High total metabolic tumor volume at baseline allows discrimination of survival even in patients responding to R-CHOP

Laetitia Vercellino et al.

Supplemental appendix

Determination of the Optimal Total Metabolic Tumor Volume Cut-off Point for Binary Outcomes

X-tile was used to define the optimal cut-off for survival prediction.[1] This cut-off was then validated by using a training/validation method. A random sample of two-thirds of the patients (n = 203; stratified by PFS event) was designated as the training cohort and the remaining one-third became the validation cohort. X-tile software identified two cut-offs for PFS and OS prediction: 220 cm^3 and 1000 cm^3 (1015 cm^3 for PFS and 1094 cm^3 for OS) , this last group involving few patients (n = 33, <11% of the study population). In order to prioritize the sensitivity, the TMTV threshold of 220 cm^3 was selected. The 220 cm^3 cut-off was validated for PFS (HR = 3.2 [95% CI, 1.4 to 7.5], *P* = .004) and OS (HR = 3.9 [95% CI, 1.3 to 11.6], *P* = .009) in the validation cohort (n = 98). The AUC for the TMTV cut-off of 220 cm^3 was 0.61 and 0.66 for PFS and OS respectively.

1. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res*. 2004;10(21):7252-7259.

TABLE A1. Clinical Characteristics of Patients

Characteristic, n (%)	Lenalidomide (n = 155)	Placebo (n = 146)	*P*
Median age, years (range)	68.0 (58-80)	68.0 (59-79)	.37
Sex			.91
Male	90 (58)	86 (59)	
Female	65 (42)	60 (41)	
Histology			.68
DLBCL NOS	107 (69)	106 (73)	
FL grade 3B	2 (1)	1 (1)	
De novo transformed	16 (10)	10 (7)	
Other	15 (10)	16 (11)	
Central review missing	15 (10)	13 (9)	
ECOG PS			.28
0–1	132 (85)	115 (79)	
≥ 2	22 (14)	27 (18)	
Missing	1 (1)	4 (3)	
IPI			.52
0–2	40 (26)	42 (29)	
3–5	114 (74)	101 (69)	
Missing	1 (1)	3 (2)	
aaIPI			.41
0–1	69 (45)	57 (39)	
2–3	85 (55)	86 (59)	
Missing	1 (1)	3 (2)	
NCCN-IPI			.67
Low-intermediate	42 (27)	34 (23)	
High-intermediate	88 (57)	80 (55)	
High	18 (12)	21 (14)	
Missing	7 (5)	11 (8)	
Extranodal sites			.82
≤ 1	73 (47)	71 (49)	
> 1	82 (53)	75 (51)	
Elevated LDH (> ULN)			.34
No	65 (42)	53 (36)	
Yes	88 (57)	91 (62)	
Missing	2 (1)	2 (1)	
Albumin			.32
≤ 35 g/L	32 (21)	39 (27)	
> 35 g/L	90 (58)	80 (55)	
Missing	33 (21)	27 (19)	
Profile (Hans score)			.39
GCB	49 (32)	42 (29)	
Non-GCB	47 (30)	54 (37)	
Missing	59 (38)	50 (34)	
BCL2 (IHC)			.99
<70%	9 (6)	9 (6)	
≥70%	37 (24)	39 (27)	
Missing	109 (70)	98 (67)	

Characteristic, n (%)	Lenalidomide (n = 155)	Placebo (n = 146)	*P*
MYC (IHC)			.31
< 70%	39 (25)	37 (25)	
≥ 70%	7 (5)	12 (8)	
Missing	109 (70)	97 (66)	
MYC (IHC)			.10
< 40%	32 (21)	27 (19)	
≥ 70%	15 (10)	26 (18)	
Missing	108 (70)	93 (64)	
R-CHOP induction cycles			.45
6 cycles	42 (27)	46 (32)	
8 cycles	113 (73)	100 (69)	
Response to R-CHOP induction			.32
CR	120 (77)	106 (73)	
PR	34 (22)	40 (27)	
ORR	154 (99)	146 (100)	.99
If PR*			-
Positive PET scan	19 (12)	19 (13)	
BM missing	30 (19)	30 (21)	

NOTE: All data are n (%) unless otherwise stated. Percentages may not sum to 100 because of rounding.

*Note that patient with PR as response at the end of induction could have a positive PET and a BM missing.

Abbreviations: aaIPI, age-adjusted International Prognostic Index; BM, bone marrow; CR, complete response; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B-cell-like; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; PET, positron emission tomography; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ULN, upper limit of normal.

CLINICAL STUDY PROTOCOL
10-10-2014
REMARC

DOUBLE BLIND RANDOMIZED PHASE III STUDY OF LENALIDOMIDE (REVLIMID®) MAINTENANCE VERSUS PLACEBO IN RESPONDING ELDERLY PATIENTS WITH DLBCL AND TREATED WITH R-CHOP IN FIRST LINE

A study sponsored by:

Date and version of Protocol: Oct 10, 2014, version N°7 Final
EUDRACT Number: 2008-008202-52

CONFIDENTIALITY STATEMENT

Table of Contents

List of abbreviations and glossary of terms 4
1. Study objectives 6
1.1. Primary objective 6
1.2. Secondary objectives 6
2. Study design 6
3. Study population 7
3.1. Target population 7
3.2. Inclusion criteria at registration 7
3.3. Exclusion criteria at registration 9
4. Study treatment 10
4.1. Revlimid® and placebo: description, storage and handling 10
4.2. Treatment schedule and design 10
4.3. Prophylactic measures 14
5. Study flow chart and schedule of assessments and procedures 15
5.1. Study flow chart 15
5.2. Screening examination and selection procedures 15
5.3. Assessment during induction phase (R-CHOP) 16
5.4. Response assessment after induction phase (R-CHOP) 16
5.5. Assessment during maintenance phase 16
5.6. Assessment at the end of maintenance 17
5.7. Follow-up assessments 18
5.8. At relapse/ progression 18
6. Study procedures 18
6.1. Informed consent 18
6.2. Registration and Randomization procedure 19
6.3. Blinding/Unblinding procedure 19
6.4. Pathological review 19
6.5. CT scan Review 20
6.6. PET scan Review 20
6.7. Study committees 20
7. Safety parameters 21
7.1. Definitions 21
7.2. Adverse Events reporting 22
7.3. Serious Adverse Events reporting 23
7.4. Obligations of the sponsor 24
7.5. Follow up of Adverse Events and Serious Adverse events 24
8. Criteria for premature discontinuation of the study 24
8.1. Withdrawal of patients under treatment 24
8.2. Procedure for withdrawal of patients from study follow-up schedule 25
9. Study criteria of evaluation 26
9.1. Safety measurements 26

9.2. Efficacy measurements 26
10. Statistical CONSIDERATIONS 26
10.1. Study design 26
10.2. Primary endpoint 26
10.3. Secondary endpoints 27
10.4. Analysis populations 28
10.5. Statistical methods 28
10.6. Hypothesis testing 29
10.7. Sample size calculation 29
11. Ethical and regulatory standards 31
11.1. Ethical principles 31
11.2. Laws and regulations 31
11.3. Informed consent 31
11.4. Ethics Review Committee (ERC) and Competent Authorities submission 31
12. Appendices 32
12.1. Appendix B: Study flow chart 32
12.2. Appendix C: Schedule of evaluations 33

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	ASpartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
BSA	Body Surface Area
CD20	antigen expressed on the surface of normal and malignant B lymphocytes
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
EC	Ethic Committee
CR	Complete Response
CRF	Case Report Form
CRu	Complete Response unconfirmed
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DLBCL	Diffuse Large cell B-Cell Lymphoma
DSMC	Data Safety Monitoring Committee
DVT	Deep Vein Thrombosis
ECOG	Eastern Cooperative Oncology Group
ERC	Ethics Review Committee
ESA	Erythropoietin Stimulating Agent
ESMO	European Society for Medical Oncology
FL	Follicular cell Lymphoma
LYSA	LYmphoma Study Association (previously GELA: Groupe d'Etude des Lymphomes de l'Adulte and GOELAMS: Groupe Ouest Est des leucémies Aigues et Maladies du Sang)
LYSA-P	LYmphoma Study Association – Pathology (previously Groupe d'Etude des Lymphomes de l'Adulte – Pathologie)
LYSARC	Lymphoma Academic Research Organisation (previously GELARC : Groupe d'Etude des Lymphomes de l'Adulte – Recherche Clinique)
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
IMIDs®	Immunomodulatory drug (structural and functional analogues of thalidomide)
IP	Investigational Product
IRB	Institutional Review Board
IV	IntraVenous

LDH	Lactic DeHydrogenase
NCI	National Cancer Institute
NCIC CTG	National Cancer Institute of Canada - Clinical Trials Group
NHL	Non-Hodgkin's Lymphoma
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PS	Performance Status
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTP	Time To Progression
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

1. STUDY OBJECTIVES

1.1. PRIMARY OBJECTIVE

The primary objective is to determine the benefit estimated by the progression-free survival associated with lenalidomide maintenance compared to placebo in responding patients treated with R-CHOP for diffuse large B-cell lymphoma.

1.2. SECONDARY OBJECTIVES

The secondary objectives are to assess:

- Percentage of patients who convert from PR to CR
- Efficacy according to the response to R-CHOP
- Overall survival in both groups of patients (with and without lenalidomide maintenance)
- The safety of lenalidomide in maintenance

2. STUDY DESIGN

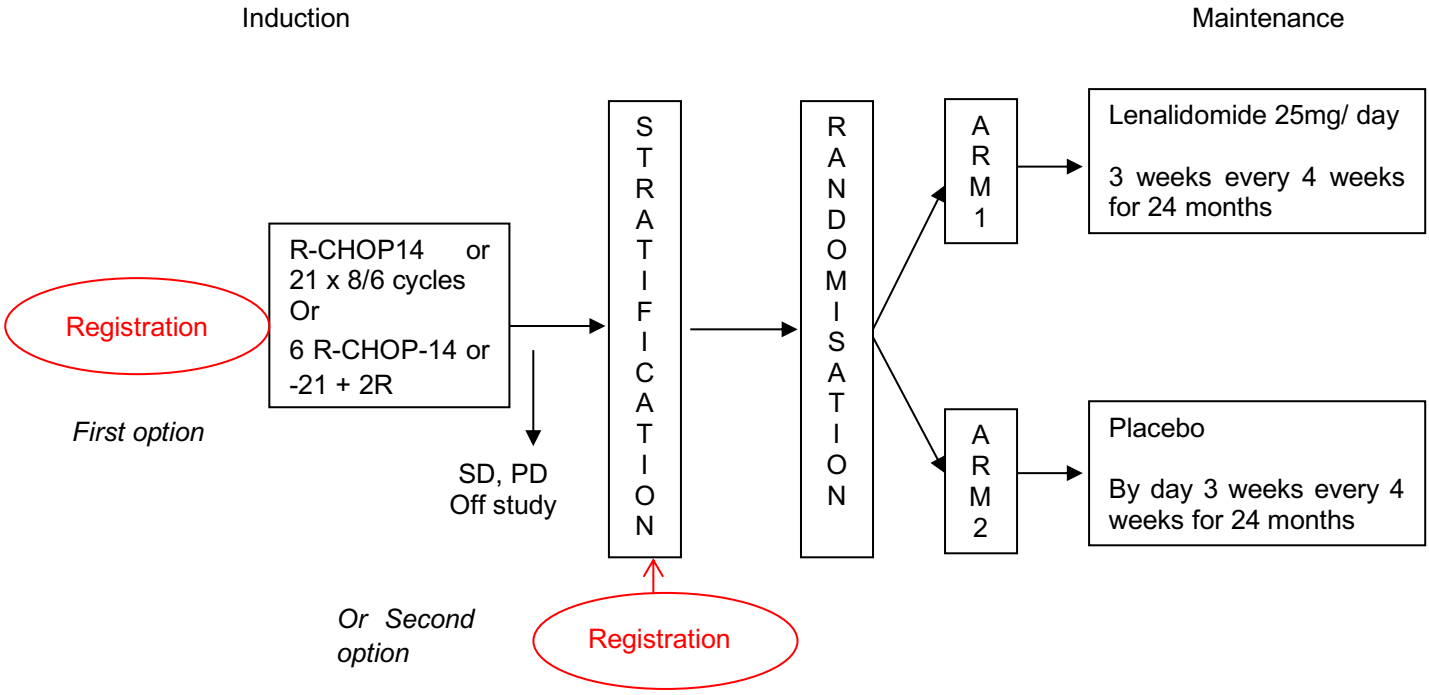
This study is a double blind, international, multicentre, randomized phase III study of lenalidomide (Revlimid®) maintenance versus placebo administered at the starting dose of 25 mg daily from D1 to D21, repeated at day 29 for 24 months (max up to 26 cycles) in patients aged from 60 to 80 years and responding to R-CHOP for a DLBCL CD20+ previously untreated.

Registration for participation in the study is done according to two pathways:

-Patients can be registered at the time of initial diagnosis and enrolment (informed consent) before the first cycle of R-CHOP.

-Patients can be registered after being treated in 1st line with R-CHOP and after the evaluation of the response, if they reached PR or CR. In these patients, the collection of data regarding the R-CHOP part would be done retrospectively.

Patients should have received at least 6 and up to 8 cycles of the R-CHOP-14 or R-CHOP-21 (or 6 R-CHOP-14 or 21 completed by 2 Rituximab alone) in accordance with local preferences. Responding patients, i.e.; those who achieve a (Complete Response) CR or (Partial response) PR will be randomized to lenalidomide maintenance (one dose daily for 3 weeks followed by one week rest, for 24 months (up to max 26 cycles) versus placebo (one dose daily for 3 weeks followed by one week rest, for 24 months).



For the maintenance phase, stratification will be according to country and the response to R-CHOP (PR and CR).

Patients registered at diagnosis before the end of recruitment could be randomized after the end of recruitment if they still meet inclusion and exclusion criteria.

Patients will be recruited over approximately 50 months, 59 months after approximate update. All randomized patients will receive 24 months treatment (max up to 26 cycles) and followed thereafter for at least three years from the last intake of study treatment in the study.

The total duration of the study is expected to be between 9 and 10 years.

3. STUDY POPULATION

3.1. TARGET POPULATION

The study population for randomization will consist of patients aged from 60 to 80 years (>59 year and <81 years old) at time of registration and responding (CR or PR) to 1st line treatment with R-CHOP for diffuse large B-cell Lymphoma, CD 20 positive.

3.2. INCLUSION CRITERIA AT REGISTRATION

Each patient must meet all of the following inclusion criteria during screening to be enrolled in the study:

For patients registered at time of initial diagnosis:

- Patient with histologically proven CD20+ diffuse large B-cell lymphoma (DLBCL) (WHO classification 2008) including clinical subtypes (primitive mediastinal, intravascular, etc.). Patients with De Novo

Transformed DLBCL from low grade lymphoma (Follicular, other..) may also be included. Patients with DLBCL associated with small cell infiltration in bone marrow may also be included.

-Or CD20+ B-cell lymphoma with intermediate features between DLBCL and Burkitt or with intermediate features between DLBCL and classical Hodgkin lymphoma

-Or CD20+ Follicular lymphoma grade 3B,

-Or CD20+ Aggressive B-cell lymphoma unclassifiable

- **Previously untreated with chemo-radiotherapy**

For patients registered after response evaluation to first line treatment with R-CHOP:

- Patient with histologically proven CD20+ diffuse large B-cell lymphoma (DLBCL) (WHO classification 2008) including clinical subtypes (primitive mediastinal, intravascular, etc.). Patients with De Novo Transformed DLBCL from low grade lymphoma (Follicular, other...) may also be included. Patients with DLBCL associated with small cell infiltration in bone marrow may also be included.

  -Or CD20+ B-cell lymphoma with intermediate features between DLBCL and Burkitt or with intermediate features between DLBCL and classical Hodgkin lymphoma

  -Or CD20+ Follicular lymphoma grade 3B,

  -Or CD20+ Aggressive B-cell lymphoma unclassifiable

- **Have reached a CR or PR (Cheson 2007) after first line treatment with at least 6-8 cycles of R-CHOP 14 or R-CHOP 21**
- **Previously untreated with radiotherapy**

For all patients:

- **Aged from 60 to 80 years at time of registration**
- **Eastern Cooperative Oncology Group [ECOG] performance status 0, 1 or 2**
- **Ann Arbor stages II-IV at time of initial diagnosis**
- **aaIPI $\geq$ 1 at time of initial diagnosis**
- **Minimum life expectancy of 3 months**
- **Voluntary signed informed consent** before performance of any study related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care
- The following laboratory values at screening
  - Absolute neutrophil count (ANC) $\geq$ 1 000 $.10^6$/L and Platelets $\geq$ 60 000 $.10^6$/L, unless these abnormalities are related to bone marrow infiltration.
  - Aspartate transaminase (AST) $\leq$ 5 x ULN; Alanine transaminase (ALT) $\leq$ 5 x ULN; Total bilirubin $\leq$ 1.5 x ULN; unless related to disease involvement
  - Creatinine clearance ≥ 30 ml/min (as calculated by the Cockcroft-Gault formula – see Appendix H 20.8)
- Females of childbearing potential (FCBP)[†] must:
  - Have a negative medically supervised pregnancy test prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the patient practices complete and continued sexual abstinence.
  - Either commit to continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study

[†] Definition found in appendix M 20.13

therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.

- Male patients must:
  - Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and for one week after cessation of study therapy.
  - Agree to not donate semen or sperm during study drug therapy and for one week after end of study drug therapy (see specifics.
- All patients must:
  - Understand that the study drug could have a potential teratogenic risk.
  - Be counseled about pregnancy precautions and risks of fetal exposure.
  - Agree to abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy.
  - Agree not to share study medication with another person.

3.3. EXCLUSION CRITERIA AT REGISTRATION

Patients meeting any of the following exclusion criteria are not allowed to be enrolled in the study:

For all patients:

- **Any other histological type of lymphoma, Burkitt included.**
- **Any history of treated or non-treated small B-cell lymphoma**
- **Central nervous system or meningeal involvement by lymphoma**
- **Contraindication to any drug contained in the chemotherapy regimen**. *For example: "cardiac contra-indication to anthracyclines (impaired Left Ventricular Function defined by LVEF<50%) neurological contra-indication to vincristine (peripheral neuropathy of WHO grade ≥ 2)*.
- **Myocardial infarction in the last 3 months or unstable coronary disease or uncontrolled chronic symptomatic congestive heart insufficiency NYHA III-IV**
- **Uncontrolled hypertension**
- **Uncontrolled diabetes mellitus as defined by the investigator**
- **Active systemic infection requiring treatment.**
- **Previously known HIV positive serology**
- **Active hepatitis B or C**
- **Prior history of malignancies other than lymphoma within 3 years** (except for complete resection of basal cell carcinoma, squamous cell carcinoma of the skin, or carcinoma in situ of breast or cervix).

  Patients previously diagnosed with prostate cancer are eligible if (1) their disease was T1-T2a, N0, M0, with a Gleason score ≤7, and a prostate specific antigen (PSA) ≤10 ng/mL prior to initial therapy, (2) they had definitive curative therapy (i.e. prostatectomy or radiotherapy) ≥2 years before Day 1 of Cycle 1, and (3) at a minimum 2 years following therapy they had no clinical evidence of prostate cancer, and their PSA was undetectable if they underwent prostatectomy or <1 ng/mL if they did not undergo prostatectomy.
- **Serious medical or psychiatric illness** likely to interfere with participation in this clinical study.

4. STUDY TREATMENT

4.1. REVLIMID® AND PLACEBO: DESCRIPTION, STORAGE AND HANDLING

4.1.1. Description

Revlimid® 25, 20, 15, 10 and 5 mg is presented in hard capsules.

Each capsule contains 25, 20, 15, 10 or 5 mg of lenalidomide and respectively 200, 244.5, 289, 294 or 147 mg of excipient anhydrous lactose.

Placebo 25, 20, 15, 10 and 5 mg is presented in hard capsules.

- Two types of placebos may be used.
  - One placebo contains the excipients used for the drug product (matching placebo): Lactose Anhydrous Microcrystalline Cellulose Croscarmellose Sodium Magnesium Stearate.
  - The other placebo is a standardized formulation containing microcrystalline cellulose (standardized placebo).
- Capsules conform in colour and size for blinded studies.

4.2. TREATMENT SCHEDULE AND DESIGN

4.2.1. Treatment in Induction phase (R-CHOP):

All patients (independent of time of registration) must be or have had at least 6 and up to 8 cycles of R-CHOP-14 or R-CHOP-21 or 6 R-CHOP-14 or-21 completed by 2 Rituximab.

Details of administration of Rituximab, doxorubicin, cyclophosphamide, vincristine, methotrexate vials and prednisone will also be documented in the CRF for patients that have been registered at the time of initial diagnosis. For patients registered after having been treated in first line with R-CHOP these data will be collected retrospectively.

Patients with an international prognostic index ≥1 will be treated according to Institutional practice.

Debulking in pre-phase treatment is permitted:

-Prednisone or

-Prednisone + Vincristine or

-Prednisone + Cyclophosphamide or

-Prednisone + Vincristine + Cyclophophamide. Vincristine could be replaced by Etoposide in case of neurological toxicity.

Local radiotherapy is not permitted

All patients will be treated with at least **6 and up to 8 cycles of R-CHOP-14 or R-CHOP-21 or 6 R-CHOP-14 or -21 completed by 2 Rituximab alone.**

Standard Doses :

R- CHOP		Dose (mg/m²)	Days
CYCLOPHOSPHAMIDE	IV	750	1
DOXORUBICINE	IV	50	1
VINCRISTINE	IV	1,4 (max 2 mg)	1
PREDNISONE	PO	40	1 to 5
RITUXIMAB	IV	375	1

-Vincristine 1.4mg/m² (max 2mg) could be replaced by Etoposide 100mg/m² (max 200mg) in case of neurological toxicity.

-Intrathecal (IT) methotrexate is permitted.

-IT methotrexate can be replaced by IV methotrexate as follows:

- First injection of IV methotrexate 1.5g/m² 3 weeks after the day 1 of the last cycle of R-CHOP or after the last Rituximab alone
- Second injection of IV methotrexate 1.5g/m² 2 weeks after the 1st injection

-Use of liposomal doxorubicin is permitted.

While the patient must commence on full dose R-CHOP dose appropriate reductions for toxicity are permitted.
Contrariwise the induction phase with R-mini CHOP is not allowed.

Prophylactic use of G-CSF or ESA **is allowed. G-CSF use is allowed in case of febrile neutropenia**. ESA can be used for the treatment of anaemia in symptomatic patients with non-myeloid tumors receiving chemotherapy according to the EMEA guidance from June 2008. For patients receiving ESA, DVT prophylaxis must be either LMW heparin or warfarin.

4.2.2. Treatment in Maintenance phase (lenalidomide vs placebo)

All patients responding to R-CHOP will be randomized and treated with lenalidomide or placebo administered daily from D1 to D21, repeated at day 29 for 24 months (max up to 26 cycles). For the randomization procedure see chapter 10.2

Day 1 of cycle 1 of study drug (lenalidomide/placebo) treatment must occur within 12 weeks (84 days) after the first day of the last R-CHOP cycle or the last Rituximab alone.

LENALIDOMIDE VS PLACEBO		Total Dose (mg)	Days
LENALIDOMIDE	PO	Starting dose 25mg*	1 to 21
PLACEBO	PO	Starting dose 25mg*	1 to 21

*For patients with creatinine clearance between 30-60 ml/min calculated by the Cockcroft-Gault formula the starting dose of study drug is 10mg. It is the responsibility of the investigator to make sure that creatinine clearance is calculated according to Cockcroft- Gault formula. The use of MDRD should be limited to the sites where Cockcroft is not available. (See Appendix H 20.8)

- **Dose-modifications of study drug (lenalidomide/ placebo):**

  - ✓ **Start Dose 25mg (if creatinine clearance ≥ 60ml/min)**

Study drug will be given at the starting dose of 25 mg daily from D1 to D21, repeated at day 29 for 24 months (up to max 26 cycles).

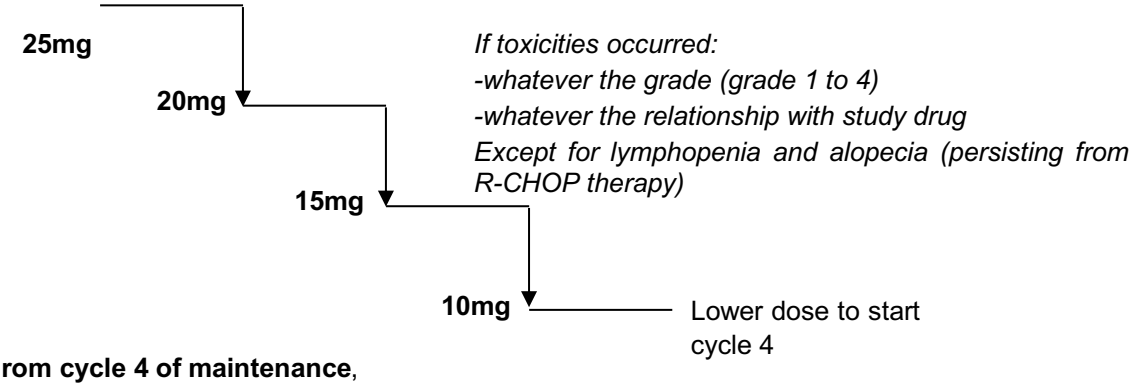
Patient must have an ANC ≥ 1 000.10^6/L, Platelets ≥ 60 000.10^6/L, and any other toxicity resolved to grade 1 or less before the first intake for day 1 of each cycle including cycle 1

During the first 3 cycles (Cycle 1, 2 and 3) of maintenance in case of toxicity occurrence whatever the grade (1 to 4) and regardless its relationship to the study drug, the dose of the study drug must be decreased at the next cycle by step of 5mg. It will be done **only for patient starting at 25mg.**

In case of toxicity grade 1-2 (for infection and neurological toxicities only grade 1) study drug should not be stopped during the current cycle but the dose reduced at the next cycle.

In case of toxicity grade 3-4 (grade 2 for infection and neurological toxicities) the study drug must be stopped during the current cycle and the dose reduced at the next cycle**.**

Dose reduction steps are as follows **during the first three cycles**:



From cycle 4 of maintenance,

After the third cycle, the study drug tolerance seems to be less compromised and the policy for decreasing the dose from cycle 4 will resume as follow.

The **study drug should be stopped during the current cycle and** dosing reduced in the next cycle in the event of the following drug-**related toxicities**:

- **Haematological toxicities**: if ANC < 1 000.10^6/L or platelets < 60 000.10^6/L,
- **Neurological and Infection toxicity** ≥ grade 2
- **Liver Enzymes see table below**
- **Any other toxicity** ≥ grade 3 except for lymphopenia , DVT or alopecia

The study drug should be stopped during the current cycle and dosing reduced directly to 10mg in the next cycle in the event of **Creatinine clearance degradation** between 30 and 60 ml/min

The study drug dosing should be permanently discontinued in the event of the following drug-related toxicities:

- **Desquamating (blistering) rash ≥ Grade 3 or non desquamating rash Grade 4**
- **Grade 3 / 4 allergic reaction or hypersensitivity.**
- **Creatinine clearance < 30 ml/min**

After study drug cessation for toxicity the next cycle may not commence until at least day 29 of the preceding cycle. Toxicities must have resolved to ≤ grade 1 with the exception of the following haematology parameters:

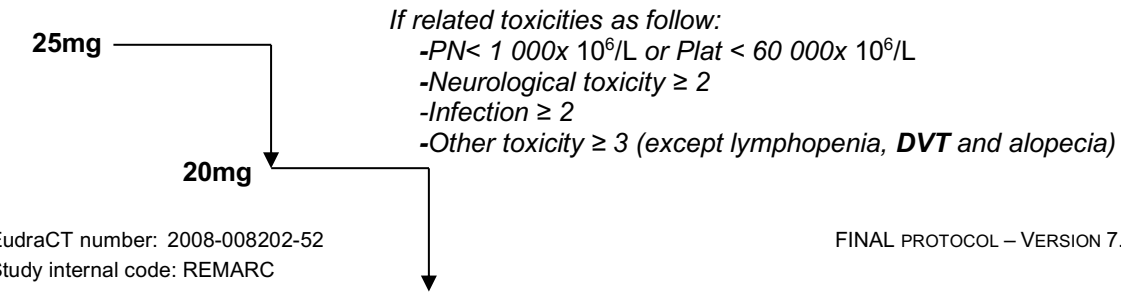
ANC ≥ 1 000.10^6/L

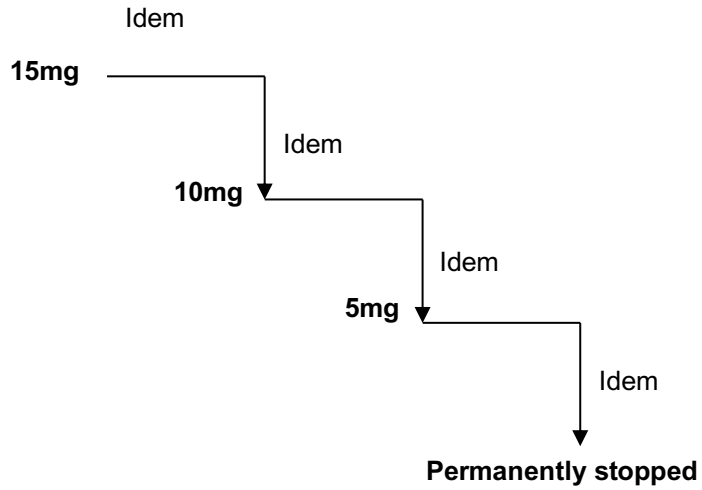
Platelets ≥ 60 000.10^6/L

If toxicity is not resolved within 6 weeks following the last intake of study drug, it must be stopped permanently.

Patient must have an ANC ≥ 1 000.10^6/L and Platelets ≥ 60 000.10^6/L and any other toxicity resolved to grade 1 or less before the first intake for day 1 of each cycle including cycle 1.

Starting from Cycle 4, the dose reduction steps are as follows:





✓ **Start Dose 10mg (If Creatinine clearance < 60ml/min AND ≥ 30ml/min)**

➔ **In case of creatinine clearance between 30 and 60 ml/min as calculated by the Cockcroft-Gault formula,** study drug will be started at 10 mg daily from D1 to D21, repeated at day 29. The dose can be escalated to 15 mg after 2 cycles if tolerated (i.e. absence of grade 3 or 4 toxicity). It is the responsibility of the investigator to ensure that creatinine clearance is calculated according to the Cockcroft- Gault formula (see Appendix H 20.8). The use of MDRD should be limited to the sites where Cockcroft is not available.

The creatinine clearance could vary but should remain above 30 ml/min (≥30 - < 60 ml/min).

For patient starting at 10mg from cycle 1 of maintenance,

The study drug should be stopped and dosing reduced in the next cycle in the event of the following drug-related toxicities:

- **Haematological toxicities**: if ANC < 1 000.10^6/L or platelets < 60 000 .10^6/L,
- **Neurological and Infection toxicity ≥** grade 2
- **Liver Enzymes, see table below**
- **Any other toxicity ≥** grade 3 except for lymphopenia, DVT or alopecia

The study drug should be permanently discontinued in the event of the following drug- related toxicities:

- Desquamating (blistering) rash ≥ Grade 3 or non-desquamating rash Grade 4
- Grade 3/4 allergic reaction or hypersensitivity
- Creatinine clearance < 30 ml/ min

After study drug cessation for toxicity the next cycle may not commence until at least day 29 of the preceding cycle. Toxicities must have resolved to ≤ grade 1 with the exception of the following haematology parameters:

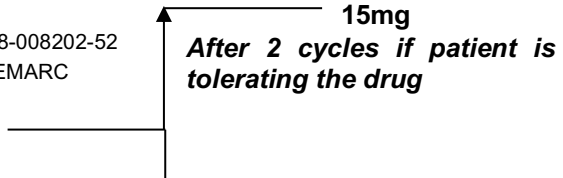
ANC≥ 1 000.10^6/L

Platelets ≥ 60 000 .10^6/L

If toxicity is not resolved within 6 weeks following the last intake of study drug, it must be stopped permanently.

Patient must have an ANC ≥ 1 000.10^6/L, Platelets ≥ 60 000.10^6/L, and any other toxicity resolved to grade 1 or less before the first intake for day 1 of each cycle including cycle 1

Dose reduction steps are as follows for patients with calculated creatinine clearance between 30-60ml/min:



10mg

If related toxicities as follow:
-PN< 1 000x10^6/L *or Plat < 60 000 x*10^6/L
-Neurological toxicity ≥ 2
-Infection ≥ 2
-Other toxicity ≥ 3 (except lymphopenia, DVT and alopecia)

5mg

5mg every other day → Idem

↓

Permanently stopped

✓ **Whatever the start dose, 25mg or 10mg**

➔ **In the event of Deep Venous Thrombosis (DVT),** study drug must be temporarily ceased. Antithrombotic treatment (heparin/coumadin [INR 2-3]) must be started; Anticoagulation must be maintained during the study treatment with study drug. On resolution of symptoms, at the discretion of the local investigator, the study drug can be resumed without dose reduction.
For patient starting at 25mg if DVT occurred during the first 3 cycles, a dose reduction should be done.

Dose modifications are as follows for Liver Enzymes:

Chemistry value	**Action**	**Study Drug Dose Modification**
ALT > 3 but ≤ 5 x ULN and Total bilirubin ≤ 1.5 x ULN	Continue study drug: re-test at next scheduled visit	No change
ALT > 3 but ≤ 5 x ULN and Total bilirubin > 1.5 x ULN	Temporarily cease study-drug; re-test weekly until ALT and total bilirubin return to baseline	– Resume the same dose of study drug if recovery from the event is ≤ 14 days. If recovery is prolonged beyond 14 days, then the study drug dose should be decreased by one level, and weekly testing of liver functions should occur during that cycle. If the values do not return to baseline within 28 days, the medical monitor must be notified.
ALT >5 x ULN or Total bilirubin > 1.5 x ULN	Temporarily cease study-drug; re-test weekly until ALT and total bilirubin return to baseline	– Resume the same dose of lenalidomide if recovery from the event is ≤ 14 days. If recovery is prolonged beyond 14 days, then the lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. If the values do not return to baseline within 28 days, the medical monitor must be notified.

If a patient has had a dose reduction, then dose re-escalation of study drug is not permitted at any time.

4.3. PROPHYLACTIC MEASURES

It is recommended that patients at high risk for a thromboembolic event (high risk is defined for example as a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/ or a known hypercoagulable state regardless of thromboembolic history)

receive prophylactic aspirin [ASA] (70-100mg) daily unless contraindicated. If ASA is contraindicated use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the International Normalization Ratio (INR) in the range of 2-3 or other anti-venous thrombotic prophylaxis according to hospital guidelines or physician preference is acceptable. However the choice of anticoagulant for prophylaxis for VTE relies upon the investigator's discretion and should be tailored to the patients' individual risk/ benefit profile by taking into account the individual thrombotic risk (e.g: history of venous thrombosis), bleeding risk, and the quality of compliance with antithrombotic treatment

Prophylactic use of G-CSF or ESA is allowed during the 2 phases of study (induction and maintenance). G-CSF use is allowed in case of febrile neutropenia. ESA can be used for the treatment of anaemia in symptomatic patients with non-myeloid tumours receiving chemotherapy according to the EMEA guidance from June 2008. For patients receiving ESA, DVT prophylaxis should be either LMW heparin or warfarin.

5. STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS AND PROCEDURES

5.1. STUDY FLOW CHART

See Appendix.

5.2. SCREENING EXAMINATION AND SELECTION PROCEDURES

See Appendix.

The patient will be required to give written informed consent to participate in this study before any non routine screening tests or evaluations are conducted.

The inclusion and exclusion criteria (see section 5.2 and 5.3) will be assessed during the screening period. Patients must continue to meet all eligibility criteria on Day 1 of Cycle 1.

Patients registered at time of initial diagnosis:

The following assessments must be conducted during the screening period (up to 30 days **before first cycle of chemotherapy R-CHOP**)

- Patient demographics including birth date and sex.
- Complete relevant medical history including complete lymphoma history.
- Concomitant medication assessment.
- ECOG Performance Status (see Appendix F 20.6).
- Weight, height, body surface area (BSA – see Appendix E 20.5)
- Physical examination.
- Stage and extent of the current disease according to the American Joint Committee on Cancer Non Hodgkin's Lymphoma (AJCC – see Appendix D 20.4) (35)
- Biochemical tests: calcium, sodium, potassium, creatinine, creatinine Clearance, LDH, ALT, AST, total bilirubin, alkaline phosphatise, β2-microglobuline.
- Serum electrophoresis
- Bone marrow biopsy
- Cervical, Chest, abdomen and pelvis CT scan with IV contrast (**up to 28 days before first cycle of chemotherapy**). The scans may be performed with oral contrast only, if a patient is allergic to IV contrast agents.
- Positron Emission Tomography (PET) scan (**up to 28 days before first cycle of chemotherapy**). Is suggested but **it is not mandatory**
- Any other evaluation/ procedures required to assess baseline disease for other sites of disease will be performed (cerebral CT scan, Lumbar puncture if clinically indicated) (**up to 28 days before first dose of study drug**).

- Complete blood cell counts.
- Echocardiography or isotopic method to determine resting ejection fraction
- Electrocardiogram
- HIV, HBV, HCV serology
- For patients registering after completion of 1st line induction treatment the above information will be collected retrospectively.
- Tumour biopsy be done even if patient is registered after induction phase (R-CHOP phase)

5.3. ASSESSMENT DURING INDUCTION PHASE (R-CHOP)

Patients registered at time of initial diagnosis:

The adverse events serious	AE related to SAE must be reported and followed during induction phase (until induction evaluation) Second malignancies must be reported as serious adverse event regardless of when they occur and regardless of their relationship to study treatments/procedures
Any other procedures if clinically relevant	During induction phase

5.4. RESPONSE ASSESSMENT AFTER INDUCTION PHASE (R-CHOP)

For all patients:

Evaluation must be performed between 3 weeks (21 days) and 8 weeks (56 days) after the day 1 of the last R-CHOP cycle or the last Rituximab alone.

- Physical examination
- ECOG PS (see Appendix F 20.6)
- Cervical Chest, abdomen and pelvis CT scan with IV contrast. The scans may be performed with oral contrast only, if a patient is allergic to IV contrast agents.
- **Positron Emission Tomography (PET) scan**
- Complete blood cell counts
- Biochemical tests: calcium, sodium, potassium, creatinine, creatinine clearance, Total Bilirubine, **LDH**, ALT, AST,
- Bone marrow biopsy if initially involved
- Adverse events serious
- Evaluation of the disease response (Cheson 2007)
- Any other procedures if clinically relevant
- Stratification of responding patients

Patients with at least a Partial Response will be randomized after evaluation and maintenance treatment will start within 12 weeks after the first day of the last R-CHOP cycle or the last Rituximab alone.

5.5. ASSESSMENT DURING MAINTENANCE PHASE

The following assessments must be conducted during the maintenance period (See Appendix C 20.3):

Physical examination (including vital signs)	Day 1 of each cycle for the first 3 cycles, then every 3 cycles
ECOG PS (see Appendix F 20.6)	Day 1 of each cycle for the first 3 cycles, then every 3

	cycles
Biochemical tests: calcium, sodium, potassium, creatinine, creatinine clearance, LDH, ALT, AST, total bilirubin.	Day 1 of each cycle for the first 3 cycles, then every 3 cycles
Complete blood cell counts	Once a week during the first cycle Then each 15 days (at D1 and D15) during cycle 2 and cycle 3 And monthly at day 1 of each cycle thereafter, unless clinically indicated. Next cycle can be postponed for 6 weeks after last intake of study drug until ANC ≥ $1{,}000.10^6$/L and platelets ≥ $60{,}000.10^6$/L. The next cycle will be done at the appropriate dose (reduction dose) After 6 weeks, if ANC < $1{,}000.10^6$ or platelets < $60{,}000.10^6$ study drug will be permanently stopped
The adverse events	AE reported and followed during the entire maintenance phase. Next cycle can be postponed for 6 weeks after last intake of study drug until toxicity resolved to at least grade 1 (except for ANC and platelets see above) Next cycle will be done at the appropriate dose (reduction dose) After 6 weeks, if toxicity is not resolved to at least grade 1 (except ANC and platelets), study drug will be permanently stopped. Second malignancies must be reported as serious adverse event regardless of when they occur and regardless of their relationship to study treatments/procedures
Cervical, Chest, abdomen and pelvis CT with IV contrast.	At cycle 6 (6months), cycle 12 (12 months) and cycle 21 (18 months)
PET scan	-For patients with a positive PET scan at randomization an additional PET scan will be done before the end of maintenance (whenever response status has improved to CR during maintenance treatment)

5.6. ASSESSMENT AT THE END OF MAINTENANCE

The following assessments must be conducted during the 2 months (60 days) after day 1 of last cycle: (See Appendix):

- Physical examination.(including vital signs)
- ECOG PS. (see Appendix)
- Biochemical tests: calcium, sodium, potassium, creatinine, creatinine clearance, LDH, ALT, AST,
- Complete blood cell counts.
- Bone marrow biopsy if positive before maintenance.
- Cervical, Chest, abdomen and pelvis CT scan with oral and IV contrast.
- Evaluation of the disease response (Cheson 2007).
- Any other evaluations or procedures performed at baseline for evaluation of the disease response.

- Adverse events.

In case of premature withdrawal during the study treatment period (maintenance period), the evaluation should be performed 2 months after day 1 of last cycle or before the start of any new treatment.

Toxicities (see Safety section) must be reported during the study period up to 60 days after the last drug administration.

5.7. FOLLOW-UP ASSESSMENTS

The following assessments must be conducted at each follow-up visit every 6 months until the number of events (160) for final PFS analysis are met (See Appendix 20.2) and until at least 3 years from the last intake of study treatment in the study:

- Physical examination.
- ECOG PS (see Appendix 20.6).
- Complete Blood cell counts.
- Bone marrow biopsy if clinically indicated.
- Cervical, Chest, abdomen and pelvis CT with IV contrast (once a year until end of study)
- Evaluation of the disease response (Cheson et al., 2007).
- Any other evaluations or procedures performed at baseline for evaluation of the disease response (every 6 months).
- Survival Status
- Second Primary Malignancies (SPMs)
- Subsequent lines of treatment

5.8. AT RELAPSE/ PROGRESSION

Relapse/ progression will be determined as per Cheson 2007 criteria (see Appendix 20.7).

Progressive disease will be based on CT scan or histologic documentation or clinical measurable tumor, and not on PET finding only.

At relapse, peripheral blood and if feasible / clinically indicated, tumour biopsy and bone marrow examination will be performed.

6. STUDY PROCEDURES

6.1. INFORMED CONSENT

Written informed consent in compliance with local regulatory authority will be obtained from each patient prior to entering the trial, there are two entry pathways:

-Registration before R-CHOP, at diagnosis

-Registration after R-CHOP, before randomization

The patient and the investigator will date and sign the informed consent form, and registration of patient in the study will be done by IVRS before patient starting R-CHOP chemotherapy or starting maintenance treatment.

The investigator shall provide a copy of the signed consent to the study patient; a copy shall be maintained in the investigator's study file.

When allowed by local regulation, an original copy of the signed consent form will be recovered by the LYSARC or representative sponsor in a sealed envelope.

6.2. REGISTRATION AND RANDOMIZATION PROCEDURE

A patient will be registered after verification of eligibility. Patients will be able to be either:

- Registered at time of initial diagnosis, then a new IVRS call/ IWRS connection will be done for randomization after response evaluation at the end of 1st line treatment.

- Or Registration will take place after 1st line treatment with R-CHOP, directly at randomization

Randomization to the maintenance (lenalidomide vs placebo) will be done only for patients achieving a CR or PR after induction treatment and being eligible for randomization. Response evaluation to determine eligibility for randomization should be performed within 56 days (8 weeks) after day 1 of last cycle of R-CHOP or last Rituximab alone.

Randomization should occur after documentation of CR or PR and maintenance treatment will start within 12 weeks after the first day of the last R-CHOP cycle or last Rituximab alone.

Registration should be done before the start of the protocol treatment.

Stratification will be done according to the response to R-CHOP (PR or CR) and the country

6.3. BLINDING/UNBLINDING PROCEDURE

Maintenance phase will be blinded.

Blinding

Treatment with lenalidomide or placebo will continue in 28-day cycles until disease progression, unacceptable toxicity or treatment discontinuation for any other reason.

Emergency Unblinding

The blind must not be broken during the course of the study unless in the opinion of the investigator it is absolutely needed to safely treat the patient. Blind may be broken using IVRS/ IWRS. Every effort should be made to contact the Medical Monitor prior to breaking the blind.

The reason for breaking the blind must be documented in the patient's CRF and in the patient's medical records. Documentation of contact or attempted contact with the clinical research physician prior to breaking the blind must also be documented in the patient's medical records.

6.4. PATHOLOGICAL REVIEW

The pathological diagnosis of DLBCL should have been performed locally before the registration/ randomization for each patient.

Histopathology central review process has become in recent years a common prerequisite procedure for clinical trials in the field of lymphoma. It requires both a histopathological and immunohistochemical approach using an appropriate panel of antibodies according to the morphological pattern and, in some instances, further molecular or genetic analysis.

A mandatory pathological review will be performed 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.

Therefore for each patient, the investigator will be requested to join with the inclusion form a copy of the histopathological report with the name and address of the pathologist having diagnosed the lymphoma easily identified **as well as a copy of the bone marrow report**.

When bone marrow biopsy was involved at inclusion and becomes negative after treatment, the bone marrow biopsy will be reviewed.

6.5. CT SCAN REVIEW

A central review of CT scan is mandatory and organized for each randomized patient from randomization to assess primary criteria, the images will be reviewed by a panel of CT experts.

For each patient, when applicable, data and images of CT scans must be uploaded on Imagys webplatform:

- prior to R-CHOP if available,
- prior to randomization,
- at cycle 6,
- at cycle 12,
- at cycle 21
- at final response evaluation and
- once a year during follow-up and
- all other unscheduled CT scans

In case of MRI modality used, MRI will be reviewed by a panel of CT experts.

6.6. PET SCAN REVIEW

A central review of the PET scan is mandatory and organized for each randomized patient from randomization.

For each patient when applicable, the data and DICOM images of:

- PET before randomization and
- PET during maintenance for patient with a PET positive at randomization (whenever response status has improved to CR during maintenance treatment)
- And all other PET done during the study for any reasons will be reviewed by a panel of PET experts.

6.7. STUDY COMMITTEES

6.7.1. Independent Data Safety Monitoring Committee

A data safety monitoring committee (DSMC), including at least four independent members (2 experts in NHL, 1 expert in medical ethics and one independent statistician) has been established. The DSMC will meet periodically to review the safety and efficacy data from the trial prepared by the independent statistician. All data presented at the meeting will be confidential. Following each meeting the DSMC will prepare a report and may recommend changes in trial conduct.

The first DSMC will be conducted after the first 60 patients have been randomized and treated for 3 cycles.

The second DSMC will be conducted after the first 207 patients have been randomized and treated for 2 cycles.

The third DSMC will be conducted after the first 414 patients have been randomized and treated for 2 cycles.

Additional “safety” DSMC could be organized every 6 months according to the occurrence of serious toxicities.

6.7.2. Independent Review Committee

For PFS assessment as the primary endpoint an external CRO will conduct independent review of all CT and PET scans according to an independent review charter.

An independent hematologist expert will be appointed to independently confirm first progression based on data of the independent review of CT and PET scans and clinical data, and to evaluate conversion to CR if any.

Bone Marrow examination will be reviewed by the pathological platform to evaluate conversion into CR in patients with positive bone marrow at time of randomization.

7. SAFETY PARAMETERS

7.1. DEFINITIONS

7.1.1. 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 adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

7.1.2. 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 in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically significant event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriated in 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.

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

7.1.3. Intensity

The **intensity of the event** will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) grading system v3.0 in the toxicity categories that have recommended grading.

Adverse events not listed on this grading system will be graded according to the four-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)

Any toxicity of any intensity grade occurred during **maintenance phase** will be recorded and graded on the appropriate toxicity page in the CRF (following CTCAE, version 3.0).

7.2. ADVERSE EVENTS REPORTING

Adverse events (AE) regardless of seriousness or relationship to Investigational Product that occurred **after the informed consent up to 60 days after the last study drug administration** are to be recorded in the AE pages of the Case Report Form (CRF) in accordance with General AE/SAE reporting rules.

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 adverse events and his opinion as to whether the adverse event can be related to the study drugs

All events that meet one or more criteria of seriousness (see Section 11.1.2.) will be reported as Serious Adverse Event (see Section 11.3).

General AE/SAE reporting rules:

- Any episode of any grade of toxicities, related to a Serious Adverse Event must be reported as "Adverse Event" in the appropriate CRF pages, regardless the time of occurrence.
- Non-serious adverse events are not to be reported if occurred during the induction phase up to the patient's randomization to maintenance.
- Haematological toxicities (anaemia, thrombocytopenia, leucopenia, neutropenia), febrile neutropenia and nausea, requiring hospitalization less than 8 days, are not to be reported as SAE during induction phase.
- During maintenance period, **Adverse Event of grade 2-5 for infections and neurological toxicities and Adverse Event of grade 3-5 for other toxicities (CTCAE – version 3.0) must be reported as "Adverse Event" in the appropriate CRF pages.**

- Only during **the first 3 cycles** of maintenance period, any Adverse Events leading to the doses modification and whatever their grade should be reported as “Adverse Event”.
- Sign, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as “Adverse Event” or “Serious Adverse Event”.
- “Alopecia” toxicity (any grade) will never be reported as “Adverse event”.

7.3. SERIOUS ADVERSE EVENTS REPORTING

All defined **Serious Adverse Events (SAEs)** occurred **after the informed consent up to 60 days after the last study drug administration**, whether or not ascribed to the study, will be recorded in the Serious Adverse Event pages in accordance with General AE/SAE reporting rules.

A Serious Adverse Event that occurs after this time, including during the follow-up period, **if considered related to the study medication**, will be reported (and the AE also).

All Serious Adverse Events must also be reported on the Adverse Event page of the CRF.

Second malignancies must be reported as serious adverse event (and AE also) regardless of when they occur and regardless of their relationship to study treatments/procedures including during the follow-up period.

- 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 (eg surgery was performed earlier than planned).

OBLIGATIONS OF THE INVESTIGATOR

In a case of Serious Adverse event The Investigator must immediately:

- **SEND (within 1 working day, preferably by fax) the SAE pages to**

  LYSARC Pharmacovigilance department:

  All SAE forms must be dated and signed by the responsible Investigator or one of his/her authorized staff Members.
- 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 Serious Adverse Event that is fatal or life threatening should be provided within one calendar week.

For serious adverse events, the following must be assessed: relationship to test substance, action taken, and outcome to date. The Causality is initially assessed by the investigator. For serious adverse events, causality can be one of two possibilities:

- **Unrelated :**The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
- **Related** The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event

7.4. 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 lenalidomide, to the Health Authorities, Ethic Committees in each country in accordance with international and local regulations, and to the Investigators.

The expectedness of an adverse reaction will be determined by the Sponsor according to the Investigator's Brochure for lenalidomide.

In this study, the SAE related to the underlying condition will not be considered unexpected unless their course, intensity or other specific features are such that the Investigator considers these events as exceptional.

Any other Serious Adverse Reaction during maintenance phase not consistent with the SAEs listed in the Investigator's brochure for lenalidomide and consistent with the events listed in the reference safety information (SmPC) for Rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone will be considered as unexpected.

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

7.5. FOLLOW UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

- Any SAEs 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 adverse events must be documented and the outcome must be followed up until the return to normal or consolidation of the patient's condition.

8. CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

8.1. WITHDRAWAL OF PATIENTS UNDER TREATMENT

Circumstances that lead to premature withdrawal of a patient from the trial must be clearly reported by the investigator on the appropriate CRF page. Patients withdrawn during the maintenance will continue to be assessed and followed in the study unless the patient refuses.

Patients can be withdrawn from the study under the following circumstances:

- death,
- disease progression
- initiation of alternate anti-neoplastic therapy,
- toxicity,
- intercurrent illness,
- non compliance (including loss of patient to follow-up),
- voluntary withdrawal,
- failure to meet the eligibility criteria.

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, 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 (60 days after last drug administration for the "Assessment at the end of maintenance" – see Section 7.6).

If the patient explicity 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 CRF. However, data up to the time of consent withdrawal will be included in the data reported for the study.

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 there must be documented attempts to contact the patient either by phone or letter.

Patients who are withdrawn from the study will not been replaced. Furthermore, those patients may not re-enter the study at any time.

8.2. PROCEDURE FOR WITHDRAWAL OF PATIENTS FROM STUDY FOLLOW-UP SCHEDULE

The patients may withdraw from the study follow-up schedule, before study completion if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision:

- All study withdrawals should be recorded by the Investigator in the appropriate CRF pages and in the patient's medical records when considered as confirmed (at least date of withdrawal and reason for);
- If possible, the patients are assessed using the procedure normally planned for the assessment at the end of maintenance.

The Investigator should make every effort to recontact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who did not complete the study and for whom no endpoint data are available will be considered as lost to follow-up.

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

9. STUDY CRITERIA OF EVALUATION

9.1. SAFETY MEASUREMENTS

The detailed and schedules for the procedures listed below are presented in Appendices C 20.3, respectively:

- Adverse events
- Physical examination
- Vital signs
- Weight
- Clinical laboratory evaluations

9.2. EFFICACY MEASUREMENTS

9.2.1. Criteria for response categories

See Appendix G 20.7

10. STATISTICAL CONSIDERATIONS

10.1. STUDY DESIGN

This study is designed as a phase III, randomized, double-blind, placebo-controlled trial to explore the effect of maintenance therapy with lenalidomide versus placebo on progression-free survival (PFS) in patients treated with R-CHOP responding to induction therapy.

10.2. PRIMARY ENDPOINT

The primary endpoint is progression-free survival (PFS). PFS will be measured from the date of randomization to the date of first documented disease progression or relapse assessed by a blinded independent response adjudication committee, or death from any cause whichever occurs first.

The central assessment procedure will be detailed in a separate charter.

The progression data will be assigned to the earliest time when any progression is observed without prior missing assessments during the study up to the end of the follow up phase.

Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

Any documented progression occurring after a withdrawal of the study for other reasons than “lost to follow up” or after any change of therapy will be considered as an event. If no event has been observed for these patients, the last tumor assessment date will be use as censor date.

PFS based on investigator judgment will be used as secondary endpoint.

Sensitivity analysis will be performed based on different censoring rules:

The progression data will be assigned to the earliest time when any progression is observed without prior missing assessments during the study up to the end of the follow up phase. If withdrawal from the study due to adverse events or change of therapy occur before documented progression or death then these observations will be censored at the date when the last adequate assessment determines a lack of progression.

For patients who discontinue the study before being evaluated for response, the date of randomization will be used as censor date.

For patients who do not develop progressive disease during the study, the most prior visit date with an adequate assessment indicating no progressive disease will be used as the censor date.

10.3. SECONDARY ENDPOINTS

10.3.1. Efficacy endpoints

Secondary efficacy endpoints will include:

OVERALL SURVIVAL (OS)

Overall survival will be measured from the date of randomization to the date of death from any cause. Patients who have not died at the time of the analysis or who are lost to follow-up will be censored at the date of last contact.

Sensitivity analysis could be conducted in which patients will be censored at the first dose date of another lymphoma therapy. In case of cross over methods to handle it will be specified in the Statistical Analysis Plan document.

RESPONSE RATE AT THE END OF MAINTENANCE TREATMENT

Response will be assessed at the end of the 24 months maintenance if patient received all planned cycles otherwise at withdrawal. Complete (CR) and Overall (CR/PR) response rates will be presented. Patient without response assessment (due to whatever reason) will be considered as non-responder. An additional analysis will also be performed considering as non-responders all patients who relapsed or died during treatment phase even if they were prematurely withdrawn as responder.

PERCENTAGE OF PATIENTS WHO CONVERT FROM PR TO CR

The number and percentage of patients who were in partial response (PR) at the end of induction treatment and who were in complete response (CR) at the end of maintenance treatment will be described.

10.3.2. Safety endpoints

All patients who receive any amount of trial drug (either Lenalidomide or Placebo) will be considered evaluable and analyzed for safety of maintenance treatment.

Analysis of safety will be performed by summarizing adverse events, laboratory data and vital signs. When applicable, summary of safety data will also be performed by cycle.

All adverse events will be tabulated and graded according to the NCI-CTCAE (Version 3.0) for each patient. Toxicities will be summarized for each designation by worst grade per patient and by grade by cycle. Verbatim descriptions of AEs reported during the study period will be mapped to MedDRA-Preferred Term and System Organ Class. All treatment-emergent AEs (i.e., occurring from 1st cycle of maintenance treatment) will be summarized in frequency tables. All treatment-emergent SAEs, grade 3 and higher, study drug related events, AEs leading to death will be listed and summarized in frequency tables. All deaths will be listed and also summarized by cause of death.

Clinical laboratory tests and their change from baseline will be summarized in terms of mean, standard deviation, median, minimum and maximum values by visit. The frequencies of the worst severity grade observed during the treatment will be displayed in cross-tabulations by baseline status for each study arm.

Vital signs and their change from baseline will be summarized in terms of mean, standard deviation, median, minimum and maximum values by visit.

Graphical displays will be provided where useful to aid in the interpretation.

10.4. ANALYSIS POPULATIONS

10.4.1. Induction phase

- **Induction Full Analysis Set (FAS-Induction)**

The Induction Full Analysis Set includes all patients who were registered in the trial regardless whether they have received induction treatment or not (following an intent-to-treat principle). Patients will be analyzed according to the induction therapy they received at the first cycle.

This population will also be the **Included Set**.

- **Induction Safety Set (SS-Induction)**

All registered patients who have received at least one component of the planned induction treatment regimen (R-CHOP) will be included in the Induction Safety Set. Patients will be analyzed according to the induction therapy they received at the first cycle.

10.4.2. Maintenance phase

- **Maintenance Full Analysis Set (following an intent-to-treat principle) (FAS-Maintenance)**

The maintenance full analysis set contains all patients who were formally randomized to the maintenance phase of the trial regardless whether they have received maintenance or not (following an intent-to-treat principle). Patients will be analyzed according to the maintenance therapy they were randomized to receive.

This will be the primary analysis population for this study.

- **Maintenance Safety Set (SS-Maintenance)**

The maintenance safety set includes all patients who have received at least one dose of maintenance treatment. The safety parameters will be summarized according to the therapy the patient actually received, i.e. a patient will be included in the lenalidomide arm for safety analyses if he/she received at least one dose of lenalidomide during any maintenance visit; otherwise, he/she will be included in the placebo arm.

10.5. STATISTICAL METHODS

The primary analysis between the two study arms in the maintenance phase will be an unstratified two-sided log-rank test based on the data from the independent assessment. The primary analysis will be conducted based on the maintenance full analysis population. Estimates of the treatment effect will be expressed as hazard ratios including two-sided 95% confidence intervals. In addition Kaplan-Meier estimates of median progression-free survival as well as progression-free survival rates at one, two and three years after randomization with 95% confidence intervals will also be reported. To account for the stratified randomization, a log-rank test stratified by response to induction therapy (CR vs PR) will be performed in addition to the unstratified analysis described above.

Continuous variables will be summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles will also be presented when considered relevant.
Categorical data will be described in counts and percentages (of non-missing data). Response rates at the end of maintenance therapy and percentage of patients who convert from PR to CR will be expressed with 95% confidence limits according to Pearson-Clopper method and compared using a chi-square test.
Censored data 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% CIs. The median time to event will be calculated (if reached) with 95% confidence intervals. Secondary time to event endpoints will be analyzed by using the same tests and significance levels as the primary endpoint.

The Cox proportional hazards model will be used in exploratory analyses to determine which demographic and prognostic variables most affect treatment outcome and to adjust the treatment comparisons for these

variables. Only those variables that differ at the 0.10 level for a preliminary univariate Cox regression analysis will be included in the multivariate model. A forward selection stepwise procedure will be used to identify the subset of relevant factors. After a final model has been determined, treatment will be added to assess its effect on the model.

10.6. HYPOTHESIS TESTING

A two-sided log-rank test will be used for testing the difference in progression-free survival between the two treatment groups. The significance level for the final analysis will be 0.05 to account for the interim analysis (the overall alpha level is 5%).

The hypothesis will be:

H_0: PFS (lenalidomide) = PFS (placebo)

versus

H_A: PFS (lenalidomide) ≠ PFS (placebo)

Where PFS denotes the survival distribution of the parameter time to progression-free survival.

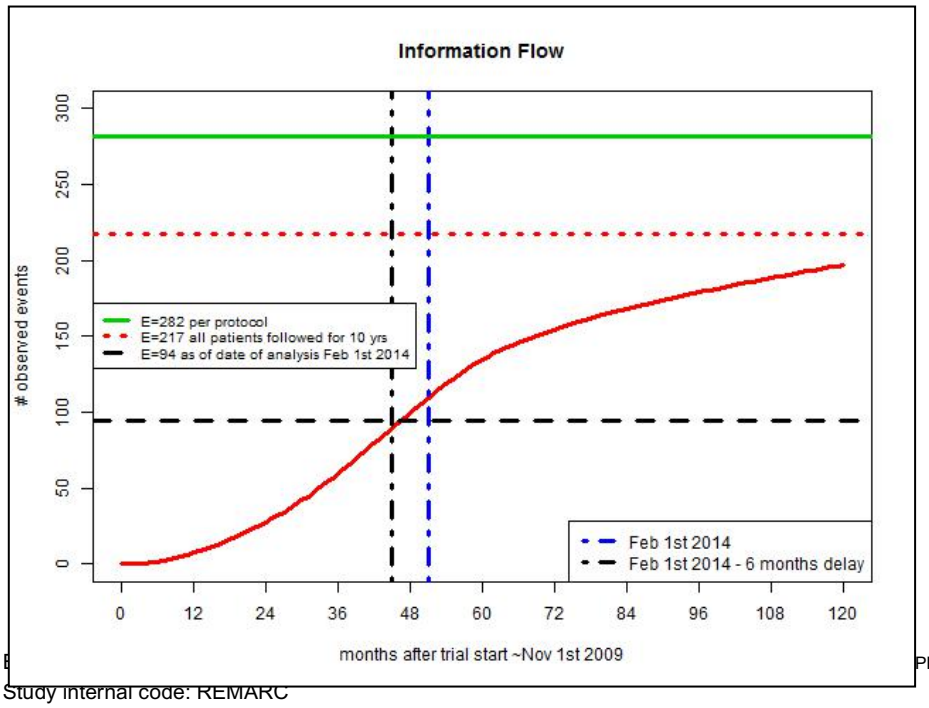
For secondary parameters, statistical tests will be two-sided and performed using a 5% level of significance. Given the exploratory nature of the analyses, no adjustment for multiple comparisons will be made.

10.7. SAMPLE SIZE CALCULATION

The DSMC met in June 2013 to monitor safety of the study. There were no safety concerns; however the DMSC recommended to re-evaluate the planned number of PFS events for the primary analysis due to lower number of events being observed. The DSMC observed that the PFS event rate was lower than envisaged in the protocol. Based on observed overall PFS curve (calculated with REMARC study blinded data), 2-year PFS rate is 80% instead of 69% assumed in the study protocol version6.

Figure 15.7.1 illustrated the projected cumulative number of progression/death events over time based on observed blinded data so far. Based in Figure 15.7.1 the originally targeted 287 PFS events (solid green horizontal line) will never be reached.

Figure 15.7.1: Simulation of the number of expected events during time (using projection from Remarc study blinded data)



As a result, the total number of progression/death events required for final PFS analysis is reduced from 287 to 160 events. With 160 events, it provides adequate power (80% or more) if the true Hazard Ratio is 1.55 or better (Placebo versus Revlimid).

The final analysis will occurred when the 160 events has been reached or at the latest when 5 years median follow-up has been achieved. The occurrence of the 160 events is projected to be around September 2016 (see Figure 15.7.1). At that time it is also projected to have 97 deaths for the interim OS analysis.

See more details on statistical approach used for this simulation in Appendix 20.14

Previous version indicating the sample size calculation which is not changed:

The primary analysis for the study is to compare progression free survival (PFS) between Treatment Arm A (lenalidomide) and Treatment Arm B (Placebo) using a group sequential log-rank test corresponding to 2 equally spaced analyses: one interim analysis at 50% information and one final at 100% information. The boundary for declaring superiority of Arm A over Arm B is based on an alpha-spending function of the O'Brien-Fleming type with overall α = 0.05, two-tailed. The boundary for stopping futility is based on an beta-spending function of the O'Brien-Fleming type with an overall 80% power and a 2-sided type I α = 0.05.

For the primary efficacy variable, PFS, an improvement in median PFS from 38.6 months for Treatment Arm B to 54 months for Treatment Arm A (corresponding to a 2-year PFS of 65% vs 73.6%), is considered clinically relevant.

It is assumed that the overall PFS distribution is exponential with a constant failure (hazard) rate and that accrual is uniform during the accrual period (for the first 5 months and afterwards). It is also assumed that annual drop-out rate is about 6% and that the drop-out is exponentially distributed.

With a 50-month of accrual period and 25-month follow-up after the study closes to randomization, about 311 patients in each treatment group would have 80% power to detect a hazard rate ratio of 1.4 using a two-sided log rank test with overall significance level of 0.05 and significance level of 0.05 for the final analysis (adjusted for one interim analysis).

Therefore a total of approximately 621 patients will be randomized, with accrual of about 6 patients the first 5 months and then 13 patients per month.

Full information necessary for a log rank test to have 80% power will be achieved when approximately 282 patients across all treatment arms have progressed or died (PFS).

Additional cut-off for overall survival will be set when 278 deaths have been observed or at least when the number of events for PFS (287) has been reached or at the latest when the last patient into the study will finish follow up.

With an estimate of a median survival of 63 months in Treatment Arm A and 45 months in Treatment Arm B, assuming the survival distribution is exponential, for 621 randomized patients overall, a total of 278 deaths would be expected in the two arms. In a test of survival curves reflective of a 40% improvement in median OS, a two-sided log rank test at the 0.05 significance level performed when there are 278 deaths in the two arms would have a power of 80%.

Overall survival will be compared approximately 78 months after the first patient randomized. There were not enough events to perform a relevant simulation of the updated schedule for this analysis.

The table below gives the nominal two-sided p-values for rejecting the null hypothesis or the alternative corresponding to the O'Brien-Fleming boundaries.

Analysis	*Bound for efficacy*	*Reject Null Hypothesis if p less than or equal to*	*Bound for futility*	*Reject Alternative Hypothesis if p more than or equal to*
Interim (50%)	*2.963*	*0.003*	*0.348*	*0.7275*

Final Analysis	*1.951*	*0.051*	*1.951*	*0.051*

Calculations were performed using East5, Cytel Inc.

11. ETHICAL AND REGULATORY STANDARDS

11.1. ETHICAL PRINCIPLES

This protocol 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.

11.2. LAWS AND REGULATIONS

This protocol is also in accordance with laws and regulations of the country(ies) in which the trial is performed, as well as any applicable guidelines.

11.3. INFORMED CONSENT

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

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. It must be made completely and unambiguously clear to each patient that they are free to refuse to participate in the study, or that they can withdraw their consent at any time and for any reason, without incurring any penalty or withholding of treatment on the part of the investigator. Patients 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/ randomization process will be documented in each patient's medical records.

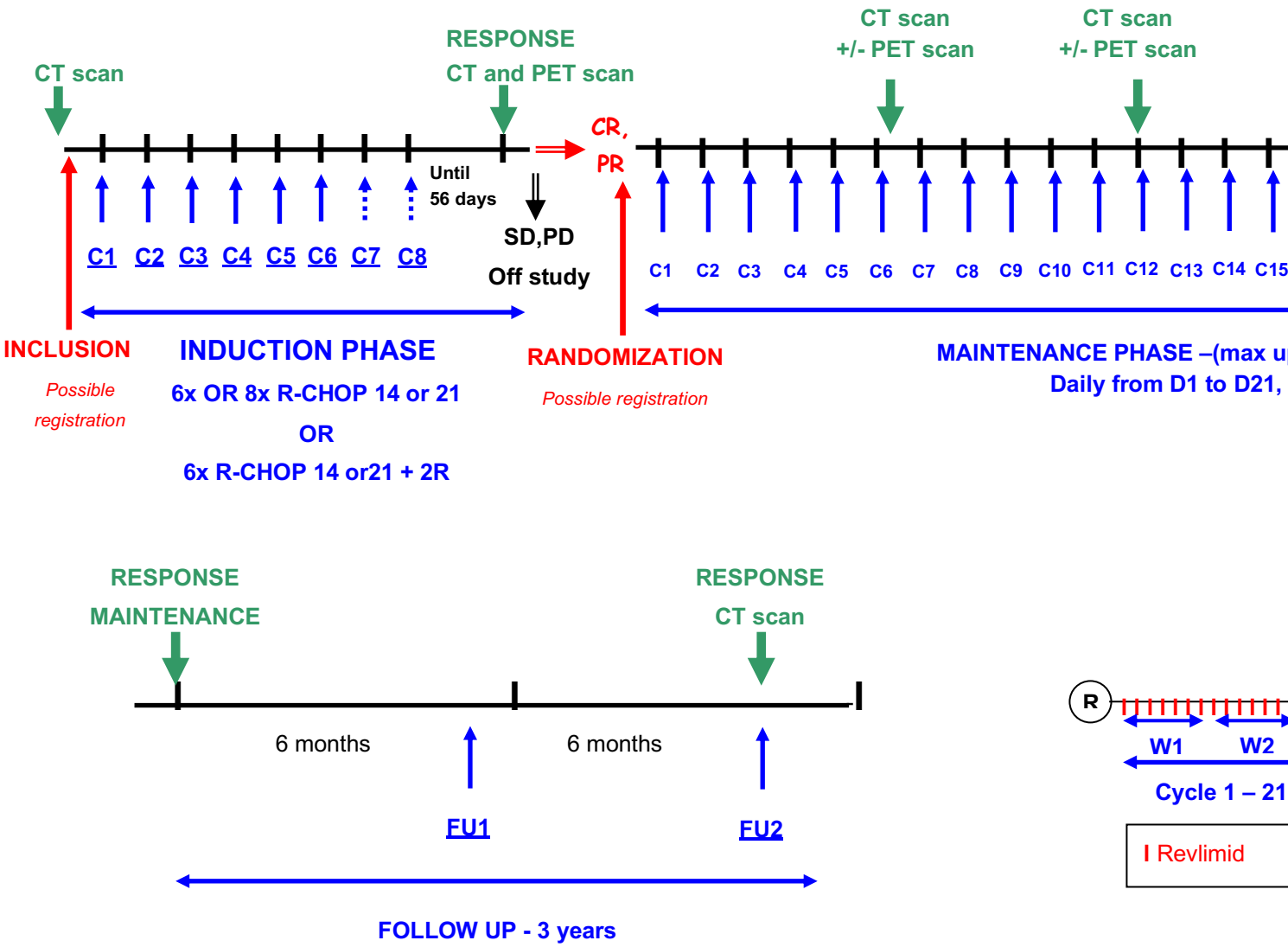
The informed consent document used by the investigator for obtaining patient's informed consent must be reviewed and approved by LYSARC prior to Ethical Committee / IRB submission.

11.4. ETHICS REVIEW COMMITTEE (ERC) 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.

12. APPENDICES

12.1. APPENDIX B: STUDY FLOW CHART



12.2. APPENDIX C: SCHEDULE OF EVALUATIONS

Events	Screening	INDUCTION PHASE	Evaluation for Randomization (Cheson 2007)	@	MAINTENANCE PHASE	EVALUATION END OF TTT (Cheson 2007)	FOLLOW-UP (Cheson 2007)
Date	within 30 days before first dose	Before each cycle	Within 56 days after the day 1 of last cycle of CT			Within 2 months after last drug administration	every 6 months, during at least 3 years
Informed consent	X						
Inclusion/Non inclusion criteria	X						
Patient characteristics	X(a)						
Physical examination (including vital signs)	X		X		X(h)	X	X
Complete relevant medical history	X						
ECOG PS	X		X		X(h)	X	X
Serologies HIV, HCV, HBV	X						
Serum electrophoresis	X						
Cardiac exams (ECG and echo)	X						
Cervical, Chest, abdomen, pelvis CT with oral and IV contrast	X(b)		X		X (L)	X	X(g)
PET scan	X(b) not mandatory		X		X (J)		
Any Other procedure if clinically relevant	X	X	X		X	X	X
Bone marrow biopsy	X		X(f)			X(f)	X(f)
Complete Blood cell counts	X		X		X(i)	X	X
Clinical biochemistry	X(d)		X(e)		X(e)(h)	X(k)	
Samples for genetic and proteomic analyses	X			X (n)			
PBMC Cytometry	X			X	X (m)		
QlQ-C30 questionnaire				X	X (L)	X	X (g)
Stratification			X				
Concomitant medications					X		
Adverse events (AE)					X		

@ Stratification and randomization

(a) Demographic, weight, height, body surface area, stage and extend of the current disease,
(b) May be performed up to 28 days before first dose of study drug.
(c) May be performed up to 56 days before first dose of study drug.
(d) Calcium, sodium, potassium, creatinine, creatinine clearance, LDH, ALT, AST, total bilirubin, alkaline phosphatase, β2-microglobuline
(e) Calcium, sodium, potassium, creatinine, creatinine clearance, LDH, ALT, AST, total bilirubin,
(f) Bone marrow biopsy to be performed to assess CR in patients with a positive bone marrow result

at screening (not required for patients with already cleaned bone marrow at previous evaluation)

(g) once a year after end of maintenance

(h) Day 1 of each cycle for the first 3 cycles, then every 3 cycles.

(i) Once a week during the first cycle then every 2 weeks (D1 and D15) at cycle 2 and cycle 3 and then at day 1 for each cycles thereafter.

(j) PET scan if positive at randomization

(k) Calcium, sodium, potassium, creatinine, creatinine clearance, LDH, ALT, AST

(l) At cycle 6, cycle 12 and cycle 21

(m) At 6 months of maintenance

(n) If blood samples were not carried out with Inclusion and if applicable according to country.