DISCLOSURE

REDACTED PROTOCOL AMENDMENT 4

CC-5013-DLC-002

PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTICENTER STUDY TO COMPARE THE EFFICACY AND SAFETY OF LENALIDOMIDE (CC-5013) PLUS R-CHOP CHEMOTHERAPY (R2-CHOP) VERSUS PLACEBO PLUS R-CHOP CHEMOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED ACTIVATED B-CELL TYPE DIFFUSE LARGE B-CELL LYMPHOMA

The "ROBUST" Study

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PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTICENTER STUDY TO COMPARE THE EFFICACY AND SAFETY OF LENALIDOMIDE (CC-5013) PLUS R-CHOP CHEMOTHERAPY (R2-CHOP) VERSUS PLACEBO PLUS R-CHOP CHEMOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED ACTIVATED B-CELL TYPE DIFFUSE LARGE B-CELL LYMPHOMA

The "ROBUST" Study

INVESTIGATIONAL PRODUCT (IP):	**Lenalidomide (CC-5013)**
PROTOCOL NUMBER:	**CC-5013-DLC-002**
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Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

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Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

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PROTOCOL SUMMARY

Study Title

Phase 3 Randomized, Double-Blind, Placebo Controlled, Multicenter Study to Compare the Efficacy and Safety of Lenalidomide (CC-5013) Plus R-CHOP Chemotherapy (R2-CHOP) Versus Placebo Plus R-CHOP Chemotherapy in Subjects with Previously Untreated Activated B-cell Type Diffuse Large B-cell Lymphoma

Indication

Previously untreated, activated B-cell (ABC) type diffuse large B-cell lymphoma (DLBCL).

Objectives

To evaluate the efficacy and safety of lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R2-CHOP) chemotherapy versus placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (placebo-R-CHOP) chemotherapy in subjects who have previously untreated ABC type DLBCL.

Study Design

This randomized, placebo controlled study is designed to evaluate the efficacy and safety of R2-CHOP chemotherapy versus placebo-R-CHOP chemotherapy in previously untreated ABC type DLBCL. The study is divided into the Screening Period, Treatment Period, and Follow-up Period. Approximately 560 subjects will be randomized over approximately a 34-month accrual period.

The Screening Period for eligibility determination may begin after the subject signs the informed consent form. During the Screening Period subjects will undergo safety and other assessments, including central pathology confirmation of DLBCL diagnosis and determination of ABC type. Following confirmation of eligibility, subjects will undergo randomization to either the experimental or control arm in a 1:1 ratio.

The Treatment Period begins with Cycle 1 Day 1 dosing. Subjects will receive protocol-specified treatments for 6 cycles. Treatment will continue to completion; or until the outcome of the computed tomography (CT) scan at Midcycle (between Weeks 9 – 12 which is after Cycle 3 but before Cycle 4) indicates a treatment change based on response assessment; disease progression; unacceptable toxicity; death; or withdrawal of consent, whichever occurs first. End of Treatment is defined as the later date of either End of Lenalidomide/Placebo or End of R-CHOP.

The Follow-up Period for each subject begins immediately after their End of Treatment date. Subjects will be followed for first and second progressions, subsequent antilymphoma therapy, development of any second primary malignancies (SPMs), and overall survival (OS) according to the schedule described in Table 5. After the 12 Apr 2019 primary analysis, subjects will only be followed for SPM and OS data collection.

The pharmacokinetic (PK) substudy is designed to evaluate the PK of lenalidomide when co-administered with and without R-CHOP. It will be conducted at selected sites and will be optional for subjects at those sites. Approximately 20 subjects will be included in the PK substudy.

Study Population

Subjects must have a diagnosis of ABC type DLBCL, be previously untreated, have at least one measurable lesion by CT scan, and have adequate liver, renal, cardiac, and bone marrow function.

Length of Study

The primary analysis will occur when the required 192 progression free survival (PFS) events (progressions/deaths) in the intent-to-treat (ITT) population have occurred, which is approximately 42 months from the start of enrollment. After the primary analysis, those subjects who are alive will still be followed exclusively for second primary malignancies and overall survival for up to 5 years from the date the last subject is randomized. The total study duration is approximately 8 years (34 months accrual period + 5 years SPM follow-up).

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

Study Treatments

Study treatments in a 21-day cycle are: lenalidomide / placebo Days 1 – 14; rituximab, cyclophosphamide, doxorubicin, and vincristine Day 1; prednisone Days 1 – 5. Refer to Table 7 for complete details.

Overview of Efficacy Assessments

The International Working Group (IWG) Response Criteria for non-Hodgkin's lymphoma (NHL) (Cheson, 2014), and the Deauville Criteria for scan interpretation (Itti, 2013; Meignan, 2013), will be used for efficacy assessments. The local investigator will perform real time efficacy review to guide subject management, with the exception of the assessment performed 3 – 4 weeks after Cycle 6 which will be reviewed in real time by the Independent Response Adjudication Committee (IRAC). The IRAC will also perform a subsequent batched review of all assessments. Additional efficacy evaluation includes a CT scan to support disease restaging at Midcycle (once between Weeks 9 – 12 which is after Cycle 3 but before Cycle 4).

Overview of Safety Assessments

Safety will be monitored throughout the study. Safety evaluations will include adverse event (AE), SPM, and concomitant medication assessment, physical examinations, vital sign measurements, and clinical laboratory safety tests.

Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report any SPMs as serious adverse events (SAEs), regardless of causal relationship to investigational product (IP) (lenalidomide, placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, or prednisone), occurring at any time for the duration of the study, from the time of signing the Informed Consent Document (ICD) for up to 5 years from the date the last subject is randomized.

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1. INTRODUCTION

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of lenalidomide.

1.1. Diffuse Large B-cell Lymphoma

Diffuse large B-cell Lymphoma is a distinct histological type within mature B-cell NHL that is characterized by large tumor cells and aggressive clinical behavior. This type accounts for approximately 31% of all newly diagnosed malignant lymphomas (Armitage, 1998).

CHOP chemotherapy in combination with the anti-CD20 monoclonal antibody rituximab on a 21-day schedule is a standard of care in newly diagnosed cases in most countries worldwide (Feugier, 2005; Ketterer, 2013). In the GELA study of R-CHOP versus CHOP front line therapy in elderly subjects, following R-CHOP treatment the 5-year event-free survival (EFS) was 47%, the 5-year progression free survival (PFS) was 54%, and the 5-year overall survival (OS) was 58% (Feugier, 2005). While approximately 50% to 60% of patients are cured (Feugier, 2005; Micallef, 2011), for those patients who are refractory or who progress following R-CHOP, treatment options are limited and outlook is poor; most die within the next two years. Since roughly 40% to 50% of patients are not cured on initial therapy, evaluating other front line treatment options is warranted. Other attempts to improve cure rate, including R-ACVBD, CHOEP, dose dense regimens (R-CHOP14), and high dose regimens (DA-EPOCH), have not replaced R-CHOP21 as a standard of care (Ketterer, 2013; Micallef, 2011; Recher, 2011).

1.2. Biological and Clinical Significance of DLBCL Typing

As initially described by Staudt and colleagues, DLBCL is composed primarily of two biologically distinct pathophysiologic entities (Alizadeh, 2000). The authors classified DLBCL by gene expression profiling (GEP) into the germinal center B-cell (GCB) and the activated B-cell (ABC) types, derived from different cells of origin. Subsequently, an additional type was noted by GEP called type III, (Rosenwald, 2002), which has since been renamed as unclassifiable type. Although GEP is now capable of discerning all three types, GCB, ABC, and unclassifiable; immunohistochemistry (IHC) is capable of discerning only two, GCB and non-GCB. The less precise IHC method groups ABC and unclassifiable together as the non-GCB type. The Lymphoma/Leukemia Molecular Profiling Project reported approximately 60% GCB and 40% non-GCB (including ABC and unclassifiable) in 240 newly diagnosed DLBCL subject biopsy samples examined by GEP (Fu, 2008; Lossos, 2004; Rosenwald, 2002).

The different DLBCL types have been reported to have different clinical outcomes with CHOP (Rosenwald, 2002) and R-CHOP (Fu, 2008) therapy, supporting the concept that these are distinct clinical and molecular subtypes. In the first line setting the 5-year OS rates for the GCB, unclassifiable, and ABC types were 60%, 39%, and 35%, respectively, with CHOP treatment (Rosenwald, 2002). With R-CHOP, the 3-year EFS for GCB and non-GCB subtypes was 67% and 52% respectively, and the 3-year OS was 85% and 69%, respectively (Fu, 2008). With R-CHOP and predominantly higher risk patients (IPI 0/1 = 21%, IPI 2/3 = 63%, and IPI 4/5 = 15%) the median PFS for the ABC type was 1.5 years (Lenz, 2008). In the relapsed setting, the prognosis appears to be approximately the same for both the GCB and non-GCB subtypes

(Costa, 2008; Wilson, 2008), which may possibly reflect the selection of GCB subjects with poorer prognosis not cured initially by R-CHOP.

1.2.1. GCB versus ABC Gene Expression Profiling Assay Used in This Protocol

The cell of origin (COO) as characterized by GEP and performed on fresh tissue biopsy samples is considered a gold standard. However defining COO is not currently the routine diagnostic work-up in clinical practice. Moreover, it is not a practical method for subject selection in clinical trials due to the fresh biopsy sample requirement as well as the substantial time and technological expertise required to perform the assay.

This protocol will use a validated GEP based assay performed on with formalin-fixed paraffin-embedded (FFPE) biopsy material to identify eligible subjects with the required ABC type. The was validated against the original COO model defined by Lenz (Lenz, 2008) using an independent cohort of 68 FFPE biopsies. In the validation cohort the assay was accurate, as only one case with definitive COO was incorrectly assigned by and robust, with >95% concordance of COO assignment between two independent laboratories (Scott, 2014). Although the assay is technically verified, it has not received marketing approval by a health authority beyond being *Conformité Européenne* (CE) marked in the European Union (EU). The assay is being developed as a companion diagnostic to lenalidomide in conjunction with the assay manufacturer, . Analytical assay validation is not a part of this CC-5013-DLC-002 protocol.

1.3. Biomarkers in DLBCL

1.3.1. Biomarkers in DLBCL Pathogenesis

In recent years a number of chromosomal rearrangements, acquired mutations, or aberrant expression of genes coding for proteins as well as for micro ribonucleic acid (miRNA) have been identified in DLBCL. Many are associated with a particular DLBCL subtype or yield prognostic information. For example, BCL2 is a commonly affected gene in the GCB subtype, and EZH2 is also mutated in the GCB subtype (Morin, 2010; Schuetz, 2012). Activation of NF-κB and mutation of MYD88 are more common in the ABC type (Compagno, 2009; Ngo, 2011). Co-expression of MYC/BCL2 is associated with a very aggressive clinical course in both subtypes, although it has been reported to be more common in the ABC type (Green, 2012; Hu, 2013; Johnson, 2012). Additionally, mutations in MYC, CDKN2A, SOCS1, MYD88, CARD11, TP53, and other genes have demonstrated prognostic information in patients with DLBCL receiving front line treatment (Gisselbrecht, 2012; Horn, 2013; Jardin, 2008; Schif, 2013). Single nucleotide polymorphisms (SNPs) are also reported to be associated with prognosis (Ding, 2013; Li, 2013).

1.3.3. Mechanistic Biomarkers

Recent research on the mechanism of action of lenalidomide, pomalidomide, and thalidomide suggest that in tumor cells and T cells, cereblon, a component of E3 ubiquitin ligase complexes, is a target for binding by these compounds. These studies showed that the loss of cereblon or a binding partner, such as DDB1, decreases or eliminates the antitumor and immunomodulatory activity of lenalidomide and pomalidomide (Ito, 2010; Zhu, 2011; Lopez-Girona, 2012). A number of recent studies have reported correlation between pre-treatment levels of cereblon measured by GEP or by IHC methods to clinical outcomes in subjects treated with regimens containing lenalidomide, pomalidomide or thalidomide. Very recently multiple groups have described Aiolos (*IKZF3*) and Ikaros (*IKZF1*) as two direct substrates of the CRL4 CRBN E3 ligase complex. These proteins act as transcriptional repressors in T-cells and are also drivers of proliferation in multiple myeloma (MM) cells (Lu, 2013; Gandhi, 2013; Krönke, 2013).

1.4. Preclinical Data on Lenalidomide in DLBCL

There is biological plausibility and also preclinical data that provide strong support for why lenalidomide should be expected to significantly enhance the efficacy of the current standard of care R-CHOP in the treatment of the ABC type of DLBCL.

In DLBCL cell line models, lenalidomide preferentially suppresses the proliferation of ABC cells in vitro and delays tumor growth in a human tumor xenograft model, with minimal effect on GCB cells. This tumoricidal effect was associated with down-regulation of interferon regulatory factor 4 (IRF4, also known as MUM1), a hallmark of ABC cells (Zhang, 2013). IRF4

inhibition by lenalidomide induced down-regulation of B-cell receptor (BCR)-dependent NF-κB, and this effect was reported to require co-expression of cereblon, a molecular target of lenalidomide (Zhang, 2013). It has also been reported that NF-κB mediates resistance to chemotherapy and that decreased NF-κB expression may restore sensitivity to chemotherapy agents (Bottero, 2001; Luo, 2005). Independently, Yang also reported on the activity of lenalidomide in ABC type DLBCL cell lines (Yang, 2012). Lenalidomide killed ABC cells by augmenting autocrine interferon beta (IFN-ß) production, which was dependent on oncogenic MYD88 mutations in these lymphomas. In a cereblon-dependent fashion, lenalidomide down-regulated IRF4 and SPIB transcription factors which repress IFN-ß production.

In addition to the direct antitumor effects on the ABC tumor cells, lenalidomide exerts potent immunomodulatory activity. Preclinical studies have shown an enhancement of antibody dependent cell mediated cytotoxicity (Wu, 2008) and antitumor effects in vivo (Hernandez-Ilizaliturri, 2005; Zhang, 2009) when lenalidomide was combined with rituximab. In a murine NHL model, lenalidomide induced significant increase in the recruitment of NK cells to tumor sites, resulting in enhanced antitumor activity of rituximab (Reddy, 2007). When combined with rituximab, lenalidomide improved survival in a mouse NHL model and the antitumor activity was shown to be NK cell-mediated (Hernandez-Ilizaliturri, 2005).

Preclinical studies suggest that lenalidomide may promote restoration of antitumor immunological effects in patients with certain hematological malignancies. Impaired T-cell immunological synapse formation has been reported in chronic lymphocytic leukemia (CLL), follicular lymphoma (FL) and DLBCL patients and is thought to be a mechanism of cancer immune evasion (Ramsay, 2008; Ramsay, 2009). Lenalidomide treatment of the T-cells and the tumor cells collected from these patients repaired the immune synapse defects by enhancement of the F-actin synapse. In vitro studies have shown that lenalidomide induced actin cytoskeleton reorganization and polarization of NHL cells as early as 30 minutes, a process termed “capping,” which is considered an important subcellular component of the immune synapse formation (Gaidarova, 2009). Additionally it has been shown that the combined use of lenalidomide and rituximab enhances NK cell-mediated immune synapse formation and the resultant cytotoxicity, versus using each agent alone. Lenalidomide induces CD20-localization within the “cap,” and the addition of rituximab can enhance immune synapse formation (Gaidarova, 2009). The capping of CD20 is accompanied by redistribution of other proteins that become part of the immune synapse complex. Therefore, the capping process induced by lenalidomide appears integral to immune synapse formation and may coordinately enhance the clustering of both the CD20 antigen and the attached rituximab, potentially further enhancing its activity, which would support the clinical combination of these agents.

1.5. Clinical Efficacy Data on Lenalidomide in DLBCL

1.5.1. Relapsed / Refractory DLBCL

Single agent lenalidomide activity in relapsed or refractory DLBCL subjects has been noted in two Celgene-sponsored single arm clinical trials in aggressive NHL: study CC-5013-NHL-002 (Wiernik, 2008) and study CC-5013-NHL-003 (Witzig, 2011). Data from both studies were combined for a revised analysis of 134 DLBCL subjects as study design was nearly identical and subject baseline characteristics were similar. Results showed an overall response rate (ORR) of

26.1% (35/134), a median PFS of 2.7 months, and a median response duration of 6.0 months (Czuczman, 2010). In these clinical trials, COO typing was not conducted.

Hernandez-Ilizaliturri et al reported in a retrospective analysis of 40 relapsed/refractory aggressive NHL subjects (34 DLBCL, 6 composite/transformed DLBCL) treated with single agent lenalidomide at Roswell Park Cancer Institute, Mayo Clinic, University of Bologna, and Hackensack University that there was a preferential clinical activity of lenalidomide in patients with the non-GCB subtype DLBCL (Hernandez-Ilizaliturri, 2011). The tumor response rate was 52.9% (5 CR, 4 PR) in the non-GCB subtype (n=17) compared to 8.7% (1 CR, 1 PR) in the GCB subtype (n=23). Median PFS for lenalidomide was 6.2 months for the non-GCB and 1.7 months for the GCB subtype (p=0.004). There were no differences in age, disease stage at time of treatment, international prognostic index (IPI) scores, or number of prior therapies between the GCB and non-GCB groups.

These observations led to the CC-5013-DLC-001 Phase 2/3 randomized clinical trial of single agent lenalidomide versus investigator's choice in subjects with relapsed/refractory DLBCL in GCB and non-GCB subtypes. In this trial, subjects with relapsed DLBCL underwent GCB versus non-GCB typing during the screening phase, and the typing information was used to assign subjects to two different cohorts defined by the subtype. The subjects were then randomized to receive lenalidomide or single agent of investigator choice. This study is still ongoing.

At the time of planned final analysis (N=102 mITT; 54 non-GCB, 48 GCB), the CC-5013-DLC-001 study showed a statistically significant improvement of median PFS for lenalidomide versus investigator's choice treatment in the non-GCB subtype as assessed by the IRAC (control 7.1 weeks versus lenalidomide 15.2 weeks; p = 0.021, HR [95% CI] = 0.50 [0.27, 0.92]). There was a favorable trend in ORR as assessed by IRAC (control 11.5% versus lenalidomide 28.6%, p=0.179) and dORR (control 3.8% versus lenalidomide 21.4%, p = 0.102). There was also a favorable trend in median OS in the non-GCB subtype (control 20.4 weeks versus lenalidomide 32.3 weeks; p = 0.253, HR [95% CI] = 0.70 [0.38, 1.30]). Of note, 16/26 (61.5%) of non-GCB subjects in the control arm crossed over to lenalidomide upon radiological evidence of disease progression on the comparator treatment (Czuczman, 2014).

The CC-5013-DLC-001 study also included exploratory objectives related to gene expression profiling. If medically feasible, subjects were required to provide a fresh frozen lymph node or tumor biopsy at study enrollment; biopsies for 65 subjects were provided. Samples were then typed as ABC, GCB, or unclassifiable using Affymetrix U133 Plus 2.0 GeneChip microarrays. At the time of planned final analysis (N= 65 mITT, 27 ABC type, 8 unclassifiable type, 30 GCB type) the study showed a favorable trend in median PFS for lenalidomide versus investigator's choice treatment in the ABC type as assessed by IRAC (control 6.3 weeks versus lenalidomide 82.0 weeks; p = 0.105, HR [95% CI] = 0.44 [0.15 – 1.23]). There was also a favorable trend in median OS in the ABC type (control 18.6 weeks versus lenalidomide 108.4 weeks; p = 0.144, HR [95% CI] = 0.47 [0.17, 1.33]).

Taken together, these data of lenalidomide single agent in subjects with relapsed DLBCL suggest that lenalidomide has preferential activity in non-GCB and ABC types of DLBCL. Further evidence supporting this preferential activity in the non-GCB subtype is observed in preclinical models (Section 1.4).

1.5.2. Front Line DLBCL

The chemo-immunotherapeutic regimen of R-CHOP is a standard of care worldwide for the treatment of patients with newly diagnosed DLBCL. Two academic clinical research groups have developed the combination regimen of lenalidomide + rituximab + CHOP (R2-CHOP) in patients with newly diagnosed DLBCL: the Mayo Clinic Cancer Center in the US and the Italian cooperative group, Fondazione Italiana Linfomi (FIL).

1.5.2.1. Mayo Clinic R2-CHOP Data

Protocol MC078E is an investigator initiated Phase 1/2 study of R2-CHOP in subjects with newly diagnosed, previously untreated DLBCL and follicular grade IIIA/B B-cell lymphoma, sponsored by the Mayo Clinic.

The objective of the Phase 1 cohort of this study was to establish the maximum tolerated dose (MTD) of lenalidomide that could be combined with R-CHOP. A total of 24 subjects with newly diagnosed, untreated CD20-positive DLBCL or follicular grade III NHL were enrolled. Twenty of these 24 subjects had DLBCL. Subjects received oral lenalidomide on Days 1-10 with standard dose R-CHOP every 21 days. The lenalidomide dose levels tested were 15, 20, and 25 mg. The median age was 65 (35-82) years and 54% were over 60 years. Three subjects received 15 mg, 3 received 20 mg, and 18 received 25 mg of lenalidomide. No dose-limiting toxicity was found, and 25 mg on Days 1-10 was the recommended dose for the Phase 2 portion of this study. The incidence of Grade 4 neutropenia and thrombocytopenia was 67% and 21%, respectively. Febrile neutropenia was rare (4%) and there were no deaths due to toxicity. The ORR was 100% with a CR rate of 77%. It was concluded that lenalidomide at the dose of 25 mg/day administered on Days 1 to 10 of 21-day cycle can be safely combined with R-CHOP in the initial chemotherapy of aggressive B-cell lymphoma (Nowakowski, 2011).

Based on these phase 1 results, the phase 2 cohort of the study was conducted to assess the efficacy of this combination. Response was evaluated using positron emission tomography or computed tomography (PET/CT) by standard criteria (Cheson, 2007). The study is still ongoing; data from this study were presented at ASH 2012 and at the International Conference on Malignant Lymphoma (ICML) 2013 (Nowakowski, 2012, Nowakowski 2013). Sixty-seven subjects were accrued to the Phase 2 cohort with median follow up of 2.1 years; 55 (88%) subjects had previously untreated DLBCL. All subjects received R-CHOP21 for 6 cycles plus lenalidomide 25 mg (R2-CHOP) on Days 1 – 10 of each cycle. Although not prospectively planned, subjects were retrospectively subtyped by IHC using the Hans algorithm (Hans, 2004). Furthermore, 87 consecutive subjects with DLBCL and similar clinical characteristics participating in the Mayo Clinic Lymphoma Database and treated with standard R-CHOP alone served as a contemporaneously matched control. Table 1 below describes the baseline characteristics of the 55 DLBCL subjects treated with R2-CHOP in the Mayo Clinic phase 2 trial and the 87 subjects treated with R-CHOP as matched control. Subjects treated with R2-CHOP had fewer subjects with low IPI score and were also older as compared to the R-CHOP cohort.

Table 1: Mayo Clinic Study MC078E Baseline Characteristics

Characteristic	R2-CHOP (N=55)	R-CHOP (N=87)	P value
Age			
Median (range)	68 years (22-87)	61 years (41-86)	0.0077
Sex			
Male	38 (69.1%)	50 (57.5%)	0.1647
ECOG PS			0.6093
0	24 (43.6%)	32 (36.8%)	
1	25 (45.5%)	41 (47.1%)	
2	6 (10.9%)	11 (12.6%)	
3	0	3 (3.4%)	
Stage (Ann Arbor)			0.3213
II	8 (14.5%)	20 (23.0%)	
III	16 (29.1%)	14 (16.1%)	
IV	31 (56.4%)	53 (60.9%)	
IPI			0.0096
Low	3 (5.5%)	18 (20.7%)	
Low-intermediate	22 (40.0%)	16 (18.4%)	
High-intermediate	22 (40.0%)	38 (43.7%)	
High	8 (14.5%)	15 (17.2%)	
DLBCL Subtype (Hans)			n/a
GCB	34 (62%)	59 (68%)	
Non-GCB	21 (38%)	28 (32%)	

DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GCB = germinal center B-cell; IPI = international prognostic index (Nowakowski, 2013).

Safety data of the R2-CHOP regimen showed the most common Grade 3 and 4 toxicities with R2-CHOP were neutropenia (12% Grade 3, 74% Grade 4), thrombocytopenia (30% Grade 3, 16% Grade 4), anemia (20% Grade 3, 0% Grade 4), febrile neutropenia (12% Grade 3, 0% Grade 4), pneumonia (2% Grade 3, 0% Grade 4), sepsis (0% Grade 3, 2% Grade 4), venous thrombosis (0% Grade 3, 2% Grade 4), fatigue (2% Grade 3, 0% Grade 4) and dehydration (2% Grade 3, 0% Grade 4). Overall, R2-CHOP is considered well tolerated (Nowakowski, 2013).

Efficacy data from 51 evaluable subjects treated with R2-CHOP showed CR 73%, PR 27%, ORR 100% (Table 2), and 3-year PFS 65% overall. The ORR, CR, and PFS compare favorably with the matched control cohort Figure 1.

Although not prospectively planned, subjects were retrospectively subtyped as GCB or non-GCB by IHC using the Hans algorithm (Hans, 2004). Table 2 summarizes the phase 2 efficacy data for the overall population and also by GCB vs. non-GCB subtype reported thus far (Nowakowski, 2012, Nowakowski 2013). In non-GCB subjects, the ORR and CR were better in subjects treated with R2-CHOP when compared with the subjects treated with R-CHOP (ORR 100% vs 69%; CR 80% vs 50%). This level of difference was not observed in the GCB subtype.

An updated manuscript was recently published (Nowakowski, 2015).

Table 2: Mayo Clinic Study MC078E Efficacy Results

	R2CHOP[1] N=55		**R-CHOP "control"[2] N=87**	
ORR	51/51 (100%)		68/83 (82%)	
CR	37/51 (73%)		56/83 (67%)[3]	
PR	14/51 (27%)		12/83 (14%)	
	GCB N=31	**Non-GCB N=20**	**GCB N=57**	**Non-GCB N=26**
ORR	31 (100%)	20 (100%)	50 (88%)	18 (69%)
CR	23 (74%)	16 (80%)	43 (75%)	13 (50%)
PR	8 (26%)	4 (20%)	7 (12%)	5 (19%)
NR/PD	0 (0%)	0 (0%)	7 (12%)	8 (31%)

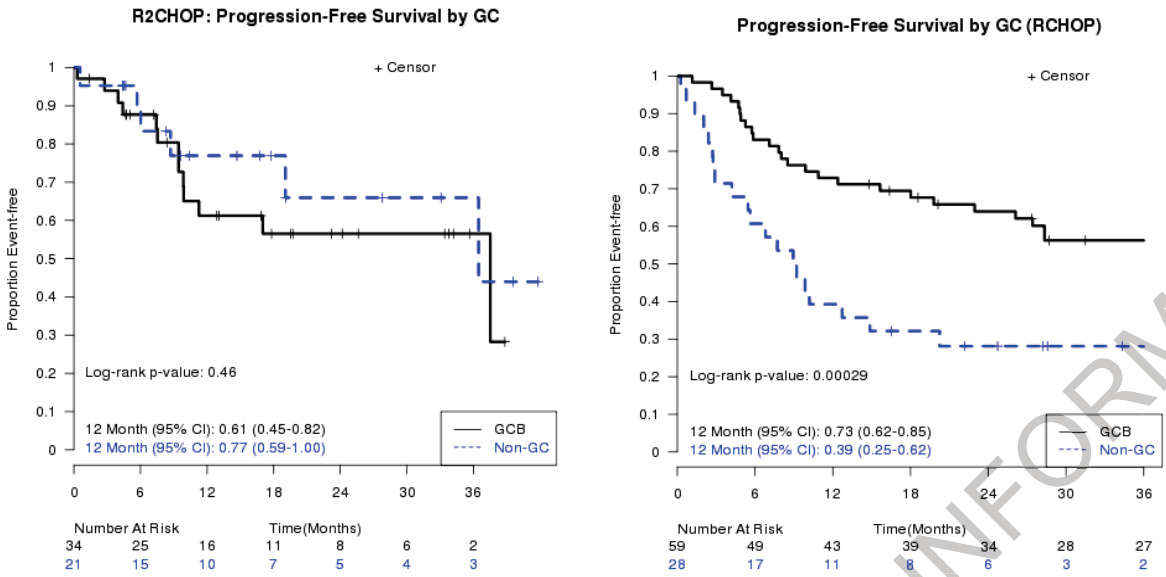
CR = complete response; GCB = germinal center B-cell; NR = no response; ORR = objective response rate; PD = progressive disease; PR = partial response (Nowakowski, 2013).

[1] Assessment by Cheson 2007 criteria; 4 subjects were not evaluable because of refusal (n=3) or death before evaluation (n=1)

[2] Assessment by Cheson 1999 criteria; 4 subjects unevaluable for response assessment

[3] Including CR=54, complete response unconfirmed (CRu)=2

Figure 1: Mayo Clinic Study MC078E PFS by Subtype



GC = germinal center; GCB = germinal center B-cell; (Nowakowski, 2013).

1.5.2.2. FIL R2-CHOP Data

The Italian cooperative group FIL conducted a prospectively designed multicenter phase 1/2 study to evaluate the toxicity and efficacy of lenalidomide plus R-CHOP21 in untreated elderly DLBCL subjects, the REAL07 trial.

The objective of the Phase 1 cohort of the REAL07 trial was to determine the maximum tolerated dose of this combination. Four lenalidomide doses (5, 10, 15, and 20 mg/day on Days 1-14) using the continual reassessment method were planned in combination with each course of R-CHOP for a total of 6 courses. Seven subject cohorts (n=3 each) were treated (total n=21) at 10, 20, 15, 15, 15, 10, and 10 mg of lenalidomide. Dose-limiting toxicities occurred in seven subjects during the first three treatment courses. The third dose-level of lenalidomide (15 mg/day) was selected as the maximum tolerated dose, with an estimated dose-limiting toxicity probability of 0.345 (95% credibility interval 0.164-0.553). Grade 3-4 hematologic adverse events were: neutropenia in 28% of the courses, thrombocytopenia in 9%, and anemia in 3%. Non-hematologic toxicities were moderate: grade 4 increase of creatinine phosphokinase (n=1), grade 3 cardiac (n=2), grade 3 neurologic (n=3), and grade 3 gastrointestinal (n=1). In this phase 1 study, 90% of subjects achieved an overall response with 81% achieving complete remission. It was concluded that this combination is tolerable in elderly DLBCL subjects, and lenalidomide given at 15 mg on Days 1-14 of each cycle in combination with standard R-CHOP21 was the recommended dosing schedule for Phase 2 study (Chiappella, 2013a). Nine subjects were treated at this dosing schedule in the Phase 1 cohort.

Phase 2 of the REAL07 trial was a study to investigate the efficacy of R2-CHOP in CD20+ elderly DLBCL or FL grade IIIB subjects. Key inclusion criteria included age 60-80, Ann Arbor stage II-IV, and IPI $\geq$ 2. The primary endpoints were ORR and CR rate after 6 courses of R2-CHOP by using Cheson, 2007 criteria and included PET negativity as a requirement for CR. The secondary endpoints were 2-year OS, 2-year PFS, and relationship between response and

histopathological features. Subjects were treated with lenalidomide given at 15 mg on Days 1-14 of each cycle in combination with standard R-CHOP21 for 6 cycles. Subjects were retrospectively subtyped by IHC using the Hans algorithm (Hans, 2004), although this analysis was not prospectively planned.

Forty subjects were enrolled. The phase 2 cohort data analyses included these 40 subjects plus 9 subjects from the phase 1 cohort treated at the recommended phase 2 dose/schedule (total N=49). Table 3 describes the subject baseline characteristics.

Table 3: FIL Study REAL07 Baseline Characteristics

R2-CHOP, N = 49			
Median age (range)	69 (61-79)	Bone marrow	17 (35%)
Male	29 (59%)	B symptoms	21 (43%)
Stage III/IV	8/35 (16/71%)	LDH > normal	22 (45%)
PS ≥1	31 (63%)	IPI IH/H risk	29 (59%)
DLBCL/FLgIIIb	45/3 (92/8%)	β2m > normal	34 (69%)

PS = performance status, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, LDH = lactase dehydrogenase, IPI = international prognostic index, IH = intermediate / high risk, H = high risk, β2m = beta 2 microglobulin (Chiappella, 2013b).

The most significant common hematological toxicities recorded in 277 cycles of treatment were neutropenia (9% grade 3, 22% grade 4), leukocytopenia (15% grade 3, 13% grade 4), febrile neutropenia (3% grade 3, 1%, grade 4), thrombocytopenia (5% grade 3, 7% grade 4), and anemia (4% grade 3, < 0.5% grade 4) (Chiappella, 2013b).

Table 4 summarizes the response data reported thus far from the REAL07 trial, for the 40 subjects enrolled in the phase 2 cohort plus 9 subjects from the phase 1 cohort treated at the recommended phase 2 dose/schedule (total N=49). The overall results for all 49 subjects showed a CR rate of 86%, ORR 92%, 2-year PFS 73%, and 2-year OS 92%.

Among these 49 subjects, GCB vs. non-GCB typing assignment was achieved in 34 subjects (17 subjects with GCB, and 17 subjects with non-GCB) by Hans criteria (Table 4). The CR rate in subjects with non-GCB subtype appears to be better than the in GCB subtype subjects (88% vs 76%). In addition, as was observed in the Mayo Clinic study, among the subjects treated with R2-CHOP regimen, the PFS and OS curves of the subjects with the non-GCB subtype appear to be about the same as or better than the GCB subtype subjects, suggesting that adding lenalidomide to standard therapy improved treatment outcome in non-GCB subjects who have a poor prognosis and typically have a worse outcome to treatment (Figure 2).

An updated manuscript was recently published (Vitolo, 2014).

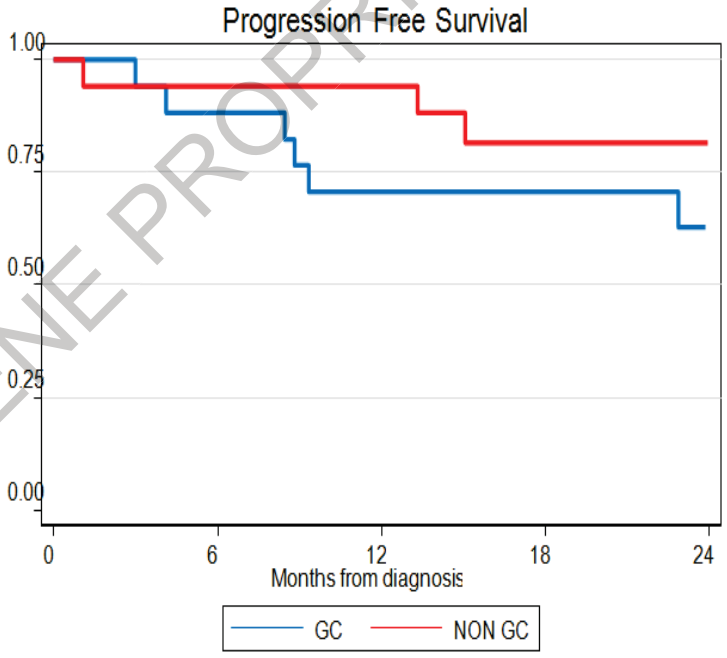
Table 4: FIL Study REAL07 Efficacy Results

	Total N=49	GCB N=17	Non-GCB N=17
ORR	45/49 (92%)	15/17 (88%)	15/17 (88%)
CR	42/49 (86%)	13/17 (76%)	15/17 (88%)
PR	3/49 (6%)	2/17 (12%)	0/17
NR	3/49 (6%)	2/17 (12%)	1/17 (6%)
NA (death)	1/49 (2%)	0/17	1/17 (6%)
PFS	73%[1] (95% CI: 57-84)	71%[2] (95% CI: 43-87)	81%[2] (95% CI: 53-94)
OS	92%[1] (95% CI: 79-97)	88%[2] (95% CI: 59-97)	94%[2] (95% CI: 65-99)

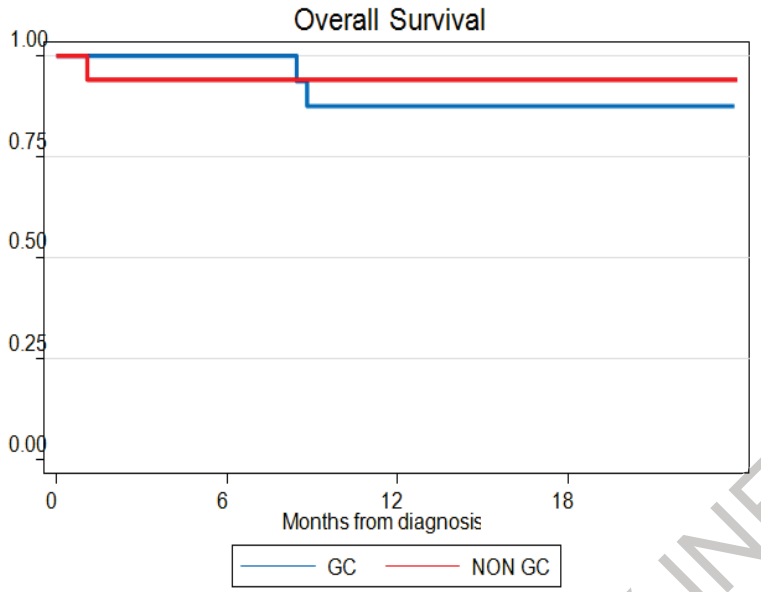
ORR = overall response rate, CR = complete response, PR = partial response, NR = no response, NA = not applicable, PFS = progression free survival, OS = overall survival (Chiappella, 2013b).
[1] At 2-years
[2] At 18 months

Figure 2: FIL Study REAL07 PFS and OS by Subtype

A. PFS



B. OS



GC = germinal center (Chiappella, 2013b).

1.5.3. Clinical Efficacy Data Conclusion

In summary, the R2-CHOP efficacy data from the Mayo Clinic MC078E study and the FIL REAL07 study compare favorably to historical R-CHOP21 data with a better CR rate at the end of induction therapy and better PFS. Furthermore, promising efficacy results were also demonstrated in the non-GCB subtype, which generally has a poorer outcome when treated with R-CHOP alone. Clinically meaningful improvements as demonstrated by higher CR rate (80% in Mayo study, 88% in FIL study, vs 50% in the R-CHOP historical control) and longer PFS (18-month PFS of 80% in Mayo study, 81% in FIL study vs 30% in 87 subjects from Mayo Clinic Lymphoma Database who were treated with R-CHOP as matched control) in non-GCB DLBCL subjects are considered significant in this difficult to treat sub-population. The addition of lenalidomide could ameliorate the poor prognosis effect of the ABC phenotype and improve treatment outcome in this subgroup of subjects.

From a safety perspective, this combination is tolerable, without unexpected toxicities. The Grade 3 and 4 toxicities are primarily hematological in nature, and manageable with supportive care.

1.6. Clinical Safety Events of Interest for Lenalidomide

1.6.1. Deep Vein Thrombosis

1.6.1.1. Deep Vein Thrombosis in Multiple Myeloma

Venous thromboembolic events (VTE), such as deep venous thrombosis (DVT) and pulmonary embolism (PE), have occurred in subjects with multiple myeloma treated with lenalidomide combination therapy, and in subjects with MDS or lymphoma treated with lenalidomide

monotherapy. A significantly increased risk of DVT and PE has been observed in subjects with multiple myeloma who were treated with lenalidomide and dexamethasone therapy (see Revlimid prescribing information). Clinical data in multiple myeloma subjects treated with lenalidomide suggests that concomitant administration of gluco-corticosteroids or erythropoietin can increase the thrombotic risk. Male gender and smoking history have also been reported to increase the risk of VTE in myeloma subjects treated with lenalidomide (Leleu, 2011).

In two randomized studies (MM-009 and MM-010) a significantly increased risk of DVT and PE was seen in subjects with multiple myeloma who were treated with REVLIMID® (lenalidomide) in combination with dexamethasone (see Revlimid Prescribing Information). In these pivotal trials for lenalidomide in subjects with multiple myeloma receiving lenalidomide plus dexamethasone, DVT and PE were reported as SAEs in 7.4% and 3.7% of subjects, respectively, compared to 3.1% and 0.9% of subjects receiving placebo and dexamethasone. The protocols did not require systematic DVT prophylaxis. An analysis of pooled data from the MM-009 and MM-010 studies demonstrated that thromboembolic events were significantly higher in subjects treated with lenalidomide/dexamethasone in the absence of prophylactic use of an anticoagulant ($p < 0.001$) (Dimopoulos, 2009). The effect of adding erythropoietin to lenalidomide/ dexamethasone demonstrated a higher, but not statistically significant rate of thrombosis in the erythropoietin group 18% versus 10% for the lenalidomide/dexamethasone group without the addition of erythropoietin ($p=0.14$) (Weber, 2007).

The Eastern Cooperative Oncology Group (ECOG) trial E4A03 evaluated lenalidomide 25 mg on Days 1-21 plus high-dose dexamethasone 40 mg on Days 1-4, 9-12 and 17-20 of a 28-day cycle (RD) versus lenalidomide plus low-dose dexamethasone 40 mg on Days 1, 8, 15, and 22 (Rd) in subjects with newly-diagnosed multiple myeloma. Overall, VTEs including DVT and PE occurred in 26% of 223 subjects in the RD arm and in 12% of 220 subjects in the Rd arm (Rajkumar, 2010). DVT prophylaxis was to be used in both arms.

1.6.1.2. Deep Vein Thrombosis in Non-Hodgkin's Lymphoma

Factors known to increase thrombotic risk in cancer patients in general, not necessarily those receiving lenalidomide, include the underlying disease, family history, immobilization, hormonal therapy, central venous catheter placement, recent DVT, doxorubicin and other factors (Zhou, 2010; Park, 2012; Lyman, 2013).

Venous thrombotic events, including DVT and PE, have been reported in patients during treatment for NHL, generally occurring at incidences from ~7% up to 20% (Komrokji, 2006; Mohren, 2005; Ottinger, 1995; Zhou, 2010). The risk is significantly higher for females, patients with renal dysfunction or high hemoglobin levels, and patients receiving doxorubicin- or methotrexate-based regimens (Zhou, 2010). Ottinger et al analyzed incidence, risk factors, causes and prognostic significance of VTE in high-grade NHL in a prospective clinical trial of 593 subjects. They reported a 6.6% incidence of VTE, with 77% of all cases occurring before or within the first 3 months of chemotherapy. Vessel compression by high-grade NHL was identified as the leading cause of VTE (Ottinger, 1995).

In lymphoma lenalidomide clinical trials, DVT and PE were reported in 7 (2.6%) and 6 (2.2%) of 266 subjects with relapsed or refractory aggressive NHL receiving lenalidomide in clinical studies NHL-002 and NHL-003 (Wiernik, 2008; Witzig, 2011). In clinical study NHL-001, DVT and PE were reported in 0 (0%) and 1 (2.3%) of 43 subjects with indolent relapsed or

refractory NHL (Witzig, 2009). Antithrombotic prophylaxis was not suggested in NHL-001 or NHL-002 but was required for subjects considered to be at high risk of developing DVT in NHL-003. In the recent CALGB 50401 Phase 2 study evaluating lenalidomide plus rituximab versus lenalidomide single-agent therapy in relapsed FL subjects (N=89), thrombosis was reported in 2 (4%) of 44 subjects in the lenalidomide plus rituximab arm versus 7 (16%) of 45 subjects in the lenalidomide arm (Leonard, 2012). In a study evaluating lenalidomide plus rituximab in relapsed / refractory mantle cell lymphoma (MCL) subjects (n=44), 3 thromboembolic events were reported (2 [5%] Grade 3; 1 [5%] Grade 4) after 379 cycles of lenalidomide plus rituximab (Wang, 2012).

In two front line DLBCL clinical trials evaluating lenalidomide plus R-CHOP, VTE rates were reported. In REAL07 (n=49), which required LMWH heparin as VTE prophylaxis, the Grade 3 VTE rate was 2% and the grade 4 rate was 0% (Chiappella, 2012). In a Mayo Clinic study (n=47) which required 325 mg aspirin daily as VTE prophylaxis, the grade 3 VTE rate was 0% and the grade 4 rate was 2% (Nowakowski, 2015).

It cannot be excluded that the risk of VTE is increased in the subjects participating in this study treated with R-CHOP and lenalidomide. For recommendations on VTE prophylaxis in the present study see Section 9.3.6.

1.6.2. Tumor Flare Reaction

Tumor flare reaction (TFR) is defined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3 as a constellation of signs and symptoms of tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances in direct relation to initiation of therapy (Cancer Therapy Evaluation Program, 2003).

TFR is an adverse effect of lenalidomide previously reported in subjects with CLL (Chanan-Khan, 2008a). In clinical studies of lenalidomide in subjects with NHL, TFR has also been reported, but at a lower rate than in CLL patients (Corazzelli, 2010; Eve, 2010; Witzig, 2011). The clinical manifestations of TFR seen in subjects treated with lenalidomide are similar for CLL and lymphoma subjects, and typically occur in the first cycle. Symptoms include a sudden increase in the size and tenderness of the disease bearing sites, including the lymph nodes, spleen and/or the liver, often accompanied by pain and sometimes accompanied by low-grade fever and non-pruritic diffuse rash (Chanan-Khan, 2008a; Witzig, 2009). The increase in lymphadenopathy may be localized or generalized. In lymphoma patients, TFR is not usually accompanied by lymphocytosis. The onset of TFR has been as early as within a few hours after the first dose, but in the vast majority of cases is within the first 2-3 weeks of the first cycle (Witzig, 2009). Tumor flare reaction can recur to a lesser extent if the dose is increased (Witzig, 2009). Based on experience in Celgene-sponsored clinical studies, TFR subsides over time and usually resolves in 1-2 weeks with or without intervention (Witzig, 2009).

TFR data on single-agent lenalidomide in over 400 subjects with relapsed or refractory aggressive or indolent NHL who received lenalidomide in four Celgene sponsored Phase 2 clinical studies (NHL-001, NHL-002, NHL-003, and MCL-001) are now available. These were Phase 2 multicenter, single-arm, open-label studies that evaluated lenalidomide 25 mg/day for 21 days of a 28-day cycle. In NHL-001 there were 43 previously treated subjects with indolent NHL (Witzig, 2009), in NHL-002 49 subjects with relapsed/refractory aggressive NHL

(Wiernik, 2008), in NHL-003 217 subjects with relapsed/refractory aggressive NHL (Witzig, 2011), and in MCL-001 134 subjects with MCL (Goy, 2012). Tumor flare reaction occurred in 4 subjects (Grade 1 [n = 1] and Grade 2 [n = 3]) in the NHL-001 study; none in the NHL-002 study; 7 of 217 subjects in the NHL-003 study (Grade 1 [n = 2], Grade 2 [n = 2] and Grade 3 [n = 3]); and 13 of 134 subjects in the MCL-001 study (Grade 1 [n = 7], and Grade 2 [n = 6]). The data from these protocols suggested that subjects experienced TFR during the first 1 to 2 weeks of Cycle 1 and that the TFR may be treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDs).

In a single-center, open-label Phase 2 investigator initiated study, Ahmadi et al evaluated the use of lenalidomide, dexamethasone and rituximab (cohort 1) versus lenalidomide plus rituximab (cohort 2) in subjects with relapsed or refractory indolent B-cell or MCL resistant to rituximab (Ahmadi, 2011). Tumor flare was reported in 12 (5 in cohort 1 and 7 in cohort 2) of the 45 subjects (MCL and FL).

It is important to note that the increased lymphadenopathy seen in TFR may mimic progressive disease (PD). Therefore, careful monitoring and evaluation to differentiate TFR from PD is necessary for addressing treatment of individual subjects including making decisions whether to discontinue treatment (Chanan-Khan, 2008b). There are currently no laboratory or radiological tests that distinguish TFR from PD. The distinction may be made on clinical grounds, incorporating observations such as timing of the event relative to the start of lenalidomide, associated physical findings, laboratory findings, and pace of disease before and after institution of lenalidomide treatment. Also, in the case of TFR, inflammation and edema may be reduced or disappear after short-term treatment with NSAIDs and/or corticosteroids.

1.6.3. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a well-known constellation of metabolic abnormalities resulting from spontaneous or treatment-related tumor necrosis or fulminant apoptosis. The metabolic abnormalities include: hyperkalemia, hyperuricemia and hyperphosphatemia with secondary hypocalcaemia with risk of renal failure. TLS has been reported in subjects receiving rituximab plus lenalidomide, and rituximab plus chemotherapy.

The presence of known risk factors such as bulky disease, pre-existing (moderate) renal insufficiency, high ALC and high uric acid levels (> 8 mg/ dL) prior to therapy are known to increase the likelihood of TLS. Early identification of subjects at risk, initiation of prophylactic measures, as well as the careful monitoring for early signs of laboratory TLS, and prompt initiation of supportive care are critical to prevent potentially life-threatening metabolic derangements (Cairo, 2010).

The experience with tumor lysis syndrome in Celgene-sponsored studies of single-agent lenalidomide in NHL is summarized below. Four Phase 2 multicenter, single-arm, open-label studies evaluated lenalidomide 25 mg/day for 21 days of a 28-day cycle: NHL-001 in 43 previously treated subjects with indolent non-Hodgkin lymphoma (Witzig, 2009), NHL-002 in 49 subjects with relapsed/refractory aggressive NHL (Wiernik, 2008), NHL-003 in 217 subjects with relapsed/refractory aggressive NHL (Witzig, 2011), and MCL-001 in 134 subjects with relapsed/refractory MCL (Goy, 2012). All four protocols suggested that subjects receive TLS prophylaxis (allopurinol or equivalent) and be well hydrated during the first 7 days of

lenalidomide administration in the first cycle or as clinically indicated. Grade 1 TLS occurred in 1 of the 433 (< 0.3%) subjects receiving lenalidomide.

In an investigator initiated study, a single-center, open-label Phase 2 study, Dutia et al (Dutia, 2010) evaluated the use of lenalidomide and rituximab in subjects with relapsed or refractory indolent B-cell NHL. Two of the first 4 subjects treated using the lenalidomide dose of 25 mg developed TLS. Thus, the lenalidomide dose was reduced to 20 mg and allopurinol prophylaxis was used in all subsequent subjects with no further TLS events recorded.

For recommendations on TLS prophylaxis in the present study see Section 9.3.5.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to compare the efficacy of R2-CHOP versus placebo-R-CHOP.

2.2. Secondary Objective

The secondary objective of this study is to compare the safety of R2-CHOP versus placebo-R-CHOP.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- Progression-free Survival (PFS)

3.2. Secondary Endpoints

Key secondary endpoint

- Event-free Survival (EFS)

Other secondary endpoints

- Overall Survival (OS)
- Complete Response (CR) rate
- Duration of CR
- Time to next lymphoma therapy (TTNLT)
- Objective response rate (ORR)
- Health-related quality of life (HRQoL) as measured by the EuroQol 5 Dimension Scale (EQ-5D) and the Functional Assessment of Cancer Therapy for Patients with Lymphoma (FACT–Lym) standardized measures of health status

4. OVERALL STUDY DESIGN

4.1. Study Design

This randomized, placebo-controlled study is designed to evaluate the efficacy and safety of R2-CHOP chemotherapy versus placebo-R-CHOP chemotherapy in subjects with previously untreated CD20+, ABC type DLBCL. Stratification for randomization will be employed to reduce bias related to subject IPI score, presence of bulky disease, and age. Randomization in this parallel treatment design is in a 1:1 ratio to either R2-CHOP or placebo-R-CHOP. Celgene, as well as the investigator and subject, will be blinded to treatment assignment.

This study is divided into Screening (4.1.2), Treatment (4.1.3) and Follow-up Periods (4.1.7). Details of the study treatments are described in Section 8.

Approximately 560 subjects will be randomized. Subjects who discontinue or withdraw from the study will not be replaced. There is one planned interim analysis for futility at 50% information level and one planned final analysis for superiority. See Section 10 for a detailed description of Statistical Analyses.

The study will be conducted in compliance with Good Clinical Practice (GCP).

4.1.2. Screening Period

Screening for eligibility determination may begin after the subject signs the informed consent form. All screening assessments must be completed within 28 days prior to Cycle 1 Day 1. The only exceptions to the 28-day time period are for the lymph node/tumor biopsy and the bone marrow biopsy/optional aspirate, which may occur up to 8 weeks prior to C1D1; and the PET and CT scans, which may occur up to 6 weeks prior to C1D1.

During the Screening Period, subjects will undergo safety and other assessments to determine eligibility for the study as shown in Section 5 Table of Events and as described in detail in Section 6 Procedures. If subject eligibility is confirmed, then randomization via the interactive voice response system (IVRS) is the final part of the Screening Period. Pre-specification of optional therapies such as the extra two doses of single agent rituximab or consolidation radiotherapy will also be registered in IVRS prior to randomization.

Key aspects of screening include Central Pathology assessment of disease diagnosis, typing by GEP, and CD20+ status; local assessment of bone marrow involvement by lymphoma;

documentation of measurable disease by CT scan; collection of a PET scan; and verification of adequate liver, renal, cardiac, and bone marrow function.

4.1.3. Treatment Period

The Treatment Period begins with the first dose of lenalidomide/placebo or of the chemotherapy drugs as described in Section 8. Subjects will receive protocol-specified treatments for 6 cycles, and if standard of care per local practice, may also receive two additional doses of single agent rituximab if pre-specified in IVRS prior to randomization. Treatment will continue to completion, or until the outcome of the Midcycle CT scan (once between Weeks 9 – 12 which is after Cycle 3 but before Cycle 4) indicates a treatment change; disease progression; unacceptable toxicity; death; or withdrawal of consent, whichever occurs first.

In order to manage toxicity and allow subjects to complete 6 cycles of treatment, dose delay and modification rules will be followed (Section 8). Key aspects of ongoing safety monitoring include physical exam, AE assessment, and hematology/chemistry laboratory testing prior to the initiation of every cycle, and at additional time points as shown in the Table of Events, Table 5.

Key aspects of ongoing efficacy assessment include: CT scans at Screening, Midcycle (once between Weeks 9 – 12 which is after Cycle 3 but before Cycle 4), once between 3 – 4 weeks after completing Cycle 6, and in follow-up at specified time points; and PET scans at Screening and once 3 – 4 weeks after completing Cycle 6. A subject's withdrawal from study treatment due to the outcome of the Midcycle CT scan or for disease progression will be based upon investigator assessment. However, the response evaluation 3 – 4 weeks after completing cycle 6 will be based on real time IRAC review per Section 4.1.5.

4.1.4. Treatment Decisions Based on Midcycle CT Scan

Following the Midcycle CT scan, it is acceptable to change therapies if the CT shows evidence of lack of response or progression.

Only a CT scan is required for the Midcycle assessment. If a combined PET-CT is performed, measurements, response assessment, and treatment decisions should be based on the diagnostic quality CT portion of the PET-CT scan. If a combined PET-CT without contrast is performed, then progression may not be scored on PET positivity alone, but must be confirmed by CT with contrast or a biopsy of the PET positive lesion. As noted by the ICML Imaging Working Group, the positive predictive value of an interim PET in DLBCL is variable; therefore, the decision to change therapies solely on the basis of Midcycle PET is not recommended, unless there is clear evidence of progression (Barrington, 2014).

4.1.5. Treatment Decisions Based on End of Treatment CT and PET Scans

After Cycle 6, response will be evaluated in real time by Central Radiology and this evaluation should guide immediate decisions regarding the subject's next treatment. The radiological assessment schedule is the same for *all subjects*, regardless of whether the optional two doses of single agent rituximab are administered. Therefore, the CT and PET scans required at 3 – 4 weeks after completing Cycle 6 must be completed before the optional Cycle 7 dose of rituximab is administered. The scans acquired 3 – 4 weeks after Cycle 6 should be forwarded immediately to Central Radiology. All prior scans should be sent to Central Radiology at that time if for some reason they were not forwarded already.

If a combined PET-CT is performed, measurements, response assessment, and treatment decisions should be based on the diagnostic quality CT portion of the PET-CT scan. If a combined PET-CT without contrast is performed, then progression may not be scored on PET positivity alone, but must be confirmed by CT with contrast or a biopsy of the PET positive lesion. The same modality should be used throughout all post-baseline assessment time-points for a given subject if possible.

4.1.6. End of Treatment Date

The End of Lenalidomide/Placebo Date is defined as the date of Cycle 6 Day 21 for subjects who complete 6 full cycles of lenalidomide/placebo treatment per protocol; or it is the date either the investigator or subject decided to permanently discontinue lenalidomide/placebo treatment. The End of R-CHOP Date is defined as the date of Cycle 6 Day 21 for subjects who complete 6 full cycles of R-CHOP treatment per protocol; or it is the date either the investigator or subject decided to permanently discontinue R-CHOP treatment. The optional, extra 2 doses of rituximab do not extend the End of R-CHOP Date. Study treatment includes both lenalidomide/placebo and R-CHOP, and these may be completed or discontinued at different times. Therefore, the End of Treatment Date is defined as the later date of either End of Lenalidomide/Placebo or End of R-CHOP.

4.1.7. Follow-up Period

The Follow-up Period for each subject begins immediately after their End of Treatment Date; this rule applies to *all* subjects. This includes subjects who complete the full course of treatment, who complete the full course of treatment plus the 2 extra dose of rituximab, who discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new antilymphoma/salvage therapy (chemotherapy, SCT, radiotherapy, etc.). Note that a subject receiving the 2 extra doses of rituximab would be in the Follow-up period during receipt of the last 2 rituximab doses. Subjects will be followed for first and second progressions, subsequent antilymphoma therapies, development of SPMs, and overall survival according to the schedule described in Table 5. CT scans continue at the protocol specified time points until first progression and must be submitted to Central Radiology.

If a combined PET-CT is performed, measurements, response assessment, and treatment decisions should be based on the diagnostic quality CT portion of the combined PET-CT scan. If a combined PET-CT without contrast is performed, then progression may not be scored on PET positivity alone, but must be confirmed by CT with contrast or a biopsy of the PET positive lesion.

After the 12 Apr 2019 primary analysis, subjects will only be followed for SPM and OS data collection.

4.1.9. Independent and Central Assessment Committees

A Data Monitoring Committee (DMC) composed of oncologists and a biostatistician, who are all independent of and external to Celgene, will review ongoing safety data throughout the study according to the DMC charter, and may review interim efficacy data for futility. The DMC will make recommendations regarding the continuation of the study, potential amendments, or necessary safety measures.

An IRAC will review all CT and PET scans and relevant clinical data for efficacy assessment using the IWG Response Criteria for NHL (Cheson, 2014). Their retrospective, batched review will be the basis for efficacy endpoint calculations. Additionally, the IRAC will perform a real time review of scans collected 3 – 4 weeks after Cycle 6. Otherwise, eligibility assessment for inclusion criterion number 4 for measurable disease and response assessment will also be performed locally by the investigator and will guide enrollment and treatment decisions.

A Central Pathology laboratory will perform screening testing of lymph node / tumor biopsy samples to determine disease diagnosis, ABC versus GCB type, and CD20+ status. Their review will serve as the basis for determining eligibility for inclusion criterion number 1 and exclusion criterion number 2.

A Central Laboratory will perform hematology and chemistry testing of screening and on-study subject blood samples. Their results will be the basis for safety endpoint calculations. Central safety laboratory data will also be the primary guide for eligibility and subject management. However, local laboratory results may be used to guide clinical decisions and dose modifications, and if used, those data will also be collected.

4.2. Study Design Rationale

The worldwide standard of care in front line, advanced stage DLBCL is R-CHOP on a 21 day schedule for 6 – 8 cycles; this includes such countries as the US (NCCN, 2013), Canada (Cheung, 2007), Japan (Ishizawa, 2007), China (Lin, 2005), and countries in Europe (Feugier, 2005; Ghielmini, 2013; Tilly, 2012). Therefore, R-CHOP is the control arm drug selection.

The local standard practice in some countries / investigative sites is to give a total of 8 cycles of rituximab. Therefore in order to accommodate local practice in this global study, investigators may choose to give two additional doses of single agent rituximab at the end of the 6 cycles of R2-CHOP or placebo-R-CHOP induction therapy. However, to minimize bias, investigators are required to pre-specify this option in IVRS before randomization.

As discussed in Section 1.5, the PFS data from the REAL07 and Mayo Clinic studies, both in front line DLBCL GCB and non-GCB subtypes, are the basis for evaluating R2-CHOP in the present study (Chiappella, 2012; Nowakowski, 2015). The 3-year PFS rate of 65% for non-GCB subjects treated with R2-CHOP shown by the Mayo Clinic suggests that R2-CHOP is particularly active in the non-GCB subject group (Nowakowski, 2015), and is the basis for selecting only the ABC type of DLBCL for this study.

The REAL07 study in subjects aged 60 - 80 years tested lenalidomide at 15 mg on Days 1 – 14 per 21-day cycle whereas the Mayo Clinic study in subjects 18 or older tested lenalidomide at 25 mg on Days 1- 10 per 21-day cycle. Both studies treated subjects for 6 cycles and required pegfilgrastim prophylaxis for neutropenia and also required DVT prophylaxis. A comparison of

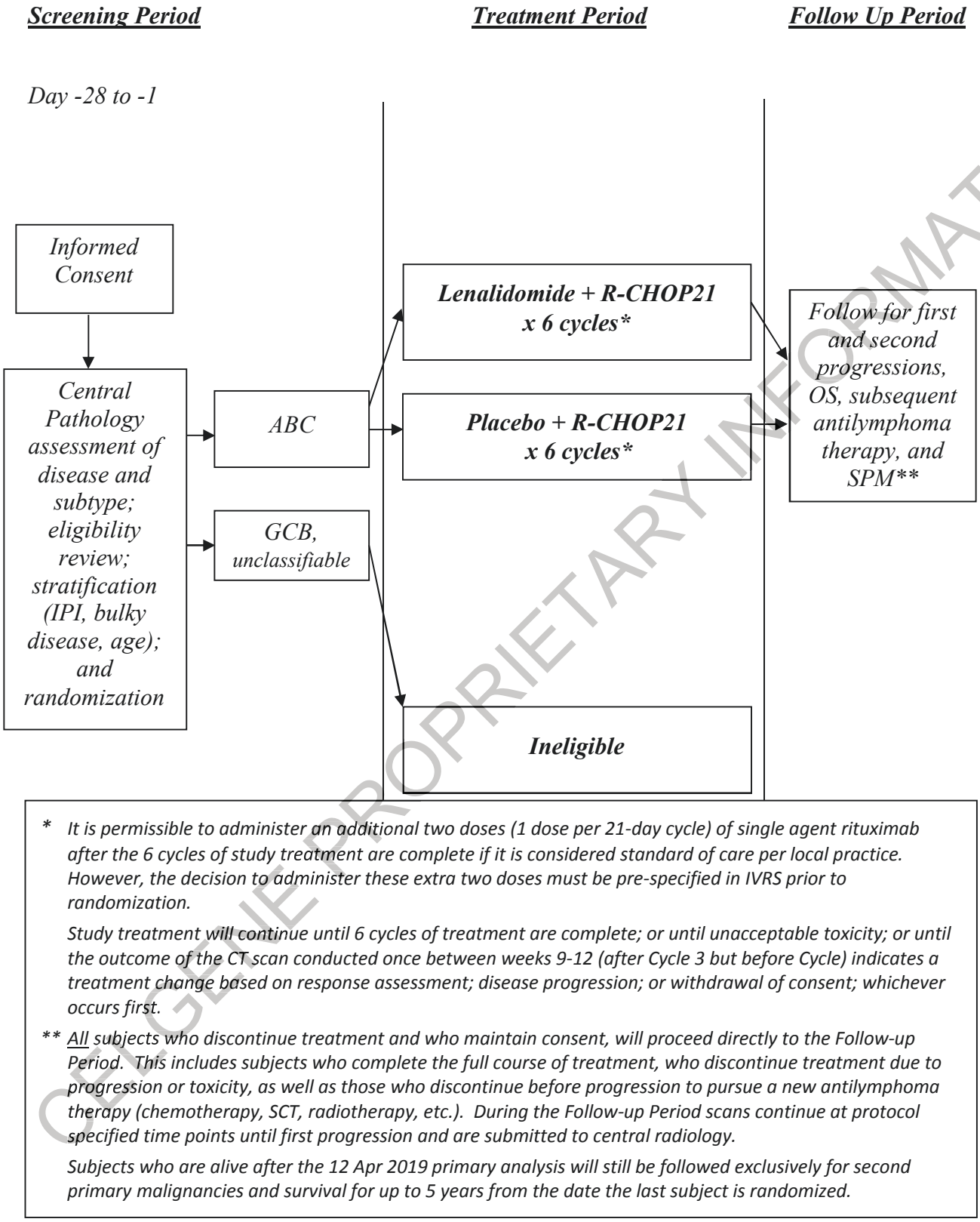
the most common, Grade 3 and 4 hematological toxicities of neutropenia, thrombocytopenia, anemia, and febrile neutropenia suggests that the 15 mg schedule is better tolerated (Chiappella, 2012; Nowakowski, 2015) and is the basis for the lenalidomide dose and schedule selected for this study.

Progression-free survival was selected as the study primary endpoint because it is a measure of clinical benefit most acceptable to regulatory authorities. PFS in the ITT population will be assessed by independent, centralized review.

Event free survival was selected as a key secondary endpoint because it is a measure of clinical benefit well accepted by clinicians in this disease setting. EFS captures information on what is considered failure of frontline chemotherapy (ie., R-CHOP), namely inadequate response such as stable disease or failure to achieve PET-negativity that often requires change in therapy and start of salvage therapy. On the other hand, the PFS endpoint does not capture such change in therapy as a PFS event. Depending on the exact definition of PFS, a subject who has inadequate response to front line therapy and thus changes to salvage therapy would either be censored or be recorded as not having a progression, requiring continued follow-up through subsequent lines of therapy until an actual progression of disease (tumor enlargement) is recorded. It is of note that in a recent meta-analysis of several clinical trials, both 3-year PFS and 3-year EFS were highly correlated with difference in 5-year OS (r_s of 0.90 [95% CI 0.73 – 0.96] (Lee, 2011).

The IWG response criteria were selected to provide an international standard for the assessment of lymphoma (Cheson, 2014). The use of this established tool and an IRAC will ensure that data across centers are evaluated consistently and will also allow for comparison to historical data.

Figure 3: Overall Study Design



* *It is permissible to administer an additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of study treatment are complete if it is considered standard of care per local practice. However, the decision to administer these extra two doses must be pre-specified in IVRS prior to randomization.*

Study treatment will continue until 6 cycles of treatment are complete; or until unacceptable toxicity; or until the outcome of the CT scan conducted once between weeks 9-12 (after Cycle 3 but before Cycle) indicates a treatment change based on response assessment; disease progression; or withdrawal of consent; whichever occurs first.

** *All subjects who discontinue treatment and who maintain consent, will proceed directly to the Follow-up Period. This includes subjects who complete the full course of treatment, who discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new antilymphoma therapy (chemotherapy, SCT, radiotherapy, etc.). During the Follow-up Period scans continue at protocol specified time points until first progression and are submitted to central radiology.*

Subjects who are alive after the 12 Apr 2019 primary analysis will still be followed exclusively for second primary malignancies and survival for up to 5 years from the date the last subject is randomized.

IPI= international prognostic index, ABC= activated B-cell, GCB= germinal center B-cell, OS=overall survival, SPM= second primary malignancy

4.3. Study Duration

The primary analysis will occur when the required 192 PFS events (progressions / deaths) in the ITT population have occurred, which is approximately 42 months from the start of enrollment. After the primary analysis, those subjects who are alive will still be followed exclusively for second primary malignancies and survival for up to 5 years from the date the last subject is randomized. Therefore, the study duration is approximately 8 years (34 month accrual period + 5 years SPM follow-up). See Section 10.3.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

5. TABLE OF EVENTS

Table 5: Table of Events

	Screening Period	Treatment Period			Follow-up Period
	Day -28 to Day -1	Cycles 1-6 Day 1 (+/- 3 days)	Cycles 1-2 Day 8 (+/- 3 days)	End of Treatment Visit (+/- 3 days)	Weeks 34,46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, 310 (± 2 weeks) until first progression
Informed Consent	X				
Complete Medical History	X				
Central Nervous System (CNS) Lymphoma Evaluation	X				
Hepatitis B Virus (HBV) Testing	X				
Hepatitis C Virus (HCV) Testing	X				
Creatinine Clearance (CrCl)	X				
Body surface Area (BSA) Calculation	X				
Electrocardiogram (ECG)	X				
Multiple Gated-Acquisition Scan (MUGA) / Echocardiography	X			X	
Saliva Sample	X				
Lymph Node / Tumor Biopsy	Within 8 weeks prior to C1D1				
Submit Lymph Node / Tumor Biopsy to Central Pathology	X				
Inclusion / Exclusion Criteria Review	X				

Detailed information for each row, if applicable, is provided in Section 6.

Table 5: Table of Events (Continued)

	Screening Period	Treatment Period			Follow-up Period
	Day -28 to Day -1	Cycles 1-6 Day 1 (+/- 3 days)	Cycles 1-2 Day 8 (+/- 3 days)	End of Treatment Visit (+/- 3 days)	Weeks 34,46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, 310 (± 2 weeks) until first progression
Pre-specify Optional Consolidation Radiotherapy and/or Additional Rituximab	X				
Randomization	X				
Modified Cumulative Illness Rating Scale (subjects >80 years)	X				
Physical Examination	X	X	X	X	X Required until the 12 Apr 2019 primary analysis
Vital Signs	X	X	X	X	
Complete Blood Count (CBC) with Differential	X	X	X	X	
Lactate Dehydrogenase (LDH)	X	X	X	X	
Serum Chemistry	X	X	X	X	
Thyroid Stimulating Hormone (TSH)	X			X	
Serum Immunoglobulin	X			X	
Lenalidomide Counselling	X	X			
Pregnancy Testing - for FCBP with Regular or No Menstrual Cycles	24 hours prior to lenalidomide/placebo dosing, and once during day -10 to -14	Weekly during first 28 days; every cycle on Day 1 thereafter		At End of Lenalidomide/Placebo and at 28 Days after End of Lenalidomide/Placebo	
Pregnancy Testing- for FCBP with Irregular Menstrual Cycles	24 hours prior to lenalidomide/placebo dosing, and once during day -10 to -14	Weekly during first 28 days; every cycle on Days 1 and 14 thereafter		At End of Lenalidomide/Placebo and at both 14 and 28 days after End of Lenalidomide/Placebo	

Detailed information for each row, if applicable, is provided in Section 6.

Table 5: Table of Events (Continued)

	Screening Period	Treatment Period			Follow-Up Period
	Day -28 to Day -1	**Cycles 1-6 Day 1 (+/- 3 days)**	**Cycles 1-2 Day 8 (+/- 3 days)**	**End of Treatment Visit (+/- 3 days)**	**Weeks 34,46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, 310 (± 2 weeks) until first progression**
Quality of Life Assessment	X	Once between Weeks 9–12, (after Cycle 3 but before Cycle 4)		Once 3 – 4 weeks after completing Cycle 6 (Prior to optional Cycle 7 rituximab)	X Required until the 12 Apr 2019 primary analysis
Performance Status	X	At Midcycle			
Computed Tomography (CT) Neck, Chest, Abdomen, Pelvis	Within 6 weeks prior to C1D1				
Response Assessment (Cheson, 2014)					
Positron Emission Tomography (PET) of Neck, Chest, Abdomen, Pelvis	Within 6 weeks prior to C1D1				
Bone Marrow Biopsy	Within 8 weeks prior to C1D1			Procedure is dependent on the post Cycle 6 PET scan results and is required only if Bone Marrow Biopsy is positive at Screening, and there is an equivocal post Cycle 6 PET scan finding in the bone marrow	
Bone Marrow Aspirate (optional)	Within 8 weeks prior to C1D1				

Detailed information for each row, if applicable, is provided in Section 6.

Table 5: Table of Events (Continued)

	Screening Period	Treatment Period			Follow-Up Period
	Day -28 to Day -1	**Cycles 1-6 Day 1 (+/- 3 days)**	**Cycles 1-2 Day 8 (+/- 3 days)**	**End of Treatment Visit (+/- 3 days)**	**Weeks 34,46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, 310 (± 2 weeks) until first progression**
Administer Investigational Product (IP) – Start Cycle		X (± 1 day)			
IP Accountability and Compliance		X		X	
Administer Mandatory Primary Neutropenia Prophylaxis		(1-3 days after chemotherapy or per local practice; details in Section 8.2.3)			
Tumor Lysis Syndrome (TLS) Assessment		Cycles 1 - 2 (same day as dosing)	X (± 1 day)		
Adverse Event	After signing the informed consent document through 28 days after last dose, which includes the optional two additional doses of single agent rituximab, if administered.				
Concomitant Medications / Procedures					
Subsequent Antilymphoma therapy and Progression	After signing the informed consent document until the subject has died, revokes consent, or until the 12 Apr 2019 primary analysis, whichever occurs first.				
Assessment of Second Primary Malignancy (SPM)	After signing the informed consent document until the subject has died, revokes consent, or for up to 5 years from the date the last subject is randomized, whichever occurs first.				
Survival Information					

Detailed information for each row, if applicable, is provided in Section 6.

6. PROCEDURES

Informed Consent must be obtained prior to performing any procedures specifically for this study that are beyond standard of care. The subject may withdraw consent at any time for all or certain aspects of the study as follows:

1. Withdraw consent for study treatment, but allow Follow-up Period assessments and data collection on subsequent antilymphoma therapy, PFS , SPM, and survival information.
2. Withdraw consent for study treatment and Follow-up Period assessments, but allow data collection on subsequent antilymphoma therapy, PFS , SPM, and survival information.
3. Withdraw all consent.

Central Nervous System (CNS) Lymphoma Evaluation will be performed at Screening. CNS involvement should be considered if paranasal sinus, testicular, epidural, or bone marrow sites are involved, or if there are ≥ 2 extra-nodal sites and elevated LDH. If CNS lymphoma is deemed possible by the investigator, then the subject is required to have a negative cerebrospinal fluid (CSF) cytology examination, and a head CT or MRI during Screening. Refer to Section 9.3.1 for permitted, concomitant CNS prophylaxis treatment.

Hepatitis B Virus (HBV) Testing will be performed at Screening by the Central Laboratory and includes hepatitis B surface antigen (HBsAg), antibody to the hepatitis B surface antigen (anti-HBs), and antibody to the hepatitis B core antigen (anti-HBc). If a subject is anti-HBc positive the Central Laboratory will automatically perform a quantitative polymerase chain reaction test to measure viral DNA load. If Screening Central Laboratory results are not available and treatment needs to be urgently started, then local laboratory results may be used to confirm eligibility, however the Celgene medical monitor must be consulted. Additionally, the data must be submitted to Celgene in the case report form (CRF) and the investigator must ensure that samples for the Central Laboratory are drawn before investigational product is administered and immediately sent to the Central Laboratory.

Hepatitis C Virus (HCV) Testing will be performed at Screening by the Central Laboratory on all subjects. If Screening Central Laboratory results are not available and treatment needs to be urgently started, then local laboratory results may be used to confirm eligibility, however the Celgene medical monitor must be consulted. Additionally, the data must be submitted to Celgene in the CRF and the investigator must ensure that samples for the Central Laboratory are drawn before investigational product is administered and immediately sent to the Central Laboratory.

For those who are HCV positive, the investigator must confirm that the subject is an acceptable candidate for R-CHOP therapy and does not have an active HCV infection or unacceptable liver damage as documented by one of the following options: FibroScan® (liver ultrasound for fibrosis), liver biopsy, zero RNA viral load by local laboratory, or other local practice test.

Creatinine Clearance will be assessed at Screening by the Central Laboratory. If Screening Central Laboratory results are not available and treatment needs to be urgently started, then local

laboratory results may be used to confirm eligibility, however the Celgene medical monitor must be consulted. Additionally, the data must be submitted to Celgene in the CRF and the investigator must ensure that samples for the Central Laboratory are drawn before investigational product is administered and immediately sent to the Central Laboratory. Creatinine clearance (CrCl) is estimated using the Cockcroft-Gault formula where CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]; for females, the formula is multiplied by 0.85 (Cockcroft, 1976).

Body Surface Area (BSA) will be calculated using the subject's height and weight according to local pharmacy practice. Height will be collected only at Screening; however, weight will be collected at the start of every cycle. It is up to pharmacist and investigator discretion whether BSA will be recalculated prior to preparing every cycle of chemotherapy from Cycle 2 onward, or whether the Screening / Cycle 1 BSA will be used throughout the study. If BSA is to be recalculated, the same calculation method should be used throughout the study per subject.

Electrocardiogram (ECG) will be performed at Screening to assess heart electrical function. If an ECG was performed as standard of care within 28 days of dosing, that data may be used to fulfill the eligibility requirement.

Multiple Gated-Acquisition Scan (MUGA) / Echocardiography will be performed at Screening and End of Treatment Visit to assess left ventricular ejection fraction (LVEF). If a MUGA/echocardiography was performed as standard of care within 28 days of dosing, that data may be used to fulfill the eligibility requirement. Note that MUGA is highly preferred, but if this testing modality is not available or is not standard local practice, then echocardiography will be acceptable.

Saliva Sample is to be collected in a 2 mL ORAgene kit tube during Screening. The sample is for germline mutational analysis and the results do not impact subject eligibility.

Lymph Node/Tumor Biopsy specimen preserved as a formalin-fixed paraffin-embedded block (FFPE) or unstained slides, and acquired within 8 weeks prior to C1D1, must be available. If submitting unstained slides, 15-20 are *highly recommend* in order to complete all testing. If an archival specimen is not available or is not acceptable, a re-biopsy is required prior to randomization. This procedure should be performed before initiating the optional pre-phase corticosteroid treatment. Refer to Inclusion Criterion 3 for more details on specimen acceptability. Refer to the laboratory manual for sample handling instructions.

Submit Lymph Node/Tumor Biopsy to Central Pathology. The Screening biopsy sample is to be submitted to Central Pathology during Screening with enough time planned to allow central confirmation of disease, subtype, and CD20 status. Central Pathology will review and provide biopsy results within three calendar days (includes Saturday and Sunday) of receiving a complete sample set, properly prepared and labeled, and accompanied by the correct paperwork.

Inclusion/Exclusion Criteria must be reviewed and cleared prior to randomization. Celgene corporate policy does not allow waivers to any eligibility criteria.

Pre-specify Optional Consolidation Radiotherapy and/or Additional Rituximab if applicable. If the investigator intends to administer optional consolidation radiotherapy (Section 8.2.2) and / or an optional two additional doses of single agent rituximab (Section 8.2.6 Rituximab), these must be pre-specified prior to randomization through the IVRS.

Randomization is accomplished through the IVRS, by a designated member of the investigator's staff once all eligibility criteria have been verified. Randomization is part of the Screening Period and may be completed up to 7 days prior to Cycle 1 Day 1 dosing (to allow pharmacy preparations) however, the Screening Period must not exceed 28 days.

Modified Cumulative Illness Rating Scale (CIRS) is to be assessed at Screening only for subjects >80 years of age. The following organ specific categories are assessed: heart; hypertension; vascular-hematopoietic; respiratory; eyes, ears, nose, throat, and larynx; upper gastrointestinal; lower gastrointestinal; liver and biliary trees; renal; genitourinary; musculoskeletal/integument; central and peripheral nervous system; endocrine-metabolic system and breast; psychiatric and behavioral diseases. DLBCL illnesses or disease related organ damage should not be assessed as part of this rating scale. If there are two or more illnesses/impairments in one organ category, the illness/impairment with the highest severity will be evaluated. Each organ category is scored separately according to Appendix 19.2 (Salvi, 2008a).

Physical Examination includes assessment of lymphadenopathy, hepatomegaly and splenomegaly, as clinically indicated. The exam is performed at Screening, at every cycle on Day 1, during Cycles 1 - 2 on Day 8, and at End of Treatment Visit. If the most recent protocol scheduled or unscheduled assessment was performed within 7 days prior to End of Treatment Visit, the assessment does not need to be repeated again at End of Treatment Visit. If a subject has discontinued treatment for any reason other than disease progression or death, the exam is required to continue during the Follow-up Period at Weeks 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, and 310 (± 2 weeks) until first progression or the 12 Apr 2019 primary analysis, whichever occurs first.

Vital Signs include blood pressure, pulse, and temperature and will be measured at Screening, every cycle on Day 1, during Cycles 1 - 2 on Day 8, and at End of Treatment Visit. If the most recent protocol scheduled or unscheduled assessment was performed within 7 days prior to End of Treatment, the assessment does not need to be repeated again at End of Treatment Visit. If a subject has discontinued treatment for any reason other than disease progression or death, the assessment is required to continue during the Follow-up Period at Weeks 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, and 310 (± 2 weeks) until first progression or the 12 Apr 2019 primary analysis, whichever occurs first.

Complete Blood Count (CBC) with Differential includes hemoglobin, hematocrit, white blood cell count (WBC) with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count. The test is performed at Screening, every cycle on Day 1, during Cycles 1-2 on Day 8, and at End of Treatment Visit. If a subject has discontinued treatment for any reason other than disease progression or death, the assessment is required to continue during the Follow-up Period at Weeks 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, and 310 (± 2 weeks) until first progression or the 12 Apr 2019 primary analysis, whichever occurs first.

At Screening, all CBC testing is performed by the Central Laboratory. If the Screening test is completed within 7 days of Cycle 1 Day 1 dosing, the test does not need to be repeated again on Cycle 1 Day 1. If Screening Central Laboratory results are not available and treatment needs to be urgently started, then local laboratory results may be used to confirm eligibility, however the Celgene medical monitor must be consulted. Additionally, the data must be submitted to

Celgene in the CRF and the investigator must ensure that samples for the Central Laboratory are drawn before investigational product is administered and immediately sent to the Central Laboratory.

After the Screening Period, testing continues by the Central Laboratory. However, in urgent cases, local laboratory results may be used to guide clinical decisions and dose modifications, however, that data must be submitted to Celgene in the CRF, and whenever possible, a concurrent sample should be sent to the Central Laboratory.

If the most recent protocol scheduled or unscheduled test was performed within 7 days prior to End of Treatment Visit, the test does not need to be repeated again at End of Treatment Visit.

Lactate Dehydrogenase (LDH) is performed at Screening, every cycle on Days 1, during Cycles 1-2 on Day 8, and at End of Treatment Visit. If a subject has discontinued treatment for any reason other than disease progression or death, the assessment is required to continue during the Follow-up Period at Weeks 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, and 310 (± 2 weeks) until first progression or the 12 Apr 2019 primary analysis, whichever occurs first.

At Screening, all testing is performed by the Central Laboratory. If the Screening test is completed within 7 days of Cycle 1 Day 1 dosing, the test does not need to be repeated again on Cycle 1 Day 1.

If Screening Central Laboratory results are not available and treatment needs to be urgently started, then a local laboratory LDH result may be used. However, the data must be submitted to Celgene in the CRF and the investigator must ensure that samples for the Central Laboratory are drawn before investigational product is administered and immediately sent to the Central Laboratory.

After the Screening Period, testing continues by the Central Laboratory. However, in urgent cases, local laboratory results may be used to guide clinical decisions and dose modifications, however, that data must be submitted to Celgene in the CRF, and whenever possible, a concurrent sample should be sent to the Central Laboratory.

If the most recent protocol scheduled or unscheduled test was performed within 7 days prior to End of Treatment Visit, the test does not need to be repeated again at End of Treatment Visit.

Serum Chemistry includes albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate transaminase (AST), bilirubin (total), calcium, chloride, creatinine, glucose, phosphorous, potassium, sodium, total protein, blood urea nitrogen (BUN), and uric acid. The test is performed at Screening, every cycle on Days 1, during Cycles 1-2 on Day 8, and at End of Treatment Visit. Unscheduled tests may be ordered at any time.

At Screening, all chemistry testing is performed by the Central Laboratory. If the Screening test is completed within 7 days of Cycle 1 Day 1 dosing, the test does not need to be repeated again on Cycle 1 Day 1. If Screening Central Laboratory results are not available and treatment needs to be urgently started, then local laboratory results may be used to confirm eligibility, however the Celgene medical monitor must be consulted. Additionally, the data must be submitted to Celgene in the CRF and the investigator must ensure that samples for the Central Laboratory are drawn before investigational product is administered and immediately sent to the Central Laboratory.

After the Screening Period, testing continues by the Central Laboratory. However, in urgent cases, local laboratory results may be used to guide clinical decisions and dose modifications, however, that data must be submitted to Celgene in the CRF, and whenever possible, a concurrent sample should be sent to the Central Laboratory.

If the most recent protocol scheduled or unscheduled test was performed within 7 days prior to End of Treatment Visit, the test does not need to be repeated again at End of Treatment Visit.

Thyroid Stimulating Hormone (TSH) is tested at Screening and at the End of Treatment Visit; the blood serum samples are analyzed by the Central Laboratory.

Serum Immunoglobulin (Ig) measurement includes IgA, IgG, IgM and will be collected at Screening and at End of Treatment Visit. Testing is performed by the Central Laboratory.

Lenalidomide Counseling is conducted for all subjects at the following times: once during Screening prior to Cycle 1 Day 1 dosing; and while on treatment, once per cycle prior to dispensing lenalidomide. Please consult the Pregnancy Prevention Risk Management Plan for details.

Pregnancy Testing is applicable to all subjects who are females of childbearing potential (FCBP). FCBP is defined as a: sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months).

Prior to starting investigational product, two negative pregnancy tests are required (sensitivity of at least 25 mIU/mL). The first test must be performed within 10 to 14 days prior to the start of lenalidomide/placebo dosing, and the second within 24 hours prior to the start of lenalidomide/placebo dosing. During the Treatment Period testing is performed weekly for the first 28 days. Thereafter, FCBP with *regular or no menstrual cycles* continue testing at a minimum of every 28 days during the Treatment Period (Day 1 of every 21-day cycle is acceptable), at the Lenalidomide/Placebo End of Treatment, and 28 days following Lenalidomide/Placebo End of Treatment. Thereafter, FCBP with *irregular menstrual cycles* continue testing every 14 days during the Treatment Period, at Lenalidomide/Placebo End of Treatment, and at both 14 and 28 days following Lenalidomide/Placebo End of Treatment.

Quality of Life Assessment will be completed using the EQ-5D and FACT-Lym questionnaires (Appendix 19.6 and 19.7). These are required to be completed at the following time points: at Screening, Midcycle, once 3 – 4 weeks after completing Cycle 6; Weeks 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, and 310 (± 2 weeks) until first progression or the 12 Apr 2019 primary analysis, whichever occurs first. To the extent possible, collect this assessment the same day the CT scan is performed. If an additional CT scan is performed earlier than the specified time points due to changes in the subject's clinical status, please also collect an additional questionnaire set at that time. Once a subject has progressed, no further questionnaires are required.

Performance Status will be scored according to Table 6 and will be measured at Screening; Midcycle; and once 3 – 4 weeks after completing Cycle 6. If a subject has discontinued treatment for any reason other than disease progression or death, the assessment is required to

continue during the Follow-up Period at Weeks 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, and 310 (± 2 weeks) until first progression or the 12 Apr 2019 primary analysis, whichever occurs first.To the extent possible, collect this assessment the same day the CT scan is performed.

Table 6: Performance Status by Eastern Cooperative Oncology Group Scale

Score	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, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

(Oken, 1982)

CT Scan of the Neck, Chest, Abdomen, and Pelvis is to be performed with contrast unless *medically contraindicated*; in this case magnetic resonance imaging (MRI) or a CT without contrast is acceptable. It is acceptable to perform a combined PET-CT, however, the CT portion should be of diagnostic quality.

If the local preference is to perform a combined PET-CT without contrast, this will be acceptable for *post baseline assessments only* (unless contrast is medically contra indicated at baseline): Midcycle (once between Weeks 9 – 12 which is after Cycle 3 but before cycle 4); End of Treatment Visit; and for *PET negative (CR) subjects only*, also during the Follow-up Period. If a combined PET-CT without contrast is performed, then progression may not be scored on PET positivity alone, but must be confirmed by CT with contrast or a biopsy of the PET positive lesion. The same modality should be used throughout all post-baseline assessment time-points for a given subject if possible. Consult the radiology manual for more detail.

This procedure should be performed before initiating the optional pre-phase corticosteroid treatment. All scans will be sent to Central Radiology on an ongoing basis for subsequent efficacy assessment. Local interpretation of scans will determine eligibility and inform real-time treatment decisions during the study. However, the CT scans collected 3 – 4 weeks after Cycle 6

should be forwarded immediately to Central Radiology for a real time assessment which will guide treatment decisions *at the post Cycle 6 time point*.

The CT scans are required at Screening, Midcycle (once between Weeks 9 – 12 which is after Cycle 3 but before Cycle 4); once 3 – 4 weeks after completing Cycle 6; Weeks 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, and 310 (± 2 weeks) until first progression or the 12 Apr 2019 primary analysis, whichever occurs first. The radiological assessment schedule is the same for *all subjects*, regardless of whether the optional two doses of single agent rituximab are administered. Therefore, the scan required at 3 – 4 weeks after completing Cycle 6 must be completed before the optional Cycle 7 dose of rituximab is administered. If an additional scan is performed earlier than the specified time points due to changes in the subject's clinical status, this extra scan should also be submitted to Central Radiology. Once a subject has experienced first progression, no further CT scans are required. Below is a bulleted summary:

- Screening
  - PET and CT with contrast to define lesions
- Once between Weeks 9 – 12
  - CT with contrast, or PET-CT without contrast per local standard of care
- Once 3-4 weeks after completing Cycle 6
  - PET and CT with contrast or PET-CT without contrast per local standard of care
    - If PET negative (CR), contrast CT not required
    - If PET positive, contrast CT or biopsy required to confirm PD before changing therapy
- Follow-up for PET negative (CR) cases
  - CT with contrast, or PET-CT without contrast per local standard of care
  - Progression must be confirmed by contrast CT or biopsy
- Follow-up for PET positive cases (PR and SD)
  - CT with contrast

Scans previously acquired as standard of care up to 6 weeks prior to Cycle 1 Day 1 may be submitted to fulfill the Screening requirement as long as they meet the minimum technical standards specified by Central Radiology and include all required fields. Fields missing from archival scans may be imaged separately during Screening and the complete set of scans may be submitted together to fulfill Screening requirements.

The scanning time points are the same for *all* subjects, including those who complete the full course of protocol specified treatment, who discontinue treatment early due to toxicity, as well as those who discontinue before progression to pursue a new antilymphoma/salvage therapy (chemotherapy, SCT, radiotherapy, etc.). All scans are submitted to Central Radiology. However, in the case where a subject receives a new antilymphoma therapy before first

progression, and as part of another clinical trial, continue the scans to the extent possible and submit if possible to Central Radiology until first progression.

Response Assessment includes review of current CT, PET, laboratory, and clinical data to determine the subject's response status per the IWG Response criteria for NHL (Cheson, 2014). The response assessments are required at: Midcycle; once between 3 – 4 weeks after completing Cycle 6; Weeks 34, 46, 58, 70, 82, 94, 106, 118, 130, 142, 154 (± 1 week); 180, 206, 258, and 310 (± 2 weeks) until first progression or the 12 Apr 2019 primary analysis, whichever occurs first. The response assessment schedule is the same for *all subjects*, regardless of whether the optional two doses of rituximab are administered. If an additional CT scan is performed earlier than the specified time points due to changes in the subject's clinical status, please also perform an additional response assessment at that time. Once a subject has progressed, no further response assessments are required.

Bone Marrow Biopsy will be performed at Screening (before pre-phase corticosteroid treatment, if applicable) for all subjects; and at the End of Treatment only if the subject has an equivocal post Cycle 6 PET scan finding in the bone marrow, and had lymphomatous involvement of the bone marrow at Screening. Therefore, if an EOT biopsy is required, the timing will be dependent on the post Cycle 6 PET scan results. Samples previously acquired as standard of care within 8 weeks prior to C1D1 may be used to fulfill the Screening bone marrow biopsy requirement. Local pathology review of the Screening and End of Treatment Visit bone marrow samples is acceptable; Central Pathology does not review bone marrow biopsy samples. The Screening results do not impact study eligibility. A unilateral biopsy is acceptable.

Bone Marrow Aspirate sample collection within 8 weeks prior to C1D1 is recommended, but is not required. This procedure should be performed before initiating the optional pre-phase corticosteroid treatment. Local pathology review of the aspirate is acceptable. If a subject develops an SPM post C1D1, and if a Screening aspirate was collected, sponsor review of the sample and/or of the local pathology report may be requested.

PET Scan of the neck, chest, abdomen, and pelvis is required once during Screening before receipt of investigational products (also before pre-phase corticosteroid treatment, if applicable); and once between 3 – 4 weeks after completing Cycle 6. The radiological assessment schedule is the same for *all subjects*, regardless of whether the optional two doses of single agent rituximab are administered. Therefore the scan required at 3 – 4 weeks after completing Cycle 6 must be completed before the optional Cycle 7 dose of rituximab is administered.

Scan interpretation is according to the Deauville Criteria with a score of 1 – 2 being negative, and score of 3 – 5 being positive (Itti, 2013; Meignan, 2013), (Appendix 19.3). Although local interpretation at Screening is acceptable, all scans will be sent to Central Radiology on an ongoing basis for subsequent efficacy assessment. However, the PET scan collected 3 – 4 weeks after Cycle 6 should be forwarded immediately to Central Radiology for a real time assessment which will guide treatment decisions *at the post Cycle 6 time point*.

Scans previously acquired as standard of care within 6 weeks prior to Cycle 1 Day 1 may be submitted to fulfill the Screening requirement as long as they meet the minimum technical standards specified by Central Radiology and include all required fields. Screening PET scan *results* do not impact eligibility.

Administer Investigational Product as described in Section 8.2.

IP Accountability and Compliance is described in Sections 8.7 and 8.8.

Administer Mandatory Primary Neutropenia Prophylaxis as described in Section 8.2.3

Tumor Lysis Syndrome (TLS) Assessment includes review of uric acid, potassium, phosphorous, calcium, and serum creatinine laboratory values; hydration status check; and clinical assessment / grading using the Cairo-Bishop Definition of TLS in Appendix 19.5. (CTCAE is not used to grade TLS in this study.) TLS assessment is to be performed at Cycles 1-2 Days 1, 8, and thereafter as clinically indicated. Note that the TLS assessment has a smaller window than the other assessments. The Day 1 TLS assessment must always be performed on the same day as dosing; the Day 8 TLS assessment must be performed within ± 1 day. TLS prophylaxis treatment is discussed in Section 9.3.5.

Adverse Events will be collected from signing of informed consent through 28 days after the last dose of investigational product, which includes the optional two additional doses of single agent rituximab, if administered.

Concomitant Medications / Procedures will be collected from signing of informed consent through 28 days after the last dose of investigational product, which includes the optional two additional doses of single agent rituximab, if administered. These also include blood products transfused (packed red blood cells, platelets, etc.).

Subsequent Antilymphoma Treatment and Progression will be recorded, specifically the individual drug names, dates of treatment, and progression date, as long as the subject does not revoke consent, and the study remains open at the investigator's center.

Data through first progression may be collected at scheduled protocol clinic visits, . After the 12 Apr 2019 primary analysis, this information will not be collected.

Second Primary Malignancy (SPM) will be monitored as an event of interest and must be reported as an SAE regardless of the treatment arm the subject is in. This includes any SPM, regardless of causal relationship to IP, occurring at any time for the duration of the study, from the time of signing the ICD until the subject has died, revokes consent, or for up to 5 years from the date the last subject is randomized, whichever occurs first. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, x-rays, CT scans, etc.). If a tissue biopsy is collected related to an SPM, sponsor review of the sample and/or a local pathology report may be requested. For this particular study, SPM will include cases of DLBCL transformation to acute lymphoblastic leukemia (ALL).

As part of the SPM follow-up on all subjects, regardless of whether the subject actually experiences an SPM, information about subsequent antilymphoma therapies, first and second progression, and survival will also be collected. This is described in the Table of Events (Table 5) and earlier in Section 6.

Survival Information will be collected on all subjects at scheduled protocol clinic visits until first progression. Thereafter, information will be collected via subject contact (phone, email, visit, etc.) as long as the subject does not revoke consent, and the study remains open at the investigator's center.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

This study will enroll approximately 560 subjects in the ITT population which are anticipated to come from the regions of North America, Europe, and Asia.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Histologically confirmed CD20+ DLBCL of the below World Health Organization (WHO) sub-classifications as assessed by Central Pathology. In the rare case that local and Central pathology disagree on DLBCL diagnosis and/or CD20+ status, **and if** ABC type is confirmed by Central Pathology (inclusion criterion 2), then the subject may still be enrolled on the basis of a local DLBCL diagnosis and/or CD20+ status at investigator discretion. A retrospective adjudication will be performed by a second Central Pathologist.
   a. Not otherwise specified (NOS)
   b. Associated with chronic inflammation
   c. Epstein-Barr virus positive (EBV+) of the elderly
2. ABC type determined using a validated GEP assay performed on as assessed by Central Pathology. (ABC type subjects are reported by the GEP assay as eligible for this inclusion criterion, whereas subjects with an indeterminate, unclassifiable, or GCB type are not eligible).
3. Adequate lymph node or tumor biopsy specimen available for Central Pathology review and GEP profiling by the . A formalin fixed paraffin embedded lymph node or tumor biopsy acquired by a surgical incision or excision biopsy is strongly preferred. Core needle biopsy is allowed, and typically 3 – 4 passes embedded in two FFPE blocks are adequate for both local and Central Pathology evaluation (one block for local and one block for Central Pathology). Other commonly used devices (e.g. endoscopy forceps or grasp biopsy) are also acceptable provided they yield an equivalent amount of tissue. Material from a fine needle aspiration is not acceptable. If an archival specimen is not available or is not acceptable, a re-biopsy is required prior to randomization.
4. Measurable disease on cross section imaging by CT that is at least 1.5 cm in the longest diameter and measurable in two perpendicular dimensions.
5. Ann Arbor stage II-IV disease.
6. No prior treatment for DLBCL, except as allowed in Section 8.2.1.
7. Appropriate candidate for 6 cycles of R-CHOP21.
8. International Prognostic Index score of 2 or greater.
9. Performance status ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) scale.

10. Must be between the ages of 18 and 80 years on the date of the informed consent document signature. At the discretion of the investigator, subjects over 80 years may be included if their ECOG performance status is ≤ 1; **each** of their individual organ system scores is ≤ 2 using the Modified Cumulative Illness Rating Scale (CIRS) for co-morbidity (Salvi, 2008; Salvi, 2008a); and if they would otherwise be eligible for full-dose R-CHOP per local practice.
11. Must fulfill the following laboratory requirements:
    a. Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3 (1.5 x 10^9/L) unless secondary to bone marrow or spleen involvement by lymphoma; in this case the limit is ≥ 1,000 cells/mm^3 (1.0 x 10^9/L). Bone marrow involvement by lymphoma is demonstrated by recent bone marrow aspiration, bone marrow biopsy, or PET scan finding. Spleen involvement by lymphoma is demonstrated by splenomegaly.
    b. Platelet count ≥ 75,000/mm^3 (75 x 10^9/L) unless secondary to bone marrow or spleen involvement by lymphoma; in this case the limit is ≥ 50,000/ mm^3 (50 x 10^9/L). Bone marrow involvement by lymphoma is demonstrated by recent bone marrow aspiration, bone marrow biopsy, or PET scan finding. Spleen involvement by lymphoma is demonstrated by splenomegaly.
    c. Hemoglobin ≥ 7.5 g/dL (4.7 mmol/L)
    d. Serum aspartate transaminase (AST/SGOT) and alanine transaminase (ALT/SGPT) ≤ 3.0 x upper limit of normal (ULN). In the case of documented liver involvement by lymphoma, the requirement is ≤ 5.0 x ULN.
    e. Serum total bilirubin ≤ 2.0 mg/dl (34 µmol/L). In the case of Gilberts Syndrome, or documented liver or pancreatic involvement by lymphoma, the requirement is ≤ 5.0 mg/dl (86 µmol/L).
    f. Calculated creatinine clearance (Cockcroft-Gault formula) of ≥ 30 mL/min
12. Understand and voluntarily sign an informed consent document prior to conducting study assessments or procedures.
13. Able to adhere to the study visit schedule and other protocol requirements.
14. Females of childbearing potential (FCBP) must:
    a. Have two negative pregnancy tests as verified by the study doctor prior to starting 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 subject practices complete abstinence [1] from heterosexual contact.
    b. Either commit to complete abstinence[1] from heterosexual contact (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 therapy, during the study therapy (including dose interruptions), and for 12 months after discontinuation of study therapy.

[1] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

15. Male subjects must:
    a. Practice complete abstinence[1] or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following investigational product discontinuation, even if he has undergone a successful vasectomy.
    b. Agree to not donate semen during investigational product therapy and for 28 days after discontinuation of investigational product therapy.
16. All subjects must:
    a. Have an understanding that the investigational product could have a potential teratogenic risk.
    b. Agree to abstain from donating blood while taking investigational product therapy and for 28 days after discontinuation of investigational product therapy.
    c. Agree not to share investigational product with another person.
    d. Agree to be counseled about pregnancy precautions and risk of fetal exposure.
    e. Females must agree to abstain from breastfeeding during study participation and for at least 12 months after investigational product discontinuation.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. The following WHO subcategories of DLBCL:
    a. Active CNS or meningeal lymphoma
    b. Primary cutaneous, leg type
    c. Primary mediastinal (thymic)
    d. Lymphomatoid granulomatosis
    e. ALK-positive lymphoma
    f. Plasmablastic lymphoma
    g. Large B-cell lymphoma arising in HHV8 associated multicentric Castleman disease
    h. Primary effusion lymphoma
    i. Intravascular large B-cell
    j. B-cell unclassifiable cases with features intermediate between DLBCL and Burkitt
    k. Unclassifiable cases with features intermediate between DLBCL and classical Hodgkin's lymphoma
    l. T cell / histiocyte rich.
2. Post-transplant Lymphoproliferative Disorder (PTLPD) cases, even if they are B-cell type and ABC subtype, are excluded.
3. Histology other than DLBCL. Evidence of composite DLBCL and FL, or of transformed NHL.

4. Seropositive for or active viral infection with hepatitis B virus (HBV):
   a. HBV surface antigen (HBsAg) positive
   b. HBV surface antigen (HBsAg) negative, HBV surface antibody (anti-HBs) positive and/or HBV core antibody (anti-HBc) positive, and detectable viral DNA

   Notes:

   c. Subjects who are seropositive because of a successfully treated, prior infection are eligible (HBsAg negative, anti-HBs positive, and/or anti-HBc positive, but viral DNA negative)
   d. Subjects who are seropositive because of HBV vaccination are eligible (anti-HBs positive, anti-HBc negative, and HBsAg negative)
5. Hepatitis C virus (HCV) positive subjects with chronic hepatitis C, or subjects with an active hepatitis C infection requiring anti-viral medication (at time of randomization).

   Note:

   a. HCV positive subjects who do not have active hepatitis C, and who are otherwise acceptable candidates for R-CHOP chemotherapy, as documented by the investigator, are eligible.
6. Known seropositive for or active viral infection with human immunodeficiency virus (HIV).
7. Contraindication to any drug in the chemotherapy regimen, and specifically:
   a. LVEF < 45% as assessed by MUGA, or LVEF < local institutional normal limits for R-CHOP administration as assessed by echocardiography
   b. Peripheral neuropathy ≥ Grade 2
8. Major surgery (excluding lymph node or bone marrow biopsy) within 28 days from signing the informed consent document, unless the subject is recovered
9. Life expectancy < 6 months
10. History of other malignancies, unless the subject has been free of the disease for ≥ 5 years. Exceptions to the ≥ 5-year time limit include history of the following:
    a. Localized non-melanoma skin cancer
    b. Carcinoma in situ of the cervix
11. Prior use of lenalidomide
12. Known allergy to thalidomide
13. Known sensitivity or allergy to murine products
14. Use of any investigational agent within 28 days or five half lives, whichever is longer, of Cycle 1 Day 1
15. Subjects who are unwilling to take VTE prophylaxis
16. Pregnant or lactating females
17. Uncontrolled intercurrent illness

18. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form
19. Any condition, such as an active, severe infection, or the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
20. Any condition that confounds the ability to interpret data from the study

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Products

Celgene will provide lenalidomide 2.5 mg, 5 mg, 10 mg, and 15 mg capsules and the respective matching placebo capsules for oral administration.

Celgene will provide commercial supplies, for countries where rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone are designated as investigational product, labeled appropriately for investigational use as per the regulations of the relevant country health authority. Subjects enrolled in countries where rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone are designated as non-investigational, should obtain commercially available product through their local hospital pharmacy or licensed distributer.

Required medications for neutropenia will be selected by the investigator according to local practice and provided by the investigative site.

Recommended medications such as aspirin and allopurinol, if used, will be selected by the investigator according to local practice and provided by the investigative site.

8.2. Treatment Schedule and Administration

Please see Section 9.3 for information about recommended prophylactic treatments related to CNS lymphoma, infections, nausea, rituximab infusion reactions, HBV reactivation, TLS, and VTE. There is a ± 1 day window for Day 1 dosing during Cycles 2-6. However, no window is applicable to Cycle 1 Day 1 dosing.

8.2.1. Optional Prephase Treatment

For elderly subjects or for subjects with bulky disease, systemic symptoms, compressive disease, elevated bilirubin due to lymphoma, or rapidly progressing adenopathies, prephase treatment with corticosteroids according to local practice is permitted prior to beginning the Treatment Period, at the discretion of the investigator (Pfreundschuh, 2010). It is recommended to limit the prephase treatment to up to 100 mg / day prednisone or equivalent for 10 days. In the case of prephase corticosteroid treatment, there is no protocol specified definition of bulky disease. A washout period is not required; prephase treatment may be given, immediately followed by the prednisone as part of R-CHOP, and then a corticosteroid taper is allowed. However, the Screening PET, CT, lymph node biopsy, and bone marrow biopsy (and if applicable, also the bone marrow aspirate) should be completed before initiating corticosteroids.

In cases of medical emergencies (e.g., superior vena cava or spinal cord compression) in which prephase treatment with corticosteroids is not considered adequate, it may be acceptable for local radiation to be administered; however, the Celgene medical monitor must be consulted. In such case, the radiated lesion(s) cannot be used as measurable (target) lesion(s).

Prephase treatment with vincristine or any other chemotherapy is prohibited.

8.2.2. Optional Consolidation Treatment (Pre-Specified)

The investigator may prospectively choose to give local radiotherapy after study chemotherapy per local practice, such as for the treatment of a particular site of bulky disease or a large mass, or in subjects at higher risk for CNS lymphoma. In the case of consolidation treatment, bulky disease is defined as ≥ 7.0 cm. However, the decision to treat and the location to be treated must be determined during the Screening Period and registered in the IVRS. In this case, the consolidation radiotherapy will not count as a treatment event for the EFS endpoint.

If the investigator should decide at anytime after Cycle 1 Day 1 to give consolidation treatment, or to switch treatment to a different lesion, receipt of consolidation treatment will count as an EFS event.

8.2.3. Mandatory Primary Neutropenia Prophylaxis

Primary neutropenia prophylaxis with either granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) is required for all subjects at every cycle during Cycles 1 – 6. The selection of a particular drug, for example filgrastim, pegfilgrastim, lenograstim, sargramostim, molgramostim, is per local practice. The dose and schedule of the selected drug is also determined per local practice. However, it is recommended that investigators follow either of the below schedules, at every cycle:

- Pegfilgrastim (or equivalent biosimilar product) once per cycle, starting on Day 2-4 (i.e. 1-3 days after chemotherapy)

  OR

- Filgrastim (or equivalent biosimilar product) for at least 7 days in each cycle, starting on Day 2-4 (i.e. 1-3 days after chemotherapy)

8.2.4. Lenalidomide/Placebo-R-CHOP Regimen

The R2-CHOP or placebo-R-CHOP regimen will be administered over a 21-day cycle (with the possible exception of Cycle 1, which may last 22 days; see Section 8.2.6 Rituximab).

Treatment will continue until the R2-CHOP or placebo-R-CHOP regimen of 6 cycles is complete, or until unacceptable toxicity, inadequate response to treatment is determined, disease progression, or withdrawal of consent, whichever occurs first.

Table 7: Lenalidomide/Placebo-R-CHOP Regimen

Drug	Dose	Dosing Days (21-day cycle)
Lenalidomide / Placebo PO	15 mg	1-14
Rituximab IV	375 mg/m^2	-1 OR 1
Cyclophosphamide IV	750 mg/m^2	1
Doxorubicin IV	50 mg/m^2	1
Vincristine IV	1.4 mg/m^2 (max of 2.0 mg total)	1
Prednisone / Prednisolone PO (Day 1 IV administration is acceptable)	100 mg	1-5

IV=intravenous, PO= per os, oral administration

8.2.5. Lenalidomide / Placebo

Lenalidomide is initiated on Day 1 of Cycle 1 at a dose of 15 mg (oral administration) PO once daily for 14 days in each 21-day cycle.

On Day 1 of every cycle, lenalidomide will be administered in the clinic. For subsequent dosing days, subjects should be instructed to take lenalidomide / placebo at approximately the same time each day as the Day 1 dosing for that cycle. There is no requirement for taking lenalidomide / placebo with or without food, or with or without certain types of foods or liquids.

A 7-day rest period following the 14 days of dosing is required, unless the allowed -1 day visit window around Day 1 is used; in this case the minimum rest period is 6 days. A rest period may be extended for toxicity as needed (Section 8.2.12).

If a subject misses a dose of lenalidomide / placebo and it is within 12 hours of their normal dosing time, the subject should be instructed to make up the missed dose, and to then take their next dose according to their regular schedule. Lenalidomide concentration is low at 12 hours post dose, therefore making up a missed dose and then resuming regular dosing with a greater than or equal to (≥) 12 hour interval between the two doses will not cause considerable drug accumulation.

Dose modifications are per Table 8. The dose may also be interrupted and/or reduced for reasons in addition to those listed in Table 8 per investigator discretion. If a dose is reduced, re-escalation is not permitted.

8.2.6. Rituximab

The investigator may choose whether to administer rituximab on Day 1 of the cycle or one day prior to the start of the cycle. During Cycle 1, if rituximab is administered one day prior to the start of the other chemotherapy drugs, then Cycle 1 may last 22 days instead of the usual 21 (Day -1 plus Days 1 – 21); and first receipt of rituximab will mark the beginning of the Treatment Period. Additionally, the investigator may choose to administer rituximab over two days at the

beginning of each cycle per local practice (for example Day -1 and Day 1; or Day 1 and Day 2; or Day 2 and Day 3).

It is permissible to administer an additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of study treatment are complete if it is considered standard of care per local practice. However, the decision to administer these extra two doses must be pre-specified in IVRS prior to randomization. The radiological and response assessment schedule is the same for *all subjects* regardless of whether the optional two doses of rituximab are administered. Therefore, the scan required at 3 – 4 weeks after completing Cycle 6 must be completed before the optional Cycle 7 dose of rituximab is administered.

Preparation, infusion rate, dose modification, and guidance on pregnancy prevention should be performed according to the locally approved rituximab prescribing information or your local institutional practice.

8.2.7. Cyclophosphamide

Preparation and infusion rate are according to the package insert and local practice.

Recommended dose modifications are provided in Table 10 and may be applied at investigator discretion. For toxicities not covered by Table 10 it is recommended to follow the package insert and local practice.

8.2.8. Doxorubicin

No other anthracycline may be substituted for doxorubicin. Liposomal doxorubicin is not permitted.

Preparation and infusion rate are according to the package insert and local practice.

Recommended dose modifications are provided in Table 10 and may be applied at investigator discretion. For toxicities not covered by Table 10, it is recommended to follow the package insert and local practice.

8.2.9. Vincristine

Preparation and infusion rate are according to the package insert and local practice.

Recommended dose modifications are provided in Table 11 and may be applied at investigator discretion. For toxicities not covered by Table 11, it is recommended to follow the package insert and local practice.

8.2.10. Prednisone

The prednisone start dose is a flat 100 mg PO or intravenous (IV) dose (Moreno, 2000). Subsequent doses may be reduced for medical reasons at investigator discretion.

Subjects should be instructed to take prednisone in the morning on scheduled dosing days.

In countries where prednisone is not available it will be acceptable to substitute prednisolone on a 1:1 basis for prednisone. It is also acceptable to administer the prednisone or prednisolone by IV rather than PO on Day 1 of the cycle for convenience. In countries where local practice is to use an IV formulation on Day 1, it will be acceptable to substitute an equivalent (80 mg) or local

practice dose of IV methylprednisone on Day 1 only of each cycle. It will also be acceptable to substitute with a local practice dose of IV dexamethasone on Day 1 only of each cycle.

8.2.11. Lenalidomide/Placebo-R-CHOP Regimen Modifications

Recommended regimen modifications are provided in Table 12 and may be applied at investigator discretion. For toxicities not covered by Table 12, it is recommended to follow the respective package inserts and local practice.

8.2.12. Requalification Criteria For Subsequent Treatment Cycles

The next cycle of treatment may begin on the next scheduled Day 1 if all of the following Requalification Criteria are met:

- ANC ≥ 1,000 cells/mm³ (1.0 x 10^9/L), unless secondary to lymphoma bone marrow or spleen involvement per investigator assessment
- Platelet count ≥ 75,000 cells/mm³ (75 x 10^9/L), unless secondary to lymphoma bone marrow or spleen involvement per investigator assessment
- All other non-hematological toxicities have resolved to ≤ Grade 2
- A 7-day rest period has elapsed following the last dose of lenalidomide/placebo (a 6-day rest period applies if the early rituximab dosing option is used; Section 8.2.6)

If the Requalification Criteria are not met (after the rest period has elapsed) on Day 1 of the new cycle, the subject will be evaluated again within 7 days. If the requalification criteria are still not met after 7 days delay, the subject will be evaluated again in another 7 days. If the requalification criteria are again not met after 14 days total delay, hold lenalidomide/placebo, and if clinically appropriate, continue R-CHOP alone (continue in the Treatment and Follow-up Periods per Table 5). Lenalidomide/placebo may be resumed later if the requalification criteria are met; however, skipped doses of lenalidomide/ placebo may not be made up, and rest periods must be observed.

Other toxicity delays for any of the individual chemotherapy drugs rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) are allowed. Other toxicity delays for R-CHOP as a unit are allowed to a maximum of two 14-day delays over all 6 cycles. At investigator discretion, lenalidomide/placebo may be continued alone if R-CHOP is discontinued, provided the above re-qualification criteria are otherwise met, and rest periods are observed.

If the requalification criteria are fulfilled, but the subject develops toxicity as described in Table 8 due to lenalidomide / placebo, the R-CHOP drugs should continue even if lenalidomide / placebo is held. There is no maximum delay limit for lenalidomide / placebo. Lenalidomide / placebo may be resumed later if the requalification criteria are met; however, skipped doses of lenalidomide/ placebo may not be made up and rest periods must be observed.

Table 8: Dose Modification Rules – Lenalidomide / Placebo

NCI CTCAE (v 4.03) Toxicity Grade	Action Required
Neutropenia* Sustained (≥ 7 days) Grade 4 (neutrophil count < 500 cells/mm³ [0.5x10^9/L]) *unless secondary to lymphoma bone marrow or spleen involvement per investigator assessment	• Withhold dose for the remainder of the cycle • Monitor CBC at least every seven days • At the next cycle, when the Requalification Criteria For Subsequent Treatment Cycles (Section 8.2.12) are met, restart at the same dose level
Febrile Neutropenia* Grade 3 or 4 *unless secondary to lymphoma bone marrow or spleen involvement per investigator assessment	• Withhold dose for the remainder of the cycle • Monitor CBC at least every seven days • At the next cycle, when the Requalification Criteria For Subsequent Treatment Cycles (Section 8.2.12) are met, restart at the next lower dose level
Thrombocytopenia* Grade 4 (platelet count < 25,000 cells/mm³ [25x10^9/L]) *unless secondary to lymphoma bone marrow or spleen involvement per investigator assessment	• Withhold dose for the remainder of the cycle • Monitor CBC at least every seven days • If at Day 1 of the next cycle, the Requalification Criteria For Subsequent Treatment Cycles (Section 8.2.12) are met, restart at the same dose level • If at Day 1 of the next cycle, the Requalification Criteria For Subsequent Treatment Cycles (Section 8.2.12) are not met, restart at the next lower dose level when Requalification Criteria are met
Rash Grade 2 or 3 non-desquamating (blistering) ---------- Desquamating (blistering) ≥ Grade 3 OR Non-desquamating Grade 4	• Determine causative investigational product and if attributable to lenalidomide then: – Hold dose; administer antihistamines or short course of ≤ 20 mg prednisone (or equivalent) – When toxicity resolves to ≤ Grade 1, restart at the same dose level ---------- • Determine causative investigational product and if attributable to lenalidomide then: – Discontinue lenalidomide / placebo
Allergic reaction or hypersensitivity Grade 2 ---------- Grade 3– 4	• Determine causative investigational product and if attributable to lenalidomide then: – Withhold dose. Follow at least every seven days – When the toxicity resolves to ≤ Grade 1, restart lenalidomide / placebo at next lower dose level ---------- – Discontinue lenalidomide

Table 8: Dose Modification Rules – Lenalidomide / Placebo (Continued)

NCI CTCAE (v 4.03) Toxicity Grade	Action Required
Constipation Grade 1–2 ---------- ≥ Grade 3	• Initiate bowel regimen and maintain dose level ---------- • Withhold dose. Follow at least every seven days • When the toxicity resolves to ≤ Grade 2, restart at same dose level
Venous thrombosis/embolism ≥ Grade 3	• Withhold dose and start therapeutic anticoagulation; restart at investigator's discretion (maintain dose level)
Tumor Lysis Syndrome (TLS) *Grading is per Cairo-Bishop, and not per NCI CTCAE,* for TLS only Lab TLS or Grade 1 TLS ---------- Grade 2 – 4	• Continue lenalidomide (maintain dose), or at the investigator's discretion, continue lenalidomide and reduce dose by one level • Provide vigorous IV hydration and appropriate medical management according to the local standard of care, until electrolyte abnormalities are corrected. Rasburicase therapy is appropriate (if approved by the local Health Authority) as needed to reduce hyperuricemia • Hospitalization will be at investigator's discretion ---------- • Withhold dose • When symptoms resolve to Grade 0, restart at same dose level • If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following re-initiation of lenalidomide
AST or ALT > 3 x ULN	• Withhold lenalidomide dose; re-test at least weekly until AST or ALT < 2.5 x ULN or return to baseline • If the event is considered *related* to lenalidomide, restart lenalidomide at *next lower dose* level • If the event is considered *NOT related* to lenalidomide, restart the *same dose* level of lenalidomide • For subjects with Gilbert's syndrome or liver involvement, consult the Celgene medical monitor regarding dose reductions
Bilirubin ≥ 3 x ULN	• Withhold lenalidomide dose; re-test at least weekly until bilirubin < 1.5 x ULN • If the event is considered *related* to lenalidomide, restart lenalidomide at *next lower* dose level • If the event is considered *NOT related* to lenalidomide, restart the *same dose* of lenalidomide • For subjects with Gilbert's syndrome or liver involvement, consult the Celgene medical monitor regarding dose reductions

Table 8: Dose Modification Rules – Lenalidomide / Placebo (Continued)

NCI CTCAE (v 4.03) Toxicity Grade	Action Required
Other lenalidomide related non-hematologic AEs ≥ Grade 3	• Withhold dose • When the AE resolves to ≤ Grade 2, restart at the same or next lower dose level per the investigator's discretion

AE= adverse event, ALT= alanine transaminase; AST= aspartate transaminase CBC= complete blood count, NCI CTCAE=National Cancer Institute Common Terminology Criteria for AE, Lab = laboratory, ULN= upper limit of normal

Table 9: Dose Reduction Levels – Lenalidomide

Starting Dose	15 mg Daily on Days 1-14, Every 21 Days
Level –1 Dose	10 mg daily on Days 1–14, every 21 days
Level –2 Dose	5 mg daily on Days 1– 14, every 21 days
Level –3 Dose	2.5 mg daily on Days 1–14, every 21 days

Table 10: Recommended Dose Modification Rules – Cyclophosphamide and/or Doxorubicin

NCI CTCAE (v 4.03) Toxicity Grade	Action Required
Neutropenia Sustained (≥ 7 days) Grade 4	• If toxicity occurs after discontinuing lenalidomide, decrease both cyclophosphamide and doxorubicin by 25% and follow standard dosing guidelines
Thrombocytopenia Sustained (≥ 7 days) Grade 4 OR ≤10,000 cells/mm^3 or 10 $x10^9$ cells/L) at any time	• If toxicity occurs after discontinuing lenalidomide, decrease both cyclophosphamide and doxorubicin by 25% and follow standard dosing guidelines
Cystitis, noninfective Grade 2	• Withhold cyclophosphamide for the current cycle and until resolution of cystitis • At next cycle decrease current cyclophosphamide dose by 50% • For subsequent cycles, if all renal / genitourinary toxicity is Grade < 2, re-escalate to the previous cyclophosphamide dose
Left ventricular systolic dysfunction ≥ Grade 3	• Discontinue doxorubicin

Table 10: Recommended Dose Modification Rules – Cyclophosphamide and/or Doxorubicin (Continued)

NCI CTCAE (v 4.03) Toxicity Grade	Action Required
Mucositis / Stomatitis ≥ Grade 2	• At next cycle decrease current doxorubicin dose by 25% • For subsequent cycles, if toxicity resolves to < Grade 2, re-escalate to the previous doxorubicin dose

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 11: Recommended Dose Modification Rules – Vincristine

NCI CTCAE Toxicity Grade (v 4.03)	Action Required
Peripheral neuropathy- motor Grade 2 ---------- Grade 3	• Withhold vincristine for the current cycle and until toxicity improves to < Grade 2 • At next cycle decrease current dose by 50% ---------- • Discontinue vincristine
Peripheral neuropathy- sensory Grade 3 ---------- Grade 4	• Withhold vincristine for the current cycle and until toxicity improves to < Grade 2 • At next cycle decrease current dose by 50% ---------- • Discontinue vincristine

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 12: Recommended Dose Modification Rules – Lenalidomide/Placebo R-CHOP Regimen

NCI CTCAE (v 4.03) Toxicity Grade (as applicable)	Action Required
Nausea / Vomiting Grade 3	• Maximize anti-emetic therapy; if anti-emetic therapy is ineffective, discontinue lenalidomide/placebo or entire regimen at investigator discretion
Infection with ANC ≥ 1000/mm^3 and requiring IV antibiotics or hospitalization ---------- with ANC < 1000/mm^3 and requiring IV antibiotics or hospitalization	• Withhold regimen; restart at the same dose level when infection is controlled. • If AE reoccurs on subsequent cycles, decrease lenalidomide/placebo to next lower dose level and consider prophylactic antibiotics ---------- • Withhold regimen; restart when infection is controlled, decrease lenalidomide/placebo to the next lower dose level.

Table 12: Recommended Dose Modification Rules – Lenalidomide/Placebo R-CHOP Regimen (Continued)

NCI CTCAE (v 4.03) Toxicity Grade (as applicable)	Action Required
	• If AE reoccurs despite discontinuation of lenalidomide/placebo, then on subsequent cycles reduce cyclophosphamide by 25% and doxorubicin by 25%; consider prophylactic antibiotics.
Viral Hepatitis B, C new infection, or reactivation	• Discontinue regimen; treat hepatitis
Other non-hematologic toxicity Grade 3	• Withhold regimen until toxicity resolves to ≤ Grade 2 or baseline, then restart

8.2.13. Overdose

Overdose, as defined for this protocol, refers to lenalidomide / placebo, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone / prednisolone. On a per-dose basis, an overdose is defined as the following amount over the protocol-specified dose of these drug(s) assigned to a given subject, regardless of any associated AEs or sequelae:

PO any amount over the protocol-specified dose

IV 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the CRF. See Section 11 for the reporting of AEs associated with overdose.

8.2.14. Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from study treatment:

- Treatment was completed per protocol
- Adverse event(s)
- Locally assessed outcome of the Midcycle CT scan indicates a treatment change
- Disease progression
- Protocol violation
- Withdrawal of consent
- Lost to follow up

- Death

The following events are considered sufficient reasons for discontinuing a subject from the overall study:

- Withdrawal of consent
- Lost to follow up
- Death

The reasons for both treatment and study discontinuation should be recorded in the CRF and in the source documents.

8.5. Method of Treatment Assignment

An IVRS will be employed to accomplish randomization, to record pre-specification of optional consolidation radiotherapy, and to manage subject medications.

Subjects will be typed as GCB, ABC, or unclassifiable by the Central Pathology laboratory as part of screening. Disease diagnosis, subtype, and CD20 status will be entered by the Central Pathology laboratory into the IVRS.

Once the subject is determined eligible, the investigator or designee will access the IVRS within the 28-day Screening Period to obtain the randomized treatment assignment for the subject.

Subjects will be stratified as follows:

- IPI score: 2 / ≥ 3
- Age: < 65 / ≥ 65
- Presence of bulky disease: ≥ 7.0 cm (bulky) / < 7.0 cm (non-bulky)

Subjects will be randomized in a 1:1 ratio to either R2-CHOP or placebo-R-CHOP. The subject identification number (subject ID) assigned by the IVRS will identify the subject for all aspects of the study, including drug re-supply requests, result reporting from all central laboratories, central radiology data submission, and CRF data. The randomization schedule will be generated by the IVRS vendor.

8.6. Packaging and Labeling

Lenalidomide / placebo will be packaged in bottles, and each bottle will contain 14 capsules.

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot

number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

8.7. Investigational Product Accountability and Disposal

The investigator(s) or designee is responsible for taking an inventory of each shipment of investigational product received and comparing it with the accompanying shipping order/packaging slip. The investigator(s) will verify the accuracy of the information on the shipping order/packaging slip and call IVRS to register receipt at the site of the investigational product.

At the study site, investigational product will be stored in a locked, safe area to prevent unauthorized access and should be stored as directed on the product label.

An accurate accounting of the dispensing and return of investigational product for each study subject will be maintained in source documents on an ongoing basis by a member of the study site staff. Additionally, if any investigational product is lost or damaged or if the study subject misses a dose, this information should be documented in the study subject's CRF and source documents.

Celgene will instruct the investigator on the return, disposal, and/or destruction of unused investigational product.

8.8. Investigational Product Compliance

For the oral medications of prednisone (or prednisolone) and lenalidomide / placebo, study personnel will review the dosing instructions with the subject prior to dispensing investigational product. The subject will be instructed to return the investigational product bottles, including any unused investigational product, to the site at the end of the applicable treatment cycle. To monitor treatment compliance, the subject will be interviewed at each applicable visit regarding whether they took their medication, and a reconciliation of capsules will be done upon bottle return. Subject compliance will be noted in the source records and on the appropriate CRFs based upon the interview and capsule count.

For the IV medications of rituximab, cyclophosphamide, doxorubicin, and vincristine, the planned and administered dosage will be recorded in the source records and on the appropriate CRFs.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Prohibited Concomitant Medications

Anticancer therapy other than R-CHOP plus lenalidomide or placebo is prohibited during the entire Treatment Period of the study.

Other investigational therapy (drug or otherwise) is prohibited 28 days prior to Day 1 dosing and during the entire Treatment Period of the study.

9.2. Permitted Concomitant Medications

9.2.1. Hematopoietic Growth Factors and Transfusions

Growth factors (eg erythropoietin, platelet growth factors) and blood product transfusions (packed red blood cells, platelets, etc.) may be prescribed during the Treatment and Follow-up Periods at the investigator's discretion and should be used in accordance with the American Society of Clinical Oncology's (ASCO) guidelines or the European Society for Medical Oncology (ESMO) guidelines. With the exception of packed red blood cells, which may be administered at any time as needed, including during Screening; other growth factors or blood product transfusions should not be administered during the Screening Period to increase a subject's blood values in order to meet entry criteria. Note that primary neutropenia prophylaxis during the Treatment Period is mandatory (Section 8.2.3).

9.2.2. Pneumocystis Pneumonia Prophylaxis

Pneumocystis prophylaxis is permitted for all subjects according to local practice.

9.3. Recommended Concomitant Medications

9.3.1. CNS Lymphoma Prophylaxis

Subjects at risk for CNS involvement may receive CNS lymphoma prophylaxis treatment. The following may be considered by the investigator: 4 – 8 doses of intrathecal methotrexate and/or cytarabine administered during the R2-CHOP or placebo-R-CHOP induction treatment. CNS prophylaxis with IV drugs is not permitted.

9.3.2. Nausea Prophylaxis

Premedication with an antiemetic is recommended according to local practice.

9.3.3. Rituximab Infusion Reaction Prophylaxis

Premedication with acetaminophen and diphenhydramine to prevent a rituximab infusion reaction is recommended according to local practice. It is acceptable to use glucocorticoid steroids to treat an active rituximab infusion reaction as per local practice.

9.3.4. HBV Reactivation Prophylaxis

Subjects who are HBsAg negative, anti-HBs positive, and or anti-HBc positive, but viral DNA negative are eligible. For these subjects, DNA monitoring and prophylactic medication for HBV reactivation are recommended per local practice.

9.3.5. TLS Prophylaxis

It is recommended that subjects receive TLS prophylaxis (allopurinol, rasrubricase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of treatment administration in the first cycle, or as clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for TLS, the subjects will have blood samples drawn for serum chemistry on Days 1, and 8 of the first 2 cycles and additionally as clinically indicated. TLS will be assessed by the Cairo-Bishop Grading system (not by CTCAE) and the assessment includes both laboratory tumor lysis syndrome (LTLS) criteria and clinical TLS criteria. If a subject develops LTLS (defined by the presence of two or more serum value abnormalities of uric acid, potassium, phosphorous, or calcium) or ≥ Grade 1 TLS (defined by the presence of laboratory TLS and one or more of the following criteria: creatinine ≥ 1.5 x ULN, arrhythmia, or seizures), appropriate medical management should be initiated according to the local standard of care in each institution, along with vigorous IV hydration. Rasburicase treatment is considered appropriate if it is approved by the local Health Authority.

Refer to Table 8 for further instructions and dose modifications for TLS.

9.3.6. Venous Thromboembolism Prophylaxis

It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolism. In this double-blind placebo-controlled clinical trial, in which the investigator does not know the subject's treatment arm assignment, the decision to take prophylactic measures should be made carefully after an assessment of an individual subject's underlying risk factors.

As reference information, for subjects receiving lenalidomide in open-label trials, it is strongly recommended that subjects at risk for VTE receive either aspirin (70 – 325 mg PO daily) or another prophylaxis agent while on lenalidomide. In those subjects with a high risk of VTE, it is strongly recommended that the subject receive prophylactic anticoagulation therapy with low molecular weight (LMW) heparin, or heparin (dose recommended for the prophylaxis of DVT/PE per the package insert), or warfarin (to maintain an INR of 2.0). These prophylactic agents should be considered for subjects enrolling in this blinded, placebo-controlled clinical trial. The choice of VTE prophylaxis agent relies upon the investigator's discretion and should be tailored to the subject's individual risk/benefit profile by taking into account the individual thrombotic risk, bleeding risk, and the quality of compliance with the VTE prophylaxis.

The use of clopidogrel or ticlopidine alone is not recommended as VTE prophylaxis in this trial.

9.4. Mandatory Concomitant Medication

9.4.1. Primary Neutropenia Prophylaxis

Please refer to Section 8.2.3.

10. STATISTICAL ANALYSES

The objectives of the statistical analyses are to investigate the efficacy and safety of R2-CHOP versus placebo-R-CHOP in subjects with previously untreated, ABC type DLBCL. One interim analysis at 50% information level for futility and one final analysis for superiority are pre-planned for the primary efficacy endpoint.

10.1. Overview

Eligible subjects will be randomized to either the R2-CHOP or placebo-R-CHOP regimen in a 1:1 ratio. Treatment will continue until 6 cycles of treatment are completed, or until unacceptable toxicity, or the outcome of the Midcycle CT scan indicates a treatment change, disease progression, or withdrawal of consent, whichever occurs first. Upon treatment completion or premature discontinuation, subjects will be followed for progression, subsequent antilymphoma therapies, and overall survival.

The efficacy analyses will be based on subjects' response to treatment evaluated by the investigator and by the IRAC using the IWG Response Criteria for NHL (Cheson, 2014).

The safety analyses will include AEs, physical examinations, vital signs, and laboratory tests.

All statistical analyses specified in this protocol will be conducted using SAS® version 9.2 or higher.

10.2. Study Population Definitions

In this study the following three populations will be defined for the analysis and used in presentation of the data.

Intent-to-Treat (ITT) Population: The ITT population is defined as all subjects who are randomized into the trial, regardless of whether they received study treatment or not.

Modified Intent-to-Treat (mITT) Population: The mITT population is defined as all subjects who satisfy the following conditions:

- are randomized
- have received at least one dose of investigational product
- are CD20+, ABC type DLBCL as determined by Central Pathology
- are previously untreated
- have measurable disease at baseline
- have at least one post-baseline tumor assessment or died after randomization but before the assessment

Safety Population: The safety population is defined as all subjects who have received at least one dose of investigational product.

The ITT population will be used for the primary efficacy analysis. Subjects will be analyzed according to the treatment arm to which they are initially assigned.

The mITT population will be used as supportive analysis for efficacy. Subjects will be analyzed according to the treatment arm to which they are initially assigned.

The safety population will be used for all safety analyses. Subjects will be analyzed according to the treatment which they actually received.

10.3. Sample Size and Power Considerations

The sample size of this study is determined to provide adequate power to evaluate the treatment effect on PFS, the primary endpoint.

Accrual

This study will accrue a total of 560 subjects over approximately a 34-month accrual period. However, if the actual number of PFS events toward the end of the accrual period is far less than expected or if the subject dropout rate is unusually high, an additional number of subjects may be enrolled.

Sample Size for the PFS Analysis

The PFS endpoint will be analyzed after a total of 192 PFS events in the ITT population have been observed. This sample size will have 90% power to detect a hazard ratio (HR) of 0.625, i.e., a 37.5% reduction in the PFS hazard rate, at a two-sided 0.05 significance level, with an interim analysis for futility at 50% of the information pre-planned. In case the event rate falls below 2 events per month before reaching 192 events, the final analysis will be performed when at least 170 events have occurred. The power of the study will be at least 86%.

With an adequate enrollment rate and the assumption that the median PFS in the control arm is about 24 months, it is estimated that the required 50% information, or 96 PFS events, for the interim PFS futility analysis will be available approximately 28 months from the start of enrollment, and the required 192 PFS events for the final PFS analysis will be available in about 42 months from the start of enrollment.

This sample size is calculated using the software EAST 5.4 with a β-spending function of Gamma(-4). Since there is no intention to declare efficacy at the interim PFS analysis, no α-spending function is specified. For a detailed description of stopping boundaries please refer to Section 10.8 Interim Analysis.

The treatment effect assumption for the sample size determination is based on limited information available from two investigator initiated studies (Section 1.5.2.1 study MC078E and Section 1.5.2.2 study REAL07). In the event that new data from an external, randomized study suggests a substantially different effect from the assumptions made in this protocol, the sample size or analysis plan of the present study may be adjusted. However, the adjustment should be made prior to any un-blinded analysis.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

Subject disposition (analysis population allocation, randomization status, discontinued treatment, primary reason for early treatment discontinuation, discontinued the study, primary reason for early study discontinuation) will be summarized using frequency and percent for both treatment arms. A summary of subjects randomized by country/site will be provided. Protocol deviations/violations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

10.6.1. Primary Efficacy Endpoint Definition

The primary efficacy endpoint of this study is PFS, which is defined as the time from randomization to objective disease progression or death from any cause, whichever occurs first.

The PFS events will be determined by the IRAC using the Revised Response Criteria for Malignant Lymphoma (Cheson, 2014). The PFS analysis based on the IRAC assessment will serve as the primary analysis. The PFS analysis based on the local investigator's assessment will serve as the sensitivity analysis.

Subjects who did not experience disease progression and who did not die before the clinical data cut-off date will be censored at the time of the last visit with adequate response assessment.

In addition, the following two sets of censoring rules will be applied to the PFS analysis.

The first set of censoring rules will follow FDA's "Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics" (FDA, 2007). Specifically, subjects who received new anticancer therapy without objective disease progression will be censored at the date of the last radiological assessment prior to the new anticancer therapy. The analysis with this set of censoring rules will serve as the primary analysis for PFS.

In order to avoid possible informative censoring, e.g. the administration of new anticancer therapy may be related to factors associated with the actual survival time, a sensitivity analysis for PFS will be performed using the second set of censoring rules that follows EMA's guideline "Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man" (EMA, 2012). Specifically, outcome data will be collected according to the intended schedule of assessment and the date of progression or recurrence will be assigned based on the time of the first evidence of objective progression or recurrence regardless of violations, discontinuation of investigational product or change of therapy. Detailed censoring rules for PFS analysis will be provided in the Statistical Analysis Plan (SAP).

10.6.2. Secondary Efficacy Endpoint Definitions

Key Secondary Endpoint

The key secondary efficacy endpoint of the study is EFS, which is defined as the time from randomization until occurrence of one of the following events, whichever occurs first:

- Disease progression
- Relapse from CR
- Initiation of subsequent systemic antilymphoma therapy
- Death due to any cause

Pre-specified consolidation radiotherapy after study chemotherapy per local practice, such as for the treatment of a particular site of bulky disease or a large mass, or in subjects at higher risk for CNS lymphoma as described in Section 8.2.2 will not count as subsequent systemic antilymphoma therapy or an EFS event if the decision to treat and the location to be treated is determined during the Screening Period. Similarly, pre-specified additional two doses of single agent rituximab as described in Section 8.2.6 will be handled in the same way.

Subjects who did not experience any of these events defined in the four categories above before the clinical data cutoff date will be censored at the last time known to be alive and without these events.

Other Secondary Endpoints

Overall Survival

The OS is defined as the time between randomization and death from any cause. Subjects who complete the study and are still alive at the time of the clinical data cutoff date will be censored at the last visit date or the last contact date, whichever is later. Subjects who were lost to follow-up prior to the clinical data cut-off date will also be censored at the time of the last contact.

CR Rate by IWG (Cheson, 2014)

The CR rate is calculated as the proportion of subjects who have achieved CR prior to any treatment change.

Duration of CR

Duration of CR is defined only for the subjects who have achieved CR prior to any treatment change. It is calculated as the time from the first CR prior to treatment change to the first event of disease progression or death. Subjects who have not progressed or died at the time of the clinical data cutoff date will be censored at the last assessment showing no progression. Subjects who change treatment without evidence of disease progression will be censored at the last assessment showing no progression prior to treatment change.

Time to Next Lymphoma Treatment

The TTNLT is defined as the time from randomization to the time of treatment change for the next lymphoma treatment. Subjects without treatment change will be censored at the last visit.

Objective Response Rate

The ORR is defined as the proportion of subjects who have achieved either CR or PR prior to any treatment change.

Health Related Quality of Life

Data on health related quality of life will be collected using the standardized EQ-5D and FACT-Lym health measurement instruments.

EQ-5D is a standardized measure of health status developed by the EuroQol Group. The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ visual analog scale records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled "Best imaginable health state" and "Worst imaginable health state." This information can be used as a quantitative measure of health outcome as judged by the individual respondents. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.

The FACT-Lym questionnaire was developed as part of the FACIT measurement system to address HRQL issues for NHL patients. The FACT-Lym questionnaire is a validated and reliable self-report instrument for assessing the impact of lymphoma on HRQL and a useful targeted endpoint in NHL clinical research (Hlubocky, 2012).

It contains 42 questions covering HRQL and common lymphoma symptoms and treatment side-effects, and consists of five general HRQL subscales (Cella, 2005). It begins with the Functional Assessment of Cancer Therapy - General (FACT-G), which contains 27 questions covering four core subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 questions) used to assess NHL-related symptoms such as pain, itching, night sweats, trouble sleeping, fatigue and trouble concentrating. The FACT-Lym also asks patients about their concerns regarding lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment. All questions are answered on a 5-point scale ranging from "not at all" (0) to "very much" (4).

Both HRQoL instruments (EQ-5D and Fact – Lym) will be examined as secondary endpoints to identify changes in HRQoL measures relative to the comparator arm. The analysis of these HRQoL instruments will be predefined in the SAP prior to database lock.

10.6.4. Analysis Method

Demographics and Baseline Characteristics

Subjects' demographics and baseline characteristics will be summarized for the ITT population, mITT population, and Safety population.

Subjects' age, weight, and baseline characteristics will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum), while gender, race, and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

Subject disposition (analysis population allocation, randomized, premature treatment discontinuation along with primary reason for treatment discontinuation, premature study discontinuation along with primary reason for study discontinuation) will be summarized using frequency and percentage for both treatment arms. Protocol deviations and violations will be summarized using frequency tabulations.

Time-to-Event Endpoints

The efficacy analysis will be performed on both ITT and mITT populations where the analysis on ITT population is the primary analysis and analysis on mITT population is supportive.

For the time-to event endpoints, the Kaplan-Meier estimates of the survival function will be calculated and graphically presented. The stratified log-rank test will be performed to evaluate

treatment efficacy. The stratification factors for analysis include subject disease severity (IPI score 2 vs 3 or above), presence of bulky disease (tumor diameter ≥ 7.0 cm vs < 7.0 cm), and age category (< 65 vs 65 or older). The experimental arm will be declared superior if the 2-sided p-value from the stratified log-rank test is ≤ 0.05 in favor of the experimental arm. The un-stratified log-rank test will be performed as sensitivity analysis.

Conventionally, hazard ratio with two-sided 95% confidence interval (CI) will be estimated using the Cox proportional hazards model. But the treatment effect will be determined by the p-value from the stratified log-rank test, not by this 95% CI for the hazard ratio. Subgroup analysis for EFS and PFS will be performed as appropriate.

Binary Endpoints

The binary endpoints such as CR rate will be summarized in frequency and percent by treatment arm. The stratified Cochran-Mantel-Haenszel (CMH) test will be performed to evaluate treatment efficacy. The stratification factors include subject disease severity (IPI score 2 vs 3 or above), presence of bulky disease (tumor diameter ≥ 7.0 cm vs < 7.0 cm), and age category (< 65 vs 65 or older). The un-stratified CMH test will be performed as sensitivity analysis.

10.7. Safety Analysis

Safety analysis will include all subjects in the Safety population.

Investigational product exposure will be summarized for each treatment arm including duration of investigational product, total dose taken, and dose reductions.

Adverse events, vital sign measurements, clinical laboratory measurements, physical examination and concomitant medications will be summarized by treatment arm.

Adverse Events

AEs will be coded according to Medical Dictionary for Drug Regulatory Activities (MedDRA) and classified using the NCI CTCAE. The incidence rates of AEs will be tabulated by system organ class and preferred term. The incidence of AEs will also be tabulated by severity within each system organ class and preferred term. The most severe grade of each preferred term for a subject will be utilized for summaries of AEs by NCI CTCAE grade.

Subsets of AEs to be summarized include SAEs, suspected treatment-related AEs, and AEs that resulted in withdrawal of investigational product.

All AEs with corresponding attributes will be displayed in a by-subject listing. AEs leading to death or to discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, suspected treatment-related events, and SAEs will also be displayed in separate by-subject listings.

Laboratory Tests

Laboratory data will be graded according to NCI CTCAE severity grade. The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by baseline status for each treatment arm.

For variables for which an NCI CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges pretreatment and during treatment will be summarized by treatment.

Change from baseline will be descriptively summarized at each post-baseline visit by treatment arm.

Lab shift tables will be produced by treatment arm.

Physical Examination and Vital Signs

Physical examination data will be tabulated by treatment. Vital signs data will be descriptively summarized by treatment in terms of means, medians, standard deviations, minimum, and maximum.

10.8. Interim Analysis

Interim Analysis for PFS

An interim analysis for futility only is planned for the PFS at 50% information level, ie, when 96 PFS events among the enrolled ITT subjects have been developed across all treatment arms. According to the projected enrollment rate and the hypothesized treatment effect, it is estimated that the required 96 PFS events will be observed in about 28 months after the first subject is randomized.

The boundary for declaring futility of the experimental arm over the control arm is based on a ß-spending function of Gamma(-4) with overall $\beta = 90\%$. A normalized log-rank statistic will be calculated and compared with the futility boundary.

If the 1-sided p-value is ≥ 0.478 at the interim PFS analysis, the alternative hypothesis may be rejected, and the DMC may recommend stopping the trial for futility. However, this futility boundary is a non-binding boundary, which means that the study does not have to stop if the futility boundary is crossed at the interim analysis. The study may continue, if so desired by the sponsor, to the final analysis for efficacy without inflating the Type 1 error or losing power.

Since there is no intention to declare efficacy at the interim PFS analysis, no penalty in α should be imposed. Treatment efficacy will be declared at the final PFS analysis if the 1-sided p-value is ≤ 0.025 in favor of the experimental arm, after the required 192 PFS events in the ITT population are observed.

11. ADVERSE EVENTS

11.1. Monitoring, Recording, and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.2.13 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the investigator from the time the subject signs informed consent until 28 days after the last dose of IP and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);

- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in (see Section 11.5). This includes any second primary malignancy, regardless of causal relationship to IP (lenalidomide / placebo or control), occurring at any time for the duration of the study, from the time of signing the ICD through follow-up for overall survival. For this particular study, SPM will include cases of DLBCL transformation to ALL. The Follow-up Period involves subject contact per Table 5, until the subject dies, revokes consent, or until 5 years from the date the last subject is randomized, whichever occurs first. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF (i.e., AE and SPM CRF) and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

11.2.2. Severity / Intensity

For both AEs and SAEs, the investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity / intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3. Causality

The investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

The investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

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

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The exposure of any pregnant female (e.g., caregiver or pharmacist) to lenalidomide is also an immediately reportable event. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in (see Section 11.2.1). This includes any second primary malignancy, regardless of causal relationship to IP (lenalidomide / placebo or control), occurring at any time for the duration of the study, from the time of signing the ICD through follow-up for overall survival. For this particular study, SPM will include cases of DLBCL transformation to ALL. The Follow-up Period involves subject contact per Table 5, until the subject dies, revokes consent, or until 5 years from the date the last subject is randomized, whichever occurs first. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF (i.e., AE and SPM CRF) and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) and any SPM occurring at any time during the study including the follow-up period, or any SAE made known to the investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g., missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to lenalidomide based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Adverse events such as disease progression, death related to disease progression (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the sponsor to regulatory authorities.

Celgene or its authorized representative shall notify the investigator of the following information (In Japan, Celgene KK shall notify the Heads of the Institutes in addition to the investigators):

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- In Japan, measures taken in foreign countries to ensure subject safety, study reports that indicates potential risk of cancer, etc., or biannual SAE report according to the local regulations.

Where required by local legislation, the investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

12. DISCONTINUATIONS

Discontinuation may be from the investigational product or from the overall study. Since this study includes overall survival as an endpoint, the reasons for discontinuing both investigational product and the study will be collected for all subjects, as long as the study remain open at an investigator's site. The reasons for discontinuation should be recorded in the CRF and in the source documents.

12.1. Discontinuation of Investigational Product

The following events are considered sufficient reasons for discontinuing a subject from investigational product:

- Completed investigational product regimen per protocol
- Locally assessed outcome of the Midcycle CT scan indicates a treatment change
- Progression
- Adverse event(s)
- Protocol violation
- Withdrawal of consent
- Death
- Lost to follow up

12.2. Discontinuation from the Study

The following events are considered sufficient reasons for discontinuing a subject from the overall study:

- Withdrawal of consent
- Death
- Lost to follow up

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the investigator should contact the responsible Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/CRO Medical Monitor, who will then contact you promptly.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study unless in the opinion of the investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued, if, in the opinion of the investigator, continuing IP can negatively affect the outcome of the subject's treatment. The investigator or authorized person may call the IVRS for unblinded dose information. The reason for breaking the blind must be documented in the source documents.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all investigators who in turn will select their staff.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRFs and queries.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

14.3. Subject Information and Informed Consent

The investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed

consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the investigator's study files and a copy given to the study subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to

determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating investigator and the IRB/EC. This statement also applies to any communication between the investigator (or coordinating investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible
- Periodic reports on the progress of the study
- Deviations from the protocol or anything that may involve added risk to subjects

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities).

In addition, the investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment
- GCP noncompliance
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/EC
- Composition of the IRB/EC
- Record of all communications between the investigator, Celgene, and their authorized representative(s)
- List of Sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures
- IP accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The investigator must obtain approval in writing from Celgene prior to destruction of any records. If the investigator is unable to meet this obligation, the investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. investigator/institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the investigator and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. At each monitoring visit, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and Good Clinical Practice.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g., FDA, EMA, Health Canada) and company authorized representatives. The investigator should make every effort to be available for the audits and/or inspections. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study will be submitted for publication in a peer reviewed, scientific journal. Study results may also be presented at one or more medical congresses, and may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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19. APPENDICES

19.1. Ann Arbor Staging System

- **Stage I:**
  - I: Involvement of a single lymph node region
  - IE: Localized involvement of a single extralymphatic organ or site.
- **Stage II:**
  - II: Involvement of 2 or more lymph node regions on the same side of the diaphragm
  - IIE: Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm
- **Stage III:**
  - III: Involvement of lymph node regions on both sides of the diaphragm
  - IIIE: Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site
  - IIIS: Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen
  - IIIS+E: Both IIIS+IIIE
- **Stage IV:**
  - IV: Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non regional) nodal involvement
  - IVE: Extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

Source: American Joint Committee on Cancer. Non Hodgkin's lymphoma. In: AJCC Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven;1997:289-94.

19.2. Modified Cumulative Illness Rating Scale (Salvi, 2008a)

RATING SUGGESTIONS (GENERAL PRINCIPLES)

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: for a patient suffering from a well-controlled angina (Rated 2) and terminal heart failure (Rated 4), only the higher rated condition would be scored in the Cardiac system (e.g. rating is 4).

The spread of a cancer may lead to rate the condition in more than one category. For example, a lung cancer with bone metastases treated with nonsteroidal anti-inflammatory drugs (NSAID) is Rated 4 in Respiratory and 2 in Musculoskeletal.

General rules for severity rating:

0 - No problem affecting that system or past problem without clinical relevance.

1 - Current mild problem or past significant problem.

2 - Moderate disability or morbidity and/or requires first line therapy.

3 - Severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen).

4 - Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

LEVEL 0

No problem or healed minor injuries; past childhood illnesses (chickenpox); minor surgery (carpal tunnel completely healed, caesarean); uncomplicated healed fractures; other past problems healed without sequel, residual or complication (pneumonia).

LEVEL 1

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations, having only minor impact on morbidity (asthma controlled with PRN bronchodilators, occasional heartburn relieved with PRN antiacids). Medical problems that are not currently active but were significant problems in the past (passage of a kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy).

LEVEL 2

Medical conditions that require daily treatment or first line therapy (asthma controlled with inhaled steroids, gastro-esophageal reflux treated with daily medication, osteoarthritis requiring daily NSAID, etc.) and/or have moderate disability or morbidity.

LEVEL 3

Chronic conditions that are not controlled with first line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, heart failure with symptoms or uncontrolled hypertension despite complex therapeutic regimen) and/or constant significant disability, but not severe disability.

LEVEL 4

Any acute condition that requires immediate treatment or hospitalization (unstable angina, acute myocardial infarction, stroke, but also bladder outlet obstruction) and/or extremely severe problems; organ failure (end-stage renal disease needing dialysis, oxygen-dependent chronic obstructive pulmonary disease, terminal heart failure); severe sensory impairment (almost complete blindness or deafness, being wheelchair bound) and/or severely affected quality of life, severe impairment in function; delirium by medical (organic) conditions.

RATING MALIGNANCIES

Consistent scoring of severity ratings for various malignancies is a difficult problem. Each malignancy has its own rating system and prognostic indicators, the complexity of which would quickly exceed the aim of the intended simplicity and ease of use of CIRS.

The following general guidelines are intended to provide a reasonably accurate delineation of medical burden for cancer without excessive complexity.

Level 1: Cancer diagnosed in the remote past without evidence of recurrence or sequel in the past 10 years or skin cancer excised in the past without major sequel (other than melanoma).

Level 2: No evidence of recurrence or sequel in the past 5 years.

Level 3: Required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past 5 years.

Level 4: Recurrent malignancy or metastasis (other than to lymph glands) or palliative treatment stage.

These ratings are to be made in the appropriate organ category for a given malignancy.

ORGAN SPECIFIC CATEGORIES

The following organ specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the "judgement strategy" that can be applied to other problems not listed.

If there are several problems in the same system, only the most severe is rated.

HEART

In this category only heart and coronary disease have to be considered (not vascular): coronary arteries disease, heart failure, valvular heart diseases, heart disease secondary to hypertension, endocardities, miocardities, pericardities, arrhythmias (extrasystoles, bundle-branch blocks, atrial fibrillation, PMK placement), heart malignancies. Functional impact must be considered too, e.g. NYHA II heart failure has different value between dependent and independent persons.

0 - No problems

1 -Remote MI (>5 years ago); occasional [exertion] angina; asymptomatic valvular disease

2 -CHF compensated with meds (NYHA I-II); daily anti-angina meds; left ventricular hypertrophy; atrial fibrillation, bundle branch block, daily anti-arrhythmic drugs (even for prophylaxis); PMK placement for asymptomatic bradycardia (relieved by Holter EKG monitoring); valvular disease requiring medical treatment

3 -Previous MI (<5 years ago); abnormal stress test; status post (previous) percutaneous coronary angioplasty, coronary artery bypass graft surgery or other cardiac surgery (valve replacement); moderate CHF (NYHA II-III) or complex medical treatment; bifascicular block; PMK placement for cardiogenic syncope; pericardial effusion or pericarditis

4 -Acute coronary syndrome, unstable angina or acute MI; intractable CHF (NYHA III-IV acute or chronic); marked restriction to the normal activity of daily living secondary to cardiac status

HYPERTENSION

Consider only hypertension severity; organ damage (complications) should be considered into the respective categories.

0 -Normotension

1 -Borderline hypertension; hypertension compensated with salt restriction and weight loss, drug free (when drug therapy is indicated, but the patient does not take meds, the score is at least 2)

2 -Daily antihypertensive meds: hypertension controlled by 1 pill therapy (even fixed doses combinations)

3 -Hypertension requiring two or more pills for control

4 -Malignant hypertension, or hypertension non controlled by complex therapeutic regimen

VASCULAR-HEMATOPOIETIC

Artery disease: carotid atherosclerosis, peripheral arteries disease (PAD), aneurysms (every site);

Venous disease: venous insufficiency, varices, deep venous thrombosis (DVT), pulmonary embolism, primary pulmonary hypertension;

Hematopoietic disease: anemia, leucopenia, thrombocytopenia, hematological malignancy;

Lymphopoietic disease: chronic lymphatic edema, lymphoma, spleen and thymus disease;

Immunologic disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity

0 -No problem

1 -Venous insufficiency, varices, lymphedema; carotid stenosis <70%; hemoglobin 10-12 g/dl (in females), 12-14 g/dl (in males); anemia of chronic "inflammatory" disease

2 -Previous DVT; one symptom of atherosclerosis disease (claudication, bruit, amaurosis fugax, absent pedal pulses) or daily meds (e.g. anti-platelets drugs); PAD IIa-IIb by Fontaine; carotid stenosis >70%; aortic aneurysm <4 cm; hemoglobin 8-10 g/dl (in females), 10-12 g/dl (in males); anemia secondary to iron, B12 vitamin or folate deficiency, or to chronic renal failure; total white blood cell (WBC) 2000-4000/mmc; mild thrombocytopenia (50000-150000/mmc)

3 -DVT or recent DVT (<6 months ago); two or more symptoms of atherosclerosis (see above); PAD Fontaine III or recent/previous angioplasty (with or without stenting); hemoglobin <8g/dl (in females), <10 g/dl (in males); dyserythropoietic anemia; WBC <2000/mmc; severe thrombocytopenia (<50000/mmc)

4 -Pulmonary embolism (acute or recent/previous); atherosclerosis requiring surgical intervention (e.g. aortic aneurysm >4 cm, symptomatic carotid stenosis >70%, PAD Fontaine IV or amputation for vascular causes, etc.); recent/previous vascular surgery; any hematological or vascular malignancy (including multiple myeloma)

In case of immunological disease, score should be assigned by considering blood abnormalities, stadium of organ damage and/or functional disability (2: symptoms controlled by daily meds; 3: symptoms not well controlled; 4: symptoms impossible to be controlled or short time poor prognosis).

RESPIRATORY

In this category we consider COPD, asthma, emphysema, restrictive pulmonary interstitial lung diseases, malignancies of lung and pleura, pneumonia, and smoking status too.

0 -No problem

1 -Recurrent episodes of acute bronchitis; currently treated asthma with prn inhalers when required; cigarette smoker >10 but <20 pack years

2 -Instrumental diagnosis of COPD or pulmonary interstitial disease (x-ray, TC, spirometry); daily prn inhalers (≤2 pharmacological classes); two or more episodes of pneumonia in the last 5 years; cigarette smoker <20 but <40 pack years

3 -exertion dyspnea secondary to limited respiratory capacity, not well controlled by daily meds; required oral steroids for lung disease; daily prn inhalers (3 pharmacological classes); acute pneumonia treated as an outpatient

4 -Chronic supplementation of oxygen; respiratory failure requiring assisted ventilation, or previous (at least one episode); any lung or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered as a disease, and it is rated according to *lifetime pack years*:

Number of cigarette packs smoked per day X Number of years smoked in their lifetime

e.g. 1 pack year = 20 cigarettes/die (1 pack) X 1 year

Ex-smokers should be rated too, but those who have been smoke free for the most recent 20 years would merit a lower rating than currently smoking

Examples:

A. Patient smoking 20 cig/die (1 pack) for 25 years = 25 pack years - CIRS score: 2

B. Patient smoking 40 cig/die (2 packs) for 25 years = 50 pack years – CIRS score: 3

C. Ex-smoker of 20 cig/die (1 pack) for 25 years, he stopped 5 years ago – CIRS score: 2

D. Ex smoker of 20 cig/die (1 pack) for 25 years, he stopped 20 years ago – CIRS score: 1

Classification of COPD could be more specific when instrumental data (objective evidence) are available: blood gases, forced expiratory volume in 1 second (FEV1), etc.

EYES, EARS, NOSE & THROAT, and LARYNX

To simplify the potential complexity of this category it was decided to score according to the severity of the disability created by sensory diseases (degree of limited autonomy and communication), and avoid rating each type of pathology. Sensory impairments should be rated **after** instrumental correction (corrective lenses, hearing aid, etc.).

Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology

Ears: otitis, dizziness, any cause of hearing impairment

Nose & Throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignancies

Larynx: dysphonia, acute and chronic laryngitis, malignancies

0 -No problems

1 -Corrected vision with glasses; mild hearing loss; chronic sinusitis

2 -Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily meds

3 -Severe low vision, partially blind (required an escort to venture out, unable to read newspaper); severe ear impairment (conversational heading still impaired with hearing aid); laryngeal dysphonia (not neurological dysarthria)

4 -Functional blindness/deafness: unable to read, recognize a familiar face, unable to conversational heading, even if "organically" he is not completely blind or deaf; laryngectomy (every cause, especially malignancies); required surgical intervention for vertigo; aphonia secondary to laryngeal impairment.

UPPER GASTROINTESTINAL SYSTEM

This category is comprehensive of the intestinal tract from esophagus to duodenum, and pancreatic trees: dysphagia, GERD, hiatal hernia, esophageal diverticula, any type of gastritis (consider also H. Pylori eradication or not), gastric/duodenal ulcer, acute or chronic pancreatitis, malignancies (comprehensive of gastric lymphoma).

Pay attention that type 1 diabetes is rated under "metabolic".

0 -No problem

1 -Hiatal hernia, GERD or gastritis requiring prn meds; previous ulcer (>5 years ago); previous H. Pylori eradication therapy (>5 years ago)

2 -Daily proton pump inhibitor/anti-acid meds; documented gastric or duodenal ulcer or H.P. eradication therapy within 5 years

3 -Active gastric or duodenal ulcer; positive fecal occult blood test; any swallowing disorder or dysphagia; chronic pancreatitis requiring supplemental pancreatic enzymes for digestion; previous episode of acute pancreatitis

4 -Any type of malignancies (see "*Rating Malignancies*"); previous gastric surgery because of cancer; history of perforated ulcer (gastric surgery not because of cancer, ulcorrhaphy); melena/heavy bleeding from upper GI source; acute pancreatitis

LOWER GASTROINTESTINAL SYSTEM

Comprehensive of the rest of the G.I. system, from small bowel to anus: Whipple's disease, diverticulosis, irritable bowel, malignancies. Constipation is rated, too, by type and frequency of laxatives required, or by history of impaction.

0 -No problems, previous appendectomy, previous hernia repair (without complications)

1 -Constipation managed with prn meds; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adherences, laparocele, etc.); irritable bowel syndrome (few symptoms)

2 -Constipation requiring daily bulk laxatives (psyllium, policarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with meds (>5 years ago)

3 -Bowel impaction/diverticulitis within the last year; daily use of stimulant (irritant) or osmotic laxatives (bysacodil, senna, glycerol, sodium docusate; lactulose, polyethylene glycol) or enemas; chronic bowel inflammation in remission with meds (<5 years ago)

4 -Diverticulitis flare up; active inflammatory disease; current impaction; hematochezia/active bleeding from lower GI source; bowel carcinoma

LIVER AND BILIARY TREES

Comprehensive of liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, autoimmune, idiopathic), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignancies. As the hepato-biliary system is difficult to assess through the physical examination, therefore, laboratory results must be used.

0 -No problem

1 -History of hepatitis (actually normal values of transaminases); cholecystectomy

2 -Cholelithiasis; chronic hepatitis or previous hepatitis (<5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with mildly elevated transaminases (within 3-times normal values); heavy alcohol use within 5 years (to rate in "psychiatric", too)

3 -Chronic hepatitis or any other liver disease with marked elevation of transaminases (>3-times normal values); elevated bilirubin

4 -Acute cholecystitis; any biliary obstruction; active hepatitis/liver cirrhosis; any liver or biliary tree carcinoma

RENAL

This category is exclusive of kidney: kidney stones, acute/chronic renal failure, glomerulonephritis; nephrosic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma.

Bence-Jones proteinuria in multiple myeloma should not be considered.

0 -No problem

1 -Asymptomatic kidney stone; kidney stone passage within the last ten years; pyelonephritis within 5 years; kidney cysts without hematuria

2 -Serum creatinine >1.5 but <3 mg/dl without diuretic or antihypertensive medication (particularly ACE-inhibitors or SRAA blockers); kidney calculi requiring daily meds

3 -Serum creatinine >3 mg/dl or >1.5 mg/dl in conjunction with diuretics, antihypertensive, or bicarbonate therapy; active pyelonephritis; nephrosic syndrome; colic symptoms treated as an outpatient

4 -Required dialysis; renal carcinoma; colic symptoms requiring hospitalization

GENITOURINARY

Ureters, bladder, urethra.

Genitals, prostate, testicles, penis, seminal vesicles.

Uterus, ovaries. *Mammary gland is rated under "metabolic"*.

This category is comprehensive of all GU tract impairments: ureteral or bladder stones, benign prostate hypertrophy (BPH), urinary tract infections (UTI's), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

0 -No problem

1 -Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)

2 -Pathological pap smear (or 2 consecutives abnormal); frequent UTI's (3 or more in the past year) in female or current UTI's; urinary incontinence (not stress) in females; BPH with urinary symptoms (frequency, urgency, hesitancy); status post TURP; any urinary diversion procedure; indwelling catheter; bladder calculi

3 -Prostatic cancer in situ (e.g. incidentally found during TURP); vaginal bleeding; cervical carcinoma in situ; hematuria (any cause); urinary incontinence (not stress) in males; bladder polyps

4 -Acute urinary retention; current urosepsis; any GU malignancies except as above

MUSCULOSKELETAL/INTEGUMENT

This is a very wide category, including: osteoarthritis, osteoporosis, any bone fracture; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized skin cancers; rheumatoid arthritis and polymyalgia rheumatica; muscular injuries (rotator cuff, long head of the biceps); pressure sores; any dermatological disease.

The scores of this category are strictly correlated to the disability they cause; for the evaluation of the level of disability, refer to BADL and IADL.

NOTICE: score the severity of each illness according to the level of disability caused by the same illness in this category, without considering the disability caused by other diseases. For example: a patient affected both by osteoarthritis and hemiplegia from a previous stroke has a high level of disability, but you have to score 2 for disability by osteoarthritis (in this category) and 4 for disability by stroke (in the neurological category); for a patient with both a deforming rheumatoid arthritis and a previous stroke without remaining outcomes you have to score 4 for disability from arthritis (in this category) and 2 for disability from stroke (in the neurological category).

0 -No problem

1 -Requires PRN meds for osteoarthritis (NSAID) or has mildly limited IADL from joint pathology; excised skin cancers (except melanoma); skin infections requiring antibiotics within a year

2 -Daily anti-osteoarthritis meds (NSAID) or use of assisitive devices or little limitation in ADL (previous arthroprosthesis or treated fracture with a low level of remaining disability); osteoporosis without vertebral fractures; daily meds for chronic skin diseases (even local, as psoriasis or pressure sores); non metastatic melanoma; daily meds for rheumatoid arthritis (except steroids) with a low level of disability

3 -Osteoarthritis with a moderate level of disability in ADL; requires chronic treatment with steroids for arthritic conditions or joints' deformities or severely impaired; osteoporosis with vertebral compression fractures

4 -Wheelchair bound for osteomuscular disease; severe joint deformities or severely impaired usage; osteomyelitis; any bone or muscle or connective tissue neoplasm (see "Rating Malignancies"); metastatic melanoma.

Fractures and/or arthroprosthesis (both recent and old) have to be scored according to the level of disability they cause (considering outcomes too), in order to avoid confusion about possible classifications of different fractures or joints. The same for muscular diseases.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

This category includes the "somatic" pathologies of the central and peripheral nervous system: any kind of stroke, neurodegenerative diseases (Parkinson's disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological outcomes, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. It must carefully estimate the severity and prognosis of the illness but also the functional impairment that the illness causes.

0 -No problem (or fewer convulsions in childhood)

1 -Frequent headaches requiring PRN meds without impairment in Advanced ADL; previous TIA (one event); previous epilepsy, actually not treated, without crisis since more than 10 years ago.

2 -Chronic headache requiring daily meds (even for prophylaxis) or with regularly functional impairment in Advanced ADL (bed rest, job withdrawal, etc.); actual TIA or more than one previous TIA; previous stroke without significant residual; mild severity neurodegenerative diseases (see above), treated and well controlled; epilepsy controlled with drugs.

3 -Previous stroke with mild residual dysfunction (hemiparesis, dysarthria); any neurosurgical procedure; moderate severity neurodegenerative diseases (see above), not well controlled by meds; epilepsy in treatment but with periodic crisis.

4 -Acute stroke or previous stroke with severe residual dysfunction (hemiplegia, aphasia, severe vascular dementia) or more than one previous stroke (multi-infarct encephalopathy); severe neurodegenerative diseases (see above) causing disability in ADL; neurological coma.

Alzheimer's disease and dementia should not be rated into this category (Psychiatric and behavioral diseases): Alzheimer's disease should be listed only under psychiatric disorders; if dementia stems from vascular and/or mixed dementia and/or other neurological condition (e.g.

Parkinson's Disease), both "neurologic" and "psychiatric" categories should be endorsed at the appropriate level for severity, considering in this category the stroke and the multi-infarct encephalopathy responsible for the cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

ENDOCRINE-METABOLIC SYSTEM AND BREAST (systemic infections and poisonings too)

Type 1 and type 2 diabetes (organ damage should be considered into the respective categories, like for hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; it includes also hypo- and hyper-thyroidism, hypo- and hyper-parathyroidism, adrenal pathologies (Cushing' or Addison' disease), hypogonadism, hypopituitarism, etc. Malignancies of these glands, both benignant (like thyroid nodules) and malignant (like thyroid or adrenal cancer, vipoma, etc.) are included too.

Even if it is an exocrine gland, breast was included in this category because the authors didn't find a more appropriate one; so it includes the breast cancer too.

Moreover, it includes: electrolyte disorders, sepsis, systemic infections (like tuberculosis, syphilis, AIDS) scored according to their severity and the functional impairment they cause (see general indications) and poisonings (chronic by metals or acute by pesticides or carbon monoxide).

0 -No problem

1 -Diabetes and/or dyslipidemia compensated with diet; mild obesity (BMI 30-35 kg/m^2); hypothyroidism in replacement therapy (L-thyroxin); hyperthyroidism caused by Plummer' adenoma surgically treated.

2 -Diabetes compensated with oral hypoglycemic drugs or insulin (hemoglobin A1c <7%); dyslipidemia well controlled by daily meds (c-LDL lower than the recommended target according to the individual global cardiovascular risk); moderate obesity (BMI 35-45 kg/m^2); hyperthyroidism (Basedow, Plummer) in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease.

3 -Diabetes not well compensated by therapy (hemoglobin A1c 7-8.5%, presence of complications); dyslipidemia not well controlled (c-LDL higher than the recommended target according to the individual global cardiovascular risk; for instance, c-LDL>100 mg/dl in patients with previous myocardial infarction or stroke); severe obesity (BMI >45 kg/m^2); symptomatic hyperparathyroidism (for instance, hypercalcaemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization.

4 -Uncontrolled diabetes (hemoglobin A1c >8.5%) or one diabetic ketoacidosis or nonketotic hyperosmolar coma during the past year; genetic uncontrolled dyslipidemia; acute adrenal failure during hormonal replacement therapy; any neoplasm of thyroid, breast, adrenal gland (see "Rating Malignancies").

NOTICE: when the patient is not treated with drug therapy for diabetes or dyslipidemia but he should be for the optimal control of the pathology (for instance, hemoglobin A1c >7%, total cholesterol >250 mg/dl), score the pathology according to the laboratory values, which really define its severity.

PSYCHIATRIC AND BEHAVIORAL DISEASES

This category includes both dementia and related behavioral disorders (psychosis, anxiety, depression, agitation) and all the pre-existing and/or not related to dementia psychiatric disorders. Since this is the only item analyzing patient's mental status (all the others refer to physical status), it is very important to evaluate it considering carefully further information derived from the Comprehensive Geriatric Assessment (MMSE; Geriatric Depression Scale, Neuro-Psychiatric Inventory if available) (8, 9).

0 -No psychiatric problem or history thereof

1 -Minor psychiatric condition or history thereof: previous (occasional) psychiatric treatment without hospitalization; major depressive event and/or use of antidepressants more than 10 years ago without hospitalization; occasional use of minor tranquilizers (e.g. BDZ; even if as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25-28).

2 -A history of major depression (according to DSM-IV criteria) within the last 10 years (treated or untreated); mild dementia (MMSE 20-25); previous admission to Psychiatric Department for any reason; history of substance abuse (more than ten years ago, including alcoholism).

3 -Current major depression (according to DSM-IV criteria) or more than two previous major depression episodes in the past 10 years; moderate dementia (MMSE 15-20); current and usual usage of daily anti-anxiety meds (even as hypnotherapy for insomnia); current or within the past ten years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.

4 -Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management (psychiatric emergency, as attempt at suicide or severe depression with suicide purpose, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse; severe agitation from dementia); severe dementia (MMSE <15); **delirium** (acute confusion or altered mental status for medical (organic) reasons: in this case you have to codify also the medical cause in its own category with the appropriate level of severity).

It could be requested psychiatric consult for this category; dementia and depression, the most frequent diseases in the elderly, can be scored in details using the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse and all the others) has to be scored according to the level of functional impairment or disability they cause.

19.3. Deauville Criteria for PET Scan Interpretation (Meignan, 2009)

Interpretation

- A visual analysis using the 5-point scale should be applied
- The preferable reference scale should be the mediastinum and the liver

Scoring per the five point scale

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately increased compared to the liver at any site.
5. Uptake markedly increased compared to the liver at any site and/or new sites of disease.

19.4. IWG Response Criteria for NHL (Cheson, 2014)

Table 16: IWG Response Criteria for NHL (Cheson, 2014)

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Table 16: IWG Response Criteria for NHL (Cheson, 2014) (Continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

19.5. Cairo-Bishop Definitions of Tumor Lysis Syndrome

Table 17: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Laboratory Parameter	Laboratory Result
Uric Acid	≥ 476 µmol/L(≥ 8.0 mg/dL) or 25% increase from baseline
Potassium	≥ 6.0 mmol/L (≥ 6.0 mEq/L) or 25% increase from baseline
Phosphorous	≥1.45 mmol/L (≥ 4.5 mg/dL) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/L(≤ 7.0 mg/dL) or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s) (Cairo, 2004).

Table 18: Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted)
2. Cardiac arrhythmia / sudden death
3. Seizure[a]

ULN = Upper limit of normal. (Cairo, 2004)
[a] Not directly attributable to a therapeutic agent.

Table 19: Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death[a]	Death[a]

ADL= activities of daily living; LTLS = laboratory tumor lysis syndrome; TLS= tumor lysis syndrome; ULN = upper limit of normal (Cairo, 2004)
[a] Probably or definitely attributable to clinical TLS.

19.6. EQ-5D

Health Questionnaire

(English version for the UK)

(validated for use in Eire)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*eg work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

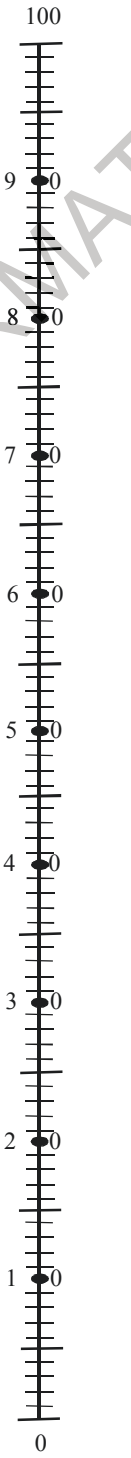
Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

Best imaginable health state



Worst imaginable health state

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

19.7. FACT-LYM

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
E83	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

19.8. Pregnancy Prevention Risk Management Plan

The Pregnancy Prevention Risk Management Plan is a standalone document.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName:
Title:
Date: Monday, 24 June 2019, 08:41 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

The ROBUST clinical database was locked on 12 Apr 2019 for the primary analysis. All patients have been off study treatment for over 1 year. The study did not meet the primary endpoint of demonstrating superiority in progression-free survival (PFS) compared to placebo plus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone therapy (R-CHOP). Protocol Amendment 4 removes the requirement of follow-up assessments for subjects continuing in the study except for overall survival (OS) and second primary malignancy (SPM) follow-up. Given the study outcome, observed significant slowing of the event rate, and expected course of the disease, it is reasonable to make this change.

For many patients, diffuse large B-cell lymphoma (DLBCL) is a curable disease. Most relapses occur within the first 12 to 18 months and the event rate slows significantly approximately 12 months after diagnosis, as has been observed in the ROBUST Study. While some patients may relapse after 2 years (defined as late relapses), the rate of late relapse after this time is low and patients who are event free at 24 months are considered to have an overall survival equivalent to that of the age- and sex-matched general population (Maurer, 2014; Feldman 2014). Therefore, extensive follow-up of the remaining patients in the ROBUST study would place a significant burden on patients and clinical professionals without any reasonable expectation of acquiring data which would benefit patients or add to the scientific understanding of the disease.

These changes will also decrease study related radiation exposure and blood draws and allow greater flexibility to investigators and patients for overall disease management. The specified assessments (summarized in Table 5) will no longer be required after the 12 Apr 2019 final analysis and will not be subject to case report form data collection. Long-term follow-up and data collection for OS and SPM remain mandatory. Specific guidance is provided in the amendment.

Changes to the protocol due to the above rationale are summarized below:

- Protocol Summary: Study Design and Length of Study - After the primary analysis, only SPM and OS information will be collected.
- Section 4.1.7: Follow-up Period - After the primary analysis, only SPM and OS information will be collected.
- Section 4.2: Figure 3 Overall Study Design - After the primary analysis, only SPM and OS information will be collected.
- Section 4.3: Study Duration - After the primary analysis, only SPM and OS information will be collected.
- Table 5: Table of Events - Clarified that the following assessments will no longer be required for data collection after the 12 Apr 2019 primary analysis:
  - Physical examination, vital signs, complete blood count with differential, lactate dehydrogenase, quality-of-life assessment, performance status, , computed

tomography, response assessment, subsequent antilymphoma therapy, and progression

- Section 6: Procedures - Select follow-up assessments (specified in Table 5), are no longer required after the 12 Apr 2019 primary analysis.

Minor grammatical edits were included to ensure consistent word use and clarity in protocol changes described above.

The following administrative change was also made:

- Changed the Medical Monitor from due to internal Celgene staff changes.

References

Feldman T, Gromko L, Protomastro EA, Starovoitova L, Mato AR, Glisch C, et al. Relapses of diffuse large b-cell lymphoma in rituximab era are limited to the first two years after frontline therapy. Blood 2014;124:1307.

Maurer MJ, Ghesquieres H, Jais JP, Witzig TE, Haioun C, Thompson CA, et al. Event-free survival at 24 months is a robust endpoint for disease-related outcome in diffuse large b-cell lymphoma treated with immunochemotherapy. JCO 2014;32(10):1066-73.

1. JUSTIFICATION FOR AMENDMENT

The amendment includes two changes:

- Changed the Medical Monitor from due to internal Celgene staff changes (Page 2).
-

For many patients DLBCL is a curable disease. However, approximately a third of patients will either not respond well to initial therapy or respond but relapse early, usually in the first year after the first treatment. Most relapses occur within the first 12 to 18 months and the event rate slows significantly approximately 12 months after diagnosis. While some may relapse after 2 years (defined as late relapses) the rate of late relapse after this time is low and patients who are event free at 24 months are considered to have an overall survival equivalent to that of the age- and sex-matched general population (Maurer, 2014; Feldman 2014). Therefore, incorporation of these late events can be complicated by competing risks, especially in older patients with comorbid health conditions.

A recent retrospective study demonstrated that relapse rate after 2 years was low (5.9%) in patients with DLBCL who achieved complete response (CR) after R-CHOP (Kang, 2018). Of particular interest, late relapse was associated with favorable baseline clinical characteristics such as GCB subtype and lower IPI scores (IPI 2 versus IPI2) compared with patients with early relapse. Early relapses were associated with the ABC subtype and higher IPI scores which have substantially worse outcomes (Kang, 2018).

The ROBUST trial is Phase 3 study of oral lenalidomide plus R-CHOP21 × 6 versus placebo-R-CHOP21 × 6 in patients with previously untreated ABC-type DLBCL. These patients have the highest unmet need with associated worse outcomes and early relapse (within first year) following initial therapy. However, those who respond and achieve 2 years event free could be considered to have an overall survival rate similar to people in the general population.

A significant slowing of the PFS event rate in the ROBUST study was observed over the past year and this may be explained by the information described above. An early relapse is expected in the ABC population followed by a falling event rate as subjects have a decreasing probability of progression the longer they remain event free and reach the 18 months to 2-years post treatment start time period. (The median follow-up for the ROBUST study subjects through the end of 2018 was approximately 24.4.months.) Following this time period, it is anticipated that future events can be characterized as late events that are potentially not lymphoma related, and that will potentially complicate analysis.

Over the course of the past year the Independent Radiology Adjudication Committee (IRAC) assessed PFS event rate has fallen from approximately 8 events per month to the current rate of 2 to 3 events per month (~6 per quarter)

2. REFERENCES

Feldman T, Gromko L, Protomastro EA, Starovoitova L, Mato AR, Glisch C, et al. Relapses of diffuse large b-cell lymphoma in rituximab era are limited to the first two years after frontline therapy. Blood 2014;124:1307.

Kang J, Lee K, Hong JY, Yoon DH, Kim S, Park JS, et al. Low relapse rate after 2 years in patients with diffuse large b-cell lymphoma (DLBCL) treated with R-CHOP and achieved complete response [abstract]. In: The 60th Annual Meeting of the American Society of Hematology; 2018 Dec 2; San Diego, CA. Abstract nr 2996.

Maurer MJ, Ghesquieres H, Jais JP, Witzig TE, Haioun C, Thompson CA, et al. Event-free survival at 24 months is a robust endpoint for disease-related outcome in diffuse large b-cell lymphoma treated with immunochemotherapy. JCO 2014;32(10):1066-73.

1. JUSTIFICATION FOR AMENDMENT

Major changes included in this amendment are summarized below:

- Revised lenalidomide / placebo dose modification rules for neutropenia and thrombocytopenia toxicities. Considering the aggressive nature of the disease under study, diffuse large B-cell lymphoma (DLBCL), and the known overlapping hematologic toxicity of R-CHOP and lenalidomide, the dose modification rules were re-evaluated based on the investigators' feedback. This revision has been recommended by the Study Steering Committee (SSC) after careful benefit/risk evaluation. The purpose of this revision is to maintain the dose and intensity of the regimen as much as possible, while managing the hematology toxicity effectively, thus aiming to provide optimized overall benefit for the patients (Table 8).

The amendment also includes several other minor clarifications and corrections:

- The 'All Cycles Day 1' column under the Treatment Period of the Table of Events was revised to state 'Cycles 1-6 Day 1' (Table 5).
- Changed the 3 months prior to Cycle 1 Day 1 (C1D1) tumor biopsy and bone marrow biopsy/aspirate collection windows to 8 weeks prior to C1D1. Upon further evaluation with the SSC, it was assessed that subjects enrolling after an 8-week interval are likely to have a more indolent course of disease than the expected patient population for this study, which takes into account the aggressive nature of DLBCL. Therefore, patient selection bias may be introduced if a significant number of these subjects are enrolled (Table 5, Section 4.1.2, and Section 6).
- Clarified that 'Pregnancy Testing – for FCBP with Regular or No Menstrual Cycles' and 'Pregnancy Testing – for FCBP with Irregular Menstrual Cycles' is required 24 hours prior to lenalidomide/placebo dosing (instead of 24 hours prior to C1D1), and once during day -10 to -14 to highlight that the timing of the pregnancy testing is dependent on lenalidomide/placebo dosing and not on other components of R-CHOP dosing. The abbreviation 'FCBP' stated above means females of childbearing potential (Table 5 and Section 6).
- Typographical error was deleted for Quality of Life Assessment in the Table of Events, as it incorrectly indicated a collection time point at Cycle 6 Day 1. The timing of this assessment is the same as for computed tomography (CT) scan collection and was correctly stated in Section 6 (Procedures). Consequently, this table has been updated to align with the timing stated in Section 6 (Table 5).
- Clarification that the need to perform a Bone Marrow Biopsy at the End of Treatment Visit is dependent on the post Cycle 6 positron emission tomography (PET) scan results, and is required only if the Bone Marrow Biopsy at Screening is positive and there is an equivocal post Cycle 6 PET scan finding in the bone marrow. The post Cycle 6 PET scan is performed once, 3-4 weeks after completing Cycle 6 (Table 5 and Section 6).

- Administration of Mandatory Primary Neutropenia Prophylaxis added to the Table of Events and Procedures section, to emphasize the protocol requirement of primary neutropenia prophylaxis at every cycle during Cycles 1-6 (Table 5 and Section 6).
- Further clarified that the Tumor Lysis Syndrome (TLS) Assessment at Cycles 1-2 Day 8 has a window of ± 1 day (Table 5 and Section 6).
- Clarification added to Adverse Event and Concomitant Medications/Procedures collection schedule to emphasize that the period through 28 days after the last dose of investigational product, applies to the optional two additional doses of single agent rituximab, if administered (Table 5 and Section 6).
- Allowed local laboratory results to confirm eligibility if Screening Central Laboratory results are not available and it is necessary to urgently start treatment. This applies to eligibility laboratory requirements for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Creatinine Clearance, Complete Blood Count (CBC) with Differential, and Serum Chemistry. In this case, the Celgene medical monitor must be consulted, the data submitted on the case report form (CRF), and a central laboratory sample must still be collected prior to first dose. Due to the aggressive nature of DLBCL, there are cases in which treatment must be urgently and immediately started at the investigator's discretion. In these cases, it may be possible for eligibility criteria to be confirmed against local laboratory results instead of Central Laboratory results (Section 6).
- Allowed Lactate Dehydrogenase (LDH) local laboratory results to be used at Screening, if Central Laboratory results are not available and it is necessary to urgently start treatment (Section 6).
- Clarified that if RNA viral load for Hepatitis C Virus (HCV) testing is needed, the test is done by local laboratory, as it is not automatically performed by the Central Laboratory (as opposed to HBV viral DNA load testing, which is automatically performed by the Central Laboratory when indicated by the protocol) (Section 6).
- Clarified that local pathology CD20+ status may be used to determine eligibility, instead of the Central Pathology result, if the local and Central Pathology disagree on CD20+ status for patients with activated B-cell (ABC) type confirmed by Central Pathology. The intent of protocol amendment 1 was for the disagreement on diagnosis between local and Central Pathology to also apply to CD20+ status (Section 7.2).
- Added PET scan finding as another option to determine bone marrow involvement by lymphoma, when assessing absolute neutrophil count (ANC) and platelet count for eligibility (Section 7.2).
- Corrected typographical error to state that both AST and ALT values must be ≤ 3.0 x upper limit of normal (ULN) or ≤ 5.0 x ULN in the case of documented liver involvement by lymphoma. The intent was to always require both values to determine eligibility (Section 7.2).

- Allowed possibility for local radiation to be administered as optional prephase treatment to subjects in cases of medical emergencies, in which prephase treatment with corticosteroids is not considered adequate. This is not expected to be a common occurrence (Section 8.2.1).
- Revised situations in which an investigator may prospectively choose to give local radiotherapy after study chemotherapy per local practice, including subjects at higher risk for central nervous system (CNS) lymphoma, which may be standard practice for these subjects (Section 8.2.2, Section 10.6.2).
- Added recommended dosing schedules for administration of mandatory primary neutropenia prophylaxis, along with clarification that this requirement applies to all subjects at every cycle during Cycles 1 – 6. These two schedules of administration were recommended by the SSC and was endorsed by the Data Monitoring Committee (DMC) (Section 8.2.3).
- Removed requirement to administer lenalidomide as the first investigational product taken on Day 1 of every cycle.

  (Section 8.2.5).
- Clarified that dose interruptions (in addition to reductions) can be done for reasons in addition to what is stated in Table 8, per the investigator's discretion. In previous protocol versions, only reductions are mentioned (Section 8.2.5).
- Allowed intravenous dexamethasone as a substitution for prednisone on Day 1 of every cycle to accommodate local practice and formulation availabilities (Section 8.2.10).
- Clarified the intent of the Requalification Criteria for Subsequent Treatment Cycles is for non-hematological toxicities to be resolved to ≤ Grade 2, instead of all other toxicities, as originally stated. Exceptions to ANC and platelet count criteria were also clarified for cases of spleen involvement secondary to lymphoma, per investigator assessment (Section 8.2.12).
- Clarified exceptions to neutropenia and thrombocytopenia lenalidomide / placebo dose modification rules for cases of spleen involvement secondary to lymphoma, per investigator assessment (Table 8).
- Clarification added to the titles of Tables 8, 10, 11, and 12 (Table 8, Table 10, Table 11, and Table 12).
- Corrected typological errors throughout the document (Table 2, Section 7.2, Section 18, and Table 19).

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

-
- Allowed submission of core needle tumor biopsy material for eligibility. provided technical validation data in showing that core needle biopsy tissue was acceptable for use in the gene expression profiling (GEP) assay that is the basis for Activated B-cell (ABC) subtype subject selection in this protocol. The validation data demonstrates that the GEP assay can be performed with core needle tumor biopsy specimens without compromising assay performance. In certain situations a surgical biopsy would pose an unacceptable risk and previously such subjects had to be excluded. With this amendment it will be possible to screen subjects who must use a core needle biopsy. (Sections 6 and 7.2)
- Allowed local pathology diffuse large B-cell lymphoma (DLBCL) diagnosis to prevail in the event that Central Pathology confirms ABC subtype but is not able to confirm a DLBCL diagnosis. In this case, the subject may enroll at investigator discretion. A retrospective adjudication by a second Central Pathologist will be performed for the purposes of defining the modified intent to treat (mITT) population; primary analysis is per the intent to treat (ITT) population. According to an internationally recognized, expert hematopathologist, , this should be a rare (< 1%) occurrence, and therefore does not pose a major risk to the existing ITT sample size. This provision was added to allow the possibility of adjudication by an expert pathologist in difficult cases. (Section 7.2)
- Changed the hemoglobin inclusion criterion 11c from ≥10 g/dL (6.2 mmol/L) to ≥7.5 g/dL (4.7 mmol/L) for all subjects, and allow packed red blood cell (PRBC) transfusions as needed during Screening (PRBC transfusions were already permitted during the Treatment Period). Many DLBCL patients will have depressed hemoglobin values regardless of whether they have documented bone marrow involvement by lymphoma. Additionally, lenalidomide impact on hemoglobin value is much less common than neutropenia and thrombocytopenia and the protocol does allow transfusions as needed. (Sections 7.2 and 9.2.1)
- Included, at investigator discretion, subjects > 80 years if their Eastern Cooperative Oncology Group (ECOG) performance status is ≤ 1; each of their individual organ system scores is ≤ 2 using the Modified Cumulative Illness Rating Scale (CIRS); and if they would otherwise be eligible for full-dose rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) per local practice. (Other entry criteria address specific co-morbidities such as cardiac function [left ventricular ejection fraction < 45% excluded] and adequate bone marrow, kidney, and liver function [minimum laboratory values]). In the ECOG MC078E study, 9% of the subjects were ≥ 80 years, and the safety profile of the elderly study subjects was approximately the same as for the study subjects < 80 years, with no significant safety

signal. Additionally, this option will more closely align the protocol with standard practice in some countries. (Table 5 and Sections 6, 7.2, and 19.2)

- Included hepatitis C virus (HCV) positive subjects who do not have an active hepatitis C infection and who are otherwise acceptable candidates for R-CHOP chemotherapy. All subjects will be tested for HCV antibodies at Screening by the Central Laboratory, and the investigator must further test HCV+ subjects by either FibroScan® (liver ultrasound for fibrosis), liver biopsy, ribonucleic acid (RNA) viral load or other local practice. Within the current Revlimid® Investigator's Brochure (edition 18) Hepatitis C reactivation is not noted as a treatment-emergent adverse event. In addition, there was an effective HCV drug (Gilead) approved recently, and DLBCL subjects with acceptable liver function and fully controlled infection are routinely treated with R-CHOP in areas of high endemic HCV infection. (Table 5, Sections 6, 7.2, and 7.3)
- Excluded T-cell / histiocyte rich DLBCL cases from the study population. This change was made on the recommendation of the expert hematopathologist, The GEP of such subjects would not be typical because of the limited number of large B cells that are embedded within a background of abundant T cells and histiocytes, resulting in a very low tumor cellularity. Additionally, the high inflammatory component of the microenvironment could potentially overlap with Hodgkin's Lymphoma, potentially making it difficult to discriminate from ABC type DLBCL. (Sections 7.2 and 7.3)
- Excluded Post-transplant Lymphoproliferative Disorder (PTLPD) cases from the study population even if they are a B-cell type and the ABC subtype. The rationale is that PTLPD is considered a separate entity from mature B-Cell neoplasms, which include DLBCL, according to the World Health Organization 2008 classification. (Section 7.3)
- Allowed pre-phase corticosteroid treatment per local practice, with a recommended limit of 100 mg/ day prednisone or equivalent for 10 days; rather than mandating a limit of 1 mg/kg/day for 7 days. This would accommodate the variety among local practices without unnecessarily excluding an otherwise eligible subject and without impacting the essential intent of no prior anti-lymphoma treatment. Additionally, pre-phase corticosteroid treatment for elderly subjects in general may be useful (Pfreundschuh 2010). (Sections 7.2 and 8.2.1)
- Changed pneumocystis prophylaxis from "required" for all subjects to "permitted". At most sites pneumocystis prophylaxis is a local standard of care for all patients receiving R-CHOP-14, and for the elderly who receive R-CHOP-21; however, the practice varies for patients < 65 years who receive R-CHOP-21. Additionally, there is potential overlap with the myelotoxicity profile of Bactrim®, a common prophylactic drug, and lenalidomide + R-CHOP. Therefore, the protocol requirement was changed to accommodate local practice and to allow the investigator to weigh the risk / benefit on an individual subject basis. (Section 9.2.2)

- Allowed lenalidomide/placebo - R-CHOP *regimen* modifications, at investigator discretion, in the event of HCV infection or reactivation; or for the following grade 3 toxicities: nausea/vomiting, infection requiring intravenous (IV) antibiotics or hospitalization, or other non-hematologic toxicities. For other toxicities, modification should be in accordance with respective product labels. (Section 8.2.11 and Table 12)
- Allowed individual drug dose modifications for cyclophosphamide, doxorubicin and vincristine. Certain clinical situations may require the modification of individual drugs of the R-CHOP regimen, for example if the toxicity is clearly attributable to just one or two of these drugs, and when it would still be reasonable to continue with the chemotherapy regimen. (Sections 8.2.7; 8.2.8; 8.2.9; Table 10 and Table 11)
- Allowed rituximab administration over two days at the beginning of each cycle from Day – 1 through Day 3 to better manage potential infusion reactions on account of high tumor burden or bulky disease; and to accommodate various standard regional practices on this global study. (Section 8.2.6)
- Allowed IV methylprednisone as a substitution for either IV or PO prednisone on Day 1 only of every cycle to accommodate local practice, compound, and formulation availability. (Section 8.2.10)
- Changed to the most current International Working Group (IWG) Response Criteria for non-Hodgkin's lymphoma (NHL) (Cheson 2014 from Cheson 2007). As a consequence, the End of Treatment bone marrow biopsy for subjects otherwise in CR was removed; this is according to the new criteria where a positron emission tomography (PET) negative bone marrow will suffice to confirm a complete response (CR). (A subject with lymphomatous involvement of the bone marrow at Screening, who has an equivocal post Cycle 6 PET scan finding in the bone marrow, requires a repeat bone marrow biopsy; if the biopsy is negative the subject may then be classified as a CR.) However, the baseline bone marrow biopsy will be retained to document any discordant small cell component; it is also useful to screen out myelodysplastic syndrome; and there are other entry criteria related to neutrophil and platelet counts that require confirmation of baseline bone marrow involvement. As a second consequence, the B-symptom assessment will also be removed as this is not a component of the revised criteria. (Protocol Summary, Section 4.1.2, Table 5, Section 6, Appendix 19.4, and article references throughout the text)
- Allowed for combined PET-computed tomography (CT) without contrast as per local standards at Midcycle; End of Treatment; and *for PET negative (CR) subjects only*, also during the Follow-up Period. There is a key restriction that progression may not be scored on PET positivity alone, but must be confirmed by CT with contrast or a biopsy of the PET positive lesion. This option is consistent with the new IWG Response Criteria for NHL (Cheson 2014). (Sections 4.1.3, 4.1.4, 4.1.5. and 6)

Minor clarifications and corrections included in this amendment are summarized below:

- Added the informal study name "ROBUST" to the title page. The study was named to allow easier conversational identification for subjects and health care professionals.
- Explained that the assay used for ABC subtype subject selection is technically validated, but that it does not have the marketing approval by a health authority beyond *Conformité Européenne* (CE) marking in the European Union. (Section 1.2.1)
- Defined the protocol specific meaning of the term Midcycle (once between Weeks 9 – 12 which is after Cycle 3 but before Cycle 4) and thereafter treated it as a proper noun with capitalization. (Protocol Summary; Sections 4.1.3, 6; and throughout the text)
- Clarified that while it is acceptable to perform a combined PET-CT, or a standalone PET in addition to the protocol required CT scan at the Midcycle evaluation, treatment decisions to switch therapy should not be based solely on the PET results. This position is supported by the International Conference on Malignant Lymphoma Imaging Working Group recommendations which explain that the positive predicative value of interim PET in DBLC is variable. (Section 4.1.4)
- Corrected the visit window inconsistencies for the Day 1 assessments for Cycles 2-6. Dosing and tumor lysis syndrome (TLS) assessment have a ± 1 day window and should occur on the same day. All other assessments have a ± 3 day window. (Table 5, and Sections 6 and 8.2)
- Split and re-ordered the first few inclusion criteria, so that more precise reasons for screen failure may be quantitatively tracked. (Section 7.2)
- Clarified that the eligible antibody and antigen profile described in exclusion criterion 4c describes a successfully treated hepatitis B-virus (HBV) infection. (Section 7.3)
- Removed the requirement to take prednisone after lenalidomide on Days 2-5. The two drugs are not expected to have any PK interactions. (Section 8.2.10)
- Confirmed that mandatory neutropenia prophylaxis is "primary" prophylaxis where growth factors are to be administered at the beginning of R-CHOP treatment and prior to a decrease in absolute neutrophil count (ANC) value. (Sections 8.2.3 and 9.2.1)
- Changed the 2 months prior to Cycle 1 Day 1 (C1D1) tumor biopsy and bone marrow biopsy/aspirate collection windows to be 3 months prior to C1D1. This minor change will reduce re-biopsies just for this trial in subjects who have already been diagnosed and staged. (Table 5, and Sections 4.1.2 and 6)
- Changed the 28 days prior to C1D1 PET and CT scan collection windows to be 6 weeks prior to C1D1. This change will require fewer subjects who have already had imaging to repeat their scans just for this trial, and thus reduce radiation exposure. (Table 5, and Sections 4.1.2 and 6.)
- Revised pregnancy testing to occur at a *minimum* of every 28 days rather than exactly at every 28 days. The option to do more frequent testing was actually more

convenient for study subjects as the treatment cycles, which are followed by a safety and pregnancy assessment, are 21 days in length, not 28 days. This schedule is consistent with the Pregnancy Prevention Plan applicable to all lenalidomide studies and with the RevAssist pregnancy prevention guidelines applicable to Revlimid marketed product. (Table 5, Section 6.0)

- Corrected pregnancy counseling at baseline to require a single counseling session one time between signing the informed consent form (ICF) and Day 1 dosing. This is consistent with the Pregnancy Prevention Plan which requires one counseling session prior to every dispensing of lenalidomide. (Table 5, Section 6.0)
- Deleted the explanation of how to subdivide tumor biopsy formalin-fixed paraffin-embedded (FFPE) blocks for Central Pathology submission. Central Pathology will be responsible for sample slide preparation from a submitted tumor block; and the separate Central Pathology Laboratory Manual will provide necessary sample processing details. (Section 6.0)
- Allowed the lower threshold for ANC and / or platelet counts to include lymphoma involvement of the spleen, in addition to the previously allowed lymphoma involvement of the bone marrow. Patients with spleen involvement by lymphoma (as evidenced by splenomegaly) often have depressed ANC and / or platelet values and R-CHOP treatment would still be warranted. (Section 7.2)
-
- Changed the 2-sided p-value to a 1-sided p-value in the interim analysis section at the recommendation of the data monitoring committee statistician since the 1-sided p-value is more appropriate and easier to understand for futility analysis. (Section 10.8)
- Clarified that in medical emergency cases, investigators are free to un-blind their subject's treatment assignment via the IVRS. In such cases it is not required to contact the Medical Monitor prior to breaking the blind; Celgene permission is not required. Additionally, there is no emergency unbinding PIN required. (Section 13.2)
- Added the requirement for investigators to share a summary of study results with their subjects at the time results of the study are made available to the public. Celgene will provide the relevant summary written for a lay person to the investigator. (Section 14.2.)
- Added additional references to Section 18 and cited throughout the document as appropriate.