DISCLOSURE

REDACTED PROTOCOL AMENDMENT 4

CC-5013-NHL-007

A PHASE 3, DOUBLE-BLIND RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE (CC-5013) VERSUS RITUXIMAB PLUS PLACEBO IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENT LYMPHOMA

The "AUGMENT" Trial

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A PHASE 3, DOUBLE-BLIND RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE (CC-5013) VERSUS RITUXIMAB PLUS PLACEBO IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENT LYMPHOMA

The "AUGMENT" Trial

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CCI [redacted]

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{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
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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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
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, International Council for Harmonization (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SUMMARY

Study Title:

A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Placebo in Subjects With Relapsed/Refractory Indolent Lymphoma.

Indication: Relapsed/refractory indolent lymphoma

Objectives: To evaluate the efficacy and safety of rituximab plus lenalidomide combination therapy in subjects with relapsed/refractory indolent lymphoma

Study Design:

This Phase 3 multicenter, double-blind, randomized study is designed to evaluate the efficacy and safety of rituximab plus lenalidomide versus rituximab plus placebo. The overall study design is described in Figure 1. The study is divided into the Screening Period, Treatment Period, and Follow-up Period. It is planned to randomize 350 subjects.

Upon giving written informed consent, the subject enters the Screening Period to determine eligibility. All Screening assessments must be completed within 28 days prior to randomization. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either the experimental arm (rituximab plus lenalidomide) or control arm (rituximab plus placebo) at 1:1 ratio.

The subject will enter the Treatment Period once the subject has fulfilled the required assessments in the Screening Period and has been randomized. The treatments will be given as described in detail in Section 8 and must begin as soon as possible after randomization but no later than 1 week after randomization. The subjects will receive protocol-specified treatments for a maximum of 12 cycles or until relapse or progression of disease, withdrawal of consent, or unacceptable toxicity. All randomized subjects will be assessed for disease progression (PD) and overall survival (OS) during the study using the schedule described in Table 1. This includes all subjects who discontinue the protocol-specified treatment for any reason without documented evidence of clinical and/or radiological disease progression. If a subject withdraws consent, but agrees to continued collection of outcome data, these follow-up activities will continue.

Upon completion or early discontinuation of the protocol-specified treatments (see Section 8, Description of Study Treatments), all subjects will enter the Follow-up Period. In the Follow-up Period, subjects will be followed for disease progression, subsequent anti-lymphoma therapy and CCI development of any second primary malignancies (SPMs) and OS using the schedule described in Table 1.

Efficacy determination for the primary endpoint will be based upon progression-free survival (PFS) as determined by the Independent Review Committee (IRC). See Section 10 for a description of the Statistical Analysis Plan (SAP).

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study according to DMC charter.

The study will be conducted in compliance with Good Clinical Practices (GCPs).

Study Population

Subjects must have an investigator-assessed diagnosis of relapsed/refractory indolent lymphoma, defined in this clinical trial as Grade 1, 2 or 3a follicular lymphoma or marginal zone lymphoma. Subjects must have been previously treated for their lymphoma with systemic therapy (chemotherapy, immunotherapy, or chemoimmunotherapy), must be refractory to or have relapsed after their last treatment, as of Amendment 3, must have received at least two previous doses of rituximab and must not be rituximab-refractory. Subjects must have at least one measurable lesion by computed axial tomography (CT) or magnetic resonance imaging (MRI) scan, and must have adequate bone marrow function, liver function and renal function.

Length of Study

The expected accrual duration is 40 months. Subjects will receive protocol-specified treatment for a maximum of 12 months or until relapse or progression of disease, withdrawal of consent or unacceptable toxicity. Subjects will be followed for survival, disease progression, subsequent anti-lymphoma therapies, and second primary malignancies (SPMs) until 5 years after the last subject has been randomized. Thus, the duration of the entire study will be approximately 8 years (accrual period of approximately 3 years plus 5 years from last subject randomized).

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 CCI [redacted] analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

Study Treatments

Experimental arm: Rituximab + Lenalidomide

- Rituximab - 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

  plus

- Lenalidomide - 20 mg once daily on Days 1 - 21 every 28 days up to 12 cycles.

Versus

Control arm: Rituximab + placebo

- Rituximab - 375 mg/m^2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5

  plus

- Placebo (identical matched capsule) - once daily on Days 1-21 of every 28-day cycle up to 12 cycles.

Overview of Efficacy Assessments

The IRC will utilize the 2007 International working group (IWG) criteria for malignant lymphoma (Cheson, 2007), without the use of PET scan, for efficacy determination to assess response and PFS, as described in details in the IRC charter. The investigator will also use the 2007 IWG criteria for assessment of response and progression/relapse. In addition to CT/MRI scan and bone marrow biopsy to assess response and progression, subjects with gastric MALT

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lymphoma will also undergo upper gastrointestinal endoscopy as part of response assessment. Overall survival (OS), event free survival (EFS), time to next anti-lymphoma treatment (TTNLT), CCI [redacted]

Overview of Safety Assessments

Safety will be monitored throughout the study. Safety evaluations will include adverse event (AE) reporting, SPM reporting, physical examinations, vital sign measurements, concomitant medications/procedures, and clinical laboratory safety tests. All AEs and concomitant medications will be assessed and recorded from the time informed consent is obtained.

Dose modification rules and rules for discontinuation due to toxicity are outlined in Section 8. Subjects who discontinue treatment due to toxicity will enter the Follow-up Period.

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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 the investigational product (IP).

1.1. Indolent Lymphoma

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies with differing patterns of clinical behavior and responses to treatment (Armitage, 1993). Most of the NHLs are of B-cell origin. Indolent NHLs (iNHL), also referred to as low grade lymphomas, are a group of incurable slow-growing lymphoma and represent more than half of NHL (Swerdlow, 2008; Arcaini, 2012; Sousou, 2010). The major types of iNHL include follicular lymphoma (FL), marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia (WM), and small lymphocytic lymphomas (SLL). The most common subtype of iNHL is FL, constituting approximately 70% of the iNHL (Sousou, 2010; Bello, 2012). MZL accounts for 5 to 17% of all NHL in the adults (Zinzani, 2012), while SLL constitutes approximately 6% and WM approximately 1%.

1.1.1. Follicular Lymphoma

Follicular lymphoma (FL) is one of the most common indolent NHLs. BCL-2 gene deregulation involving a t(14,18) translocation is frequently seen in FL, although it is not diagnostic of FL (Rambaldi, 2002). Mutations in histone-modifying genes have recently been described as being involved in its pathogenesis (Morin, 2012). Follicular lymphoma typically follows an indolent course with a median overall survival (OS) of 7-10 years. Although FL initially responds well to treatment it is characterized by recurrent relapses or progressions with progressively shorter intervals in between (Salles, 2007). Transformation to diffuse large B-cell lymphoma and other aggressive lymphoma occurs at a rate of approximately 2% to 3% per year (Bastion, 1997).

The prognosis depends on the histologic grade, stage, treatment and age of the patient. The disease is considered incurable in advanced stage, and eventually most FL patients die of lymphoma regardless of the treatment. Follicular Lymphoma International Prognostic Index (FLIPI) score and its revised version, FLIPI2 (Federico, 2009), have been developed for the assessment of newly diagnosed FL patients, but their use in relapsed FL has not yet been fully studied.

In addition to clinical demographic parameters in prognostic indices, biological (immune signature) prognostic factors (Solal-Celigny, 2004; Federico, 2009; Dave, 2004; Gribben, 2010) and lymphoma-mediated immunosuppression (Ramsay, 2009a) have been noted to be common in FL, pointing to the importance of the impaired host immune response in the pathogenesis of this disease.

1.1.1.1. Therapy in Follicular Lymphoma

There is no standard treatment for relapsed/refractory FL patients. Treatment options include radiation, single-agent or combination chemotherapy, rituximab monotherapy, rituximab containing chemoregimens such as BR (bendamustine, rituximab), fludarabine plus rituximab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), R-CVP

(rituximab, cyclophosphamide, vincristine, prednisone), R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone), radioimmunotherapy or autologous/allogeneic stem cell transplant in some select patients (NCCN guideline, 2013 and Ghielmini, 2013 [European Society for Medical Oncology (ESMO) guideline]. In addition, repetition of a previously applied regimen is a valid option depending on the duration of the response obtained previously. A watch-and-wait strategy is sometimes employed for patients with low tumor burden progressing after the first-line therapy.

Rituximab is approved in the US, Europe and other countries for treatment of relapsed or refractory FL as single agent and is extensively used in the treatment of FL as monotherapy or in combination with chemotherapy. Several studies have demonstrated the efficacy and safety of rituximab monotherapy in relapsed/refractory FL or other low grade NHL patients, and three multicenter single-arm studies have led to regulatory approval in the US, Europe and other countries. In the first study 166 relapsed/refractory FL patients were treated with 375 mg/m^2 of rituximab weekly for 4 doses. Results demonstrated a 48% overall response rate (ORR) with 6% CR and median duration of response of 11.2 months (McLaughlin, 1998). In the second study, 37 relapsed/refractory low-grade NHL patients received an additional 4 weekly doses of rituximab for a total of 8 doses, resulting in increased ORR of 57% and CR of 14% (Piro, 1999). The third study demonstrated that the retreatment of 60 relapsed/ refractory patients who had clinical response to prior rituximab treatment with 4 weekly doses of rituximab resulted in ORR of 38% and CR of 10% (Davis, 2000a). Thus, in some countries, the approved number of rituximab doses is four to eight. A recent update of the results from the SAKK 35/98 trial evaluating prolonged single agent rituximab (Martinelli, 2010) in relapsed/refractory FL patients treated with 4 weekly doses of rituximab followed by additional 4 maintenance doses every 2 months reported a durable response with 35% of responders still in remission at 8 years. In a Phase 3 study to evaluate the safety and efficacy of rituximab in patients with bulky relapsed or refractory low-grade or FL (Davis, 1999), the ORR was 43% with a median TTP of 8.1 months and median DOR of 5.9 months. The average decrease in lesion size in patients who achieved a partial response was 76%, and patients with stable disease had a decrease in average lesion size of 26%.

The importance of rituximab has also been demonstrated in clinical trials that evaluated the addition of rituximab to combination chemotherapy and as a maintenance agent after chemotherapy in patients with relapsed FL. Forstpointner et al (Forstpointner, 2004) reported the results from a Phase 2 randomized study evaluating R-FCM versus FCM (fludarabine, cyclophosphamide, mitoxantrone) in FL (N = 93) and MCL (N = 40) patients showing improved response rate (79% versus 58%, respectively) and median PFS (16 months versus 13 months, respectively) in R-FCM group compared to FCM. Van Oers (Van Oers, 2010) evaluated the role of rituximab (R) both in remission induction and maintenance treatment of relapsed/refractory FL; patients were randomized to induction with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or R-CHOP, and those in complete or partial remission were randomized to maintenance or observation. The median PFS from first randomization was 20.2 months after CHOP versus 33.1 months after R-CHOP (hazard ratio [HR], 0.65; P < .001). Rituximab maintenance yielded a median PFS from second randomization of 51.5 months versus 14.9 months with observation. A randomized Phase 3 trial (RESORT) comparing two different rituximab dosing strategies (rituximab continuous maintenance until treatment failure, RM) or rituximab re-treatment at progression, RR) for untreated, low tumor burden (LTB) FL was not

able to demonstrate differences in time to treatment failure (TTF) (Kahl, 2011). The mean number of rituximab doses per patient (including the 4 induction doses) was 15.8 (range 5– 31) for MR and 4.5 (range 4–16) for RR. The time to initiation of cytotoxic therapy was delayed in both arms compared to historical watch and wait strategies. Rituximab re-treatment at progression produces outcomes comparable to MR in this patient population.

The combination of rituximab and bendamustine, an alkylating agent, is approved in the US, Europe and many other countries for the treatment of rituximab refractory iNHL and showed a response rate of 90% and median PFS of 2 years in relapsed/refractory indolent low grade lymphoma and MCL in single-arm Phase 2 studies (Robinson, 2008; Rummel, 2005). Major reported toxicities of bendamustine were myelosuppression (Grade 3 or 4 neutropenia and thrombocytopenia), nausea, infection, and fatigue. The two anti-CD20 radioimmunotherapy agents, yttrium Y90 ibritumomab tiuxetan and iodine I131 tositumomab, have demonstrated high activity in patients relapsed/refractory to chemotherapy or rituximab. Patients achieved a response rate of 60% to 80% but with significant toxicities including prolonged myelosuppression with potential risk of treatment-associated myelodysplastic syndrome (MDS) and acute myelogenous leukemia (Cheson, 2003). A randomized Phase 3 trial comparing yttrium Y90 ibritumomab tiuxetan to rituximab in relapsed indolent NHL demonstrated significantly higher ORR (80% versus 56%) and CR rate (30% versus 16%) but with no significant differences in median time to progression (11.2 months versus 10.1 months) (Witzig, 2002).

More recently, efforts have been made to find novel regimens for the treatment of relapsed FL that do not contain cytotoxic agents. Such efforts include combinations of rituximab with a second monoclonal antibody, such as galiximab (Czuczman, 2005; Czuczman, 2012) and anti-CD22 epratuzumab (Leonard, 2005), and with targeted agents such as bortezomib (Baiocchi, 2010), interferon (Davis, 2000b; Sacchi, 2001) and cytokines granulocyte macrophage colony stimulating factor (GM-CSF) (Cartron, 2008) and IL-12 (Ansell, 2002), as well as lenalidomide. Of these combinations, a Phase 3 study comparing bortezomib plus rituximab versus rituximab single agent has been reported (Coiffier, 2011). In this study 676 rituximab-naïve or rituximab-sensitive patients with relapsed Grade 1 or 2 FL were randomly assigned in 1:1 ratio to receive rituximab alone (weekly during first cycle x 4 doses and then on Day 1 of cycles 2 to 5) or in combination with bortezomib (weekly x 4 doses of cycles 1 to 5). While the difference in the PFS was statistically significant ($p = 0.039$), the magnitude of the difference in the median PFS was < 2 months (11.0 months in the rituximab-only arm and 12.8 months in the rituximab-bortezomib arm).

1.1.2. Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is a subtype of B-cell lymphoma, constituting approximately 8% of NHL. Considered an indolent NHL, it is distinguished from other NHLs in that it is negative for CD5, CD10, Cyclin D1 and CD23 (Higgins, 2008; Stamatopoulos, 2000).

Three types of MZL have been described: Extranodal mucosa-associated lymphatic tissue (MALT) lymphoma, splenic MZL and nodal MZL. Although these subtypes of B-cell lymphoma share morphologic, immunophenotypic and genetic characteristics, there are also important differences in their frequency, clinical presentation, and pathogenesis. MALT is most common and accounts for approximately 70% of all MZLs; splenic MZL accounts for approximately 20%

of all MZLs; and Nodal MZL is the least common, representing approximately 10% of all MZLs (Isaacson, 2008; Matutes, 2008; Campo, 2011; Arcaini, 2009).

There is no specific immunohistochemical marker for MALT lymphoma. MALT lymphoma usually arises in mucosal sites where lymphocytes are not normally present and where MALT is acquired in response to either chronic infectious conditions or autoimmune processes, such as Hashimoto thyroiditis or Sjogren syndrome. *Helicobacter pylori* gastritis is the best studied condition, but other infectious agents have been implicated in the pathogenesis of MALT lymphomas arising in the skin (*Borrelia burgdorferi*), in the ocular adnexa (*Chlamydophila psittaci*), and in the small intestine (*Campylobacter jejuni*) (Bertoni, 2005).

Splenic MZL patients present with an enlarged spleen, involvement of abdominal lymph nodes, and bone marrow disease. Liver and leukemic involvement occurs in a subset of patients. Approximately 40% to 50% of splenic MZLs are associated with deletions of chromosome 7q (Isaacson, 2008).

Patients with nodal MZL, predominantly have lymph node-based disease. The molecular pathogenesis of nodal MZL is not well understood.

1.1.2.1. Therapy in Marginal Zone Lymphoma

Front-line treatment of MZL depends on the stage of disease, histological subtype, location of disease and the presumed source of antigenic stimulation. *H. pylori* eradication therapy is recommended in all *H. pylori* positive gastric MALT lymphoma patients independent of stage or histological grade [Dreyling, 2013 (ESMO guideline); NCCN guideline, 2013]. For *H. pylori* negative patients and non-gastric MALT lymphoma patients, radiation therapy is the preferred option, while rituximab monotherapy or in combination with chemotherapy is treatment of choice for patients with contraindications to RT or for patients in need of systemic treatment [NCCN guideline, 2013; Dreyling, 2013 (ESMO guideline)].

Advanced stage disease and relapsed disease requiring systemic treatment is managed like follicular lymphoma - rituximab with or without chemotherapy, being the preferred option [NCCN guideline, 2012 and Dreyling, 2013 (ESMO guideline)]. Nodal MZL is also treated like follicular lymphoma, although no studies of large series have been published so far in this type of MZL.

1.2. Lenalidomide

Lenalidomide (REVLIMID® Celgene Corp., NJ, USA) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiD®) and has potent immuno-stimulatory, anti-angiogenic, and pro-apoptotic activities in vitro.

It offers potential benefit over the first commercially available IMiD® compound, thalidomide, in terms of both safety and efficacy in human patients (Galustian, 2004). The key to its therapeutic potential lies in the fact that it has multiple mechanisms of action in vitro, which act to produce both immunomodulatory and antitumor effects. These effects are thought to be contextual in that they depend on both the cell type and the triggering stimulus. Lenalidomide has been associated with TNF-α inhibitory, T-cell costimulatory, and antiangiogenic activities (Galustian, 2004).

Lenalidomide is approved in the United States and other countries for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a

deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities and in combination with dexamethasone for patients with previously treated multiple myeloma. In addition, it is approved in the US for the treatment of patients with mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

Lenalidomide is being investigated as treatment for various hematologic and oncologic indications.

1.3. Preclinical Studies of Lenalidomide and Rituximab in Lymphoma

The direct tumoricidal and immunomodulatory activities of lenalidomide are likely important for its clinical activity in the treatment of various hematologic malignancies. This activity is at least in part mediated by enhanced T-cell and NK-cell effector function to eliminate tumor B cells, attributed to restoration of impaired T-cell activity and formation of immunologic synapses. There are also direct effects on tumor cells, including upregulation of tumor suppressor genes, leading to cell cycle arrest.

Preclinical studies have shown an enhancement of antibody-dependent cellular cytotoxicity (ADCC) (Wu 2008) and anti-tumor effects in vivo (Hernandez-Ilizaliturri, 2005; Zhang, 2009) when lenalidomide was combined with rituximab. Lenalidomide has shown to augment ADCC mainly by increasing CD16 expression on NK cells (Zhang, 2009). In a murine NHL model, lenalidomide induced significant increase in the recruitment of NK cells to tumor sites resulting in enhanced anti-tumor activity of rituximab (Reddy, 2008). When combined with rituximab, lenalidomide improved survival in a mouse NHL model and the anti-tumor activity was shown to be NK-mediated. (Hernandez-Ilizaliturri, 2005).

Recent preclinical studies also suggest that lenalidomide may promote restoration of anti-tumor immunological effects in patients with certain hematological malignancies. Ramsay et al reported that impaired T cell immunological synapse formation was seen in both CD4 and CD8 T cells from chronic lymphocytic leukemia (CLL) and FL patients compared to age-matched healthy donors (Ramsay, 2008; Ramsay, 2009a; Ramsay, 2009b; Gorgun, 2009) and that the immune synapse defects were repaired by treatment of the cells in vitro with lenalidomide. In both FL and CLL, treatment of both tumor B cells and autologous T cells with lenalidomide was required to repair the defective immunological synapse formation (Ramsay, 2009a; Ramsay, 2009b), by preventing the induction of impaired actin synapse formation by down-regulating tumor-cell-inhibitory molecule expression (Ramsay, 2012). These findings are supported by preclinical studies conducted by the sponsor. Lenalidomide treatment induced actin cytoskeleton reorganization and polarization in a process termed “capping,” which is considered an important subcellular component of the immune synapse formation (Gaidarova, 2009), and lenalidomide induces CD20-localization within the “cap.” The combined use of lenalidomide and rituximab enhances NK cell-mediated immune synapse formation, the resultant cytotoxicity (Gaidarova, 2009). The capping of CD20 is accompanied by redistribution of proteins such as Vav1 and Rac1 that become part of the immune synapse complex. More recently, lenalidomide has been reported to bind to a target protein cereblon in T cells, which then induces certain biochemical events of T cell activation such as IL-2 secretion (Lopez-Girona, 2012).

These laboratory observations of direct lenalidomide and rituximab effects on tumor cells and on the host immune cells serve as the biological basis for the use of rituximab-lenalidomide combination described in this clinical trial protocol.

1.4. Clinical Studies of Lenalidomide or Rituximab-Lenalidomide in FL

Single agent lenalidomide was studied in patients with relapsed/refractory indolent NHL, including FL (Witzig, 2009). The dose/regimen used in this study was 25 mg once daily (QD) x 21 days every 28 days for maximum of 52 weeks. Forty-three subjects were enrolled. Patients had received a median of three prior systemic therapies (range, 1 to 17) and half were refractory to last therapy. ORR was 23% (10 of 43), including a 7% complete response (CR) or unconfirmed (CRu) rate. Twenty-seven percent (six of 22) of patients with FL Grade 1 or 2 responded to therapy. Median duration of response (DOR) was not reached, but was longer than 16.5 months with seven of 10 responses ongoing at 15 to 28 months for the entire group including FL. Median PFS for the whole group was 4.4 months (95% CI, 2.5 to 10.4 months). The most common Grade 3 or 4 AEs were neutropenia (30% and 16%, respectively) and thrombocytopenia (14% and 5%, respectively).

Recently, Leonard et al (2015) updated results and provided the final analysis on data first reported in 2012 from a multicenter, randomized, Phase 2 clinical trial conducted by the US cooperative group Cancer and Leukemia Group B (CALGB). This study evaluated the lenalidomide-rituximab (LR) combination therapy versus lenalidomide monotherapy in patients with recurrent FL who had prior therapy with rituximab alone or in combination, and time to progression of ≥ 6 months from last rituximab dose. Subjects were randomly assigned 1:1 to lenalidomide alone or LR. Lenalidomide 15 mg/day was administered during Cycle 1 on Days 1 to 21, followed by 7 days of rest and then 20 mg/day on Days 1 to 21, followed by 7 days of rest in Cycles 2 through 12. Ninety-one patients in total received treatment with lenalidomide, (n=45; LR, n=46). The median age was 63 and most patients had advanced-stage disease with low (42.2%) and intermediate (35.3%) risk by FLIPI. In the lenalidomide and LR arms, Grade 3 to 4 adverse events occurred in 58% and 53% of patients, with 9% and 11% of patients experiencing Grade 4 toxicity, respectively. Grade 3 to 4 adverse events included neutropenia (16% versus 20%, respectively), fatigue (9% versus 13%, respectively), and thrombosis (16% versus 4%). Thirty-six percent of lenalidomide patients and 63% of LR patients completed 12 cycles. Lenalidomide alone was associated with more treatment failures, with approximately 20% of patients in both arms discontinuing treatment as a result of adverse events. Overall response rate was 53% (20% complete response) for lenalidomide alone and 76% (39% complete response) for LR. At a median follow up of 2.5 years, median time to progression was 1.1 years for lenalidomide alone and 2 years for the LR combination.

The results of the CALGB study are further supported by findings from two smaller single institution studies reported by Tuscano et al (Tuscano, 2014) and Ahmadi et al (Ahmadi, 2014). Tuscano et al (Tuscano, 2014) conducted a clinical trial of the combination of rituximab and lenalidomide in 30 patients with relapsed/refractory indolent lymphoma. Patients received lenalidomide 20 mg daily for three weeks in 4-week cycles and also rituximab 375 mg/m^2 weekly x 4 doses starting on Day 15. Lenalidomide was continued until disease progression. The median age was 60.5 years old, median lines of prior therapy was 3, and 13 patients were refractory to rituximab. Of the 27 evaluable patients, 22 had FL. In this subset of FL patients, the ORR was 77% and CR/CRu was achieved in 9 patients (40.9%).

Activity of the rituximab plus lenalidomide combination has been also demonstrated in patients refractory to rituximab (defined as relapse within 6 months of last rituximab). Ahmadi et al (Ahmadi, 2014) reported the results from a Phase II trial of lenalidomide-dexamethasone-

rituximab in patients with indolent B-cell or mantle cell lymphomas refractory to rituximab. Patients initially received two 28-day treatment cycles of lenalidomide 10 mg daily and dexamethasone 8 mg once weekly. After assessment of response at 8 weeks (part 1), all patients received the addition of rituximab 375 mg/m^2 weekly for 4 doses starting with cycle 3. Lenalidomide-dexamethasone therapy continued with the addition of rituximab (part 2). Of the 27 patients enrolled, the histologies were follicular (n = 18), mantle cell (n = 5), small lymphocytic (n = 3), and marginal zone (n = 1) lymphomas. For 24 patients, the overall response rate after part 1 was 29% (4 patients had a CR or CRu, and 3 patients had a PR), and the ORR after part 2 was 58% (8 patients had a CR, and 6 patients had a PR). For 27 patients, at a median follow-up of 12.2 months, the median PFS was 23.7 months.

The rituximab plus lenalidomide combination has also been studied as frontline therapy in FL. In 2012, Fowler et al (Fowler, 2012) reported the results of an ongoing Phase 2 study evaluating the efficacy and safety of rituximab-lenalidomide in patients with untreated, Stage III/IV, indolent NHL. Patients with previously untreated indolent NHL received 20 mg/day of lenalidomide on Days 1 to 21 and rituximab 375 mg/m^2 on Day 1 of each 28 day cycle for up to 6 cycles. Response was assessed after every 3 cycles using the International Working Group (IWG) (Cheson, 1999) criteria. At the time of this report, 110 patients had completed treatment or were off-study. The median age was 58 (34-84) years, 53% of patients were male, and 103 patients were evaluable for response. Among all evaluable patients, the overall response rate was 90%. Complete responses (CR) were attained in 64% of patients, 27 patients (26%) had a partial response (PR), and stable disease (SD) was seen in 8 (8%). Among the subset of patients with FL, 40/46 (87%) evaluable patients attained a CR. Forty five evaluable pts with FL had a positive PET scan prior to therapy and 42 (93%) attained a complete metabolic response following treatment. At a median follow up of 22 months, the estimated two year PFS was 83% for all patients and 89% in patients with FL. Grade 3/4 AEs were rash (8 patients), neutropenia (44 patients), muscle pain (7 patients), thrombocytopenia (4 patients), fatigue (3 patients), and thrombosis (3 patients). Six patients were removed from treatment due to AEs but were eligible for toxicity assessment.

Martin et al (2013) reported the results of a Phase 2 clinical trial of the rituximab-lenalidomide combination given for 12 months in previously untreated FL in a multi-center cooperative group study, CALGB 50803. Lenalidomide 20 mg/day was administered on days 1-21 of a 28-day cycle for 12 cycles plus rituximab weekly x 4 in Cycle 1 and on day 1 of Cycles 4, 6, 8, and 10. Sixty-six patients were enrolled. Three patients did not receive protocol treatment and were dropped from analyses. The median age of the remaining 63 patients was 53 years; 49.2% were male; 31% were FLIPI < 2. Grade 3 or 4 toxicity that occurred in >5% of patients included neutropenia (20%), lymphopenia (8%), rash (8%), fatigue (6%), and leukopenia (5%). Grade 2 or more toxicity in > 5% of patients included fatigue (25%), infusion reaction (17%), upper respiratory reaction (13%), nausea (8%), constipation (7%), increased ALT (7%), hyperglycemia (7%), hypophosphatemia (7%), pain (6%), oral mucositis (5%), and myalgia (5%). Febrile neutropenia occurred in 1 patient (2%). Fifty-one patients (81.0%) completed 12 cycles of lenalidomide. Reasons for early termination included adverse events (6) and patient refusal (5). One patient stopped due to disease progression after initial response. Among the 54 patients with adequate data to evaluate response, the overall response rate was 92.6%, including 39 (72.2%) complete responses and 11 (20.4%) partial responses. Complete responses were not associated

with FLIPI, grade, or bulky disease. At a median follow-up of 1.3 years, 6 patients had progressed.

1.5. Clinical Studies of Lenalidomide or Rituximab-Lenalidomide in MZL

Single agent lenalidomide has been studied in patients with histologically confirmed advanced stage MALT lymphoma (Kiesewetter, 2012). The patients received 25 mg once daily (QD) x 21 days every 28 days for maximum of six cycles if the patient had achieved at least stable disease (SD) after third cycle. A total of 18 patients were enrolled with 11 previously untreated and 7 relapsed/refractory patients. An overall response rate of 61% was seen (11 of 18; 6 complete and 5 partial remissions). Three patients had stable disease while 2 progressed. The most common Grade 3 or 4 AE was neutropenia (Grade 3 in 3 patients). After a median follow up of 20.3 months, one patient has died from lymphoma while the other patients were alive and relapse-free.

The rituximab and lenalidomide combination therapy is being studied in previously untreated and also relapsed/refractory MZL patients. In the recent report discussed in Section 1.4 , Fowler et al (Fowler, 2012), the combination therapy was also evaluated in MZL lymphoma. Twenty-seven of the 100 NHL patients enrolled were MZL. Eighty-nine percent (n=24) of the patients with MZL responded with 67% patients achieving CR/CRu (Fowler, 2012). At a median follow-up of 22 months, the estimated 2 year PFS was 83% for all (FL, MZL, SLL) patients.

In the study already discussed above in Section 1.4 (Tuscano, 2014), 3 patients had MZL. In this subset of MZL patients, CR/CRu was achieved in 2 patients and the ORR was 66.7%.

Early data of rituximab and lenalidomide combination therapy in relapsed/refractory MZL patients was recently reported by Kiesewetter et al (Kiesewetter 2013). A total of 21 patients were included in the trial, and at the time of reporting, 10 patients were evaluable for response. Three patients had completed six cycles and achieved CR, whereas seven additional patients had CR after cycle 3 with treatment currently ongoing. Hematologic adverse events were mild with neutropenia Grade 2 in three patients, thrombocytopenia Grade 1 in three patients and anemia Grade 1 in one patient. Other adverse events reported were mild fatigue (n = 5), pruritus (n = 6, Grade 3 in one patient), mild constipation (n = 4), vertigo (n = 4, Grade 3 in one patient) and mild exanthema (n =3). Dose reduction was required in four patients to manage toxicity (nausea/emesis, headache/exanthema and infection).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to compare the efficacy of rituximab plus lenalidomide to rituximab plus placebo in subjects with relapsed/refractory indolent lymphoma. Efficacy determination will be based upon PFS as the primary endpoint, as assessed by the Independent Review Committee (IRC) using the 2007 International working group (IWG) criteria (Cheson, 2007) but without PET.

2.2. Secondary Objectives

The secondary objectives of the study are:

- to compare the safety of rituximab plus lenalidomide versus rituximab plus placebo
- to compare the efficacy of rituximab plus lenalidomide versus rituximab plus placebo using other parameters of efficacy:
    - Durable complete response rate (DCRR), overall response rate (ORR), complete response (Cr) rate, duration of response (DoR) and duration of complete response (DoCR) by IWG 2007 without PET See Section 18.1
    - OS, EFS, time to next anti-lymphoma treatment (TTNLT)

CCI [redacted]

CCI [redacted]

3. STUDY ENDPOINTS

Progression free survival (PFS), best overall response including ORR, CR rate, durable CR rate, and DoR will be assessed per 2007 IWG criteria (Cheson, 2007). In addition to CT/MRI scan to assess response and progression, subjects with gastric MALT lymphoma will also undergo endoscopy as part of response assessment (see Section 18.1.3). See section 10 for details and definitions.

3.1. Primary Endpoint(s)

- PFS, as assessed by the IRC using the 2007 IWG criteria

3.2. Secondary Endpoint(s)

- DCRR
- OS
- ORR
- CR Rate
- DoR
- DoCR
- EFS
- TTNLT
- Safety

CCI [redacted]

CCI [redacted]

4. OVERALL STUDY DESIGN

4.1. Study Design

This Phase 3, multicenter, double-blind, randomized study is designed to evaluate the efficacy and safety of rituximab plus lenalidomide versus rituximab plus placebo in subjects with relapsed/refractory indolent lymphoma. The overall study design is described in Figure 1. The study is divided into the Screening Period, Treatment Period, and Follow-up Period. It is planned to randomize 350 subjects at a 1:1 ratio.

All efficacy assessments will be based on central review including central radiology and clinical review by an IRC. For gastric MALT patients, results of upper gastrointestinal endoscopy will be included in the clinical data review by the IRC which will be composed of two external radiologists (with an additional radiologist in case adjudication is needed) and a hematologist/oncologist. The IRC will perform a blinded, independent assessment of radiological data and selected clinical data for each patient to determine response, date of response, and date of disease progression. The IRC will utilize the 2007 IWG criteria (Cheson, 2007; see Section 18.1) without PET for primary efficacy determination based on CT/MRI scan to assess progression, which will be used to calculate PFS. Best overall response including ORR, CR rate, DOR, and durable complete response rate will also be evaluated by IRC using the 2007 response criteria (see Section 18.1). CCI [redacted] In addition to CT/MRI scan to assess response and progression, subjects with gastric MALT lymphoma will also undergo endoscopy as part of response assessment (see Section 18.1.3). Details of the efficacy assessments will be described in the IRC charter.

Since the study primary endpoint is PFS based on CT/MRI scan as determined by IRC, progression or relapse will be based on CT/MRI scans and/or clinical data supporting progression or relapse of disease. Because all protocol-specified analyses including the planned interim analysis are based on IRC review, all CT/MRI scans and all biopsies performed must be sent for central radiology and pathology review respectively as described in Section 6.2.1.

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study according to DMC charter. In addition the DMC will conduct the planned interim analysis at approximately 50% information (96 events) for futility only.

See Section 10 for a detailed description of Statistical Analyses.

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

4.1.1. Screening Period

Upon giving written informed consent, the subject will enter the Screening Period to determine eligibility (the Screening Period timing begins on the day (Day -28) the first study procedure is performed after the subject has provided written informed consent). All screening assessments must be completed within 28 days prior to randomization. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either the experimental arm (rituximab plus lenalidomide) or control arm (rituximab plus placebo).

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Subject eligibility will be based on investigator assessment of the pathologic diagnosis. However, subject's disease diagnosis will be assessed retrospectively by central pathology to confirm the FL or MZL diagnosis. Thus, the investigator must confirm that archival formalin-fixed paraffin embedded (FFPE) tumor or lymph node tissue specimen exists during the Screening Phase. If an archival specimen is not available for submission, then a rebiopsy is required prior to randomization. All tumor specimens must be sent to the central pathology laboratory, preferably during the screening period and no later than 8 weeks after randomization. Subjects with a diagnosis of splenic MZL for whom a spleen specimen is not available, will undergo central pathology review based on the following: (1) clinical information including a CT scan of the spleen, WBC count and differential; (2) available bone marrow biopsy specimen and report for morphological evaluation and local bone marrow aspirate smear report. Flow cytometry analysis of the peripheral blood or bone marrow, HCV status, Coomb's test results and M-protein test results may be requested.

Confirmation of FL or MZL by the central pathologist is not required for entry into the study.

4.1.2. Treatment Period

The Treatment Period begins with Cycle 1 Day 1 dosing of the therapy drugs as described in Section 8 and must begin as soon as possible after randomization but no later than 1 week after randomization. The subjects will receive protocol-specified treatments and undergo efficacy and safety assessments for a maximum of 12 cycles, or until relapse or progression of disease, withdrawal of consent, or unacceptable toxicity. A central laboratory will be used for the analysis of hematology and serum chemistry. Clinical decisions and dose modifications during the study can be based on local laboratory results.

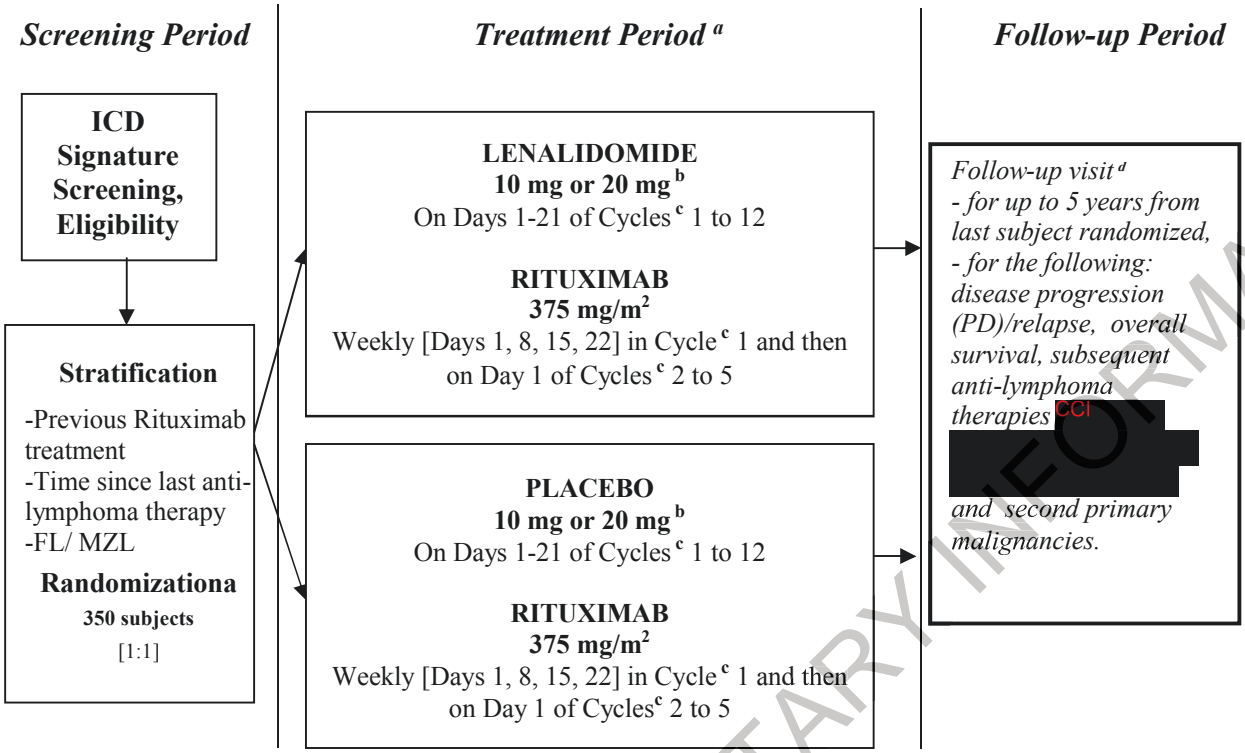
All randomized subjects will be followed for disease progression and OS using the same schedule described in Table 1. This includes all subjects who discontinue the protocol-specified treatment for any reason without documented evidence of disease progression. A subject's withdrawal from the protocol-specified treatment for disease progression will be based upon investigator assessment.

4.1.3. Follow-up Period

The Follow-up Period begins upon study treatment completion or discontinuation. 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 anti-lymphoma / salvage therapy (chemotherapy, Stem cell transplants, radiotherapy, etc.). In the Follow-up Period, the subjects will be followed for disease progression, OS, subsequent anti-lymphoma therapies, CCI [redacted], and SPMs.

CCI [redacted]

Figure 1: Overall Study Design



ICD: informed consent document; FL: Follicular lymphoma; MZL: Marginal zone lymphoma.

[a] Treatment must begin as soon as possible after randomization but no later than 1 week after randomization.
[b] 10 mg if CrCl ≥ 30 mL/min but < 60 mL/min; 20 mg if CrCl ≥ 60 mL/min.
[c] Cycle defined as Lenalidomide/ Placebo cycle of 28 days (21 days treatment and 7 days rest period)
[d] All randomized subjects are followed for disease progression and overall survival using the same schedule described in Table 1.This includes patients who discontinue the protocol-specified treatment or the study early for any reason without documented evidence of PD or relapse.

4.2. Study Design Rationale

Follicular lymphoma and marginal zone lymphoma are distinct histologic types within the broad category of B-cell NHL according to the WHO classification (Harris, 2008). For FL, this histology is further divided into three different grades – Grades 1 to 3 – based on histologic appearance. These grades reflect some degree of heterogeneity in the biology of the disease, and in fact, follicular Grade 3 is often further subdivided in Grades 3a and 3b. This 3a versus 3b distinction has implications for treatment decisions, since Grade 3b FLs are clinically more similar to aggressive lymphomas, with more infiltration of large cells. Grade 3a is typically treated as a FL, while Grade 3b is treated as an aggressive lymphoma. Thus, FL Grade 3b is excluded from this study.

Marginal zone lymphoma is also a group of individual subtypes: extranodal MZL of MALT-lymphoma, nodal MZL and splenic MZL. As with FL grades, these individual histologies are

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associated with different clinical behavior and require different management. For example, gastric MALT stage 1 (that is, stage IE) is often treated with antibiotics to eradicate *H. pylori*.

Despite these heterogeneities in the biology and treatment practices between FL and MZL, it is important to note that in advanced stage disease and in relapsed disease, the clinical behavior and treatments are very similar among the indolent lymphomas. These similarities for example are reflected in the nearly identical treatment guidelines for the management of advanced stage FL versus advanced stage MZL [NCCN guideline, 2013; Dreyling, 2013 (ESMO guideline)]. For this reason, FL and MZL are studied together in this clinical trial.

Rituximab is approved in a number of countries for the treatment of relapsed/refractory low-grade NHL or FL. "Low-grade" is a terminology which in the recent years has been replaced by the term "indolent." Clinically, "low grade" lymphoma can be used interchangeably with "indolent lymphoma".

Subsequent to the initial rituximab approval, the treatment of relapsed/refractory indolent lymphoma, including FL and MZL has continued to evolve, so that multiple options now are available. Thus, rituximab has become the backbone of combination therapy. In some instances, rituximab is used in combination with cytotoxic regimens such as cyclophosphamide-containing regimens, anthracycline-containing regimens, fludarabine containing regimens, and bendamustine, but these regimens have not been proven to increase OS compared to rituximab monotherapy. Among the available options, rituximab monotherapy remains an appropriate treatment option for relapsed indolent lymphomas of the FL and MZL types. As reviewed in Section 1.4, the combination of rituximab and lenalidomide has been reported to have activity in indolent lymphomas. Waldenstrom macroglobulinemia (WM) is assessed by different response criteria (Owen, 2013) and the rituximab-lenalidomide combination has been previously reported to be associated with acute anemia in patients with this disease (Treon, 2009). Small lymphocytic lymphomas (SLL) is considered to be the same disease entity as chronic lymphocytic leukemia. Lenalidomide has been noted to have a different safety profile in previously conducted trials in CLL (Wiernik, 2013) and is being investigated in separate CLL clinical trials. For these reasons, WM, and SLL are not studied in this clinical trial.

The current study is a Phase 3, double-blind, randomized, multicenter, placebo-controlled study, designed to evaluate the efficacy and safety of lenalidomide plus rituximab combination therapy in subjects with relapsed/refractory indolent lymphomas of the FL and MZL types. The multicenter nature of the study provides assurance that the results are likely to have general applicability. The double-blinding and placebo control will reduce bias.

Subjects are required to have measurable disease according to the IWG criteria and will have frequent periodic disease assessments for an accurate determination of PFS, the primary endpoint of this study. The IWG response criteria were selected to provide an established international standard for the assessment of lymphoma, including both nodal and extranodal disease as measurable lesions (Cheson, 2007; Cheson, 1999). The use of this established tool and an IRC will ensure that data across centers are evaluated consistently and also allow for comparison to historical data. In addition, in this clinical trial, these criteria exclude the use of positron emission tomography (PET) scan, which is less established as an indicator of response to treatment in indolent lymphomas compared to other lymphomas such as aggressive lymphomas.

The primary endpoint of PFS is a measure of clinical benefit well accepted by clinicians and by regulatory authorities in view of the long OS of subjects with this disease.

Safety will be assessed by evaluation of AEs and laboratory data. Adverse events and abnormal laboratory value severity will be graded using version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Tumor flare reaction (TFR) will be graded using NCI CTCAE v 3.0.

Monitoring for certain events (see Section 6.2.2 for details), including tumor flare reactions (TFR), TLS, and thromboembolic events (TE), will be performed along with safety assessments routinely conducted in investigational studies of hematologic malignancies. Thromboembolic events prophylaxis is recommended for subjects who are at risk for a TE. Thromboembolic events, TFR and TLS will be recorded as AEs.

4.3. Study Duration

The expected accrual duration is 40 months. Subjects will receive protocol-specified treatment for a maximum of 12 months, until relapse or progression of disease, withdrawal of consent or unacceptable toxicity. Subjects will be followed for survival, disease progression, subsequent anti-lymphoma therapies, and SPMs until 5 years after the last subject has been randomized. Thus, the duration of the entire study will be approximately 8 years (accrual period of approximately 3 years plus 5 years from last subject randomized).

4.4. End of Trial

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 CCI [redacted] analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date. After completion of the primary efficacy analysis, follow-up tests including but not limited to CT scans/ MRI, biopsies (bone marrow, tumor, gastric) and blood tests are no longer required for the study protocol and may be performed at the investigator's discretion. A central review of these tests is no longer mandatory (see Section 5 for details on the tests). CCI [redacted]

For subjects who have completed treatment or discontinued treatment due to reasons other than progressive disease or relapse, subjects will be followed every 6 months (± 2 weeks) and the follow-up assessments will include:

- OS
- SPM
- CCI [redacted]

For subjects who discontinue treatment due to progressive disease or relapse, subjects will be followed every 6 months (± 2 weeks) and the follow-up assessments will include:

- OS
- SPM

CCI [redacted]

- Next subsequent anti-lymphoma therapy
- CCI [redacted]

CCI [redacted]

5. TABLE OF EVENTS

Table 1: Schedule of Study Assessments

Procedure	Screening (Day -28 to Day -1)	Treatment Period 12 Months						At Treatment Discontinuation or Completion	Follow-up	
		Cycles 1 to 12: Every Cycle Day 1 (±3 days)	Additional Assessments: Cycle 1 Days 1, 8, 15, 22 (±1 day) Cycles 2 to 5 Day 1 (±3 days)	Cycle 1 Days 1, 8, 15 (±1 day)	Cycles 2 to 4 Day 15 (±1 day)	Cycle 4 & Cycle 7 Day 1 (± 3 days)	Cycle 10 Day 1 (±3 days)		If no PD then follow the CT scan assessment schedule[6] or otherwise specified	If progressed then every 6 months (±2 weeks)
Informed Consent	X	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	-	-	-	-	-	-	-	-	-
Complete Medical History	X	-	-	-	-	-	-	-	-	-
CNS Lymphoma Evaluation	X	-	-	-	-	-	-	-	-	-
Creatinine Clearance (Cockcroft-Gault estimation)	X	-	-	-	-	-	-	-	-	-
12-Lead ECG	X	-	-	-	-	-	-	-	-	-
HBV Screening	X	-	-	-	-	-	-	-	-	-
FFPE Tumor Specimen[1]	X	-	-	-	-	-	-	-	-	-
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X	-	-	-	-	-	X	X[12]	-
Vital Signs[2, 13]	X	X	-	-	-	-	-	X	-	-
Hematology [3, 13]	X	X	-	X	X	-	-	X	X[12]	-
Serum Chemistry[3, 13]	X	X	-	X	X	-	-	X	X[12]	-
Serum Immunoglobulin (IgG, IgA, IgM)	X	-	-	-	-	-	X	-	-	-
Thyroid Stimulating Hormone (TSH)	X	-	-	-	-	X	X	-	-	-

CCI [redacted]

Table 1: Schedule of Study Assessments (Continued)

Procedure	Screening (Day -28 to Day -1)	Treatment Period 12 Months						At Treatment Discontinuation or Completion	Follow-up	
			Additional Assessments							
		Cycles 1 to 12: Every Cycle Day 1 (±3 days)	Cycle 1 Days 1, 8, 15, 22 (±1 day) Cycles 2 to 5 Day 1 (±3 days)	Cycle 1 Days 1, 8, 15 (±1 day)	Cycles 2to 4 Day 15 (±1 day)	Cycle 4 & Cycle 7 Day 1 (± 3 days)	Cycles 10 Day 1 (±3 days)		If no PD then follow the CT scan assessment schedule[6] or otherwise specified	If progressed then every 6 months (±2 weeks)
Tumor Flare and Tumor Lysis Assessments[4]	-	-	-	X	-	-	-	-	-	-
Pregnancy Testing - for FCBP with Regular or No Menstrual Cycles	Once between Days -10 to -14, and within 24h prior to C1D1	Weekly during first 28 days; every cycle on Day 1 thereafter						X	-	-
Pregnancy Testing - for FCBP with Irregular Menstrual Cycles	Once between Days -10 to -14, and within 24h prior to C1D1	Weekly during first 28 days; every cycle on Days 1 and 14 thereafter						X	-	-
Birth Control and Lenalidomide Counseling[5]	Once between Days -10 to -14	X	-	-	-	-	-	X	-	-
Distribute Lenalidomide Counseling Sheet[5]	X	X	-	-	-	-	-	X	-	-
Adverse Events	X	After signing the informed consent document through 28 days after last dose.								
Assessment of Second Primary Malignancy (SPM)[6]	X	After signing the informed consent document up to and including a follow-up period of up to 5 years from the date of the last subject randomized								
Prior/Concomitant Medications/ Procedures / Record Hospitalizations	X	After signing the informed consent document through 28 days after last dose.								
Physical Examination [13]	X	X	-	-	-	-	-	X	X[12]	-
B Symptoms [13]	X	X	-	-	-	-	-	X	X[12]	-

CCI [redacted]

Table 1: Schedule of Study Assessments (Continued)

Procedure	Screening (Day -28 to Day -1)	Treatment Period 12 Months						At Treatment Discontinuation or Completion	Follow-up	
		Cycles 1 to 12: Every Cycle Day 1 (±3 days)	Additional Assessments: Cycle 1 Days 1, 8, 15, 22 (±1 day) Cycles 2 to 5 Day 1 (±3 days)	Cycle 1 Days 1, 8, 15 (±1 day)	Cycles 2 to 4 Day 15 (±1 day)	Cycle 4 & Cycle 7 Day 1 (± 3 days)	Cycles 10 Day 1 (±3 days)		If no PD then follow the CT scan assessment schedule[6] or otherwise specified	If progressed then every 6 months (±2 weeks)
CT or MRI of Neck, Chest, Abdomen and Pelvis and Response Assessment [7, 13]	X	**Years 1-3:** Every 12 weeks (± 1 week) **Year 4:** Every 16 weeks (± 1 week) **Year 5:** Every 6 months (± 2 weeks) **Years onwards:** Every year (± 3 weeks) **and up to PD**								-
CCI [redacted]										
Bone Marrow Biopsy[13]	X[9]	For subjects with radiological CR/CRu and conditions as defined in section 6.2.1								
Upper Gastrointestinal Endoscopy and Gastric Biopsy[10, 13]	X	**Years 1:** Cycle 7 Day 1 (± 2 weeks); After cycle 12 (+ 2 months) **Year 2-3:** Every 6 months (± 2 weeks) **Year 4 onwards**: Every year (± 2 weeks) **and up to PD or CR**								-
Dispense Study Drug[11]	-	X	-	-	-	-	-	-	-	-
Rituximab[11]	-	-	X	-	-	-	-	-	-	-
Study Drug Return/ Accountability	-	X	-	-	-	-	-	X	-	-
Subsequent Anti-Lymphoma Therapies CCI [redacted]	-	-	-	-	-	-	-	X	-	X

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

Note: Safety assessments (including labs) must be performed prior to dosing at each treatment visit.

C1D1: Cycle 1 Day 1; CBC: Complete blood count; CNS: Central nervous system; CRF: Case report form; CT: Computed tomography; ECG: Electrocardiogram; FCBP: females of childbearing potential; FFPE: Formalin-fixed paraffin embedded; HBV: Hepatitis B virus; MRI: magnetic resonance imaging; PD: disease progression; TLS: Tumor lysis syndrome; TSH: Thyroid stimulating hormone.

1. If an FFPE tumor block cannot be sent, one hematoxylin and eosin (H and E) stained slide and 10 unstained slides or 11 unstained slides will be acceptable.
2. Vital signs include weight, height (only at Screening), blood pressure, temperature, and pulse.
3. If Screening labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on C1D1.

CCI [redacted]

4. The site should make every effort to contact the subject on Day 5 (± 1 day) of the first cycle to inquire about the subject's condition and to make sure that he/she is continuing with TLS prophylaxis measures by keeping hydrated and taking the TLS prophylaxis as instructed (see Section 9.3.1 for more details).
5. All subjects enrolled into this study must conform to all aspects of the lenalidomide pregnancy prevention risk management plan (standalone document, see Section 18.6).
6. Medical history of any prior cancer other than the disease under study will be reported and, in addition, SPMs will be monitored as events of interest and must be reported as serious adverse events (SAE) regardless of the treatment arm the subject is in. This includes any second primary malignancy, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the Informed Consent (ICD) up to and including the follow-up period and until 5 years after the last subject randomized. 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 second primary malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, X-ray reports, CT scan reports, etc.).
7. Efficacy assessment to be performed until progression or relapse. See section 6.2.1 for details.
8. [redacted]
9. Bone marrow biopsy is required at Screening (for staging) only for subjects with abnormal CBC. See section 6.1 and 6.2.1 for more details.
10. Upper gastrointestinal endoscopy including biopsies (from stomach, duodenum, gastroesophageal junction and from any abnormal-appearing site) is required only in subjects with gastric mucosa-associated lymphatic tissue (MALT) lymphoma. See section 6.1 and 6.2.1 for more details.
11. See Sections 8.1 and 8.2 for more details regarding treatment administration. There is no window for study drug administration.
12. During Follow-up, at same time as the CT/MRI scan evaluation and every 6 months (± 2 weeks) after year 5 (see section 6.4).
13. Once the primary efficacy analysis is done; follow up specified tests are no longer required per protocol and may be performed at the investigator's discretion. (see Section 4.4)

CCI [redacted]

6. PROCEDURES

6.1. Screening Procedures

Subjects must approve and sign the informed consent document (ICD) prior to undergoing any study-related screening assessments.

Subjects will be screened for protocol eligibility (see Section 7) during a period of no more than **28 days** prior to randomization as outlined in the Schedule of Study Assessments (the screening period timing begins on the day [Day -28] the first study procedure is performed after the subject has provided written informed consent).

Screening assessments including physical exam, medical history, prior concomitant medication or procedures, B symptoms (fever (>38°C), night sweats, weight loss greater than 10% within the prior 6 months), Eastern Cooperative Oncology Group (ECOG) performance, vital signs, and recording of AEs/serious adverse events (SAEs) including SPMs will begin once the subject has signed the informed consent form.

The physical examination should include height (Screening only), weight, vital signs (including BP, temperature, and pulse), and an assessment of the ECOG performance status (see Section 18.4).

A medical history will be obtained by the investigator or qualified designee. Medical history (including HIV and HCV infection) judged as relevant to the study and to the safety of the study subject will be recorded in the source documents and CRF. Subjects with a presence of **CNS lymphoma involvement** are excluded from the study. Subjects with suspicion of CNS involvement must undergo neurologic evaluation and a CT/MRI of the brain and lumbar puncture to exclude active CNS disease.

A12-lead **ECG** is performed at Screening and as clinically indicated thereafter.

Hepatitis B screening is required in all subjects and includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs). If subjects are anti-HBs positive and/or anti-HBc positive, and HBsAg negative, additional HBV-DNA testing is required. See Exclusion Criterion # 6 (Section 7.3) for further details. Eligibility for the study is based on the local HBV tests. HBV tests performed as standard of care may be used as screening HBV tests if they are obtained within 28 days prior to Cycle 1 Day 1 (in such case the Screening Period would start at the HBV tests date).

Bone marrow biopsy (BMB) is required at Screening for subjects with abnormal CBCs (defined as per local laboratory lower ranges for ANC, Platelets and Hemoglobin values). For all subjects, if a BMB was performed within 12 weeks prior to Cycle 1 Day 1 and is available, it may be used as the screening biopsy. BMB samples must be submitted to central pathology within 8 weeks after randomization. The biopsy may be unilateral or bilateral at the discretion of the investigator. A block is preferred, but if a block cannot be sent, then an H&E slide and representative unstained slides must be submitted. If no such recent bone marrow biopsy samples are available, then rebiopsy will be required prior to randomization. The details of sample requirement will be discussed in the pathology manual. Pathology reports associated with these tissues also must be sent to the central pathology laboratory with the tissue and/or slides.

The **FFPE tumor block** of diagnostic tumor mass or lymph node must be confirmed to be available at the time of randomization and must be submitted to central pathology within 8 weeks after randomization. A fresh biopsy is ideal, but if not available, an archival biopsy preferably should be 2 years old or less. If the archival tissue sample is between 2 and 5 years old, the Celgene Medical Monitor must be notified to determine if the biopsy can be used. However, if archival tumor tissue was not available prior to randomization or the archival sample is older than 5 years old, a newly obtained tumor biopsy (excisional or core) is required prior to randomization. If a block cannot be sent, one Hematoxylin and Eosin (H and E) stained slide and 10 unstained slides, or 11 unstained slides will be acceptable. Details will be discussed in the separate pathology manual. Pathology reports associated with these tissues are also required and must be sent to the central pathology laboratory with the tissue and/or slides. Detailed instructions and materials for sample handling and shipping will be provided. It is noted that diagnosis based on core biopsy is acceptable but fine needle aspiration is not considered acceptable pathologic data for entry into this study.

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Eligibility will be based on local pathology review; confirmation of diagnosis by central pathology laboratory is not required for entry or initiation of treatment. However, if archival tumor tissue was not available prior to randomization, a newly obtained tumor biopsy (excisional or core) is required prior to randomization.

For subjects with gastric MALT lymphoma, upper gastrointestinal endoscopy including biopsies (from stomach, duodenum, gastroesophageal junction and from any abnormal-appearing site) is required during screening. A recent endoscopy and histological evaluation conducted within 12 weeks prior to Cycle 1 Day 1, is acceptable as the screening assessment. If no such recent evaluation is available, then gastric rebiopsy and histological evaluation will be required prior to randomization. Histological evaluation will be based on local pathology for study entry but tumor tissue samples must be submitted to central pathology within 8 weeks after randomization. The sample requirement will be discussed in detail in the pathology manual.

Hematology and serum chemistry tests will be required during Screening and Day 1 (± 3 days) and at additional times of every treatment cycle as described in Table 1. However, if Screening labs are drawn within 1 week before receipt of study drug on Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1. Eligibility for the study is based either on the central laboratory or the local laboratory results. However, the eligibility value concerning the creatinine clearance (CrCl) will be calculated only by the central laboratory.

- A central laboratory will be used for the analysis of hematology and chemistry tests. Clinical decisions and dose modifications during the study can be based on local laboratory results as long as the reason is reported accordingly. Hematology laboratory tests will include hemoglobin, hematocrit, total white blood cell (WBC) count without differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.

- Serum chemistry will include total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, chloride, blood urea nitrogen or urea, creatinine, and lactate dehydrogenase (LDH).
- Thyroid stimulating hormone (TSH)
- Serum immunoglobulin assessment (IgG, IgA, IgM). Immunoglobulin is measured to assess any risks for infections not associated with neutropenia and to determine any effect of treatment on immunoglobulin levels.
- Creatinine clearance will be calculated by the central laboratory utilizing actual body weight (Cockcroft, 1976; Luke, 1990; Griggs, 2012) and the creatinine clearance data will be sent to the site. Cockcroft-Gault estimation of creatinine clearance (CrCl) will be used:

  CrCl (mL/min) = (140 – age) (weight [kg]) / 72 x (serum creatinine [mg/dL]); for females, the formula is multiplied by 0.85.

  By SI units, CrCl (mL/min) = (140-age) x weight x 1.23 / serum creatinine [µmol/L]; for females, the formula is multiplied by 0.85.

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted. During counseling, subjects must be reminded to not share study drug and to not donate blood. For females of childbearing potential (FCBP)[1], two pregnancy tests must be performed (medically supervised; urine tests are provided and preferred method; if use of other test method (blood), the minimum sensitivity is 25 mIU/mL): (1) one during Screening Period (all FCBP, between Day -10 and -14) and (2) one within 24 hours prior the start of lenalidomide (for FCBP only) (See Pregnancy Prevention Risk Management Plan document for more details).

The preferred imaging modality is **CT with contrast**. The imaging modality used for lesion evaluation at Screening must be consistently used throughout the study for each subject (see Section 6.2.1- for details on modalities). A CT of neck, chest, abdomen and pelvis is required to confirm one measurable disease greater than 1.5 cm in diameter or at least one extranodal lesion greater than 1.0 cm in both long and short diameter. A CT (or MRI) scan performed as standard of care may be used as screening CT (or MRI) scan if it is obtained within 28 days prior to Cycle 1 Day 1 (in such case, the Screening Period would start at date of CT or MRI).

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6.2. Assessments During Treatment Phase

Treatment will start on Cycle 1 Day 1. A 1-week window between randomization and Cycle 1 Day 1 is allowed, but should not be exceeded.

Serial assessments of safety and efficacy will be performed as outlined in the Schedule of Study Assessments (Table 1). A central laboratory will be used for the analysis of hematology and

[1] See Section Appendix 18.6 for details.

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chemistry. Clinical decisions and dose modifications during the study can be based on local laboratory results.

6.2.1. Efficacy Assessments

Radiological assessments for efficacy will be CT (preferred) or MRI scan. A CT (or MRI) scan should be performed with contrast unless it is medically contraindicated. MRI may be used only if CT with contrast is medically contraindicated as assessed by the investigator or if CT scans at a frequency as per the defined schedule of assessment are not accepted by local IRB/Ethics Committee. If scans with and without contrast are performed at the same time-point, both modalities should be submitted for central review. All CT or MRI scan assessments will be determined from first dose date and will follow the counting of calendar days and not the dosing cycles. The same imaging modality (CT or MRI) and technique (e.g. the use of contrast, slice thickness for scans) that was used at Screening should be used throughout the study for each subject. The scans must be performed at:

- every 12 weeks (± 1 week) for 3 years (Years 1-3)
- then every 16 weeks (± 1 week) for 1 year (Year 4)
- then every 6 months (± 2 weeks) for 1 year (Year 5)
- and then every year (± 3 weeks) until disease progression or relapse

All CT/MRI scans performed must be submitted for central review no later than 4 weeks after they are performed.

All randomized subjects are followed for disease progression (PD) or relapse using the schedule described in Table 1. This includes subjects who discontinue the protocol-specified treatments or the study early for any reason without documented evidence of PD or relapse. If a subject withdraws consent, but agrees to continued collection of outcome data, these follow-up activities will continue. For equivocal progression, the investigator is strongly recommended to contact the sponsor Medical Monitor or Steering Committee Members for evaluation in a "real time" manner.

Protocol-defined efficacy endpoints except OS and time to next treatment will be assessed by an **IRC**. The IRC review includes central radiology and clinical review. Since the study endpoint is PFS based on CT as determined by IRC, progression will typically be based on CT scans. In limited instances where progression is evident only by assessments other than CT, CT scans must still be provided along with the non-CT documentation of progression.

The radiological assessments (CT or MRI) are considered the primary method of response assessment. The additional assessments – clinical assessments, bone marrow biopsy assessments and endoscopic assessments (including gastric biopsy) are considered confirmatory. Bone marrow assessments are considered in the response assessment in all subjects (see below paragraph for more details). Endoscopic gastric biopsy and evaluation of the biopsy findings are required only in subjects with an investigator-assessed diagnosis of gastric MALT lymphoma. In those subjects whose CT/MRI response assessments require consideration of biopsy findings before a final response assessment can be determined, the date of achievement of a response status will be the initial date of CT or MRI showing a response.

Bone marrow assessments: all subjects who have achieved a CR/CRu by radiological imaging will need to undergo a BMB to confirm the radiological response, unless a BMB collected at baseline (within 12 weeks of Cycle 1 Day 1), was negative. The confirmatory BMB should be performed within 28 days after the criteria for CR/CRu have otherwise been met. The BMB sample must be submitted to central pathology within 8 weeks.

Subjects with gastric MALT lymphoma will have an upper gastrointestinal endoscopic assessment and repeat gastric biopsy for histological evaluation during the study if the subject has fulfilled the IWG criteria for response of at least a SD and had positive biopsy at baseline. The endoscopic assessment and repeat biopsies will be performed at Cycle 7 Day 1 (±2 week), within 2 months after Cycle 12 (treatment completion), then every 6 months for 2 years, and thereafter annually. For subjects achieving radiological CR/CRu, two biopsies performed at two separate time points within 3 months after the criteria for CR/CRu were first met are required to confirm response. The biopsy samples must be submitted to central pathology review within 8 weeks. Histological evaluation will be performed using the Groupe d' Etude des Lymphomes de l' Adulte (GELA) grading system (Copie-Bergman, 2003; Copie-Bergman, 2012). The Investigator may make treatment decisions based on histological evaluation of bone marrow biopsy, gastric biopsy or other biopsies by local pathology. However, response assessments and determination of progression will be by central pathology. For equivocal biopsy findings, the investigator is strongly recommended to contact the sponsor Medical Monitor for evaluation of the equivocal biopsy by the central pathologist in a "real time" manner.

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Subjects who relapse or progress will continue to be followed for OS, TTNLT, CCI [redacted], all subsequent anti-lymphoma therapy CCI [redacted].

6.2.2. Safety Assessments

Adverse events will be assessed, concomitant medication or procedure and hospitalizations recorded from signing of informed consent form until 28 days post-last dose of treatment.

The physical examination including **ECOG PS and B symptoms** assessments should be repeated at the beginning of each cycle, at treatment discontinuation, according to the CT scan schedule during the follow-up, every 6 months (±2 week) after year 5 and at any additional times as deemed necessary by the Investigator.

Vital signs (including blood pressure, pulse, and temperature) will be measured on Day 1 of every cycle, at treatment discontinuation and at designated times thereafter. Investigators are to report any clinically significant abnormal findings as AEs.

Hematology laboratory evaluations and serum chemistry laboratory evaluations will be collected at Day 1 (± 3 days) of every treatment cycle, Days 8 and 15 (± 1 day) of Cycle 1, Day 15 of Cycles 2 to 4 (± 1 day), and at treatment discontinuation. During the follow-up period, hematology and serum chemistry assessments will follow the CT scan schedule, and will be collected every 6 months (±2 weeks) after year 5.

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TSH will be collected every 3 months after screening up to Cycle 10 (Cycle 4 Day1, Cycle 7 Day1, and Cycle 10 Day 1; ± 3 days) and thereafter as clinically indicated.

Serum immunoglobulin assessment (IgG, IgA, IgM) is performed on Cycle 10 Day 1 (± 3 days).

In addition, any or all laboratory evaluations may be repeated more frequently if clinically indicated.

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted on Day 1 of every treatment cycle. All subjects must also be counseled against sharing lenalidomide and donating blood during and within 28 days of discontinuing protocol-specified therapy. Pregnancy tests for FCBP will be performed weekly during the first cycle, every 28 days (Day 1 of every cycle) during treatment. *FCBP with regular or no menstrual cycles* must have pregnancy tests at treatment discontinuation and at Day 28 following lenalidomide or placebo discontinuation and if *menstrual cycles are irregular*, the pregnancy testing must occur at treatment discontinuation and at Days 14 and 28 following lenalidomide or placebo discontinuation (Section 18.6).

All subjects including the subjects who relapse or progress will continue to be followed for **SPMs**. 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 SPM as SAEs regardless of causal relationship to the study drug[s], occurring at any time for the duration of the study, from the time of signing the ICD up to and including the Follow-up Period (up to 5 years from last subject randomized).

6.2.2.1. Assessments for Tumor Flare

Assessments for tumor flare reaction (TFR) are conducted in Cycle 1: Days 1, 8, and 15 (±1 day), and when clinically indicated thereafter.

Tumor flare reaction 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).

Tumor flare reaction 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 at a lower rate than in CLL patients (Witzig, 2011; Eve, 2010; Corazzelli, 2010). The clinical manifestations of TFR seen in lymphoma subjects treated with lenalidomide are similar to those subjects with CLL; a sudden and tender increase in the size of the disease bearing sites, including the lymph nodes, spleen and/or the liver, typically accompanied by pain and sometimes accompanied by low-grade fever and non-pruritic diffuse rash, typically occurring in the first cycle (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 and is within the first 2-3 weeks of the first cycle in the vast majority of TFR cases (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).

The experience with tumor flare in Celgene-sponsored studies of single agent lenalidomide in NHL is now summarized. Over 400 subjects with relapsed or refractory aggressive or indolent non-Hodgkin's lymphoma have received lenalidomide in four Phase 2 clinical studies. Four studies (NHL-001, NHL-002, NHL-003, and MCL-001) were Phase 2 multicenter, single-arm, open-label studies that evaluated lenalidomide 25 mg/day for 21 days of a 28-day cycle in 43 previously treated subjects with indolent NHL (Witzig, 2009), 49 subjects with relapsed/refractory aggressive NHL (Wiernik, 2008), 217 subjects with relapsed/refractory aggressive NHL (Witzig, 2011), and 134 subjects with MCL (Goy, 2012), respectively. TFR 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)], 13 of 134 subjects in the MCL-001 study [Grade 1 (n = 7), and Grade 2 (n = 6)] and in 17 (10.2%) out of 167 subjects in the lenalidomide arm in the MCL-002 study. These protocols suggested that subjects experienced TFR during the first 1 to 2 weeks of Cycle 1 and the TFR may be treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDs).

In a single-center, open-label Phase II investigator initiated study, Ahmadi et al evaluated the use of lenalidomide, dexamethasone and Rituximab in subjects with relapsed or refractory indolent B-cell or MCL resistant to rituximab (Ahmadi, 2014). Tumor flare was reported in 1 of the 27 subjects.

It is important to note that the increased lymphadenopathy seen in TFR may mimic PD. Therefore, careful monitoring and evaluation to differentiate TFR from PD is necessary for addressing treatment of individual subjects including making decisions 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 case of TFR, inflammation and edema may reduce or disappear after short term treatment with NSAIDs and/or corticosteroids.

Management of TFR is described in Section 9.1.1.

6.2.2.2. Assessments for tumor lysis

Tumor lysis syndrome assessments are conducted in Cycle 1: Days 1, 8, and 15 (± 1 day), and when clinically indicated thereafter.

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 and the prevention of TLS development with the initiation of preventive measures, as well as the careful monitoring for early signs of laboratory TLS and the 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 in 43 previously treated subjects with indolent non-Hodgkin lymphoma (NHL-001; Witzig, 2009), 49 subjects with relapsed/refractory aggressive NHL (NHL-002; Wiernik, 2008), 217 subjects with relapsed/refractory aggressive NHL (NHL-003; Witzig, 2011) and 134 subjects with relapsed/refractory MCL (MCL-001; Goy, 2012). In addition, in the MCL-002 study, a Phase 2 randomized, two-arm, open-label study of lenalidomide versus Investigator's Choice in relapsed/refractory MCL, 167 subjects received lenalidomide 25 mg/day for 21 days of a 28 day cycle. One subject CCI had Grade 1 TLS reported. CCI [redacted]

In an investigator initiated study, a single-center, open-label Phase II study, Tuscano et al (Tuscano, 2014) 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 tumor lysis. Thus, the lenalidomide dose was reduced to 20 mg and allopurinol prophylaxis was used in all subsequent subjects with no further TLS events recorded. In the current study, it is required that subjects receive prophylaxis (allopurinol, rasburicase, or equivalent as per institutional guidelines) during the first week of the first cycle or for a longer period if clinically indicated (see Section 9.3.1 for more information).

6.2.2.3. Deep vein thrombosis

6.2.2.3.1. Deep vein thrombosis in Multiple Myeloma

Venous thromboembolic events (VTE), such as deep venous thrombosis and pulmonary embolism, have occurred in patients with multiple myeloma treated with lenalidomide combination therapy, and patients with MDS or lymphoma treated with lenalidomide monotherapy. A significantly increased risk of DVT and PE has been observed in patients with multiple myeloma who were treated with lenalidomide and dexamethasone therapy (Hussein, 2006; Revlimid prescribing information USA, February 2013). Clinical data in multiple myeloma patients treated with lenalidomide suggest 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 patients treated with lenalidomide (Leleu, 2011).

In the two pivotal randomized studies (MM-009 and MM-010) in subjects with multiple myeloma receiving lenalidomide plus dexamethasone, deep venous thrombosis and pulmonary embolism were reported in 9.3% and 4.3% of subjects, respectively compared to 4.0% and 0.9% of subjects receiving placebo and dexamethasone. The studies did not require systematic DVT prophylaxis. An analysis of pooled data from the MM-009 and MM-010 studies demonstrated thromboembolic events were significantly higher in subjects treated with lenalidomide/dexamethasone in 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

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erythropoietin (P=0.14) (Weber, 2007). The 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 venous thromboembolism (VTE) including DVT and PE occurred in 26% of 223 subjects in the RD arm and 12% of 220 subjects in the Rd arm (Rajkumar, 2010). DVT prophylaxis was to be used in both arms.

6.2.2.3.2. 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 but not limited to the underlying disease, family history, age, obesity, immobilization, hormonal therapy, central venous catheter, recent DVT, and doxorubicin (Zhou, 2010; Park, 2012; Lyman 2013).

Venous thromboembolism including deep venous thrombosis (DVT) and pulmonary embolism (PE) has been reported in patients during treatment for NHL, occurring at incidences from ~7% up to 20% (Ottinger, 1995, Komrokji, 2006, Mohren, 2005, Zhou, 2010), the risk being 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 (Ottinger, 1995) analyzed incidence, risk factors, causes and prognostic significance of VTE in high-grade non-Hodgkin's lymphoma in a prospective clinical trial. In 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.

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) and in 5 (4%) and 3 (2%) of 134 subjects with relapsed or refractory MCL receiving lenalidomide in the clinical study MCL-001 (Goy 2012). In the Lenalidomide arm of the MCL-002 study, pulmonary embolism was the most frequently reported VTE event (7 subjects, 4.2%), followed by deep vein thrombosis (3 subjects, 1.8%). Most events of both pulmonary embolism and deep vein thrombosis occurred within the first 5 cycles of treatment. All events of pulmonary embolism were considered Grade 3-5 AEs and all but one event were SAEs, whereas no events of deep vein thrombosis were SAEs and only one event was Grade 3-5. DVT and PE were reported in 0 (0%) and 1 (2.3%) of 43 subjects with indolent relapsed refractory NHL (Witzig, 2009). Anti-thrombotic prophylaxis was not suggested in NHL-001 or NHL-002 but required for subjects considered to be high risk of developing DVT in NHL-003. In the recent 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 lenalidomide plus rituximab arm versus 7 (16%) of 45 subjects in lenalidomide arm (Leonard, 2012).

Thus, when the available data are taken together, the increased risk of DVT reported thus far with lenalidomide monotherapy in lymphoma patients does not appear to be as high as when lenalidomide is added to dexamethasone in multiple myeloma subjects. However, we cannot rule out that the risk of VTE is increased in the subjects participating in this study treated with rituximab and lenalidomide. Thus, in the current study, it is recommended that all subjects at risk

for thromboembolic events receive anti-thrombotic prophylaxis (see Section 9.1.2) and all subjects will be closely monitored for VTE.

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6.3. Assessments at Treatment Discontinuation/Completion

- Physical examination including vital signs, and ECOG PS
- B symptoms
- Hematology and serum chemistry laboratory tests
- Pregnancy testing for FCBP
- Lenalidomide counseling
- Adverse events including SPM
- Hospitalization
- Concomitant medication and procedure
- Study drug return/accountability
- Subsequent anti-lymphoma therapy
- CCI [redacted]

6.4. Follow-up Assessments

Follow-up Period will start at the end of treatment (end of cycle 12, day 28) or at treatment discontinuation.

Adverse events, concomitant treatments, pregnancy testing for FCBP, and hospitalization will be recorded up to 28 days after the last dose of study drug(s).

Subjects will be followed until 5 years after the last subject is randomized, for disease progression, long-term follow-up for OS, subsequent anti-lymphoma therapy, CCI [redacted] and SPM. The frequency of the visit and assessments will be based on the disease status. If a subject withdraws consent, but agrees to continued collection of outcome data, these follow-up activities will continue.

For subjects who have completed treatment or discontinued treatment due to reasons other than progressive disease or relapse, follow-up assessments include the following and will follow the

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CT scan assessment schedule (as described in Section 6.2.1), and every 6 months (± 2 weeks) after year 5 or as specified below:

- Physical examination including ECOG PS
- B symptoms
- Hematology laboratory evaluations (hemoglobin, hematocrit, WBC count, ANC, and platelet count)
- Serum chemistry laboratory evaluations
- CT or MRI scans will follow the assessment schedule as described in Section 6.2.1.
- Upper gastrointestinal endoscopy and gastric biopsies every 6 months (± 2 weeks) in year 2 and 3 and then annually until disease progression. For subjects achieving radiological CR/ a biopsy performed at two separate time points within 3 months after the criteria for CR were first met is required to confirm response
- OS
- SPM

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For subjects who discontinue treatment due to progressive disease or relapse, subjects will be followed every 6 months (± 2 weeks) and the follow-up assessments will include:

- OS
- Next subsequent anti-lymphoma therapy

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- SPM

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Once the primary efficacy analysis is completed, follow-up tests including but not limited to CT scans, biopsies (bone marrow, tumor, gastric) and blood tests are no longer required for the study protocol and may be performed at the investigator's discretion. A central review of these tests will no longer be required (see Section 4.4 for details).

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7. STUDY POPULATION

Subjects must have an Investigator-assessed diagnosis of relapsed indolent lymphoma, defined in this clinical trial as Grade 1, 2 or 3a FL or MZL, must have been previously treated for their lymphoma with systemic therapy, must be refractory or must have relapsed after their last treatment, must have at least one measurable lesion by CT or MRI scan, and must have adequate bone marrow function, liver function and renal function.

7.1. Number of Subjects

It is planned to randomize 350 subjects in this study.

7.2. Inclusion Criteria

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

1. Must be ≥ 18 years at the time of signing the ICD.
2. Understand and voluntarily sign an ICD prior to any study related assessments/procedures are conducted.
3. Histologically confirmed MZL or Grade 1, 2 or 3a FL (CD20+ by flow cytometry or histochemistry) as assessed by investigator or local pathologist:
    a. A formalin fixed paraffin embedded specimen must be available for central review. If an archival specimen is not available, a rebiopsy is required prior to randomization.
4. Must have been previously treated with at least one prior systemic chemotherapy, immunotherapy or chemoimmunotherapy and must have received at least 2 previous doses of rituximab (as of Amendment 3):
    a. Systemic therapy does not include, for example:
        i. Local involved field radiotherapy for limited stage disease
        ii. *H. Pylori* eradication
    b. Prior investigational therapies will be allowed provided the subject has received at least one prior systemic therapy.
5. Must have documented relapsed, refractory or progressive disease (PD) after treatment with systemic therapy, and must not be rituximab-refractory.
    a. Relapsed lymphoma: relapsed after initial response of CR to prior therapy.
    b. Progressive lymphoma: PD after initial response of PR or SD to the prior therapy.
    c. Refractory lymphoma: Subject who received a non-rituximab containing systemic therapy and who experienced the best response of PD to this therapy is considered to have refractory lymphoma.
    d. Rituximab-refractoriness is defined as:
        i. Did not respond (at least a PR) to rituximab or R-chemoregimen therapy and/or

ii. Time to disease progression < 6 months after last rituximab dose.

e. Rituximab-sensitive MZL or FL defined as

i. Responded (at least a PR) to rituximab or R-chemoregimen therapy and

ii. Time to disease progression ≥ 6 months after last rituximab dose

f. Subjects with gastric MALT lymphoma and evidence of *H. pylori* (HP) infection must have documented non-response to antibiotic therapy as judged by a minimum follow up of 12 months after successful HP-eradication.

6. Investigator considers that rituximab monotherapy is appropriate.
7. Bi-dimensionally measurable disease on cross sectional imaging by CT or MRI with
   a. At least one nodal lesion > 1.5 cm in diameter or
   b. At least one extranodal lesion > 1.0 cm in both long and short diameter
8. Must be in need of treatment for relapsed, progressed or refractory disease as assessed by the investigator
9. Performance status ≤ 2 on the ECOG scale (Appendix 18.4)
10. Must fulfill the following laboratory requirements:
    a. Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3 (1.5×10^9/L) unless secondary to bone marrow involvement by lymphoma as demonstrated by recent bone marrow biopsy
    b. Platelet count ≥ 75,000/mm3 (75×10^9/L) unless secondary to bone marrow involvement by lymphoma as demonstrated by recent bone marrow biopsy
    c. Hemoglobin ≥ 8.0 g/dL (80.0 g/L; 5 mmol/L)
    d. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≤ 3x upper limit of normal (ULN) except in subjects with documented liver involvement by lymphoma
    e. Serum total bilirubin ≤ 2.0 mg/dL (34 µmol/L) except in cases of Gilberts Syndrome, or documented liver or pancreatic involvement by lymphoma
    f. Creatinine clearance of ≥ 30 mL/min (≥0.5mL/sec), from central laboratory calculation
    g. Absolute lymphocyte count ≤ 25,000/mm^3 (25×10^9/L)
11. Must be able to adhere to the study visit schedule and other protocol requirements
12. 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

† See Appendix 18.6 for details

the study, and after end of study therapy. This applies even if the subject practices true abstinence‡ from heterosexual contact.

b. Either commit to true abstinence‡ 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 drug, during the study therapy (including dose interruptions), for 28 days after discontinuation of lenalidomide/placebo therapy and according to the approved rituximab product/prescribing information.

13. Male subjects must†:

a. Must practice true abstinence‡ 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 study drug discontinuation, even if he has undergone a successful vasectomy.

b. Agree to not donate semen during study drug therapy and for 28 days after discontinuation of study drug therapy.

14. All subjects must:

a. Have an understanding that the study drug could have a potential teratogenic risk.

b. Agree to abstain from donating blood while taking study drug therapy and for 28 days after discontinuation of study drug therapy.

c. Agree not to share study medication 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 28 days after lenalidomide/placebo discontinuation and according to the approved rituximab product/prescribing information.

7.3. Exclusion Criteria

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

1. Histology other than FL and MZL or clinical evidence of transformed lymphoma by investigator assessment.
2. Grade 3b follicular lymphoma.
3. Subjects taking corticosteroids during the last 1 week prior to Cycle 1 Day 1, unless administered at a dose equivalent to ≤ 20 mg/day prednisone or prednisolone (over this week).
4. Major surgery (excluding lymph node or bone marrow biopsy) within 28 days prior to signing informed consent.

‡ True abstinence: When this is in line with the preferred and usual lifestyle of the subject. [*Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception*].

5. Systemic therapy within 28 days prior to Cycle 1 Day 1 dosing or use of the following:
   a. Antibody agents within 8 weeks prior to Cycle 1 Day 1 dosing
   b. Radioimmunotherapy within 6 months prior to Cycle 1 Day 1 dosing
6. Seropositive for or active viral infection with hepatitis B virus (HBV):
   - HBsAg positive
   - anti-HBs positive and/or anti-HBc positive, and HBsAg negative and detectable viral DNA

   Notes:- Subjects who are anti-HBs positive and/or anti-HBc positive, and HBsAg negative but viral DNA negative are eligible (see Section 9.3.3)

   - Subjects who are seropositive because of HBV vaccination are eligible (anti-HBs positive, anti-HBc negative, and HBsAg negative)
7. Hepatitis C virus (HCV) positive subjects with chronic HCV hepatitis or subjects with an active HCV infection requiring anti-viral medication (at time of randomization).

   Note: - HCV positive subjects who do not have active HCV hepatitis and are otherwise acceptable candidates for the study treatment, as documented by the investigator, are eligible. The Investigator must confirm that the patient does not have an active HCV infection or unacceptable liver damage as documented by one of the following options: liver ultrasound for fibrosis, liver biopsy, zero RNA viral load, or other local practice test.
8. Known seropositive for or active viral infection with human immunodeficiency virus (HIV)
9. Life expectancy < 6 months
10. Known sensitivity or allergy to murine products
11. Prior history of malignancies, other than FL or MZL, unless the subject has been free of the disease for ≥ 5 years. Exceptions include a history of previously treated:
    a. Basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and related localized non-melanoma skin cancer
    b. Carcinoma *in situ* of the cervix
12. Prior use of lenalidomide
13. Known allergy to thalidomide
14. Neuropathy > Grade 1
15. Presence or history of CNS involvement by lymphoma.
16. Subjects who are at a risk for a thromboembolic event and are not willing to take VTE prophylaxis.
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. Pregnant or lactating females.
20. Any condition, including for example coronary artery disease, congestive heart failure, pulmonary disease, active, severe infections, chronic renal or immunological disease, or the presence of laboratory abnormalities that places the subject at unacceptable risk if he/she were to participate in the study or that confounds the ability to interpret data from the study.

CCI [redacted]

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg capsules and the respective matching placebo capsules for oral administration. Subjects will receive 21 days of lenalidomide or placebo per cycle.

Study drug will be packaged in bottles containing study capsules for 21 days. Commercially available IV formulation of rituximab background therapy will be used. Celgene will provide commercial supplies of rituximab for IV administration, labeled appropriately for investigational use as per the regulations of the relevant country health authority. Subjects enrolled in countries where rituximab is designated as non-investigational product, should obtain commercially available product through the local hospital pharmacy or licensed distributor. Subjects enrolled in countries where rituximab is designated as IP, will have rituximab supplied and packaged by Celgene Corporation.

8.2. Treatment Administration and Schedule

Eligible subjects entering the Treatment Phase will be randomized in a 1:1 ratio using an Interactive Voice Response System (IVRS) into one of two arms (experimental or control). Randomization will be stratified as described in Section 8.6.1.

- Experimental: Rituximab + Lenalidomide
  - rituximab 375 mg/m^2 every week in cycle 1 (Days 1, 8, 15, 22) and on Day 1 of every 28-day cycle from Cycle 2 to 5

    plus
  - Lenalidomide once daily (please see Section 8.2.1 for details) on Days 1 to 21 of every 28-day cycle
- Control: Rituximab + placebo
  - rituximab 375 mg/m^2 every week in cycle 1 (Days 1, 8, 15, 22) and on Day 1 of every 28-day cycle from Cycle 2 to 5

    plus
  - Placebo (identical matched capsule) once daily (please see Section 8.2.1 for details) on Days 1 to 21 of every 28-day cycle

Treatment must begin as soon as possible after randomization but no later than 1 week after randomization. There is no window for study drug administration.

Co-administration (ie, lenalidomide intake during the rituximab infusion) should be avoided. Due to the duration of the rituximab infusion and potential infusion-related reactions to rituximab, administration of lenalidomide before rituximab should be considered.

The Treatment Period for each subject starts with first intake of study drug, which is defined as Study Day 1 of Cycle 1.

8.2.1. Lenalidomide or Placebo dosing

Lenalidomide or placebo dosing will be based on subjects creatinine clearance calculated using the Cockcroft-Gault formula utilizing actual body weight. This calculation will be performed by the central laboratory based on actual body weight.

- Subjects who have a creatinine clearance ≥ 60 mL/min (≥1.0 mL/sec) will receive oral lenalidomide or placebo at a dose of **20 mg** once daily on Days 1 to 21 in each 28 day cycle.
- Subjects who have moderate renal insufficiency (creatinine clearance ≥ 30 mL/min but < 60 mL/min; ≥ 0.5 mL/sec but < 1.0 mL/sec) will receive a lower starting dose of lenalidomide or placebo of **10 mg** once daily on Days 1 to 21 of 28-day cycle in Cycle 1 and in Cycle 2. If the subject remains free of drug-related Grade 3 or 4 toxicities for at least 2 cycles, the dose may be increased to **15 mg** once daily on Days 1 to 21 of a 28-day cycle at the discretion of the treating physician from Cycle 3 onwards.

Lenalidomide or placebo should be taken at approximately the same time every day. There is no requirement for taking lenalidomide or placebo with or without food, or with or without certain types of foods or liquids. If a subject misses a dose of lenalidomide or 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.

8.2.2. Rituximab therapy

The planned dose of rituximab is 375 mg/m^2 every week in Cycle 1 (days 1, 8, 15, 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5. Premedication should be administered (see package insert or where applicable refer to the instruction in pharmacy manual and protocol Section 9.3.2).

All dosage calculations for rituximab will be based on the subject‘s body surface area (BSA), using actual weight for calculations. This will be determined within 1 week prior to or on the first day of study drug administration of Cycle 1. For rituximab, no dosage adjustments for changes in subjects’ weight during the study should be performed.

Refer to approved product/prescribing information for further information on rituximab therapy including warning, precautions, contraindications, and guidance on pregnancy prevention.

8.2.3. Requalification Criteria for Subsequent Treatment Cycles

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

- A 7-day rest period has elapsed following the last dose of lenalidomide / placebo;
- The ANC is ≥ 1,000 cells/mm³ (1.0 X 10^9/L);
- The platelet count is ≥ 50,000 cells/mm³ (50 X 10^9/L);

- Study-drug-related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity;
- Any other study-drug-related AE not requiring discontinuation has resolved to ≤ Grade 2 severity.

If these Requalification Criteria are not met, the subject will be evaluated at least once every seven days and a new cycle of study drug will not be initiated until the criteria have been met as described above. If a new cycle is delayed for more than 28 days, the Celgene Medical Monitor must be notified. The treatment can be resumed according to the treating physicians' and Medical Monitor's clinical judgment.

The criteria above do not apply to laboratory abnormalities of subjects who are randomized with these laboratory abnormalities due to lymphoma infiltration of the bone marrow or documented liver involvement by lymphoma. In the absence of evidence of treatment emergent toxicity, the new cycle of treatment may begin at the discretion of the investigator.

The study assessments should remain in line with dosing days (actual number of days that lenalidomide or placebo plus rituximab has been administered) but the tumor assessments will be determined from Cycle 1 Day 1 and will follow the counting of calendar days and not the dosing cycles.

If a subject experiences an AE that requires a dose interruption, the subject cannot be re-started on study medication (lenalidomide or placebo) until the AE has resolved or reached acceptable grade as described in Table 2. Once the AE has resolved, the subject may restart study drug (at the dose level required in Table 2, and refer to Table 3 and Table 4 for the actual dose) for the remainder of the cycle. Doses that were missed, because of toxicity or any other reason, will not be rescheduled.

If the start of the next cycle is delayed due to an AE, the subject can re-start study drug (lenalidomide or placebo) for that next cycle once the AE has resolved and the requirements mentioned above have been met.

8.2.4. Dose Modification or Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE Version 4.03 used as a guide for the grading of severity. However, TFR will be graded using NCI CTCAE Version 3.0. Prior to dose modification or interruption, the investigator should first determine which is the offending study drug(s) causing the toxicity.

8.2.4.1. Dose Adjustment for Lenalidomide or Placebo

a) Dose modification or interruption

The dose of lenalidomide or placebo for each subject will be interrupted and modified following toxicity as described below. Refer to Table 2 for instructions on dose modifications and Table 3 and Table 4 for dose reduction instructions for study drug.

If lenalidomide or placebo has been discontinued due to toxicity, rituximab treatment may continue as per protocol. If rituximab treatment is continued following discontinuation of

lenalidomide or placebo, the subject will continue study treatment with rituximab alone and will be followed as per protocol after the last dose of rituximab (Cycle 5 Day 1 at the latest).

Table 2: Dose Modification for Lenalidomide or Placebo

NCI CTCAE Toxicity Grade	ACTION REQUIRED
Grade 3 Neutrophil count decreased (neutropenia) Absolute neutrophil count <1,000 cells/mm³ [1.0x10⁹/L] **(one time reading)**	• Follow CBC at least every seven days
Neutrophil count decreased (Neutropenia) Sustained (≥ 7 days) Grade 3 OR ≥ Grade 3 associated with fever (temperature ≥ 38.5° C) OR Grade 4	• Hold (interrupt dose) • Follow CBC at least every seven days • If neutropenia has resolved to ≤ Grade 2 restart at next lower dose level • Use of growth factors (G-CSF, GM-CSF) is permitted as per ASCO and ESMO guidelines
Platelet count decreased (Thrombocytopenia) ≥ Grade 3 (platelet count < 50,000 cells/mm³ [50x10⁹/L])	• Hold (interrupt dose) • Follow CBC weekly • If thrombocytopenia resolves to ≤ Grade 2 restart at next lower dose level
Rash[a] Grades 1-2	• Start supportive measures[b] if Grade 2 • No dose adjustment
Grade 3 (Non-desquamating or non-blistering)	• Hold (interrupt dose) • Start supportive measures[b] • Evaluate at least weekly • If rash resolves to ≤ Grade 1 restart at next lower dose
Grade 4[c]	• Discontinue lenalidomide or placebo • Dermatology evaluation • Consider supportive measures[b]

Table 2: Dose Modification for Lenalidomide or Placebo (Continued)

NCI CTCAE Toxicity Grade	ACTION REQUIRED
Desquamating (blistering) rash Any Grade[c]	• Discontinue lenalidomide or placebo • Dermatology evaluation • Consider supportive measures[b]
Stevens-Johnson Syndrome or Toxic epidermal necrolysis	• Discontinue lenalidomide or placebo • Dermatology evaluation
Allergic reaction or hypersensitivity Grade 2	• Hold (interrupt) dose. • Follow at least every seven days. • When the toxicity resolves to ≤ Grade 1 restart at next lower dose level
Grade 3-4	• Discontinue lenalidomide or placebo
Constipation Grade 1-2	• Initiate bowel regimen and maintain dose level
≥ Grade 3	• Hold dose and initiate bowel regimen • When the toxicity resolves to ≤ Grade 2 restart at next lower dose level
Vascular access complication (Venous thrombosis/embolism) ≥ Grade 3	• Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level)
Peripheral Neuropathy Grade 3	• Hold (interrupt dose) • When toxicity resolves to ≤ Grade 1 or to screening, restart at the next lower dose
Grade 4	• Discontinue lenalidomide or placebo
Tumor Flare Reaction (TFR)[a] Grade 1-2	• Continue lenalidomide or placebo, maintain dose level • At the investigator's discretion may initiate therapy with NSAIDs, limited duration corticosteroids, and/or narcotics

Table 2: Dose Modification for Lenalidomide or Placebo (Continued)

NCI CTCAE Toxicity Grade	ACTION REQUIRED
Grade 3-4	• Hold (interrupt dose) and initiate therapy with NSAIDs, corticosteroids, and/or narcotics • When symptoms resolved to ≤ Grade 1, restart at same dose level for the rest of the cycle
Hypothyroid If the TSH is > ULN and subject is clinically euthyroid	• Repeat TSH on Day 1 of next cycle • No dose decrease or interruption
If TSH is > ULN for more than 2 cycles, or if subject has clinical symptoms of hypothyroidism;	• Endocrinology evaluation is recommended and thyroid hormone replacement is allowed if clinically indicated • No dose decrease or interruption
Hyperthyroid If TSH < LLN and subject is clinically euthyroid,	• Repeat TSH every 3 months • No dose decrease or interruption
If TSH <LLN at repeat evaluation and subject is clinically euthyroid	• Recommend endocrine evaluation • No dose decrease or interruption
If TSH < LLN and subjects have symptoms of hyperthyroid (tremor, tachycardia, unintentional weight loss, or *new onset* night sweats),	• Hold (interrupt dose) • Obtain endocrine evaluation and workup for alternative etiologies • Repeat TSH level on day 1 of next cycle and contact medical monitor • If endocrine evaluation rules out hyperthyroidism, restart lenalidomide or placebo at the same dose • If hyperthyroidism confirmed and alternative etiologies eliminated, restart lenalidomide or placebo dosing at next lower dose.

Table 2: Dose Modification for Lenalidomide or Placebo (Continued)

NCI CTCAE Toxicity Grade	ACTION REQUIRED
Liver Function[d]	
ALT or AST Grade 2 (>3 - 5 x UNL) **and** Total bilirubin Grade 1 (> ULN - 1.5 x ULN)	• Continue study drug: re-test at next scheduled visit • No dose modification
ALT or AST ≥ Grade 3 (>5 x ULN) **or** Total bilirubin ≥ Grade 2 (> 1.5 x ULN)	• Hold (interrupt dose) and follow weekly ALT and total bilirubin until return to baseline (value at Screening) • Resume the same dose of study drug if recovery (return to baseline) from the event is ≤ 14 days • If recovery is prolonged beyond 14 days, weekly testing of liver functions should occur during that cycle and then decrease the dose by one level when recovered (returned to baseline)
Cairo-Bishop Toxicity Grade (see Appendix 18.5)	
Laboratory TLS or Grade 1 TLS	• Continue lenalidomide or placebo (maintain dose), or at the investigator's discretion, continue lenalidomide or placebo and reduce dose by one level • Provide vigorous intravenous hydration and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy is appropriate (if approved by the local Health Authority) as needed to reduce hyperuricemia • Hospitalization will be at investigator's discretion
Clinical TLS ≥ Grade 2	• Hold (Interrupt dose) • When the AE resolves to Grade 0, restart at next lower dose per investigator's discretion
Other ≥ Grade 3 study drug-related AEs	• Hold dose and restart at same or next lower level per investigators discretion when toxicity resolves to ≤ Grade 2

[a] AEs are graded using the NCI CTCAE v 4.03; however TFR will be graded using NCI CTCAE v 3.0.
[b] Suggested supportive measures for rash – 1) initiate daily oral antihistamines, for example, loratadine 10 mg PO daily, cetirizine 10 mg PO daily or diphenhydramine 25 mg PO daily; 2) Short courses of low-dose steroids for example, prednisone 10 mg PO x 3 days (or equivalent) or hydrocortisone 20 mg PO QAM, 10 mg PO QPM x 3 days. It is recommended that the daily oral anti-histamines treatment be continued for the rest the of the lenalidomide treatment.

[c] In cases of Grade 4 or desquamating rash, prompt dermatologic evaluation with skin biopsy is strongly recommended.
[d] For subjects with Gilberts Syndrome or liver involvement by lymphoma, dose reductions should be made in consultation with the Medical Monitor.

b) Dose Reduction Levels Based On Starting Dose

The daily dose of lenalidomide or placebo may be reduced successively by one level from the starting dose. There will be no more than one dose reduction from one cycle to the next. No dose (re)escalation is permitted at any time unless as specified in Table 4.

For subjects with starting dose of 20 mg of lenalidomide/placebo daily on Days 1 to 21 every 28 days (for subjects with a creatinine clearance ≥ 60 mL/min), the daily oral dose of study drug shall be reduced by one level (decrements of 5 mg –refer to Table 3) at the next treatment cycle if toxicity requiring dose modifications (as per Section 8.2.3) has occurred during the previous treatment cycle.

Subjects who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min] (Refer to dose reduction steps in Table 4):

- Will receive a lower starting dose of study drug of 10 mg once daily in Cycle 1 and Cycle 2 Days 1 to 21 for 28 days.
- If the subject remains free of drug-related Grade 3 or 4 toxicities for at least 2 cycles, the dose may be increased to 15 mg once daily on Days 1 to 21 of a 28-day cycle at the discretion of the treating physician from Cycle 3 onwards.
- The daily oral dose of study drug may be reduced successively by one level on event of toxicity as described in Table 2. Only 1 dose reduction should occur for concurrent AEs that require a dose reduction.

Table 3: Dose Reduction Steps for Adverse Events Related to Study Drug for Subjects Initiating Treatment at 20 mg Daily on Days 1 to 21, Every 28 Days

Dose	Once Daily on Days 1-21, Every 28 Day Cycles
Level 1 (starting dose)	20 mg daily on Days 1-21, every 28 days
Level 2[a]	15 mg daily on Days 1-21, every 28 days
Level 3[a]	10 mg daily on Days 1-21, every 28 days
Level 4[a,b]	5 mg daily on Days 1-21, every 28 days

[a] Once a subject's dose has been reduced, no dose re-escalation will be permitted.
[b] Subjects who cannot tolerate Dose Level 4 are to be discontinued from the Treatment Phase of the study.

Table 4: Dose Modification Steps for Subjects Initiating Treatment at 10 mg Daily on Days 1 to 21, Every 28 Days

Dose	Once Daily on Days 1-21, Every 28 Days
Level -1[a]	15 mg daily on Days 1-21, every 28 days
Level 1 (starting dose)[a,b,c]	10 mg daily on Days 1-21, every 28 days
Level 2[c,]	5 mg daily on Days 1-21, every 28 days
Level 3[c,d]	2.5 mg daily on Days 1-21, every 28 days

[a] If the subject has not experienced any drug-related Grade 3 or 4 toxicity for at least 2 cycles, the dose may be increased to 15 mg once daily on Days 1 to21 of each 28 day cycle at the discretion of the treating physician from cycle 3 onwards
[b] Once the dose is escalated to 15 mg once daily for 21 days every 28 day, dose may be reduced successively by 1 level, ie, to 10 mg.
[c] Once a subject's dose has been reduced, no dose re-escalation is permitted.
[d] Subjects who cannot tolerate Dose Level 3 are to be discontinued from the Treatment period of the study.

8.2.4.2. Dose Adjustment for Rituximab

The dose of rituximab should not be reduced. The dose of rituximab may be interrupted and modified according to the clinical practice of the Investigator's institution (e.g., dose splitting or dose banding), and in line with the approved prescribing information including administration, warnings, precautions, contraindications, and adverse reactions, as applicable.

In case a dose of rituximab is missed during the first cycle because of toxicity, it will not be rescheduled. In such situations, treatment with lenalidomide or placebo does not need to be interrupted.

In case of delay in the start of next cycle during (Cycles 2 to 5) due to toxicity, rituximab administration will be postponed until AE has resolved, at which point the next cycle is started.

If rituximab is discontinued due to toxicity, lenalidomide/placebo should be continued as per protocol and the subject should continue on the study.

8.2.4.3. Overdose

Overdose, as defined for this protocol, refers to lenalidomide / placebo and rituximab. 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 case report form. See Section 11.1 for the reporting of AEs associated with overdose.

8.3. Blinding

For this trial, study subjects, Investigators, staff, and Celgene Corporation clinical and medical representatives will all be blinded to the treatment assignments until disease progression as determined by IRC. Both lenalidomide and placebo capsules are identical in appearance.

Randomization, drug dispensing, dose reduction/escalation, and drug discontinuation will be accomplished by an IVRS system. Authorized site personnel must contact the IVRS for randomization, study drug assignment at the beginning of each cycle, to register dose reductions or escalations, and treatment discontinuation. Confirmation of each call will be sent to the investigational site and Celgene.

8.4. Emergency Unblinding

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 decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, the investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The investigator should ensure that the code is broken only in accordance with the protocol. The investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the investigator in the subject's source documentation.

Emergency unblinding should only be performed by the investigator through the IVRS by using an emergency unblinding personal identification number (PIN), and the investigator should call the IVRS for unblinded dose information.

8.5. Discontinuation

8.5.1. Treatment Discontinuation

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

- Adverse Event(s)
- PD or relapse
- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation

The reason for discontinuation should be recorded in the CRF and in the source documents.

The decision to treatment discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

8.5.2. Study discontinuation

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

- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation

The reason for discontinuation should be recorded in the CRF and in the source documents.

The decision to study discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

8.6. Method of Treatment Assignment

The treatment assignment will occur in the Screening period, once all the required screening procedures have been completed, and all required data have been submitted to the IVRS/IWRS system.

8.6.1. Stratification

Subjects will be stratified by: previous rituximab treatment (yes/no), time since last anti-lymphoma therapy (≤ 2, > 2 year), and disease histology (FL or MZL).

8.7. Packaging and Labeling

The IP (lenalidomide or matching placebo) will be packaged in bottles and each bottle will contain 21 capsules.

The label(s) for IP will include Celgene 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.

8.8. Study Drug Receipt and Storage

The Investigator(s) is responsible for taking an inventory of each shipment of study drug received and comparing it with the accompanying study drug shipping order form. The

Investigator(s) will verify the accuracy of the information on the form and call the IVRS to register the study drug received at the site and retain a copy of the form in the study file.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored as directed on the package label.

8.9. Investigational Product Accountability and Disposal

An accurate accounting of the dispensing/return of study drug 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 study drug 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 (or designee) will review with the Investigator or relevant site personnel the process for investigational product return, disposal and/or destruction including responsibilities for the site versus Celgene (or designee).

8.10. Investigational Product Compliance

For the oral medications of lenalidomide or placebo, study personnel will review the dosing instructions with the subject prior to dispensing the study drug. The subject will be instructed to return the study drug bottle, including any unused study drug, to the site at the next visit. Subject compliance will be noted on the appropriate CRFs and source records based on a capsule count. To monitor treatment compliance, reconciliation of capsules will be done at each scheduled study visit.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

Therapies considered necessary for the subject's well being may be administered at the discretion of the Investigator. All medications (prescription and non-prescription), growth factors, transfusions, treatments and therapies taken from 28 days prior to start of study drug through the last dose of study drug, must be recorded on the appropriate page of the CRF.

9.1.1. TFR Treatment

Treatment of TFR is up to the discretion of the investigator depending upon the severity and clinical situation. It is suggested that Grades 1 and 2 TFR be treated with NSAIDs (ie, ibuprofen 400 to 600 mg orally every 4 to 6 hours as needed), corticosteroids, and/or narcotic analgesics for pain management. Refer to Table 2 for further instructions and dose modifications for Grade 3 and 4 TFR.

In mild to moderate (Grades 1 and 2) cases, it is suggested that study drug be continued along with symptomatic treatment as above. In more severe cases, study drug should be interrupted, as indicated Table 2.

During the Treatment Phase, emergency use of corticosteroids at any dose to treat TFR symptoms for a subject is allowed at the Investigator's discretion.

9.1.2. Thromboembolism Prophylaxis

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

As reference information, for subjects receiving lenalidomide in open-label trials, it is strongly recommended that subjects at risk for a thromboembolic event receive prophylactic aspirin (70 to 325 mg) daily or another prophylaxis agent while on lenalidomide. In those subjects with high risk of VTE, it is strongly recommended that the subject receive a 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.

9.1.3. Growth Factors and Transfusions

Growth factors (eg, G-CSF, erythropoietin, etc) may be prescribed by the Investigator for rescue from severe hematologic events and should be used in accordance with the American Society of Clinical Oncology's (ASCO) guidelines or the ESMO guidelines. Growth factors or platelet transfusions should not be used to meet eligibility.

Growth factors or platelet transfusions are not to be administered prophylactically, except for high risk subjects in accordance with the ASCO guidelines or the ESMO guidelines.

9.2. Prohibited Concomitant Medications and Procedures

Systemic chronic corticosteroid use at doses above 20 mg / day (prednisone/ prednisolone or equivalent) is prohibited during the Treatment Phase. For subjects receiving systemic corticosteroids at doses above 20 mg / day (prednisone/ prednisolone or equivalent), a 7 day washout period prior to Cycle 1 Day 1 study drug dosing is required.

Systemic doses above 20 mg/day (prednisone/ prednisolone or equivalent) are allowed for the treatment of TFR at any time, for rituximab cytokine release syndrome prophylaxis with each rituximab infusion, and treatment of infusion related reactions at any time.

In addition, short courses of steroids are permitted at high doses for short-term use if necessary for the well being of the subject. Examples of such short-term use include the treatment of exacerbation of chronic obstructive pulmonary disease and other conditions for which short-term steroid treatment is considered standard of care.

All investigational therapies (drug or otherwise) and anticancer therapies, other than lenalidomide or rituximab are prohibited during the entire Treatment Period of the study.

9.3. Required Concomitant Medications and Procedures

9.3.1. TLS Prophylaxis

All subjects must receive tumor lysis prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of the first cycle or for a longer period if clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for TLS and cytopenia(s), the subjects will have a complete blood count (CBC) and chemistry drawn on Days 1, 8 and 15 of the first cycle and additionally as clinically indicated. The site should make every effort to contact the subject on Day 5 (± 1 day) of the first cycle to inquire about the subject's condition and to make sure that he/she is continuing with TLS prophylaxis measures by keeping hydrated and taking the TLS prophylaxis as instructed. Any subject contact that is made on Day 5 (± 1 day) should be documented in subject's medical record and any AEs that are discovered should be captured on the CRF. TLS will be assessed by Cairo-Bishop Grading system (See Section 18.5).

9.3.2. Rituximab premedication

Premedication consisting of acetaminophen and an antihistamine should be administered before each rituximab infusion (see package insert or where applicable refer to the instruction in pharmacy manual). Steroids may also be administered before the start of the rituximab infusion according to institutional practice (see Section 9.2 for the permitted doses). Surveillance measures during and after infusion of rituximab should be applied as recommended by the manufacturer/current guidelines.

9.3.3. Rituximab and Hepatitis B

In subjects with prior HBV infection, HBV reactivation may occur during or after rituximab treatment even if HBV-DNA is undetectable. For subjects with evidence of prior HBV exposure (positive for anti-HBs and/or anti-HBc with or without detectable HBV-DNA), liver disease experts should be consulted before start of rituximab treatment. Such subjects should be monitored for clinical and laboratory signs of hepatitis and/or HBV reactivation during and following rituximab therapy. In subjects who develop HBV reactivation during rituximab treatment, rituximab should be immediately discontinued. In subjects who develop HBV reactivation during or after rituximab treatment, appropriate HBV treatment (for example lamivudine) should be instituted as per local medical practice and locally approved rituximab product/prescribing information.

10. STATISTICAL ANALYSES

10.1. Overview

The objective of the statistical analysis is to evaluate the efficacy and safety of rituximab plus lenalidomide combination therapy in subjects with relapsed/refractory indolent lymphoma.

All data will be summarized by treatment group. In addition, where appropriate, a total column will be included to summarize subjects across treatment groups. Summaries of continuous variables will present the number of subjects included in the analysis (N), the mean and standard deviation (SDev) of the mean, the median, the minimum, and the maximum statistics, counts and percentages will be presented in summaries of categorical variables. The denominator for each percentage will be the number of subjects in the population treatment group unless otherwise specified. In general, missing data will not be imputed unless otherwise specified.

All statistical analyses specified in this protocol will be conducted using SAS® version 9.1.3 or higher

10.2. Study Population Definitions

The following three populations defined below will be used in the analysis.

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.

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.

Modified ITT (mITT) population: The mITT population is defined as all randomized subjects who have received at least one dose of study medication, have confirmed diagnosis of relapsed/refractory FL or MZL by central pathology review who are naïve or sensitive to rituximab, met all eligibility criteria, have baseline (Screening) and at least one post-baseline tumor assessment for efficacy.

The efficacy analysis will also be performed on the mITT population as supportive evidence and/or sensitivity analysis. Subjects will be analyzed according to the treatment arm to which they are initially assigned.

Safety population: The safety population is defined as all subjects who have received at least one dose of study medication. The safety population will be used for all safety analysis. Subjects will be analyzed according to the treatment which they actually received.

Subgroups analysis: Analyses will also be performed to compare treatments within the following stratification subgroups: previous rituximab treatment (yes/no), time since last anti-lymphoma therapy (≤ 2, > 2 year), histology (FL or MZL).

Additional subgroups may be examined as needed.

10.3. Sample Size and Power Considerations

The basis for the power and sample size determination will be a test of the equality of the overall survival curves between experiment and control treatment groups using a stratified log-rank test.

The primary efficacy endpoint is PFS. To fulfill the primary objective of the study, it must be shown that the experimental arm is superior to the control arm on the primary endpoints at one-sided $\alpha = 0.025$ level. It is hypothesized that the median PFS is 17.6 months in the experimental arm and 11 months in the control arm (corresponding hazard ratio of 0.625. For 90% power to detect this difference with one-sided $\alpha = 0.025$, a total of 193 PFS events will be required.

Based on the rate of accrual anticipated in this study, and annual dropout rate of 5%, it is planned to randomize a total of 350 subjects in 1:1 ratio to the two treatment arms and the study duration to reach the PFS events is expected to be 43 months.

Sample size and power were calculated using the East® Version 5.4 software system (Cytel Inc., 675 Massachusetts Avenue, Cambridge, MA 02139, http:// www.cytel.com).

10.4. Background and Demographic Characteristics

Demographic and baseline (last non-missing observation prior to randomization) disease characteristics will be summarized by treatment group for the ITT, mITT and safety populations. Subjects' age, height, weight, and continuous baseline characteristics will be summarized using descriptive statistics (N, mean, SDev, median, minimum, maximum), while age group, gender, race, histology, and other categorical variables will be provided using frequency tabulations (count, percent) by treatment group. Medical history data (coded by MedDRA dictionary) will be summarized using frequency tabulations by treatment group, system organ class and preferred term for the ITT, mITT and safety populations.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Major protocol deviations will be summarized using frequency tabulations for ITT population. Supportive corresponding subject listings will be provided as well.

10.6. Efficacy Analysis

All efficacy analysis will be performed on the ITT population. Key efficacy analysis will be performed on the mITT population as supportive evidence and to assess robustness our efficacy findings. Subjects will be analyzed according to randomized treatment group.

10.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS assessed by the IRC using the 2007 IWG criteria (Cheson, 2007) but without PET imaging (see Section 18.1).

PFS is defined as the time from date of randomization into the study to the first observation of documented disease progression or death due to any cause, whichever occurs first.

The primary endpoint will be compared between the two treatment arms when the required 193 events progression/death events after applying appropriate censoring rules (detailed censoring rules will be pre-specified in the Statistical Analysis Plan) are achieved. The Kaplan-Meier estimates of PFS will be provided. The experimental arm will be declared superior if the one-

sided p-value from a stratified log-rank test is smaller than 0.025 in favor of the experimental arm. Conventionally, hazard ratio with two-sided 95% confidence interval (CI) will be estimated using the Cox proportional hazards model.

10.6.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will include overall survival, objective response rate, complete response rate, durable complete response rate, duration of response, duration of complete response, event free survival, and time to next anti-lymphoma treatment.

Overall survival (OS) is defined as time from date of randomization to death from any cause.

Durable complete response rate (DCRR) is defined as the proportion of subjects that stay in complete response (CR) for at least one year, i.e, have duration of CR no less than one year.

Objective response rate (ORR) is defined as the proportion of subjects with best response of at least PR during the trial without administration of new anti-lymphoma therapy.

Complete response rate (CR) is defined as the proportion of subjects with best response of complete response during the trial without administration of new anti-lymphoma therapy.

Duration of response (DoR) is defined as the time from the initial response (at least PR) to documented disease progression.

Duration of complete response (DoCR) is defined as the time from the first evidence of CR to documented disease progression.

Event-free survival (EFS) is defined as the time from date of randomization to date of first documented progression, relapse, institution of new anti-lymphoma treatment (chemotherapy, radiotherapy or immunotherapy) or death from any cause. Responding subjects and subjects who are lost to follow up will be censored at their last tumor assessment date.

Time to next anti-lymphoma treatment (TTNLT) is defined as the time from date of randomization to date of first documented administration of a new anti-lymphoma treatment (including chemotherapy, radiotherapy, radioimmunotherapy or immunotherapy).

For binary type of endpoints (ORR, CR, DCCR), number and percent of subjects will be tabulated by treatment arm. A stratified Cochran-Mantel-Haenszel (CMH) test to adjust for possible confounding effects of the stratification factors will be performed and p-value provided.

For time to event type of endpoints (OS, DoR, DoCR, EFS, TTNLT), Kaplan-Meier estimates will be provided. Stratified log-rank tests will be performed with p-value provided.

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10.7. Safety Analysis

Safety analysis will be based on all subjects in the Safety population.

Study medication exposure will be summarized for each treatment arm including duration of study medication, total dose taken, and dose reductions.

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

AEs will be coded according to medical dictionary for drug regulatory activities (MedDRA) and classified using the NCI CTCAE Version 4.03. The incidence rates of AEs will be tabulated by system organ class and preferred term. Subsets of AEs to be summarized include serious AEs (SAEs), AEs of interest including SPM, VTE, and TFR, events of all CTCAE grade severities, suspected treatment-related AEs, and events that resulted in withdrawal of study medication. The most severe grade of each preferred term for a subject will be utilized for summaries of AEs by NCI CTCAE grade. All AEs with corresponding attributes will be displayed in a by-subject

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listing. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE Grade 3 or higher, suspected treatment-related events, all deaths, and SAEs will also be displayed in by-subject listings separately.

Clinical laboratory results will be summarized descriptively by treatment group, which will also include a display of change from baseline. Laboratory values outside of the normal ranges will be identified. Clinically significant hematologic and nonhematologic laboratory abnormalities that meet Grade 3 or Grade 4 criteria according to the CTCAE will be listed and summarized. Graphical display of selective lab parameters over the course of study will be provided.

Vital sign measurements will be listed for each subject at each visit. Descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by treatment group.

10.8. Interim Analysis

One interim analysis is planned at 50% of information (96 events) for futility only. An external IRC will review all the disease progression events at the time of interim and final analyses. For the interim analysis, the date of the approximate 96th event, as determined by the IRC, will be used as the data cut-off dates. The results of the interim analysis will be reviewed by the independent external DMC.

A conditional power approach is used for futility analysis; if the interim analysis shows less than 25% conditional power for success, the trial may stop for futility.

10.9. Other Topics

Not applicable.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An 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 below), regardless of etiology. Any worsening (ie, 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.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms. See Section 8.2.4.2 for the definition of overdose.

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 other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 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 AEs as to:

11.2.1. Seriousness

A SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, 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 (study drug[s] or control), occurring at any time for the duration of the study, from the time of signing the ICD up to and including a follow-up period of up to 5 years from the date of the last subject randomized. Events of second primary malignancy 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 second primary malignancy must be provided at the time of reporting as a serious adverse event (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 (ie, 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 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 of AEs will be graded based upon the subject's symptoms according to the current active minor version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. However, TFR will be graded using NCI CTCAE version 3.0.

AEs that are not defined in the NCI CTCAE should be evaluated for severity 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:	The temporal relationship of the AE to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

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Suspected:	The temporal relationship of the AE to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed 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 or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

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 (death due to another cause) 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 AE.

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.

11.4. Pregnancy

Refer to approved product/prescribing information for further information on rituximab pregnancy restrictions.

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 subjects 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 or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE 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).

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 to 28 days after the last dose of IP) , any SPM occurring at any time during the study including the follow-up period and those made known to

the Investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries 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 will 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 Institutional Review Board (IRB)/ethics committee (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 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 IP 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.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP (rituximab) based on the Summary of Product Characteristics (SmPC). Adverse events such as disease progression or relapse, death related to disease progression or relapse (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 (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

- Other important safety information and periodic reports 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 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Local Drug Safety Affiliate Office contact information, please refer to the SAE Report Form / Completion Guidelines or to the Pregnancy Report Form / Completion Guidelines.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/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 Clinical Research Physician/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 or Contract Research Organization (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 Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. 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. See Section 8.4 for more details.

13. REGULATORY CONSIDERATIONS

13.1. 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 GCP, as described in International Council 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.

13.2. 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, including obligations of confidentiality of Celgene information. 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.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

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.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or the subject's 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 ICD 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 ICD 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 ICD 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.

13.4. 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.

13.5. Protocol Amendments

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.

13.6. 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 ICD 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.

13.7. 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 AEs 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.

13.8. 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, etc).

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.

14. DATA HANDLING AND RECORDKEEPING

14.1. 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.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene standard operating procedures (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.

14.3. 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;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- 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.

15. 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.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during, and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an investigator meeting. 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 onsite visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

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.

15.2. 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 (eg, FDA, EMA, and 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.

16. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or 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. Selection of first authorship will be based on several considerations, including but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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CCI [redacted]

18. APPENDICES

18.1. Appendix A: Response Criteria for NHL

18.1.1. Tumor Assessment by the 2007 IWG Response Criteria

In this clinical trial CT or MRI scan will be used. PET scan will not be used for tumor assessment.

Response	Definition	Nodal Masses[a]	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	Regression to normal size on CT or MRI	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	No new sites on CT or MRI No change in size of previous lesions on CT or MRI		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis ≥ 50% increase from nadir in SPD of previously involved nodes. ≥ 50% increase in longest diameter of any single previously identified node > 10 mm in short axis.	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR = complete remission; PR = partial remission; SD = stable disease; PD = progressive disease; (Cheson, 2007)
[a] Measurable extranodal lesion will be assessed as nodal disease

CCI

[redacted]

18.1.3. Additional Response Assessment In Gastric MALT subjects with Radiological Response of at Least a PR by 2007 IWG Criteria

Subjects with gastric MALT and a radiological (CT or MRI scan) response of at least a SD will also undergo histological evaluation by endoscopy at time points specified in Table 1 (see also Sections 6.2.1 and 6.4). The histological scoring will be based on the GELA histological scoring system (Table 5). Final response assessment in subjects with gastric MALT will incorporate the IWG criteria as well as the histological findings.

Table 5: GELA Histological Scoring System for Evaluation of Gastric MALT lymphoma

Score	Lymphoid infiltrate	LEL	Stromal Changes
CHR (complete histological remission)	Absent or scattered plasma cells and small lymphoid cells in the LP	Absent	Normal or empty LP and/or fibrosis
pMRD (probable minimal residual disease)	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM	Absent	Empty LP and/or fibrosis
rRD (responding residual disease)	Dense, diffuse, or nodular extending around glands in the LP	Focal LEL or absent	Focal empty LP and/or fibrosis
NC (no change)	Dense, diffuse, or nodular	Present, 'may be absent''	No changes

MM, muscularis mucosa; LP, lamina propria; SM, submucosa; LEL, lymphoepithelial lesions. (Copie-Bergman, 2003; Copie-Bergman, 2012)

CCI [redacted]

The final response assessment of the subjects with gastric MALT lymphoma:

Complete remission (CR)

- CR by IWG criteria and
- normalization of endoscopic findings and
- histology of CHR in two subsequent follow-up investigations (the two investigation must be within 3 months after the radiological criteria for CR were first met).

Partial remission (PR)

Either

- PR by IWG criteria and
- Normalization or reduction of macroscopic findings, histological signs of lymphoma regression (rRD) or negative histology (CR or pMRD)

or

- CR by IWG criteria and rRD by histological evaluation

Stable disease (SD):

- SD by IWG criteria and no worsening of macroscopic findings or dissemination of gastric MALT lymphoma or transformation into diffuse large B-cell lymphoma

Progressive disease (PD)

- PD by IWG criteria or
- Any worsening of macroscopic findings or dissemination of gastric MALT lymphoma or transformation into diffuse large B-cell lymphoma.

Relapse

- Relapse by IWG criteria

or

- Endoscopic findings of re-occurrence of histologically-confirmed lymphoma after a histological CR was previously documented and confirmed on at least two prior repeat biopsies

CCI [redacted]

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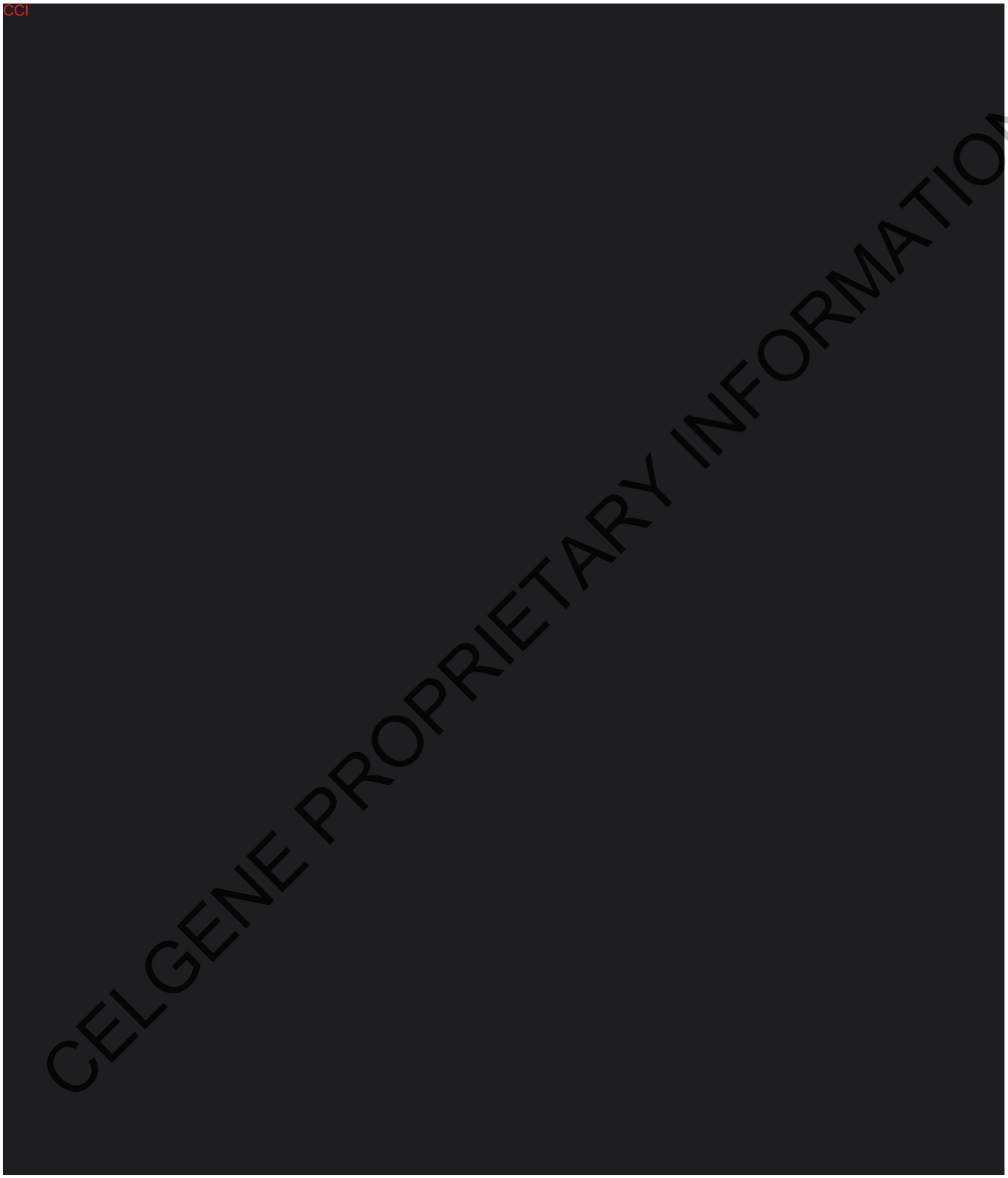

CCI

18.3. Appendix C: Ann Arbor staging

- **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;1997:289-294.

18.4. Appendix D: Performance Status Criteria

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, e.g., 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)

CCI [redacted]

18.5. Appendix E: Cairo - Bishop Definition of Tumor Lysis Syndrome

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

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 subject has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s) (Cairo, 2004).

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.
[a] Not directly attributable to a therapeutic agent.

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]

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

18.6. Appendix F: Pregnancy Prevention Risk Management Plans

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: PPD
Title: PPD
Date: Tuesday, 18 December 2018, 05:25 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

JUSTIFICATION FOR AMENDMENT

Protocol Amendment 4 is written to reduce the frequency of follow-up tests including but not limited to computed tomography (CT) scans/ magnetic resonance imaging (MRI), biopsies (bone marrow, tumor, gastric) and blood tests sincethe primary efficacy analysis has been completed for this study. These changes to the protocol are being implemented to decrease subject exposure to radiation and to reduce the risk of bleeding, pain or infection from the above procedures. These tests will now be performed at the investigator's discretion and will no longer require a central review. Further, this amendment provides specific guidance on the follow-up data that still needs to be mandatorily collected for this study in subjects who have reported progressive disease and in those who have not.

Significant changes included in this amendment are summarized below:

The following changes were made to the study protocol and the associated sections of the Protocol Summary:

Changed Medical Monitor/ Emergency Contact Information

Section 4.4: End of Trial- Added guidance regarding the follow- up process and the tests required once the primary efficacy analysis has been completed.

Rationale for change: The frequency of follow-up tests was reduced and left to the investigator's discretion now that the primary efficacy analysis for the study has been completed. The requirement for central review for those tests was also removed as the primary efficacy analysis has been completed. Specific guidance was provided for the follow-up data to be collected for subjects who have progressive disease and for those subjects who have not yet reported a progression.

Section 5: TABLE OF EVENTS- Added footnote 13 to the table clarifying that after the primary analysis is done, specified follow up tests are no longer required per protocol and may be performed at the investigator's discretion.

CCI [redacted]

Rationale for change: Since the primary efficacy end point has been reached and safety analyses for this study have been done, there is no need for a central review of the biopsy samples. An investigator diagnosis is sufficient.

Section 6.4: Follow-up Assessments- Added guidance on reducing follow-up tests, leaving them to the investigator's discretion and removing the requirement for central review of those tests during follow-up as the primary efficacy analysis has been completed.

Section 11.6: Expedited Reporting of Adverse Events

- Added a statement about the expedited reporting requirement per the United States regulations.
- Removed the statement regarding providing information on steps taken in foreign countries for subject safety specific to Japan.

- Added statement regarding providing safety information and periodic reports to investigators according to local regulations.

Section 13.2- Investigator Responsibilities- Added wording on Celgene confidentiality obligations for the investigators.

In addition, some aspects of the original protocol version were clarified, spelling, formatting and punctuation errors were corrected, and various abbreviations and acronyms were spelled out. This amendment includes several other minor clarifications and corrections.

JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Modified the Inclusion Criterion number 4 to no longer allow rituximab naïve patients onto the study. This was also reflected in the study population bullet under the protocol Summary on page 6. (Section 7.2)**

CCI [redacted] Implementing this change at this point in the study should keep the number of rituximab patients under 25%.

- **Modified Inclusion Criterion number 5 to confirm that patients must have documented relapsed, refractory or progressive disease (PD) after treatment with systemic therapy, and must not be rituximab-refractory. Also defined refractoriness as (1) did not respond (at least a PR) to rituximab or R-chemoregimen therapy and/or (2) time to disease progression < 6 months after last rituximab dose. (section 7.2)**

The modification of Inclusion criterion number 4 led us to modify Inclusion Criterion number 5 to ensure that the two criteria are in line.

- **Revised Exclusion Criterion number 7 for hepatitis C virus (HCV) positive patients who do not have an active hepatitis C infection and who are otherwise acceptable candidates for the AUGMENT study. All patients will be tested for HCV antibodies at Screening by the Central Laboratory, and the investigator must further test HCV positive patients by either liver ultrasound for fibrosis, liver biopsy, ribonucleic acid (RNA) viral load or other local practice. Within the current Revlimid Investigator's Brochure hepatitis C reactivation is not noted as a treatment-emergent adverse event (Section 7.3).**

The patients enrolled in this study are not at risk for hepatitis C reactivation, either by Revlimid or rituximab. Therefore, it was decided to allow patients who are HCV positive without active infection and who are otherwise acceptable candidates for the study, to be able to enter the study. This should allow more patients to be eligible in the Mediterranean region of Europe and Japan.

- **Revised to include a time limit on the age of the archival biopsy required for diagnosis prior to randomization. Also, clarified that if a formalin-fixed paraffin embedded (FFPE) tumor block cannot be sent, one hematoxylin and eosin (H and E) stained slide and 10 unstained slides or 11 unstained slides will be acceptable. (Section 6.1)**

CCI [redacted]

No time limit was previously defined in the protocol for the age of the archival biopsy required for diagnosis prior to randomization. In order to ensure that the disease is the same and transformation has not occurred, it was decided to limit the age of the biopsy moving forward. If a FFPE block cannot be sent, the specific slide requirements were also clarified.

- **Defined the requirement for a diagnosis of splenic marginal zone lymphoma (MZL) for patients who do not have a spleen specimen available during the screening period (Section 4.1.1).**

As more MZL patients have been enrolled into the study, a few cases of splenic MZL patients who did not have spleen specimens were seen. It was decided to define the requirements for diagnosis for these patients within the protocol.

The amendment also includes several other minor clarifications and corrections:

- Revised to allow continuation of lenalidomide/placebo if rituximab is discontinued due to toxicity (Section 8.2.4.2).
- Clarified that all patients MUST receive tumor lysis prophylaxis (Sections 9.3.1 and 6.2.2.2).
- Confirmed when end of treatment should occur: end of cycle 12, day 28. (Section 6.4)
- The study rationale in Section 1.4 (Clinical Studies) was revised to include an updated reference for the recently published CALGB 50402 (Alliance) study along with the results. (Section 1.4, Section 17) A few deletions were made to the first sentence of section 1.3.
- Added Complete Response (CR) rate to the secondary objectives (Sections 2.2 and 3.4).
- Footnote 10 (table 1) and Section 8.2 were revised to reflect "there is no time window for study drug administration."
- Updated Sections 6.2.2.1, 6.2.2.2 and 6.2.2.3.2 with information from the MCL-002 study that is now available.
- Moved the last section of Section 8.2.3.1 (Requalification Criteria for Subsequent Treatment Cycles) up to Section 8.2.3 where it fits better.
- Clarification of wording in second paragraph of Section 8.2.4.1a.
- Clarification of study medication in paragraph 2 and dose reduction occurring for concurrent adverse events (AEs) in last bullet of Section 8.2.4.1b.
- Confirmed that no investigational or anticancer therapies other than lenalidomide or rituximab are allowed during the Treatment Period of the study (Section 9.2).
- Added two paragraphs from the updated protocol template regarding Investigator Responsibilities (Section 13.2.)
- Medical Monitor phone number was updated on page 2.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Update of Exclusion Criterion #21**

The Exclusion Criterion #21 is being amended [redacted] to complete the non-inclusion criteria specifying that rituximab should not be administered in case of active, severe infections (for example, tuberculosis, septicaemia and opportunistic infection) in accordance with the recommendations of the Summary of Product Characteristics (SmPC) of the marketing authorisation (MA) of MabThera®.

A country specific protocol amendment is already available in France. The protocol has been updated globally.

- **The surveillance and safety requirements should be followed as per the Rituximab package insert or SmPC**

This protocol is also amended [redacted] that the female study subjects also need to be informed about the pregnancy prevention guidelines provided in the Rituximab/Mabthera SmPC (as long as the infertility is not definitely confirmed). Inclusion Criteria # 12 and #14 and Sections 8.2.2. and 11.4 are amended accordingly.

In Germany, the Inform Consent Document was updated. The protocol has been updated globally.

- **Revision to CT/MRI scan timing requirement after year 5 to one per year**

This change was made based on investigator feedback and an attempt to avoid delaying treatment in the setting of aggressive lymphoma. This change was made based on Scientific Steering Committee discussion and approval.

- **Revision to exclusionary time period for prior malignancies and precision on the exceptions**

This change is to decrease the exclusionary time period for prior malignancies from ≥ 10 to ≥ 5 years. Basal cell carcinoma of the skin, squamous cell carcinoma of the skin are additional exceptions. These changes are to align this particular study with the rules agreed with Health authorities.

- **Inclusion Criterion #7: Subjects with extranodal lesion are eligible**

Inclusion Criterion #7 and Section 6 were updated to clarify that subjects with extranodal lesion are eligible. This change was made based on Scientific Steering Committee discussion and approval.

[redacted]

- **HBV management**

A specific section was created to clarify the management of subjects at risk for HBV reactivation (Section 9.3.3.). This change was made based on Scientific Steering Committee discussion and approval.

- **Exclusion Criterion #7**

Subjects with a history of HCV, and who have received anti-viral treatment and who have no detectable HCV-RNA levels for at least 12 months are eligible. This change was made based on Scientific Steering Committee discussion and approval.

- **Clarify bone marrow biopsy requirement at screening and at response**

All subjects do not need BMB at screening, only in case of abnormal blood counts. The change in Sections 6.1. and 6.2.1.and inclusion criterion #10 was made based on Scientific Steering Committee discussion and approval.

- **Clarify study treatment continuation rules in case of lenalidomide or rituximab intolerance/ hypersensitivity**

These changes were made in Sections 8.2.3.1. and 8.2.3.2. were made based on investigator feedback and Scientific Steering Committee discussion and approval.

The amendment also includes several other minor clarifications and corrections:

- Change of Celgene Medical Monitor
- Updated and added new references
- Clarification of the study design
- Clarification of the Table of Events
- Time window clarified the timing of procedure at Cycle 1 Day 1, 8, 15 and 22 (±1 day), Cycles 2 to 5 Day 1 (±3 days) and Cycles 2 to 4 Day 15 (±1 day)
- Clarification of FCBP and counseling procedures
- Hematologic panel clarification, eosinophils and basophils added; WBC differential removed; urea" added.
- Clarification and additional standard units.
- Clarification to use prednisone or equivalent, prednisolone.
- Added the possibility to contact the Medical Monitor or Steering Committee Members in case of equivocal progression
- Inclusion Criterion # 8 clarification that subject will also need treatment if progressed
- Inclusion Criterion # 10 was merged with Exclusion Criterion # 17 in order to have all screening laboratory values in one inclusion criterion.
- Exclusion Criterion # 3, clarification for prednisolone
- Exclusion Criterion # 5, administrative clarification
- Exclusion Criterion # 6, administrative clarification
- Administrative clarification of unblinding and discontinuation
- Clarification of growth factor and transfusion use

- Statistical section clarification: correction of Intent-to-treat (ITT) population and Modified Intent-to-treat (mITT) population definitions. Endpoints definition added
- Durable complete response rate (DCRR), complete response rate (CR) CCI [redacted] definition and clarification
- Clarification that histological transformations are not considered SPM
- CC [redacted]
- Clarification for Japan
- Administrative correction of spelling, formatting errors, punctuation errors, and various abbreviations and acronyms were spelled out.

CCI [redacted]

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- The 2007 international working group (IWG) criteria for malignant lymphoma modified to allow the inclusion of extranodal disease as measurable disease will be utilized for efficacy determination to assess response and PFS.

  Justification:

  The current study will enroll follicular lymphoma (FL) and marginal zone lymphoma (MZL) patients.

  The 1999 IWG criteria state that only nodal disease is measurable disease. Patients with MZL often have extranodal disease without nodal disease and thus would be excluded. The 2007 IWG criteria (Cheson, 2007) allow assessment of extranodal disease as measurable disease.

  With the aim to simplify the protocol, also allow inclusion of patients with only extranodal disease, and use one set of criteria which allows accurate assessment of extranodal as well as nodal disease CCI [redacted] Celgene will be using the 2007 IWG criteria in this study. This will allow inclusion and appropriate assessments of FL and MZL patients in this study.

The amendment also includes several other clarifications and corrections

1. Updated the introduction section and the rationale with new available background information.

CCI [redacted]

3. Summary section, Figure 1, study overview section, and assessment section (section 6) updated to be consistent with regards to:
   a. Response and PD data collected during next anti-lymphoma treatment
   b. Duration for the submission of the pathology sample for central review
4. Reformatted Table 1, Schedule of study assessment to make it clear and more understandable.
5. Clarified that local HBV tests and tests done as part of standard of care will be acceptable.
6. Updated the background and prophylaxis for VTE and also the definition of patients at risk for VTE who will need prophylaxis.
7. Updated the background information for the tumor flare section.
8. Clarification regarding use of steroid prophylaxis for rituximab cytokine release syndrome during treatment.
9. Updated the exclusion criterion #21 to include examples of conditions that would put patients under unacceptable risk such as coronary artery disease, congestive heart failure, pulmonary disease, chronic renal or immunological disease.

10. Updated Table 2 dose modification for lenalidomide or placebo to clarify the action required for rash and also include dose modification for Stevens-Johnson Syndrome or Toxic epidermal necrolysis. The footnote is updated to clarify that only TFR will be graded by NCI CTCAE version 3.0.
11. Updated treatment administration section (Section 8.2) to include definition of overdose.
12. Updated the Adverse event section to provide additional clarity regarding the SPMs and also severity/intensity grading according to CTCAE version 4.0.
13. Added 'secondary endpoint' title in Section 10.6
14. Provided clarification regarding the investigational product accountability and disposal and also provided additional information regarding monitoring.
15. Updated summary section and Section 4.0 to include definition of 'end of trial'.
16. Updated the Table of Content and also corrected minor grammatical and formatting errors.