (GCB) and the activated B cell like.[19] These two entities are distinguishable even through immunohistochemistry techniques[20-22] and show different long term prognosis with ABC subtype showing significantly worse survival.

More recently, the results of the so-called bio-CORAL trial have been published, concerning the biological aspect of the CORAL trial. In 249 out of 396 patients of the original clinical study, histopathological material from biopsies performed at diagnosis or at relapse was available. The cell of origin (COO) was analysed through both microarray procedures and immunohistochemical algorithm.[23]

Patients with GCB DLBCL according to the Hans algorithm, who were treated with R-DHAP, had a better 3-year PFS than patients with non-GCB DLBCL (52% vs 32, respectively; p .01). Otherwise, patients treated with R-ICE had a poor 3-year PFS without significant difference between the GCB and non-GCB Hans phenotypes (3-year-PFS 31% vs 27% respectively; p .81;). Similar results were observed for OS. Multivariate analysis showed an independent prognostic impact of the following parameters on PFS:

- GCB/non-GCB Hans phenotype interaction with treatment (p .04)
- prior rituximab exposure (p .0052),
- secondary aaIIPI (P _ .039), and
- FoxP1 expression (p .047).

This analysis showed that R-DHAP carried more benefit than R-ICE in patients with GCB DLBCL as classified by Hans, which was independent from clinical variables, such as aaIPI.

4.3 Bortezomib

Bortezomib is a proteasome inhibitor with proven activity in different lymphoma subtypes.24-25 Its mechanism of action impacts different cellular processes, including the inhibition of the nuclear factor kappa-B, which is constitutively activated in the ABC subtypes of DLBCL. Its principal toxic effects are represented by peripheral neuropathy and by mielotoxicity, mainly thromboctophenia.

Although as single agent bortezomib has demonstrated minimal activity in pretreated DLBCL, it can be safely used in combination with R-CHOP with moderate increase in neurological toxicity.[26-27] When combined to DA-EPOCH (dose-adjusted infusional etoposide, doxorubicin, vincristine, cyclophosphamide and prednisone) ORR of bortezomib + chemotherapy was significantly higher in cases with ABC (83%) than with GCB subtype (13%).[28] Ruan and coworkers added bortezomib to RCHOP in 40 DLBCL. Unlike in DLBCL treated with R-CHOP alone, ABC and GCB subtypes had similar outcomes[29].

The addition of bortezomib to cytarabine has already been tested by the MD Anderson group within the Hyper-CVAD regimen in a mantle cell lymphoma population setting with no evidence of increased toxicity.[30] Otherwise, few clinical data are published on the association of bortezomib and cisplatinum in the solid tumor setting: cumulative peripheral neuropathy, which could be of concern in this association, has not emerged as the dose limiting toxicity.[31] In addition, recent studies demonstrated the feasibility of bortezomib administered in subcutaneous injection (SC) instead of intravenous bolus (IV). In a phase I study conducted in 24 relapsed/refractory multiple myeloma, 12 patients were treated with bortezomib SC. Results underlined that there was no significant difference in overall proteasome inhibition activity and that similar efficacy and toxicities were seen with both the IV and SC routes of administration.[32] A phase III randomised, trial was then conducted on 222 myeloma patients with the primary end-point of non-inferiority of SC versus IV bortezomib in terms of overall response rate. The study demonstrated that SC bortezomib offers non-inferior efficacy to standard IV administration, with an improved safety profile especially in terms of peripheral neurotoxicity.[33]

5 RATIONALE OF THE STUDY

The probability to achieve CR with R-chemotherapy in patients failing a rituximab containing first line regimen is quite low, in particular in cases with non GCB profile. The bioCORAL trial suggest that ABC subset have a dismal outcome whichever the induction treatment. Thus it can be argued the addition of new molecule to the RDHAP regimen could be of value. Bortezomib appears the best candidate in this setting as ABC subtypes constitutively express NFkb, which is the target of bortezomib itself. Data from the literature suggest an encouraging activity of R-chemo+ bortezomib in non GCB-derived DLBCL, although in small series. Thus, the addition of bortezomib is here justified by the need to circumvent constitutional resistance to chemotherapy. Published experience of the association between bortezomib and cytarabine are also encouraging with acceptable cumulative toxicity.

6 OBJECTIVES OF THE STUDY

6.1 General objectives

Aim of this randomised screening trial is to assess whether the addition of Bortezomib to the standard R-DHAP, as induction therapy before transplantation procedure, is a promising strategy, worthy a subsequent confirmatory phase III trial, in patients with relapsed/refractory DLBCL.

Primary objective is to assess whether the experimental treatment achieves an absolute increase of the CR proportion of at least 20% (from 30% to 50%) with respect to the standard treatment.

Secondary objectives are to compare BR-DHAP vs R-DHAP for:

- Overall Response Rate (ORR) prior to consolidation
- Progression free survival (PFS)
- Overall Survival (OS)
- Feasibility and toxicity
- The mobilizing potential
- The rate of patients actually proceeding to transplantation.

Exploratory objectives are the subgroup analyses on the efficacy and safety endpoints to assess the potential heterogeneity of effects by biological lymphoma's characteristics (Germinal Center B-cell vs non-Germinal Center, Activated B-cell, GCC vs ABC), secondary aaIIPI and other important modifying factors.

6.2 End-points

6.2.1 Primary endpoint

The complete response rate (CR) evaluated by PET scan after four cycles of R-DHAP ± Bortezomib before transplantation according to Cheson criteria [12]

6.2.2 Secondary endpoints

- Overall response rate (ORR): a patient is defined as a responder if he has a complete or partial response, evaluated by PET/TC, after four cycles of R-DHAP ± Bortezomib

- Progression free survival (PFS): measured from the date of randomization to the date of disease progression, relapse or death from any cause. Responding patients and patients who are lost to follow up will be censored at their last assessment date.
- OS: measured from the date of randomization to the date of death from any cause. Patients alive at the time of the final analysis will be censored at the date of the last contact. For both PFS and OS minimum follow up time required for all patients will be 2 years.
- Toxicity: severe, life- threatening, fatal (grade 3, 4 and 5) and/or serious adverse events are defined according to "Common Terminology Criteria for Adverse Events" (CTCAE), version 4.0.
- Mobilizing potential: amount of CD34 + stem cell collected /Kg
- Feasibility: proportion of randomized patients successfully completing transplantation

7 PATIENT SELECTION CRITERIA

Patients with DLBCL who have received one previous chemotherapy line and who have failed or have relapsed after their last therapy will be enrolled.

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

The following items are generally used in the definition of selection (eligibility) criteria:

7.1 Inclusion criteria

1. Age 18-65
2. Relapsed/refractory disease after receiving one line of standard chemoimmunotherapy (R-CHOP, GA-CHOP, R-CHOP like)
3. Diffuse Large B-cell Lymphoma at relapse. Patient has to be re-biopsied prior to study entry. If this is harmful for the patient, the patient can be enrolled if archivial tumor sample and block from first diagnosis are available.
4. No prior Bortezomib therapy
5. Measurable and/or evaluable disease
6. Any Ann Arbor stage and IPI group at relapse
7. Performance status $\leq$ 2 according to ECOG scale unless due to lymphoma
8. No Central Nervous System (CNS) disease (meningeal and/or brain involvement by lymphoma)
9. Adequate hematological counts: ANC $\geq$ 1.5 x 10^9/L, Hgb $\geq$ 9 g/dl (transfusion independent), Platelet count > 75 x 10^9/L (transfusion independent), with the exception of cytopenia due to lymphoma bone marrow involvement
10. HIV negativity, HCV negativity, HBV negativity or patients with HBcAb +, HBsAg -, HBs Ab+/- with HBV-DNA negativity (in these patients Lamivudine prophylaxis is mandatory)

11. Normal liver function (ALP, AST, ALT, GGT, conjugated bilirubin total < 2 x ULN) if not related to lymphoma

12. Normal kidney function (creatinine clearance ≥ 45 ml/min)

13. Cardiac ejection fraction ≥ 50% (MUGA scan or echocardiography)

14. Normal lung function

15. Absence of active opportunistic infections

16. Non peripheral neuropathy or active neurological non neoplastic disease of CNS

17. Non major surgical intervention prior 3 months to randomization if not due to lymphoma and/or no other disease life-threatening that can compromise chemotherapy treatment

18. Disease free of prior malignancies other than lymphoma for > 3 years with exception of currently treated squamous cell and basal cell carcinoma of the skin or carcinoma in situ of the cervix or breast

19. Life expectancy > 6 months

20. No psychiatric illness that precludes understanding concepts of the trial or signing informed consent

21. Written informed consent

22. Women must be:

    - postmenopausal for at least 1 year (must not have had a natural menses for at least 12 months)
    - surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy),
    - abstinent (at the discretion of the investigator/per local regulations), or
    - if sexually active, be practicing a highly effective method of birth control (eg, prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel, male partner sterilization) as local regulations permit, before entry, and must agree to continue to use the same method of contraception throughout the study. They must also be prepared to continue birth control measures for at least 12 months after terminating treatment.

23. Women of childbearing potential must have a negative serum or urine beta-human chorionic gonadotropin (beta-hCG) pregnancy test at screening

24. Men must agree to use an acceptable method of contraception (for themselves or female partners as listed above) for the duration of the study. Men must agree to use a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study drug.

7.2 Exclusion criteria

1. Diagnosis of Lymphoblastic Lymphoma, Burkitt Lymphoma, Non Hodgkin Lymphoma CD20 negative, Mantle Cell Lymphoma, Follicular Lymphoma g I-II-IIIa-IIIb, Primary Mediastinal Lymphoma

2. Age > 65 years

3. Patients ineligible to high-dose chemotherapy
4. Performance status > 2 according to ECOG scale if not due to lymphoma
5. Patient has known or suspected hypersensitivity or intolerance to Rituximab
6. Patient has received an experimental drug or used an experimental medical device within 4 weeks before the planned start of treatment. Concurrent participation in non-treatment studies is allowed, if it will not interfere with participation in this study.
7. CNS disease (meningeal and/or brain involvement by lymphoma)
8. History of clinically relevant liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances
9. Uncontrolled diabetes (if receiving antidiabetic agents, subjects must be on a stable dose for at least 3 months before first dose of study drug
10. Uncontrolled or severe cardiovascular disease including myocardial infarction within six months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis
11. Cardiac ejection fraction < 50% (MUGA scan or echocardiography)
12. Creatinine clearance < 45 ml/min
13. Presence of major neurological disorders
14. HIV positivity, HCV positivity, HBV positivity with the exception of patients with HBcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative
15. Active opportunistic infection
16. Major surgical intervention prior 3 months to randomization if not due to lymphoma and/or other disease life-threatening that can compromise chemotherapy treatment
17. Prior malignancies other than lymphoma in the last 3 years with exception of currently treated squamous cell and basal cell carcinoma of the skin or carcinoma in situ of the cervix or breast
18. Life expectancy < 6 months
19. Any other coexisting medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent.
20. If female, the patient is pregnant or breast-feeding.

8 STUDY DESIGN

This is a prospective, multicenter, two-arm randomized phase II screening trial34 in young patients (18-65 years) affected by relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) at diagnosis, eligible to high-dose therapy.

Aim of the study is to to assess whether the addition of Bortezomib to R-DHAP is more promising than standard R-DHAP, as induction therapy before high dose chemotherapy with transplantation with respect to response and safety. Patients will be randomized at first relapse between: a) the standard salvage therapy Rituximab in association to DHAP every 28 days (R-DHAP) for 4 cycles and b) Bortezomib in association to the same regimen (BR-DHAP). In both arms the induction therapy is followed by autologous stem cell transplantation or, if indicated, by allogeneic stem cell transplant.

A patient is considered evaluable if it is possible to assess response by PET after 4 cycle or, if a patient withdraws from the study for PD, before completion of study treatment.

After providing written informed consent, patients will be evaluated for eligibility during a 28-day screening period. If they continue to meet eligibility criteria, they will be randomized to receive the first dose of BR-DHAP or R-DHAP .

The main efficacy variable will be the response to treatment, defined as the incidence of complete response assessed by PET-scan after 4 cycles of chemotherapy. The rate of complete response will be the principal measure of efficacy. Study discontinuation because of death or worsening conditions will be considered as failures and included in the estimation of response rates.

All toxic reactions will be annotated and their grade will be assessed according to the Common Toxicity Criteria (CTC) Version (see appendix). The rate of non-hematologic toxicity of grade 3 or greater will be the principal measure of safety. All patients given at least one dose of the experimental treatment will be included in the estimation of toxicity rates.

During the treatment period of four cycles, all patients will receive a total of four 28-day courses of chemotherapy +/- bortezomib. Those randomized to BR-DHAP will be given Bortezomib 1.5 mg/m2 on Days 1 & 4 of each 4-week cycle of BR-DHAP

Duration of treatment will be 4 months (one cycle per-month) plus 30 days for response evaluation

The Bortezomib 1.5 mg/m2 dose will be administered as a s.c bolus (see Section Bortezomib administration).

Prior to each Bortezomib administration, vital signs measurements (blood pressure, pulse, respiratory rate, and temperature) and hematology tests (as listed in Study Procedures) will be obtained. In addition, prior to Bortezomib administration on Day 1 of each cycle, a physical examination (that will include neurological/peripheral neurological examination) and chemistry tests (see Section) will be performed. If examinations and tests reveal dose-limiting toxicities as described in Section Dose Adjustments for Bortezomib, then adjustments to Bortezomib dosing must be made, or dosing discontinued, as described in Section.

During the study, disease status will be evaluated after the 4th cycle by imaging test (18FDG-PET and CT scan), and every other cycle (i.e., after 2nd course) by CT scan. 18FDG-PET scan is also recommended after the 2nd course in order to assess the role of early response. Adverse events will be monitored from the first study-related procedure, throughout treatment, and for 30-42 days (i.e., until the End of Treatment Visit

before high dose chemotherapy) following Bortezomib discontinuation. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) will be used to record the intensity (severity) of adverse events.

Serious adverse events will be reported as described.

Procedures to be performed during the study are summarized on the Appendix, Time and Events Schedule.

Trial treatment and the dosage of the investigational product as well as the description of the dosage form, packaging and labeling of the Bortezomib are described in section Dosage and Administration, and in Investigational Study Drug Information.

The trial include four 4-days (RDHAP) or (BR-DHAP) courses (including the Bortezomib administration on day 4) at a 28 -days interval, followed by high dose-chemotherapy and stem cell rescue . Non-responding patients will be given salvage chemotherapy according to local policy. Thereafter, the follow-up period will last a minimum of five years as concern monitoring of the disease (See Section, Study Procedures).

8.1 Rationale for the Study Design

The study is designed to compare the efficacy of RDHAP in association to BORTEZOMIB with RDHAP alone in patients with DLBCL who have relapsed or are refractory to previous chemotherapy. The study is designed primarily for a preliminary efficacy assessment. The assessment of safety will be also made by measuring neuro and myelotoxicity during the drug administration period as described above.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical design

This is a prospective, multicenter, two-arm randomized phase II screening trial (34) designed to assess whether the addition of Bortezomib to R-DHAP is more promising than standard R-DHAP as induction therapy before high dose chemotherapy with stem cell transplant in terms of efficacy on an intermediate endpoint (CR) and safety.

A result of this screening trial in favor of the experimental combination should be interpreted as a promising result to support the rationale of a next confirmatory phase III randomized trial, with adequate statistical power to detect a clinically meaningful advantage of the experimental regimen over the standard one, using a definitive clinical endpoint.

Patients will be randomized at first relapse/progression between:

a) the standard salvage therapy Rituximab in association to DHAP every 28 days (R-DHAP) for 4 cycles and

b) Bortezomib in association to the same regimen (BR-DHAP).

9.1.1 Sample size

The principal aim is to test if the experimental therapy performs better than the standard one, assuming an absolute increase of at least 20% in CR after 4 courses of the experimental arm with Bortezomib in association to R-DHAP with respect to the standard salvage treatment R-DHAP. According to a one-sided test with an α

error of 0.10 and a β error of 0.20, and assuming a 30% CR for the standard arm R-DHAP based on the literature, a sample size of 54 patients for each arm is required. for a total of 108 patients to be enrolled This design allows only to assess whether the experimental arm achieves an enough higher proportion of CR than the standard arm, with an acceptable toxicity profile, to justify a further randomized phase III confirmative trial on a definitive primary clinical endpoint.

9.1.2 Stratification and randomization

All enrolled patients will be stratified in four groups with different prognosis, according to clinical (relapsed/refractory) characteristics.

After stratification, all patients will be randomized, with a 1:1 ratio, into two arms:

- Scheme 1: R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + R-DHAP x 2, restaging with PET evaluation

- Scheme 2: Bortezomib + R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + Bortezomib + R-DHAP x 2, restaging with PET evaluation

The web-based randomization procedure, developed centrally by the Trial Center of the Clinical Epidemiology Unit at the S. Giovanni Battista University Hospital (Turin), will be completely concealed to researchers. After registering the patient at the study dedicated area, each patient will be assigned a unique ID code. The randomization procedure will be accessible only after the baseline forms have been completely filled out. The procedure, based on computer generated random sequence in blocks of variable size and in random order, will be continuously accessible (24/24h a day).

9.1.3 Statistical analysis

The main statistical analyses will be based on all the randomized patients (the intention-to-treat – ITT-population).

The proportion of CR will be compared between the two arms with a chi-square test, without continuity correction, using a test critical value of 1.282 (corresponding to a one-sided p-value of 0.10) to reject the null hypothesis. For estimating purposes only, 95% confidence intervals will be calculated for all the study endpoints.

The frequency of other dichotomous efficacy and safety endpoints will be compared between the two arms using a chi square test or the Fisher exact test, when appropriate.

The time-to-event functions will be estimated by the Kaplan-Meier product-limit method and the difference between arms will be analyzed with the log-rank test. The Hazard Ratio (HR) will be estimated using the Cox proportional-hazards model.

Exploratory analyses to detect important effect modifications across subgroups will be performed including treatment/covariate interaction terms in the appropriate (logistic or Cox) statistical models.

9.1.4 Study duration

This study is expected to start in October 2012. The last patient is expected to be enrolled at the end ofApril 2018. After a minimum duration of follow-up of 24 months from the enrolment of the last patient the study will be concluded in April 2020.

10 PATHOLOGICAL REVIEW AND BIOLOGIC STUDIES

A centrally pathological review is planned at accrual for all patients enrolled into the trial; investigator centers will make available the archival tumor samples taken at the time of first diagnosis. The central revision will be perfomed by a panel of pathologist expert in DLBCL diagnosis and responsible of trial revision. Central revision will primarily concern the confirmation of the original diagnosis and the subdivision of DLBCL into Germinal Center Cell or non-Germinal/Activated-B-cell according to the most commonly used algorithms: Hans, Choi or Tally[20,21,22]

Re-biopsy at relapse before study accrual is mandatory, although if a new biopsy is unfeasible, a core-biopsy will be performed. If this is harmful for the patient, the patient can be enrolled if archivial tumor sample and block from first diagnosis are available. This new sample will be used for both immunohistochemical and molecular studies, including: BCL6 translocation/BLIMP1deletion, BCL2 translocation, c-MYC trans location; TP53 status (deletion and mutation); genetic profile of pathway of histone modifiers (CREBBP and EZH2); genetic profile of pathway of NF-kB (TNFAIP3, CARD11, CD79A, CD79B, MYD88); evaluation of NK-kB pathway activation in IHC (nuclear expression of p105/p50 and p100/p52).

Additional histopathological studies of immunochemistry, gene profiling, molecular biology and pharmacogenetic will be conducted with the aim of identify prognostic biological factors.

11 STUDY TREATMENT

Patients will be randomized at study entry to receive:

- Scheme 1: R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + R-DHAP x 2, restaging with PET evaluation
- Scheme 2: Bortezomib + R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + Bortezomib + R-DHAP x 2, restaging with PET evaluation

11.1 Initial dose and schedule

Scheme 1: R-DHAP

Out-patient version

Rituximab 375 mg/sqm iv day 0 or 1

Cisplatin 100 mg/sqm iv day 1 in 6-hours infusion (a 3-hours infusion is allowed)

Cytarabine 2000 mg/sqm in 3-hours infusion iv day 2 and day 3

Dexametasone 40 mg day 1-4

Pegfilgrastim 6 mg sc monodose 24 hours after the end of chemotherapy or G-CSF from day 5 till stem cell harvest during mobilization's course (II o III cycle R-DHAP)

Rituximab 375 mg/sqm iv 24 hours before apheresis as purging in vivo during second courses of therapy

Scheme 2: B-R-DHAP

Out-patient version

Rituximab 375 mg/sqm iv day 0 or 1

Bortezomib SC 1.5 mg/sqm day 1, day 4

Cisplatin 100 mg/sqm iv day 1 in 6-hours infusion (a 3-hours infusion is allowed)

Cytarabine 2000 mg/sqm in 3-hours infusion iv day 2 and day 3

Dexametasone 40 mg day 1-4

Pegfilgrastim 6 mg sc monodose 24 hours after the end of chemotherapy or G-CSF from day 5 till stem cell harvest during mobilization's course (II o III cycle R-DHAP)

Rituximab 375 mg/sqm iv 24 hours before apheresis as purging in vivo during second courses of therapy

Chemotherapy R-DHAP and BR-DHAP will be repeated every 28 days.

11.2 Mobilization and apheresis

Mobilization of peripheral stem cell is planned after II or III courses of R-DHAP or BR-DHAP, with Rituximab pre-apheresis; harvest of at least $3x10^6$ cells CD34+/kg is recommended . Apheresis after 3rd curse should be reserved to patients with bone marrow involvement by lymphoma at accrual, provided bone marrow clearance is checked after 2nd course .

Suggested regimen for transplantation according to local policies:

BEAM or FEAM (BCNU or Fotemustine 300 mg/sqm iv day -7, Cytarabine 200 mg/sqm every 12 hours iv days -6, -5, -4, -3 (8 total doses), VP-16 100 mg/sqm every 12 hours iv days -6, -5, -4, -3 (8 total doses), Melphalan 140 mg/sqm iv day -2, Reinfusion of PBSC (CD34+ > 3 $x10^6$/Kg) day 0, Pegfilgrastim 6 mg sc monodose day 0) or Thiotepa/Endoxan/Melphalan cointaining regimens.

In selected cases, in progressive DLBCL patients during first line treatment or in refractory disease, an allograft should be considered

11.3 Dose Modification and Delay

11.3.1 Dose-adjustment for Bortezomib

If a Bortezomib dose due to toxicity or another reason is missed, then that dose is skipped and

treatment continues with next planned dose.

Observed toxicities, considered by the investigator to be related specifically to Bortezomib are to be

managed as follows:

- If leucocytes are < 1.0 x 109/l (and/or platelet counts < 25,000 cells/µl), scheduled Bortezomib application will be skipped until recovery to NCI toxicity < 2.

- For any ³grade 3 non-hematologic toxicity other than neuropathic pain and/or peripheral sensory neuropathy, considered by the investigator to be related to Bortezomib, scheduled Bortezomib application will be skipped until the toxicity returns to Grade 2 or better.

- If a dose of Bortezomib was skipped due to toxicity then reduce the drug doses as follows:

- If the patient was receiving 1.5 mg/m2, reduce the dose to 1.3 mg/m2.

- If the patient was receiving 1.3 mg/m2, reduce the dose to 1.0 mg/m2.

- If the patient was receiving 1.0 mg/m2, reduce the dose to 0.7 mg/m2

- If the patient was receiving 0.7 mg/m2, discontinue study drug, unless patient is responding, in which case this should be discussed with the study coordinators. Dose reductions below 0.7 mg/m2 should be avoided, but will be considered if patient is having a good response.

- Patients who experience Bortezomib- related neuropathic pain and/or peripheral sensory neuropathy are to be managed as follows:

Peripheral Sensory Neuropathy (NCI CTCAE Grade)

Neuropathic Pain (NCI CTCAE Grade)		0 Normal	1 Loss of deep tendon reflexes or paresthesia but not interfering with function	2 Objective sensory loss or paresthesia, interfering with function, but not with ADLs	3 Sensory loss or paresthesia interfering with ADLs	4 Disabling
0	None	No action	No action	~25% dose reduction*	Skip; ~50% dose reduction**	Discontinue VELCADE
1	Mild pain not interfering with function	No action	No action	~25% dose reduction*	Skip; ~50% dose reduction**	Discontinue VELCADE
2	Moderate pain; pain or analgesics interfering with function, but not ADLs	~25% dose reduction*	~50% dose reduction	Hold; ~50% dose reduction**	Skip; ~50% dose reduction**	Discontinue VELCADE
3	Severe pain; pain or analgesics severely interfering with ADLs	Skip; ~50% dose reduction**	Skip; ~50% dose reduction**	Skip; ~50% dose reduction**	Discontinue VELCADE	Discontinue VELCADE
4	Disabling	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE

ADLs = activities of daily living

Key:

Skip: Interrupt Bortezomib (VELCADE™) until the toxicity returns to Grade 1 or better.

*~25% Dose reduction: VELCADE dose reduction from 1.5 to 1.3 mg/m^2/dose, from 1.3 to 1.0 mg/m^2/dose or from 1.0 to 0.7 mg/m^2/dose.

**~50% Dose reduction: VELCADE dose reduction from 1.5 to 1.0 or from 1.3 to 0.7 mg/m^2/dose.

11.3.2 Dose- adjustment for Rituximab

No adjustment of dose.

11.3.3 Dose- adjustment for DHAP

Before each course FBC will be taken and, if at day 28 ANC <1500/mm^3 and/or platelets <100.000/mm^3, the whole regimen will be delayed by one week. If at day 35 the ANC is >1000-1500/mm^3 and/or PLT 75-100.000/mm^3 the dosage of each chemotherapeutic drug will be reduced at 75%. If FBC has not recovered one further delay-week is admitted.

If at day 42 ANC are still <1000//mm^3, and/or platelets < 75.000/mm^3, the patient will go off-study.Drugs regimens, expected toxicity, dose modification

11.4 General information

The study drug is the bortezomib (VELCADE®).

11.5 Drug supply

Drug ordering procedures, as well as name(s) and full address(es) with phone and fax numbers of the persons from whom the drug should be ordered will be provide with specific operative procedure.

11.6 Packaging, dispensing and storage

Description of the packaging and labeling of the drugs, instructions for use, recommendations for storage will be provide with specific operative procedure.

11.7 Known Anticipated Risks of VELCADE

Adverse Events Attributed to the Natural History of the Disease Under Study and Disease ProgressionIn patients with malignancy, signs and symptoms that are consistent with the natural history of the disease under study and disease progression are common; therefore, such findings are anticipated in this patient population.

11.7.1 Consolidated Known Anticipated Risks of VELCADE

The known anticipated risks of VELCADE are presented in Table 1. Adverse events are grouped according to the combined frequency observed in a pooled analysis of studies as of 29 October 2008.

There may be risks with the use of bortezomib that are not yet known, and these may cause unforeseeable risks to the embryo or fetus (for both maternal and paternal exposure). Because of this the subjects included should not become pregnant or father of a baby while participating in this study.

11.7.2 Table 1 - Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class ***Observed Incidence***	***Preferred Term***
Blood and Lymphatic System Disorders	
Most common	*Thrombocytopenia*, anaemia**
Very common	*Neutropenia**
Common	*Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia*
Cardiac Disorders	
Common	*Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive**
Uncommon	*Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±*
Ear and Labyrinth Disorders	
Uncommon	*Deafness, hearing impaired*
Eye Disorders	
Common	*Blurred vision, conjunctivitis, conjunctival haemorrhage*
Gastrointestinal Disorders	
Most common	*Constipation, diarrhoea*, nausea, vomiting**
Very common	*Abdominal pain (excluding oral and throat)*
Common	*Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage*,*

System Organ Class *Observed Incidence*	*Preferred Term*
	lower gastrointestinal haemorrhage±* *rectal haemorrhage*
Uncommon	*Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis*, intestinal obstruction*
General Disorders and Administration Site Conditions	
Most common	*Fatigue, pyrexia*
Very common	*Chills, oedema peripheral, asthenia*
Common	*Neuralgia, lethargy, malaise, chest pain, mucosal inflammation**
Uncommon	*Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication*
Hepatobiliary Disorders	
Uncommon	*Hyperbilirubinaemia, hepatitis*±*
Immune System Disorders	
Uncommon	*Drug hypersensitivity, angioedema*
Infections and Infestations	
Very common	*Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster**
Common	*Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bactaeremia*, cellulitis*, Herpes simplex, bronchitis, gastroenteritis*, infection*

System Organ Class *Observed Incidence*	*Preferred Term*
Uncommon	*Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection*, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±*
Injury, Poisoning, and Procedural Complications	
Common	*Fall*
Uncommon	*Subdural haematoma*
Investigations	
Common	*Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased**
Uncommon	*Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased**
Metabolism and Nutritional Disorders	
Very common	*Decreased appetite, anorexia, dehydration**
Common	*Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia**
Musculoskeletal and Connective Tissue Disorders	
Very common	*Bone pain, myalgia, arthralgia, back pain*
Common	*Muscular weakness*

System Organ Class *Observed Incidence*	*Preferred Term*
Uncommon	*Limb discomfort*
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	*Tumour lysis syndrome**
Nervous System Disorders	
Most common	*Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)*
Very common	*Paresthesia, dizziness excluding vertigo, headache*
Common	*Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia*
Uncommon	*Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior encephalopathy syndrome#*
Psychiatric Disorders	
Very common	*Anxiety, insomnia*
Common	*Confusional state*
Uncommon	*Delirium*
Renal and Urinary Disorders	
Common	*Renal impairment*, renal failure*, haematuria*
Uncommon	*Micturition disorder*
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	*Cough, dyspnoea*
Common	*Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema***

System Organ Class *Observed Incidence*	*Preferred Term*
Uncommon	*Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain*
Skin and Subcutaneous Tissue Disorders	
Very common	*Rash*
Common	*Rash pruritic, rash erythematous, urticaria, petechiae*
Uncommon	*Cutaneous vasculitis, leukocytoclastic vasculitis±*
Vascular Disorders	
Common	*Hypotension*, orthostatic hypotension*
Uncommon	*Cerebral haemorrhage**

Most common = ≥ 30%, Very common = 10% to 29%, Common = 1% to 9%, Uncommon = < 1%.

** Fatal outcomes have been reported.*

± Indicates a Preferred term not listed, however the event is deemed medically important and so is included.

 # Prior to MedDRA version 14.0, posterior reversible encephalopathy syndrome (PRES) was termed "reversible posterior leukoencephalopathy syndrome (RPLS)".

8.4.3 Medical Events From Postmarketing Experience

Adverse drug reactions, as listed in the postmarketing section of the VELCADE USPI (Package Insert) or SmPC (Summary of Product Characteristics) are listed in Table 2.

Table 2 Reports of Adverse Reactions from Postmarketing Experience

System Organ Class *Preferred Term*	*Observed Incidence*[a]
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	*Rare*
Cardiac Disorders	
Atrioventricular block complete	*Rare*
Cardiac tamponade	*Rare*
Ear and labyrinth disorders	
Deafness bilateral	*Rare*
Eye Disorders	
Ophthalmic herpes	*Rare*
Optic neuropathy	*Rare*
Blindness	*Rare*
Gastrointestinal Disorders	
Acute pancreatitis	*Rare*
Ischemic colitis	*Rare*
Hepatobiliary disorders	
Hepatitis	*Uncommon*
Liver failure	*Unknown*
Immune System Disorders	
Angioedema	*Rare*

System Organ Class ***Preferred Term***	***Observed Incidence[a]***
Infections and infestations	
Herpes meningoencephalitis	*Rare*
Septic shock	*Rare*
Progressive multifocal leukoencephalopathy	*Very Rare*
Nervous System Disorders	
Autonomic neuropathy	*Rare*
Dysautonomia	*Unknown*
Encephalopathy	*Rare*
Respiratory, thoracic and mediastinal disorders	
Acute diffuse infiltrative pulmonary disease[b]	*Rare*
Acute respiratory distress syndrome (ARDS)	*Rare*
Interstitial pneumonia	*Rare*
Lung infiltration	*Rare*
Pneumonitis	*Rare*
Pulmonary hypertension	*Rare*
Skin and subcutaneous system disorders	
Acute febrile neutrophilic dermatosis	*Unknown*
Toxic epidermal necrolysis	*Unknown*

a Incidence is assigned using the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1,000 and < 1/100); rare (≥ 1/10,000 and < 1/1,000); very rare (< 1/10,000, including isolated reports).

b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

12 WITHDRAWAL AND UNBLINDING CRITERIA

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the Investigator at any time. If such withdrawal occurs, or if the patient fails to return for visits, the Investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment CRF. Therapy may be interrupted for one of the following reasons:

Adverse event(s); Abnormal laboratory value(s); Abnormal test procedure result(s); Protocol deviation; Subject withdrew consent; Lost to follow-up; Administrative problems; Death; Initiation of new cancer therapy; Disease progression.

13 CONCOMITANT TREATMENT

13.1 Recommended concomitant treatments

During treatment are recommended as concomitant therapy:

- Pegfilgrastim 6 mg sc monodose 24 hours after the end of chemotherapy or G-CSF from day 5 till stem cell harvest during mobilization's course (II o III cycle BR or R-DHAP)
- Cotrimoxazole BACTRIM 3 tablets/week (or 1 x 2/day per two days/week) or Pentamidine aerosol every 15 days in patients with Bactrim allergy or in patients with G6PD deficiency throughout the treatment and consolidation phase
- Antiviral prophylaxis with acyclovir 800-1200 mg at day since the beginning of therapy
- In patients with Ab antiHBcAg +, Ab antiHBsAg +/- prophylaxis against hepatitis B reactivation with Lamivudine 100 mg/die from one week prior the start of the treatment to at least one year after the end of the treatment
- All concomitant medications for medical conditions other than B-NHL are permitted, as clinically indicated
- All supportive therapies other than anti-cancer treatment needed for the management of patients enrolled in this study are permitted

13.2 Permitted concomitant therapy

The following medications and support therapies that may be used if needed during this study:

- Additional prophylaxis with levofloxacine or ciprofloxacine and fluconazole/itraconazole will be administrated in case of neutropenia <1.0 x 109/l.
- Mozobil- Plerixafor in addition to GSCF during mobilization was permitted
- Immunoglobulin assay is advisable once a month during the therapy with immunoglobulin replacement in case of IgG level < 0.3-0.5 gr/dl and frequent infectious events.
- Platelets and red blood cell transfusion are allowed, if needed. Packed red cells and platelets transfusions

will be given with filtered and irradiated products in case of Hb < 8 g/dL or Plts < 10 x 109/L.

- Erytropoietin therapy is allowed according to ASH/ASCO guidelines.
- Bowel care is recommended to prevent constipation and should be administered per standard practice.
- Antiemetic agents.
- Premedication for rituximab infusion with paracetamol and diphenhydramine should be considered before each infusion of rituximab, because it may reduce infusion reactions.

13.3 Prohibited concomitant therapy

The following medications and supportive therapies are prohibited at all times:

- Any antineoplastic agent other than those planned by the study program.
- Any experimental agent.

14 CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

14.1 Staging evaluation, baseline

Baseline assessment must be performed during 28 days before starting therapy.

- Complete medical history, ECOG performance status, physical examination
- ECG and echocardiogram or MUGA scan for LVEF evaluation
- Complete blood count, hematology workup and biochemistry including LDH and Beta2-microglobulin
- Lymph-node or tissue biopsy for histological diagnosis and shipment of paraffin block for centrally pathology review and for biological studies
- Aspirate and bone marrow biopsy
- Diagnostic Lumbar Puncture for determination of cell count, differential, cytologic and cytoflussimetry examination (if possible) of tumor cells; in patients with clinical suspect of CNS involvement, according to SIE criteria
- CT scan neck, chest, abdomen and pelvis
- Total body PET scan (recommended)
- Neurological visit if clinically indicated
- Other assessment: RMN brain/column, endoscopy, ORL visit, etc. according to physician judge and if clinically relevant
- Pregnancy test (if applicable)
- Written informed consent

14.2 Evaluation at each R-DHAP and BR-DHAP courses

- Blood count and complete workup with biochemistry, physical examination and hematological and extrahaematological toxicity evaluation the day before or day 1 of therapy and between two cycles and

during aplasia phase (recommended at day +8-10-12-14-16 and/or till granulocytes and platelets recovery)

14.3 Intermediate response evaluation

The evaluation of intermediate response will be assessed after 2 courses of R-DHAP or BR-DHAP.

ECOG performance status, physical examination

Blood count and complete workup with biochemistry

Aspirate and bone marrow biopsy (if positive at baseline)

CT scan neck, chest, abdomen and pelvis

Total body PET scan (recommended)

Responsive patients (in partial or complete response) after two cycles of therapy, will continue the trial and will be treated with two further courses of R-DHAP or BR-DHAP as planned.

Patients with progressive disease or stable disease after the first two cycles of therapy will stop treatment and will be considered as failure.

14.3.1 Pre-transplantation evaluation - end of study

The evaluation of pre-transplantation response will be assessed after 4 courses of R-DHAP or BR-DHAP.

ECOG performance status, physical examination

Blood count and complete workup with biochemistry

Aspirate and bone marrow biopsy (if positive at baseline)

CT scan neck, chest, abdomen and pelvis

PET total body (mandatory)

Responsive patients (in partial or complete response) after four cycles of therapy, will be treated with transplantation according to local policy.

Patients in progression disease or stable disease after the first two cycles of therapy stopped treatment and will be considered failure.

14.3.2 Follow-up

Every three months during the first two years after chemotherapy and then every 4-6 months in the third year after chemotherapy, will be evaluated :

ECOG performance status, physical examination

Blood count and complete workup with biochemistry

Every 6 months during the first two years after chemotherapy (at month 6-12-18-24) will be evaluated:

ECOG performance status, physical examination

Blood count and complete workup with biochemistry

CT scan neck, chest, abdomen and pelvis

Aspirate and bone marrow biopsy (if positive at baseline)

15 FORMS AND PROCEDURES FOR COLLECTING DATA AND DATA MANAGING

The web study area, with a dedicated database, the electronic Case Report Form (CRF) and all the required functions, will be developed in a dedicated area (https://www.filinf.it). All participating centers will receive a password to access the internet-based database.

Several systematic quality controls will be active during data entry; periodic statistical checks and personalized queries will be performed during the study.

Frequency of on-site monitoring will be planned according to the results of the statistical quality controls.

16 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and are mandated by regulatory agencies worldwide.

16.1 Definitions

Adverse Event Definitions and Classifications

16.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to the medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

The Adverse Events collection for each subject will start with the signing of informed consent form.

16.1.2 Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death
- is life-threatening

  (the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect
- ismedically important*

16.1.3 * Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical or events that may not be immediately life-threatening or result in a deathor hospitalization but that may jeopardize the patient or require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious. Unlisted (Unexpected) Adverse Event

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For a comparator product with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the summary of product characteristics (SmPC).

16.1.4 Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 1.2.

16.1.5 Product Quality Complaint

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

16.2 Attribution Definitions

16.2.1 Intensity (Severity) Reporting and Attribution

For both serious and non-serious adverse events, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Intensity for each adverse event will be determined by using Version 4.0 of the National Cancer Institute Common Toxicity Criteria (NCI CTC) as a guideline (homepage http://ctep.info.nih.gov), wherever possible. The criteria will be provided to the investigator as a separate document. In those cases where the NCI CTC do not apply, intensity should be defined according to the following criteria:

Mild: Awareness of sign or symptom, but easily tolerated, causing minimal discomfort and not interfering with everyday activities;

Moderate: Sufficient discomfort is present to cause interference with normal activities.

Severe: Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

Relationship to study drug administration will be determined as follows:

Not related

An adverse event which is not related to the use of the drug.

Doubtful
An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable
An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

16.2.2 Special Reporting Situations

The following special situations must be reported to the appropriated Sponsor-Investigator's contact person by investigational staff within 24 hours of acknowledge using the SAE form:

- Drug exposure during pregnancy (maternal, paternal)
- Suspected transmission of any infectious agent via administration of a medicinal product

The following special situations should be reported to the Sponsor – Investigator if associated with an SAE:

- Exposure to a medicinal product from breastfeeding
- Overdose of a medicinal product
- Medication error involving a medicinal product (with or without subject/patient exposure to the medicinal product, eg, name confusion)
- Suspected abuse/misuse of a medicinal product
- Unexpected therapeutic benefit
- inadvertent or accidental exposure to a medicinal product

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

16.2.3 Reporting Procedures

All Adverse Events

All adverse events will be registered in CRF from the time a signed and dated informed consent form is obtained until 30 days after the administration of the last dose of study drug. Those meeting the definition of serious adverse events must be reported using the Serious Adverse Event Form.

Serious Adverse events occurring after 30 days should be reported if considered at least possibly related to the investigational medicinal product by the investigator.

Clinically relevant changes in laboratory values must be recorded in the adverse event section of the CRF. For example, laboratory abnormalities leading to an action regarding the study drug (dose change, temporary stop, delay of the start of a cycle or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an adverse event, the following laboratory values should be reported in the laboratory section of the CRF: the value indicative of the onset of each toxicity grade, the most abnormal value observed during the adverse event, and the value supporting recovery to Grade 0 or 1 or to baseline condition.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor-Investigator instructions.

The Sponsor-Investigator assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The Sponsor-Investigators will also report to the Investigator, Independent Ethics Committee/Institutional Review Board (IEC/IRB) and to the Italian Drug Agency (AIFA) all serious adverse events of this study that are unlisted and associated with the use of the drug.

Subjects must be provided with a “study card” indicating the name of the investigational product, the study number, the investigator’s name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

<u>Pregnancies</u>

While pregnancy, in itself, is not an adverse event, any subject pregnancy or pregnancies in partners of male subjects included in the study must be submitted by investigational staff to the Sponsor-Investigator within 24 hours of their knowledge of the event using the pregnancy notification form.

Abnormal pregnancy outcomes (eg spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study.

Pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Serious Adverse Events and/or Pregnancies and/or Product Quality Complaint

All SAEs (and/or Pregnancies and/or PQC) occurring during clinical studies must be reported to the appropriated Sponsor-Investigator's contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding SAEs (and/or Pregnancies) will be transmitted to the Sponsor-Investigator using the Serious Adverse Event Form (and/or a pregnancy notification form), which must be signed by a member of the investigational staff. It is preferable that serious adverse events be reported via fax. Subsequent to a telephone report of a serious adverse event (and/or a Pregnancy), a Serious Adverse Event Form (a pregnancy notification form) must be completed by the investigational staff and transmitted to the Sponsor-Investigator within 24 hours.

The Product Quality Complaint may be reported to the appropriate Sponsor-Investigator contact person in different forms including but not limited to telephone, fax, electronic communication or in person

The SAE(s) and/or Pregnancy report(s) must be sent to the Sponsor-Investigator Pharmacovigilance Contact Person to the following fax number:

Sponsor contact:

Dr. Alessandro Levis

Address: S.C. Ematologia Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo - Alessandria

Phone no.: +39-0131-206066-

Fax no.: +39-0131-263455

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

The event resolves

The event stabilizes

The event returns to baseline, if a baseline value is available

The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts).

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Suspected transmission of an infectious agent by a medicinal product should be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for:

social reasons in absence of an adverse event

surgery or procedure planned before entry into the study (must be documented in the CRF)

study drug administration

study related procedures defined in the protocol.

17 ETHICAL CONSIDERATIONS

17.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice

The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

18 SUBJECT IDENTIFICATION PERSONAL DATA PROTECTION

All records identifying the subject must be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient initials and date of birth will also be reported on the case report forms.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection ("privacy") regulations. Breach of such regulations may result in administrative or even criminal sanctions.

Particularly, an information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data must therefore accompany the informed consent administered to the patient (see paragraph 14.3 below). Such information must (i) identify the roles of the holder ("titolare") and processor ("responsabile", appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient's prior and specific consent to such processing.

Patient information or documentation may be considered "anonymous", and as such not subject to privacy regulations, only when no key whatsoever, permitting the identification of the patient, is any longer available.

Particular attention should therefore be paid (and information/consent materials adapted accordingly) whenever patient data are supplied to third parties and may be autonomously processed, or biological samples/materials are taken and kept for future research purposes, associated or not with the pathology considered in the study.

A copy of Informed consent should be attached to this Protocol Template.

18.1 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

A copy of Informed consent should be attached to this Protocol Template.

19 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

20 DATA OWNERSHIP

According to the ICH Guidelines on Good Clinical Practice the sponsor of a study (the Institution, should the investigator or study coordinator act as sponsor in the performance of her/his institutional duties under the employment or collaboration agreement with Humanitas) is the owner of the data resulting therefrom. All

centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution's prior express consent.

21 PUBLICATION POLICY

This section should be adapted to the statutes of the cooperative group.

After completion of the study, the project coordinator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Study Coordinator for coordination and homogeneity purposes: specific advance periods for submission and review may be specified in the protocol. The timing of publications (in the event several Centers should be participating in the Study) may be coordinated, and publication delayed if patentable inventions should be involved (for the time required in order to file the relevant patent applications); otherwise, according to the MoH's Decree of May 12, 2006, investigators cannot be precluded from or limited in publishing the results of their studies (IECs must verify that no excessive restriction is contained in the protocols submitted to their review and approval).

22 STUDY INSURANCE

The Investigator-sponsor of the Study must ensure that adequate insurance coverage is available to the patients, in accordance with Section 5.8 of the ICH Guidelines of Good Clinical Practice. Such coverage must extend to all damages deriving from the study, to the exclusion of those attributable to willful misconduct or negligence of the institution or investigator. A copy, or excerpt, or insurer's certificate, attesting the existence and amount of such coverage at least for the duration of the study must be supplied as part of the study documentation to the review and approval of the IEC.

Based on section 2.4 of the MoH's decree of December 17, 2004, the insurance coverage must be supplied by the hospital or medical research department in case of no profit drug evaluation trial.

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24.1 Appendix 1: Timing of treatment and investigations

Staging	**Pre-Treatment**	**R-DHAP/BR-DHAP Treatment**					**End of Treatment**	**Follow-Up**
	Screening phase	**C1**	**C2**	**Intermediate Evaluation**	**C3**	**C4**	**Final Evaluation**	**Up to 2-years**
Informed consent	X							
Inclusion/Exclusion criteria	X							
Pregnancy test[a]	X							
Serum virology[b]	X							
Ecg/Echo/MUGA	X							
Anti-tumor activity				X			X	X
Bone marrow biopsy	X			X [e]			X [e]	X [e]
Stem cell collection			X[c]		X[c]			
GC/ABC value on diagnostic tissue	X							
PET scan	X			X			X	
CT of chest & abdomen	X			X			X	X
Adverse events		X	X		X	X		X
Hematology	X	X	X	X	X	X	X	X
Biochemistry	X[d]	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X

[a]Negative pregnancy test is required 1 week before treatment for both pre-menopausal women and women who are <1 years after onset of menopause

[b] HBsAg, HBcAb, HCV and HIV serology

[c] Stem cell mobilization will be monitored after 2nd cycle in patients with negative bone marrow biopsy at screening, and after third cycle in patients with positive bone marrow biopsy at screening.

[d] Biochemistry should include LDH and Beta2-microglobulin at screening

[e] only if positive at baseline

24.2 Appendix 2: Response Criteria

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.

24.3 Appendix 3: NCI Common toxicity criteria

In the present study, adverse events and/or adverse drug reactions will be recorded according to the:

Common Terminology Criteria for Adverse Events (CTCA), version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

24.4 Appendix 4: Dispensing information for rituximab

DESCRIPTION

Rituximab is a mouse/human chimeric antibody. The rituximab antibody is produced by a Chinese hamster ovary transfectoma. Rituximab will be provided in l00 mg (l0 mL) and 500 mg (50 mL) pharmaceutical grade vials at a concentration of l0.0 mg of protein per mL (actual concentration should be noted on the product label).

RECOMMENDED PREPARATION AND ADMINISTRATION

1. Refer to the clinical trial protocol for details about the dose and dose schedule.

2. Rituximab should be stored at 2-8°C. Do not freeze or store at room temperature. The product is a protein - HANDLE GENTLY AND AVOID FOAMING. The avoidance of foaming during product handling, preparation and administration is important, as foaming may lead to the de-naturing of the product proteins.

3. All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood.

4. Prepare the rituximab infusion solution as follows:

(a) Refrigerate (2-8°C) all materials and solutions prior to use.

(b) Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks and transfer tubing, etc.

(c) Transfer of the rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle.

(d) Transfer the appropriate amount of rituximab from the graduated syringe, into a partially filled IV pack containing sterile pyrogen-free 0.9% sodium chloride solution, USP (saline solution). The final concentration of rituximab in saline solution should be a maximum of 1 mg/ml. Mix by inverting the bag gently. DO NOT USE A VACUUM APPARATUS to transfer the product from the syringe to the plastic bag.

(e) Place an IV administration into the outflow port of the bag containing the infusion solution.

(f) NOTE: DO NOT USE evacuated glass containers which require vented administration sets because this causes foaming as air bubbles pass through the solution.

5. The administration of rituximab will be accomplished by slow IV infusion. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

6. IV pumps such as the IMED 960 may be used with the rituximab infusion. DO NOT INFUSE CONCOMITANTLY with another IV solution or IV medications. Prime the line with the rituximab solution such that approximately 30 mL are delivered

7. Administration of rituximab

Pre-administration of allopurinol (or suitable alternative):

Patients thought to be at risk of tumor lysis syndrome should be well-hydrated and treated with allopurinol (300 mg p.o.) or suitable alternative treatment for 12-24 hours before prior to the first dose of therapy with rituximab.

Caution: Do not administer rituximab as an intravenous push or bolus.

Rituximab will be administered intravenously in an out- or in-patient setting. Oral premedication (1000 mg of paracethamole and 50-100 mg diphenhydramine hydrochloride) needs to be administered 30-60 minutes prior to starting each infusion of rituximab. Prednisone/prednisolone as part of the chemotherapy protocol will be administered in the prescribed dose before the infusion of rituximab, preferably as oral medication. A peripheral or central intravenous (iv) line will be established. Before starting the infusion, there should be a ready supply of epinephrine for subcutaneous injection and diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for the emergency handling of anaphylactic reactions.

The infusion will be started at an initial rate of 50 mg/hour for the first hour. During the rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration and temperature) will be monitored every 15 minutes (4x) for one hour or until stable and then hourly until the infusion is discontinued. If no toxicity is seen during the first hour, the dose rate may be escalated gradually (by increments of 50 mg/hour at 30 minute intervals) to a maximum of 300 mg/hour. If the first dose of rituximab is well-tolerated, the starting flow rate for administration of the second and subsequent infusions will be 100 mg/hour and then increased gradually (by 100 mg/hour increments at 30 minute intervals) not to exceed 400 mg/hour. Patients may experience transient fever and rigors with infusion. If any of the effects below are noted, the antibody infusion should be temporarily discontinued, the patient should be observed, and when the symptoms improve, the infusion should be continued but at half the previous rate.

Dose Rate	**Fever**	**Rigors/chills**	**Mucosal congestion** **Edema**	**Drop in Systolic** **Blood Pressure**
Decrease to 1/2 If any of these Events seen:	> 38.5°C	Mild/Moderate	Mild/Moderate	> 30 mm Hg

Following the infusion the intravenous line should be kept open for medications, as needed. If there are no complications, the intravenous line may be discontinued after one hour of observation.Dosage: 375 mg/m² body surface.

	1st application		further Applications	
Hours	mg/h *)	mg-total	mg/h *)	mg-total
0 – 1	50	50	100	100
1 – 1.5	100	100	150	175
1.5 – 2	150	175	200	275
2 – 2.5	200	275	250	400
2.5 – 3	250	400	300	550
3 – 3.5	300	550	350	725
3.5 – 4	300	700	400	925

4 – 4.5	300	850		

*) With a concentration of 1 mg/ml the values of mg/h are equal to ml/h.

Suggested Rituximab Rapid infusion

If no adverse events occurred during first Rituximab infusion,with adeguate premedication, II-III and IV Rituximab infusion will be performed as follow:

RITUXIMAB 375 mg/m^2	First dose of 100 mg in saline solution 100 ml
	Second dose (to total dose) mg in saline solution 250 ml

time	**ml/h**
0-60	100
61-180	125

24.5 Appendix 5: Dispensing information for bortezomib

PACKAGING

BORTEZOMIB will be available as a sterile lyophilized powder in a single-use 10 mL glass vial. Each vial contains the equivalent of 3.5 mg of BORTEZOMIB in the form of a mannitol boronic ester. Each vials secured into a blister package.

LABELING

Study drug labels will contain information to meet the applicable regulatory requirements. The investigational products will be labelled and handled as open-label materials.

PREPARATION AND HANDLING

Vials for SC administration: each vial of BORTEZOMIB for Injection should be reconstituted under a laminar flow biological cabinet (hood), within 8 hours before dosing, with 1.4 mL of normal (0.9%) saline, sodium chloride injection, so that the reconstituted solution contains Velcade at a concentration of 2.5 mg/mL.

The reconstituted solution is clear and colorless, with a final pH of approximately 5 to 6. Dissolution is completed in approximately 10 seconds. Reconstituted BORTEZOMIB should be administered promptly and in no case more than 8 hours after reconstitution. In case of skin contact, wash the affected area immediately and thoroughly with soap and water and dilutedhydrogen peroxide for 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

24.6 Appendix 6: Suggested Body Surface Area Calculation

BSA should be determined using the appropriate following calculation:

$$BSA = \sqrt{\frac{Height(cm) \times Weight(kg)}{3131}}$$

OR

$$BSA = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$$

24.7 Appendix 7: Creatinine Clearance Calculation

Creatinine clearance for men and women will be calculated according to the Cockcroft-Gault formula as follows:

In men: 

In women: 

Note: Age (in years), weight (in kg), serum-creatinine (in mg/dL) 72 (normalized to 72 kg body weight and a body surface of 1.72 m^2)

24.8 Appendix 8: ECOG performance status scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about ??50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair ??50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

24.9 Appendix 9: New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	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.	Objective evidence of minimal cardiovascular disease.
III	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.	Objective evidence of moderately severe cardiovascular disease.
IV	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.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association, Inc.: Diseases of the heart and blood vessels; Nomenclature and criteria for diagnosis, 6th Ed. Boston: Little, Brown; 1964.