Official Title of Study:

A PHASE 3B RANDOMIZED STUDY OF LENALIDOMIDE (CC-5013) PLUS RITUXIMAB MAINTENANCE THERAPY FOLLOWED BY LENALIDOMIDE SINGLEAGENT MAINTENANCE VERSUS RITUXIMAB MAINTENANCE IN SUBJECTS WITH RELAPSED/REFRACTORY FOLLICULAR, MARGINAL ZONE OR MANTLE CELL LYMPHOMA

The “MAGNIFY” Trial

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The "MAGNIFY" Trial

INVESTIGATIONAL PRODUCT (IP):	**Lenalidomide (CC-5013)**
PROTOCOL NUMBER:	**CC-5013-NHL-008**
COMPOUND NUMBER:	**CC-5013 (BMS-986380)**
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SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901 USA

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

[redacted] [redacted]

Signature of Celgene Therapeutic Area Head dd mmm yyyy

[redacted]

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.

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, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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Printed Name of Coordinating Principal Investigator Institution Name:_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 5:

Considering the current rate of progression-free survival (PFS) events, which is slower than originally predicted, [redacted] the challenging follow-up of subjects in the context of the coronavirus disease 2019 pandemic, [redacted] 191 PFS events [redacted]. The final analysis is now planned to be completed at 114 PFS events.

Upon confirmation of 114 PFS events, the remaining subjects on trial will be followed for 5 years after the last subject has initiated induction therapy to meet the safety reporting requirements as outlined in the study.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 5

Section Number & Title	Description of Change	Brief Rationale
Title Page Protocol Summary Section 1.4: Lenalidomide	Added Bristol-Myers Squibb Company (BMS) Compound Number CC-5013 (BMS-986380).	For clarification purposes.
Medical Monitor/Emergency Contact Information	Updated contact information for Medical Monitor/Emergency Contact.	[redacted] has transitioned off the study and [redacted] has taken over this role.
Protocol Summary Figure 1: Overall Study Design Section 4.3: Study Duration Table 1: Schedule of Study Assessments Section 6.2.2: Second Primary Malignancies Section 10.3: Sample Size and Power Considerations Section 10.6.1: Primary Efficacy Endpoint	Updated to 114 progression-free survival (PFS) events instead of 191 PFS events for the primary efficacy endpoint.	[redacted].
Protocol Summary Section 4.3: Study Duration Section 10.3: Sample Size and Power Considerations	Updated study duration period.	For clarification purposes to align with the extended study timeline.
Section 4.1.4: Randomization to Maintenance Treatment Period Section 4.3: Study Duration	Added that all subjects who will be on treatment upon reaching 5 years after the last subject has initiated induction therapy [redacted] will continue the treatment and be followed up for safety purposes only.	For clarification purposes. Subjects will no longer be followed for efficacy upon reaching 114 PFS events, only safety purposes.
Section 4.1.6: Follow-up Period Upon Confirmation of 114 PFS Events	New section added.	This section has been included to clarify the required follow-up information to be collected after 114 PFS events are reached.
Section 4.1.6: Follow-up Period Upon Confirmation of 114 PFS Events Section 6.2.2: Second Primary Malignancies	Added that [redacted].	To clarify visit frequency and duration of the follow-up period after the confirmation of 114 PFS events.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 5		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 1: Schedule of Study Assessments	• Added new column: [redacted]. • Added footnote that upon confirmation of 114 PFS events achieved, no more computed tomography scans, [redacted] response assessment, and subsequent anti-lymphoma therapies will be performed.	For clarification purposes of the required follow-up information to be collected after confirmation of 114 PFS events.
Table 1: Schedule of Study Assessments Section 12.2: Study Discontinuation and Completion	• Updated "At Treatment Discontinuation" column to "At Treatment Discontinuation/Completion." • Updated section title and description of when subjects will be discontinued and off boarded from the study.	For clarification purposes of the required follow-up information to be collected after 114 PFS events are reached and timelines for discontinuation of subjects from the trial after 114 PFS events are reached.
Section 6.3: Efficacy Assessments	Added that scan results will be assessed by the Investigator or qualified site personnel.	For clarification purposes as to who the assessor of scan results will be.
Section 6.3: Efficacy Assessments Section 6.3.1: Subsequent Anti-lymphoma Therapy [redacted]	Added that after confirmation of 114 PFS events, no efficacy assessments will be conducted.	For clarification purposes of the required follow-up information to be collected after confirmation of 114 PFS events.
Section 10.3: Sample Size and Power Considerations	Added power calculation for 114 PFS events.	To provide additional information, ie power corresponding to the updated final analysis.
Section 10.6.2: Secondary Efficacy Endpoint	Added that overall survival (OS) rate will be collected for 5 years from the date of the last subject initiating induction therapy.	To support supplementary analysis of OS if needed.
Section 10.6.4: Analysis Methods	Updated the desired significance level for the Time-to-Event Endpoints.	To clarify that the significance level for the primary analysis needs to be adjusted due to the interim analysis.
Section 10.8: Interim Analysis	Added: "To ensure the overall 1-sided type 1 error remains at 0.025, an appropriate amount of alpha will be spent for the interim analysis."	To clarify that type 1 error for final analysis will be adjusted to preserve the overall type 1 error rate for the study.
All	Minor formatting and typographical corrections.	Minor, therefore, have not been summarized.

PROTOCOL SUMMARY

Study Title

A Phase 3b randomized study of lenalidomide (CC-5013, also known as BMS-986380) plus rituximab maintenance therapy followed by lenalidomide single-agent maintenance versus rituximab maintenance in subjects with relapsed/refractory follicular, marginal zone or mantle cell lymphoma.

Indication

Relapsed/refractory follicular lymphoma grades 1-3b, transformed follicular lymphoma, marginal zone lymphoma or mantle cell lymphoma.

Objectives

To compare the efficacy and safety of lenalidomide plus rituximab combination maintenance therapy (for 18 cycles) followed by optional lenalidomide single-agent maintenance (to progression) versus rituximab single-agent maintenance (for 18 cycles) after 12 cycles of induction therapy with lenalidomide plus rituximab, in subjects with relapsed/refractory follicular lymphoma grades 1-3b, transformed follicular lymphoma, marginal zone lymphoma or mantle cell lymphoma.

Study Design

This Phase 3b multicenter, randomized, open-label study will enroll subjects with relapsed/refractory follicular lymphoma grades 1-3b, transformed follicular lymphoma, marginal zone lymphoma or mantle cell lymphoma. All subjects enrolled will receive 12 cycles of lenalidomide plus rituximab induction therapy.

The study is designed to compare the efficacy and safety of two maintenance regimens following the induction therapy. Subjects who have stable disease (SD), partial response (PR), unconfirmed complete response (CRu) or complete response (CR) at the end of 12 cycles of induction therapy will be randomized to one of two maintenance arms: Arm A (experimental) or Arm B (control). Subjects randomized to Arm A will receive lenalidomide plus rituximab combination maintenance therapy (for 18 cycles) followed by optional lenalidomide single-agent maintenance (to progression). Subjects randomized to Arm B will receive rituximab single-agent maintenance (for 18 cycles).

Subjects will be stratified at time of randomization to the maintenance arm by histology, lines of anti-lymphoma therapy, and age.

The overall study design is described in Figure 1. The study is divided into a Screening Period, a Treatment Period (induction and maintenance), and a Follow-up Period. Approximately 500 subjects are planned to be enrolled.

Upon giving written informed consent, a subject will enter the Screening Period and undergo safety and other assessments to determine eligibility for the study. All Screening assessments must be completed within 28 days prior to the subject initiating induction therapy.

Subjects enter the Induction Treatment Period at the time they complete screening procedures and meet all eligibility criteria. Eligible subjects entering the Induction Treatment Phase will be enrolled using an Interactive Voice Response System (IVRS). The treatments will be given as described in detail in Section 8 and must begin no later than 1 week after enrollment in IVRS to receive induction therapy. Cycle length during induction and maintenance is 28 days.

Subjects may discontinue treatment earlier than described if they experience relapse or disease progression, unacceptable toxicity, or withdrawal of consent. All subjects who discontinue treatment or complete treatment will be followed for disease progression, subsequent anti-lymphoma therapy, and second primary malignancies (SPMs) for 5 years after the last subject has initiated induction therapy. Upon confirming 114 PFS events, all subjects who discontinue treatment or complete treatment will be followed for SPMs and overall survival for 5 years after the last subject has initiated induction therapy.

Assessments during the Screening, Treatment and Follow-up period are described in Table 1.

Efficacy determination for the primary endpoint will be based upon progression-free survival (PFS). See Section 10 for a description of the Statistical Analyses.

An independent external Data Monitoring Committee (DMC) will review safety data in an ongoing, periodic manner throughout the study. The frequency of DMC meetings will be documented in the 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 follicular lymphoma (FL) Grades 1, 2, 3a, or 3b(Gr 1-3b), transformed follicular lymphoma (tFL), marginal zone lymphoma (MZL), or mantle cell lymphoma (MCL), Stages I to IV, have been previously treated for their lymphoma with at least one prior line of therapy, have at least one measurable nodal or extranodal lesion by computed axial tomography (CT) or magnetic resonance imaging (MRI) scan, and have adequate bone marrow function, liver function, and renal function.

Length of Study

The expected accrual duration for 500 subjects is approximately 63 months. Subjects will receive protocol-specified treatment until relapse or progression of disease, withdrawal of consent or unacceptable toxicity. The study duration to events for primary analysis is estimated to be 105 months. The duration of the entire study will be approximately 10 years (accrual period of approximately 5 years plus 5 years from last subject initiating induction therapy).

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

Study Treatments, please see Section 8.2 for details including dose adjustments for renal insufficiency

- Induction Period (12 Cycles)

  Lenalidomide 20 mg once daily on Days 1 to 21 of every 28-day Cycle **AND** rituximab 375 mg/m^2 intra-venous (IV) every week in Cycle 1 (Days 1, 8, 15, and 22) and Day 1 of every other Cycle (Cycle 3, 5, 7, 9, 11)

Followed by Maintenance Period

- **Arm A (Experimental arm)**: Lenalidomide + rituximab (Maintenance) followed by optional lenalidomide (Maintenance)
  - Maintenance Period (18 Cycles)

    Lenalidomide 10 mg once daily on Days 1 to 21 of every 28-day Cycle (Cycle 13 through 30) **AND** rituximab 375 mg/m^2 IV on Day 1 of every other Cycle up to Cycle 30 (Cycles 13, 15, 17, 19, 21, 23, 25, 27, 29).

Followed by

  - Optional Maintenance Period (up to PD)

    Lenalidomide 10 mg once daily on Days 1 to 21 of every 28-day Cycle. This treatment will be at the discretion of the subject and/or the investigator.

VERSUS

- **Arm B (Control arm)**: Rituximab (Maintenance)
  - Maintenance Period (18 Cycles)

    Rituximab 375 mg/m2 IV on Day 1 of every other Cycle up to Cycle 30 (Cycles 13, 15, 17, 19, 21, 23, 25, 27, 29)

Overview of Efficacy Assessments

The International Working Group (IWG) 1999 response criteria (Cheson, 1999) for malignant lymphoma, modified to allow the inclusion of extranodal disease as measurable disease will be utilized for efficacy determination to assess response and progression. In addition to CT/MRI scan to assess disease, subjects with MZL involving the gastric area will undergo endoscopy as part of the response assessment.

The efficacy endpoints include:

1) Progression Free Survival (PFS)
2) Overall Survival (OS)
3) Improvement of Response (IOR)
4) Overall response rate (ORR) including partial response (PR), complete response (CR)/complete response unconfirmed (CRu) and CR/CRu rate (CRR)
5) Duration of response (DOR), duration of CR/CRu (DOCR)
6) Time to next anti-lymphoma treatment (TTNLT)
7) Time to histological transformation (TTHT)

[redacted]

Overview of Safety Assessments

Safety will be monitored throughout the study. Safety evaluations will include adverse event (AE) reporting, second primary malignancies (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.

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 informed consent document (ICD) for 5 years from the date the last subject initiated induction therapy.

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.

Once the 114 PFS events are confirmed, the follow-up period will continue for 5 years after the last subject has initiated induction therapy, and all subjects who are in the follow-up period will be deemed as completed and will be off boarded from the study [redacted].

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the Investigational Product (IP).

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

1.1 Follicular Lymphoma

Follicular lymphoma is one of the most common low-Grade non-Hodgkin lymphomas (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, 2011). Follicular lymphoma typically follows an indolent course with a median overall survival (OS) of 7 to 10 years. Although FL initially responds well to treatment it is characterized by recurrent relapses or progressions with progressively shorter intervals in between treatments (Salles, 2007). Transformation to diffuse large B-cell lymphoma (DLBCL) and other aggressive lymphoma occurs at a rate of approximately 2% to 3% per year (Bastion, 1997).

The classification of FL has evolved through major changes over the past century. The Revised European American lymphoma (REAL) classification and the World Health Organization (WHO) classification proposed the terms, follicle center cell lymphoma, follicular Grade 1, 2, 3a, and 3b. Differences in molecular genetics and clinical behavior suggest that FL Grade 3a is an indolent disease and 3b is an aggressive disease. Investigation of the cellular microenvironment of FL has provided interesting insights into prognosis, and the interaction between tumor cells and the microenvironment may determine overall clinical behavior (Vaidyanathan, 2014).

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. The 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-Céligny, 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 host immune response in this disease.

A pivotal event in the natural history of FL is histological transformation to more aggressive malignancies, most commonly diffuse large B-cell lymphoma (DLBCL). The reported frequency of higher grade FL transformation varies significantly, ranging from 10% to 60% of patients. Immunophenotypic and genetic features suggest that Grade 3b FL may be similar to de novo DLBCL, however, most clinical studies have not shown a survival difference between Grade 3a versus 3b FL. Transformation is defined as pathologically demonstrated and clonally confirmed progression of FL Grades 1, 2, 3a to DLBCL or other high grade morphology; progression from

FL Grades 1 and 2 to FL Grade 3a is not considered histologic transformation, but a common progression event during the course of therapy (Vaidyanathan, 2014).

1.1.1 Therapy in Relapsed/Refractory Follicular Lymphoma

There is no standard treatment for patients with relapsed/refractory FL. Treatment options include radiation, single-agent or combination chemotherapy, single-agent rituximab, idelalisib, rituximab-containing chemotherapy regimens 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), and radioimmunotherapy or autologous/allogeneic stem cell transplant in some selected patients (NCCN guidelines, 2015; Gopal, 2014; Ghielmini, 2013). 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 United States of America (USA), Europe and many other countries for treatment of relapsed or refractory FL as a 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 single-agent rituximab in relapsed/refractory FL or other low-grade NHL patients, and three multicenter single-arm studies have led to regulatory approval in the USA, Europe and other countries (McLaughlin, 1998; Piro, 1999; Davis, 2000a). In some countries, the approved number of rituximab doses is four or eight. A recent update of the results from the Swiss Group for Clinical Cancer Research (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 an additional 4 maintenance doses every 2 months reported a durable response with 35% of responders still in remission at 8 years.

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, 2004; Van Oers, 2010). Rituximab maintenance yielded a median PFS from second randomization of 51.5 months versus 14.9 months with observation.

The combination of rituximab and bendamustine, an alkylating agent approved in the USA, Europe and many other countries for the treatment of rituximab refractory iNHL showed a response rate of 90% and a 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 a 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 a 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).

Other recent efforts have been made to find novel regimens for the treatment of relapsed follicular lymphoma that do not contain cytotoxic agents. Such efforts include combinations 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), interferons (Davis, 2000b; Sacchi, 2001) granulocyte macrophage colony-stimulating factor (GM-CSF) (Cartron, 2008) and IL-12 (Ansell, 2002). 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 a 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).

More recently, idelalisib has been added to the treatment options for relapsed refractory FL (Gopal, 2014) and the FDA has approved idelalisib as a single agent for use in the treatment of patients with follicular lymphoma who have received at least 2 prior systemic therapies.

The treatment approach for subjects with transformed follicular lymphoma is often individualized, as there are no randomized studies in the modern era to guide practice. These patients are often excluded from clinical trial participation, therefore there is a paucity of objective data guiding optimal management. The literature suggests patients treated with rituximab-containing chemotherapy can experience significantly better overall survival compared with other published retrospective cohorts of patients treated with chemotherapy alone, who have 5-year OS rates of 20% to 30%, and median survival ranging between 1 and 2 years. However, patients receiving dose intensification and consolidation seem to have improved outcomes (Casulo, 2014).

Novel agents have been reported in transformed follicular lymphoma, including a phase 2 study using lenalidomide, an immunomodulatory agent, showing an overall response rate of 57%, with median response duration of over 1 year in patients with transformed follicular lymphoma (Czuczman, 2011). Other drugs inhibiting novel targets, such as Aurora Akinase (alisertib), Bruton tyrosine kinase (ibrutinib), the delta isoform of phosphatidylinositol 3-kinase (idelalisib), and the BCL2 protein (GDC-0199/ABT199), currently being studied in both indolent and aggressive lymphomas have the potential to significantly impact patients with transformed follicular lymphoma (Casulo, 2014).

1.2 Mantle Cell Lymphoma

Mantle cell lymphoma is a distinct subtype within B-cell type lymphoma originating from the mantle zone of the lymph node and is characterized by the overexpression of a member of the cyclin D family. Tumors with overexpression of cyclin D1 are associated with the t(11;14)(q13;q32) chromosomal translocation (Fernàndez, 2005). In rare cases, overexpression of

other cyclin D members is seen (Fu, 2005). MCL accounts for approximately 5% to 10% of all lymphomas and usually affects men over the age of 60.

Histologically, the MCL cells appear small with features similar to indolent lymphomas. For this reason, MCL was often grouped in the category of indolent lymphoma. However, the discovery of a characteristic chromosomal translocation involving the cyclin D1 gene, resulting in its unregulated overexpression, led to an improved ability to diagnose MCL and recognition that MCL had clinical behavior similar to aggressive lymphomas and has one of the poorest survival rates among the lymphomas.

1.2.1 Therapy in Relapsed/Refractory Mantle Cell Lymphoma

For the treatment of patients with newly diagnosed MCL, the National Comprehensive Cancer Network (NCCN) NHL guidelines and the recent European Society for Medical Oncology (ESMO) consensus suggest that rituximab should be part of any induction chemotherapy regimen and also that rituximab maintenance should be offered to all patients responding to frontline R-chemotherapy (NCCN guidelines, 2015; Dreyling, 2013a). Most physicians have used rituximab-containing multi-agent chemotherapy regimens such as R-CHOP, R-HyperCVAD, R-DHAP or R-FCM, often supplemented with autologous transplantation for consolidation upon completion of first-line therapy in younger patients.

Following initial chemotherapy, almost all patients experience relapse of their disease. In subjects with MCL who have relapsed after initial therapy, few effective treatment options are available. Currently, three agents have received FDA approval for use in this setting. Single agent bortezomib was approved in December 2006 for patients who received at least one prior therapy based on results from a single-arm trial. The reported objective response rate (ORR) in 155 patients was 31%, including 8% of patients achieving a complete remission (CR + CRu), median duration of response (DOR) was 9.3 months, and a median overall survival (OS) was 23.5 months (Goy, 2009; Velcade PI, 2014). Lenalidomide was approved in July 2013 for patients whose disease relapsed or progressed after two prior therapies, one of which included bortezomib. Single-agent lenalidomide approval was based on results from a single-arm trial (n = 134) resulting in an ORR of 26% that included 7% of patients who achieved a CR/CRu and median DOR of 16.6 months (Revlimid PI, 2014; Goy, 2013). More recently, single-agent ibrutinib was approved for MCL after one prior therapy based on results from a single-arm trial (n = 111) resulting in an ORR of 68% that included 21% of patients achieving a CR, and median DOR 17.5 months with OS not yet reached (Imbruvica PI, 2014; Wang, 2013a).

1.3 Marginal Zone Lymphoma

Marginal Zone Lymphoma is a distinct histology within the category of B-cell lymphomas, constituting approximately 8% of NHLs. 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 (NMZL). 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.

Extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT-lymphoma) is most common and accounts for 8% of all newly diagnosed lymphomas (Isaacson, 2008) and 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 Sjögren 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, 2011). In early stage disease, treatment of the underlying infection is the treatment of choice.

Splenic MZL patients present with an enlarged spleen, as well as 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 have lymph node-based disease without involvement of the spleen or extranodal sites. The molecular pathogenesis of nodal MZL is not understood.

1.3.1 Therapy in Relapsed/Refractory Marginal Zone Lymphoma

In patients who have relapsed after initial treatment, rituximab alone or in combination with cytotoxic agents is often used. Advanced stage disease and relapsed disease requiring systemic treatment is managed like follicular lymphoma - rituximab with or without chemotherapy, being the preferred option (NCCN guidelines, 2015; Dreyling, 2013a). Nodal MZL is also treated like follicular lymphoma, although no studies of large series have been published so far in this type of MZL.

Combination therapy with rituximab and fludarabine is a very active treatment as the initial systemic treatment for patients with extranodal MALT lymphoma (Salar, 2009). Treatment of splenic MZL patients with rituximab (either alone or in combination with chemotherapy) has shown a high response rate (Bennett, 2010).

1.4 Lenalidomide

Lenalidomide is the lead member of a proprietary series of drugs with immunomodulatory and other properties, referred to as the IMiD®s class of compounds, and is also sometimes referred to as CDC-501 and CC-5013 (also known as BMS-986380), as well as the registered name REVLIMID®.

Lenalidomide offers potential benefit over 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 anti-inflammatory 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 Tumor Necrosis Factor alpha (TNF-α) inhibitory, T-cell costimulatory, and antiangiogenic activities (Galustian, 2004).

Lenalidomide is approved in the USA for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. Lenalidomide is also approved in the USA 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 the EU for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. Lenalidomide is also approved worldwide, in combination with dexamethasone, for the treatment of patients with multiple myeloma who had been treated with at least one prior therapy. Lenalidomide is being investigated as a treatment for various hematologic and oncologic indications.

1.5 Preclinical Studies of Lenalidomide and Rituximab in Lymphoma

Lenalidomide is an immunomodulatory agent that has both direct tumoricidal and immunomodulatory activities that are likely important for its clinical activity in the treatment of various hematologic malignancies. This activity is at least in part mediated by an 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 been shown to augment ADCC mainly by increasing CD16 expression on NK cells (Zhang, 2009). In a murine NHL model, lenalidomide induced a significant increase in the recruitment of NK cells to tumor sites resulting in enhanced anti-tumor activity of rituximab (Reddy, 2007). 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 follicular lymphoma (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). 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 the rituximab-lenalidomide combination described in this clinical trial protocol.

1.6 Clinical Studies of Single-Agent Lenalidomide and Rituximab plus Lenalidomide in FL, MZL, and MCL

1.6.1 Follicular Lymphoma

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 a 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 the previous therapy. ORR was 23% (10 of 43), including a 7% complete response (CR) or unconfirmed (CRu) rate. Twenty-seven percent (6 of 22) of patients with follicular lymphoma 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% Confidence Interval (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).

In 2011,Witzig et al published the results of an international multi-center single-arm phase 2 trial (Witzig, 2011). This trial aimed to demonstrate the safety and efficacy of lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular grade 3 lymphoma (FL-3), or transformed lymphoma (TL). Two hundred and seventeen patients enrolled and received lenalidomide. The ORR was 35% (77/217), with 13% (29/217) complete remission (CR), 22% (48/217) partial remission, and 21% (45/217) with stable disease. The ORR for FL-3 was 42% (8/19) with CR/CRu rate of 11%. The ORR for TL was 45% (15/33) with CR/CRu rate of 21%. In this trial patients with TL achieved median PFS of 5.4 months with median duration of response (DOR) of 12.8 months. In patients with FL-3, median PFS was 8.9 months and median DOR was not achieved at time of publication. The most common adverse events were myelosuppression with grade 4 neutropenia and thrombocytopenia in 17% and 6% of subjects, respectively.

Leonard et al (Leonard, 2012) reported results from a randomized Phase 2 clinical trial conducted by the US cooperative group Cancer and Leukemia Group B (CALGB) evaluating rituximab-lenalidomide combination therapy versus single-agent lenalidomide in patients with

recurrent FL who had prior therapy with rituximab alone or in combination, and with a time to progression of ≥ 6 months from last rituximab dose. Ninety-four patients were enrolled to receive either lenalidomide (N = 45) or lenalidomide and rituximab combined (N = 44). Baseline characteristics included median age 63 (range, 34 to 85) and intermediate- or high-risk FLIPI (60% of patients). Grade 3 or 4 AEs were similar in both arms (49% lenalidomide, 52% lenalidomide and rituximab combination) with 9% of patients experiencing Grade 4 events in both arms. The most common Grade 3 or 4 events were neutropenia (16% lenalidomide, 19% lenalidomide and rituximab combination), fatigue (9% lenalidomide, 14% lenalidomide and rituximab combination), and thrombosis (16% [7 patients] lenalidomide, 4% [2 patients] lenalidomide and rituximab combination, p = 0.158). The treatment regimen was completed in 33% (lenalidomide) and 59% (lenalidomide and rituximab combination) of patients, with the difference due to more progressions or non-responders in the lenalidomide alone group. In both arms about 19% of patients discontinued therapy early due to adverse events (AEs) and relative dose intensity was over 80%. Objective response rates were 49% (13% CR) for lenalidomide and 75% (32% CR) for lenalidomide plus rituximab. With a median follow-up of 1.5 years (range, 0.1 to 3.6 years), median event free survival (EFS) was 1.2 years (lenalidomide) and 2.0 years (lenalidomide and rituximab).

The results of this study are further supported by findings from two smaller single institution studies reported by Dutia et al (Dutia, 2010) and Ahmadi et al (Ahmadi, 2011). Dutia et al (Dutia, 2010) conducted a clinical trial of the combination of rituximab and lenalidomide in 16 patients with relapsed/refractory indolent lymphoma. Of the 16 patients, 13 had FL. In this subset of FL patients, the ORR was 85% and CR/CRu was achieved in 5 patients (38%). Ahmadi et al (Ahmadi, 2011) reported the results from a Phase 2 trial of lenalidomide-dexamethasone-rituximab (Cohort 1) and lenalidomide-rituximab (Cohort 2) in patients with indolent B-cell or mantle cell lymphomas refractory to rituximab. Patients received two 28-day treatment Cycles of either lenalidomide 10 mg daily and dexamethasone 8 mg once weekly or lenalidomide 10 mg daily. After assessment of response, all patients received rituximab 375 mg/m^2 weekly for 4 doses starting with Cycle 3. Lenalidomide-dexamethasone or lenalidomide therapy continued with the addition of rituximab. Of the 45 patients enrolled, the histologies were follicular (n = 28), mantle cell (n = 11), small lymphocytic (n = 4), and marginal zone (n = 2) lymphomas. Of the 35 patients completing both parts of the treatment regimen, the response rate was 60% and the CR rate was 34%.

The combination of lenalidomide and rituximab in patients with grade 3 FL and transformed lymphoma has also been studied (Wang, 2013). In this phase 2 trial, 45 patients with relapsed or refractory DLBCL (n = 32), transformed lymphoma (n = 9) or grade 3 follicular lymphoma (n = 4) who had received 1 to 4 prior lines of treatment were given 20 mg oral lenalidomide on Days 1–21 of each 28-day cycle, and intravenous rituximab (375 mg/m2) weekly during Cycle 1. Grade 3/4 hematological toxicities included neutropenia (53%), lymphopenia (40%), thrombocytopenia (33%), leukopenia (27%) and anemia (18%), with a median follow-up time of 29.1 months (range, 14.7–52.0 months). The ORR was 33%; median response duration was 10.2 months. Median PFS and OS were 3.7 and 10.7 months, respectively. In this trial, patients with transformed lymphoma

achieved an ORR of 56% (5/9) and CR rate of 33%, median PFS of 4.3 months with OS of 11.5 months. Patients with grade 3 follicular lymphoma achieved an ORR of 25% (1/4) (all PR), median PFS of 2.0 months and median OS of 25.6 months.

The rituximab plus lenalidomide combination has also been studied as frontline therapy in FL. In 2013, Martin et al (Martin, 2013) reported the results of a phase 2 clinical trial of rituximab-lenalidomide combination given for 12 months in previously untreated FL, grades 1 through 3a, 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 375 mg/m^2 intravenous (IV) weekly x 4 in Cycle 1 and on Day 1 of Cycle 4, 6, 8, and 10. Sixty-five patients were enrolled. Three patients did not receive protocol treatment and were removed from analyses. The median age of the remaining 62 patients was 53 years; 49% were male; and 63% had a FLIPI score >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 higher toxicity in > 5% of patients included fatigue (25%), infusion reaction (17%), upper respiratory infection (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%). At the time of the presentation, of the 57 evaluable subjects, the ORR was 93% (72% CR), with a median time to CR of 10 weeks. Complete responses were not associated with FLIPI score, grade, or presence of bulky disease. At a median follow-up of 1.6 years, 7/57 evaluable patients had progressed; 2 stopped after 1 to 2 cycles due to toxicity, and 2 achieved best response of CR.

More recently, Fowler et al. (Fowler, 2014) published the results of a phase 2 study evaluating the efficacy and safety of rituximab-lenalidomide in patients with untreated, Stage III/IV, indolent NHL, including FL grades 1,2, small lymphocyctic lymphoma, and MZL. A total of 110 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; those subjects with a clinical benefit could continue up 12 cycles. Response was assessed after every 3 cycles using the IWG (Cheson, 1999) criteria. The median age was 58 years (range, 34 to 84), 53% of patients were male, and 103 patients were evaluable for response. Among all evaluable patients, the overall response rate was 90%. Complete responses were attained in 65 (63%) of patients, 28 patients (27%) had a PR. Among the subset of patients with follicular lymphoma, 40 of 46 evaluable patients (87%) attained a CR/CRu. As part of an [redacted], pre-and post-treatment positron emission tomography (PET) scans were obtained and available for 45 patients. Forty-four were PET-positive prior to therapy; after treatment, 42 (93%) patients were PET-negative. Median PFS for all patients was 53.8 months. The median PFS had not been reached at a median follow-up of 40.6 months for patients with FL. The most common Grade 3/4 AEs reported were neutropenia (35%), muscle pain (9%), rash (7%), pulmonary symptoms (5%), fatigue (5%), thrombosis (5%), and thrombocytopenia (4%). Six patients were removed from treatment due to AEs but were eligible for survival assessment.

The RELEVANCE study (NCT01476787) is a Phase 3, randomized two-arm comparison sponsored by the LYSARC cooperative group and designed to evaluate the effect of the combined treatment of lenalidomide and rituximab in controlling the FL disease and also increase the length

of response compared to the available standard combination chemotherapy treatment for FL (1000 patients). The study consists of Arm A = R-CHOP or R-CVP or R-bendamustine; Arm B = R-lenalidomide. A total of 1030 patients were randomly assigned to receive rituximab (R) plus lenalidomide (513 patients) or rituximab plus chemotherapy (517 patients). The median follow-up was 37.9 months. The rate of confirmed or unconfirmed complete response at 120 weeks was similar in the two groups: 48% (95% CI, 44 to 53) in the R–lenalidomide group and 53% (95% CI, 49 to 57) in the R–chemotherapy group (P = 0.13) per central review. The interim 3-year rate of progression-free survival was 77% (95% CI, 72 to 80) and 78% (95% CI, 74 to 82), respectively. A higher percentage of patients in the R–chemotherapy group had Grade 3 or 4 neutropenia (32% versus 50%) and febrile neutropenia of any grade (2% versus 7%), and a higher percentage of patients in the R–lenalidomide group had Grade 3 or 4 cutaneous reactions (7% versus 1%)(Morschhauser, 2018).

1.6.2 Marginal Zone Lymphoma

Data in MZL has also been reported. Recent data (ORR of 61%) suggested for the first time the activity of single-agent lenalidomide in MALT lymphoma with manageable side effects (Kiesewetter, 2012). In a separate Phase 2 study, the combination of lenalidomide and rituximab was administered for 6 cycles (12 cycles for responders) and was studied in previously untreated patients (Fowler, 2014). In this study, among the 27 patients with MZL, ORR was 89% with 67% CR. Two patients had an improvement in response (PR to CR) after completing therapy. In patients with MZL, median PFS was 53.8 months, 3-year PFS was 87%, and 3-year OS was 100%.

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, thrombopenia grade 1 in three patients and anemia grade 1 in one patient. Other adverse events reported were mild fatigue (n = 5), pruritus (n = 6, one patient grade 3), 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).

1.6.3 Mantle Cell Lymphoma

Patients with MCL who relapse after an initial response or do not respond to first-line treatment have a poor prognosis (Goy, 2011). With single-agent lenalidomide, response rates of 53% and 35% were seen respectively in patients with MCL and relapsed or refractory aggressive lymphomas (Habermann, 2009; Wiernik, 2008). The Celgene sponsored MCL-001, “Emerge” study demonstrated rapid and durable efficacy of single-agent lenalidomide in MCL subjects who relapsed or progressed after or were refractory to bortezomib. These results in heavily pretreated MCL patients (with a median of 4 prior treatments) support single-agent lenalidomide in patients with relapsed or refractory MCL after bortezomib (Goy, 2013). Considering the results from various Phase 2 studies (38% to 50% in response rates), the NCCN guidelines and the recent

ESMO consensus suggested that lenalidomide may be considered in advanced relapses, as toxicity seems to be manageable with some moderate myelotoxicity. Median PFS, under continuous medication, may be extended 6 to 9 months (Dreyling, 2013b). A study has reported that 25% of patients with SD at initial evaluation improved with more prolonged treatment, suggesting that a more prolonged schedule of therapy might be beneficial when administering lenalidomide (Wiernik, 2008).

The combination of lenalidomide and rituximab has also been reported in MCL (Wang, 2012). Fourteen patients have participated in the Phase 1 segment and 38 in the Phase 2 segment of the trial. During Phase 1, the dose of lenalidomide was gradually increased from 10 to 25 mg with the standard dose of rituximab administered weekly x4 during Cycle 1 only. Due to a number of toxicities and even a death in Cycle 2 with the highest dose, the dose of 20 mg of lenalidomide was finally adopted for Phase 2. Treatment in both phases continued until disease progression, stem-cell transplantation, or severe toxicity. Median age of patients was 66 years, and they had received previously a median of two treatment lines. All patients had already been treated with rituximab. During the study a dose reduction was necessary for half of the patients. In terms of efficacy, among 44 patients, 57% had an overall response: 36% had a CR and 20% had a PR. The median response duration was 18.9 months (95% CI was 17.0 months to not reached [NR]). The median PFS was 11.1 months (95% CI was 8.3 to 24.9 months), and the median OS was 24.3 months (19.8 months to NR). Interestingly, five of 14 patients who had received bortezomib treatment before enrollment achieved an overall response.

More recently Ruan et al. (Ruan, 2014) reported mature results from an ongoing multi-center phase 2 trial evaluating the combination of lenalidomide plus rituximab as initial treatment for patients with MCL followed by lenalidomide plus rituximab as maintenance therapy. Thirty-eight subjects with previously untreated MCL were enrolled at 4 centers. During the induction phase, lenalidomide was administered at 20 mg daily on Days 1-21 of a 28-day cycle for a total of 12 cycles, with dose escalation to 25 mg daily if tolerated. Standard dose rituximab was administered weekly x 4 during Cycle 1, then once every other cycle, for a total of 9 doses. During the maintenance phase, which started with Cycle 13, lenalidomide was administered at 15 mg daily on Days 1-21 of a 28-day cycle, with rituximab maintenance once every other cycle until progression of disease. Treatment was generally well tolerated with expected side effects. Grade 3-4 hematologic toxicities included neutropenia (47% in total, 42% with induction, 24% with maintenance), thrombocytopenia (13%) and anemia (8%). Grade 3-4 non-hematologic toxicities including rash (26%), tumor flare (11%), serum sickness associated with rituximab (8%) and fatigue (8%) were reported during induction phase only. At time of reporting, median follow-up was 26 months (range, 5-38 months) the ORR for all evaluable patients was 89% with 58% CR and 31% PR. Median time to objective response was 2.8 months, with median time to CR achieved at 11 months. Median progression-free survival and duration of response had not been reached. The 2-year PFS rate is estimated at 85%. Neither MIPI score nor Ki67 index correlated with response. Quality of life parameters were maintained or improved during treatment by FACT-Lym analysis.

1.7 Lenalidomide as Maintenance Therapy

Thalidomide and lenalidomide have been incorporated into the treatment paradigm of newly diagnosed and relapsed multiple myeloma (MM), as well as maintenance therapy (Munshi, 2013). Three recent trials support the use of lenalidomide maintenance therapy in MM. Lenalidomide at a 10 mg maintenance dose is highly active in MM (Palumbo, 2012; Attal, 2012; McCarthy, 2012; Boccadoro, 2013), confirming the improvement in the time to progression in all three trials and one showing an improvement in survival. At a median follow-up of 30 months, PFS was significantly prolonged in patients administered lenalidomide maintenance therapy following melphalan, prednisone, and lenalidomide induction therapy (MPR+R) (31 months) compared with those who received MPR or MP induction therapy only (14 months, $p < 0.001$ or 13 months, $p < 0.001$, respectively) (Palumbo, 2012). The trial by Attal demonstrated that PFS was 41 months with lenalidomide and 23 months with placebo maintenance. In the McCarthy study, the median time to progression, post-transplant, was 46 months with lenalidomide maintenance versus [redacted] in the placebo group ($p < 0.001$). The trial by the "Gruppo Italiano Malattie EMatologiche Dell'Adulto" (GIMEMA) reported that patients who were given lenalidomide maintenance therapy had a significantly higher PFS (37 versus 26 months) and OS (75% vs. 58%) than those with no maintenance (Boccadoro, 2013).

Lenalidomide is being studied as maintenance therapy in lymphoma (NCT01122472; NCT01415752; NCT01216683; NCT01476787).

The REMARC study (NCT01122472) is a Phase 3, randomized, double-blind, placebo-controlled study sponsored by the LYSARC cooperative group and Celgene, and is designed to explore the effect of 2-year maintenance therapy with lenalidomide versus placebo on PFS in DLBCL patients (621 planned) responding to induction therapy with R-CHOP. A total of 650 patients were randomly assigned. At the time of the primary analysis (December 2015), with a median follow-up of 39 months from random assignment, median PFS was not reached for lenalidomide maintenance versus 58.9 months for placebo (hazard ratio, 0.708; 95% CI, 0.537 to 0.933; P = 0.01). The result was consistent among analyzed subgroups (eg, male versus female, age-adjusted International Prognostic Index 0 or 1 versus 2 or 3, age younger than 70 versus ≥ 70 years), response (PR versus CR) after R-CHOP, and positron emission tomography status at assignment (negative versus positive). With longer median follow-up of 52 months (October 2016), overall survival was similar between arms (hazard ratio, 1.218; 95% CI, 0.861 to 1.721; P = 0.26). The most common Grade 3 or 4 adverse events associated with lenalidomide versus placebo maintenance were neutropenia (56% versus 22%) and cutaneous reactions (5% versus 1%), respectively (Thieblemont, 2017).

The NCT01415752 study (E1411 study; Eastern Cooperative Oncology Group [ECOG] and National Cancer Institute [NCI]) is a Phase 2, randomized, four-arm study designed to evaluate the efficacy of rituximab together with bendamustine and bortezomib compared to rituximab and bendamustine, followed by rituximab alone or with lenalidomide in older MCL patients (332 planned). Arm A = rituximab+ bendamustine followed by rituximab consolidation (RB → R); Arm B = rituximab + bendamustine + bortezomib followed by rituximab consolidation (RBV→ R); Arm C = rituximab + bendamustine followed by lenalidomide + rituximab consolidation (RB

→ LR) or Arm D = rituximab + bendamustine + bortezomib followed by lenalidomide + rituximab consolidation (RBV → LR).

The NCT01216683 study (2408 study; ECOG) is a Phase 2, randomized, three-arm comparison studying bendamustine and rituximab together with or without bortezomib followed by rituximab with or without lenalidomide in patients with follicular lymphoma. It consists of Arm A = rituximab+ bendamustine followed by rituximab consolidation (RB → R); Arm B = rituximab + bendamustine + bortezomib followed by rituximab consolidation (RBV→ R); Arm C = rituximab + bendamustine followed by lenalidomide + rituximab consolidation (RB → LR).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to compare the efficacy of lenalidomide plus rituximab combination maintenance therapy (for 18 cycles) followed by optional lenalidomide single-agent maintenance (to progression) versus rituximab single-agent maintenance (for 18 cycles) after 12 cycles of induction therapy with lenalidomide plus rituximab, in subjects with relapsed/refractory FL grades 1-3b, transformed FL, MZL or MCL. Efficacy determinations will be based upon PFS as the primary endpoint, using a modification of the IWG 1999 criteria (Cheson, 1999).

2.2 Secondary Objectives

The secondary objectives of the study are:

- To compare the safety of lenalidomide plus rituximab combination maintenance therapy (for 18 cycles) followed by optional lenalidomide single-agent maintenance (to progression) versus rituximab single-agent maintenance (for 18 cycles) after 12 cycles of induction therapy with lenalidomide plus rituximab.
- To compare other parameters of efficacy (OS, IOR, ORR, CRR, DOR, DOCR, TTNLT, TTHT) of lenalidomide plus rituximab combination maintenance therapy (for 18 cycles) followed by optional lenalidomide single-agent maintenance (to progression) versus rituximab single-agent maintenance (for 18 cycles) after 12 cycles of induction therapy with lenalidomide plus rituximab.

All efficacy assessments will be assessed using a modification of the IWG 1999 criteria (Cheson, 1999) to allow the inclusion of extranodal disease as measurable disease.

3 STUDY ENDPOINTS

All efficacy assessments will be made using a modification of the IWG 1999 criteria to allow the inclusion of extranodal disease as measurable disease (Cheson, 1999).

3.1 Primary Endpoint

- PFS

3.2 Secondary Endpoints

- OS
- IOR
- ORR
- CRR
- DOR
- DOCR
- TTNLT
- TTHT
- Safety

4 OVERALL STUDY DESIGN

4.1 Study Design

This Phase 3b randomized study is designed to compare the efficacy and safety of lenalidomide plus rituximab combination maintenance therapy (for 18 cycles) followed by optional lenalidomide single-agent maintenance (to progression) versus rituximab single-agent maintenance (for 18 cycles) after 12 cycles of induction therapy with lenalidomide plus rituximab in subjects with relapsed/refractory FL grades 1-3b, transformed follicular lymphoma, MZL or MCL. The overall study design is described in Figure 1. The study is divided into the Screening Period, Treatment Period, and Follow-up Period. Approximately 500 subjects are planned to be enrolled.

All efficacy assessments will be based on local radiology and appropriate clinical assessment using a modification of the IWG 1999 criteria (Cheson, 1999). The Cheson criteria (1999) were modified to allow the inclusion of extranodal disease as measurable disease. Evaluation of a PR allowing inclusion of sites of dominant extranodal disease (still requiring a 50% or greater decrease in the sum of the perpendicular diameters of measurable sites of disease) is adopted in this clinical trial since extranodal involvement is common in MZL and MCL. A similar modification to the Cheson criteria has been adopted in other MCL studies (Fisher, 2006; Kane, 2007). For subjects with MZL involving the gastric area, results of endoscopy will be included in the assessment of response.

An independent external DMC will review ongoing safety data throughout the study. The frequency of DMC meetings will be described in the DMC Charter.

The study will be conducted in compliance with GCP.

4.1.1 Screening Period

Upon giving written informed consent, the subject will enter the Screening Period to determine eligibility. All Screening assessments must be completed within 28 days prior to enrollment in IVRS to receive induction therapy. During the Screening Period, the subject will undergo safety and other assessments to determine eligibility for the study and undergo enrollment into the trial.

Subject eligibility will be based on investigator assessment of the pathologic diagnosis.

4.1.2 Induction and Maintenance Period

4.1.3 Enrollment in Induction Treatment Period

The subject will be enrolled into the Induction Treatment Period once all required screening assessments have been performed and the subject meets all eligibility criteria. Eligible subjects entering the Induction Treatment Period will be enrolled using an Interactive Voice Response System (IVRS). The Induction Treatment Period will start on Day 1 of the first cycle (C1D1). The lenalidomide plus rituximab induction treatment will be given as described in detail in Section 8 and must begin no later than 1 week after enrollment in IVRS to receive induction therapy. Subjects will receive induction treatment, and be evaluated for efficacy, and safety assessments for 12 Cycles or until relapse or progression of disease, withdrawal of consent, or unacceptable toxicity. The local laboratory will be used for the analysis of hematology and serum chemistry.

Clinical decisions and dose modifications during the study can be based on these results (see Section 6.2.10).

4.1.4 Randomization to Maintenance Treatment Period

After 12 cycles of lenalidomide plus rituximab induction therapy, subjects achieving CR/CRu, PR or having SD will be randomized to enter the maintenance period. During the maintenance period, subjects randomized to Arm B will receive rituximab (only) administered for 18 Cycles. Subjects randomized to Arm A will receive lenalidomide plus rituximab treatment for 18 Cycles and then lenalidomide until relapse or progression of disease. Lenalidomide (only) treatment in Arm A will be given per subject and/or physician discretion as described in detail in Section 8 and must begin no later than 1 week after the last cycle of rituximab plus lenalidomide. Subjects randomized under previous protocol (version 16 January 2014) who achieve a response of SD or better at the end of the Induction Treatment Period will remain in their originally assigned arm of maintenance therapy.

All subjects (in both Induction and Maintenance Treatment Periods) receive treatment as described unless they withdraw consent from treatment, experience unacceptable toxicities or have disease progression. Once subjects discontinue or complete treatment, they enter the follow-up period. All enrolled subjects will be followed for disease progression using the schedule described in Table 1. Subjects who progress before the end of planned treatment will enter the Follow-up Period. Determination of disease progression will be based on investigator assessment. All subjects who discontinue the protocol-specified treatment early for any reason without documented evidence of disease progression will also be followed in the Follow-up Period.

All subjects who will be on treatment upon reaching 5 years after the last subject has initiated induction therapy [redacted] will continue the treatment and will be followed up for safety purposes only.

4.1.5 Follow-up Period

Upon completion or discontinuation of the protocol-specified treatment, subjects will enter the Follow-up Period. In the Follow-up Period, all subjects will be followed for survival, time to next lymphoma treatment, and SPMs for 5 years after the last subject has initiated induction therapy unless they withdraw consent from the study, die or are lost to follow-up. Subjects whose disease has not yet progressed will also be followed for disease progression. [redacted]

4.1.6 Follow-up Period Upon Confirmation of 114 PFS Events

[redacted] SPMs for 5 years after the last subject has initiated induction therapy unless the subject withdraws from the study, dies, or is lost to follow-up.

4.2 Study Design Rationale

Follicular lymphoma, marginal zone or mantle cell lymphoma are distinct histologic types within the broad category of B-cell NHL according to the World Health Organization (WHO) classification (Harris, 2008). For FL, this histology is further divided into 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 into Grades 3a and 3b. Grade 3a versus 3b distinction has implications for treatment decisions, since Grade 3b FLs are clinically more similar to more aggressive lymphomas, with more infiltration of large cells. Grade 3a is typically treated as an indolent lymphoma, while Grade 3b is treated as an aggressive lymphoma with similar outcome.

A pivotal event in the natural history of FL is histological transformation to more aggressive malignancies, most commonly diffuse large B cell lymphomas (DLBCL) or other high-grade morphologies. In this process a more virulent subclonal population of cells emerge, typically associated with the loss of the follicular growth pattern, a rapidly progressive clinical course refractory to treatment, and short survival (commonly of less than 2 years). Although one of the earliest descriptions of FL transformation was reported more than 65 years ago, this biological process and clinical event still remains incompletely understood without a standard treatment approach (Lossos, 2011). Despite heterogeneities in the biology and treatment practices between FL, transformed lymphoma, MZL, and MCL, it is important to note that in advanced stage disease and in relapsed disease, the clinical behavior and treatments are very similar among the lymphomas that are being studied in this clinical trial. These similarities, for example, are reflected in the nearly identical treatment guidelines for the management of advanced stage FL versus advanced stage MZL (NCCN guidelines, 2015; Dreyling, 2013a). For this reason, FL and MZL are studied together in this clinical trial.

Rituximab is approved in many countries for the treatment of relapsed/refractory low-grade NHL or FL. “Low-grade” is a term based on the Working Formulation (Robb-Smith, 1982) that included lymphomas with indolent behavior solely on their histologic appearance. In recent years low-grade lymphoma has been replaced by the term “indolent.” Clinically, “low-grade” lymphoma can be used interchangeably with “indolent lymphoma.”

Subsequent to this initial rituximab approval, the treatment of relapsed/refractory low-grade NHL has evolved so that multiple options are now available. Thus, rituximab has become the backbone of combination therapy. As discussed in Section 1.6 the lenalidomide-rituximab regimen has been reported to be active in FL, transformed FL, MZL and MCL (Leonard, 2012; Fowler, 2014; Wang, 2012; Wang 2013). As mentioned in Section 1.7, lenalidomide is highly active as a single agent in FL, MCL, and MZL and as a maintenance agent in myeloma. There are ongoing trials studying lenalidomide maintenance therapy in lymphoma. Thus, in summary, sufficient evidence exists that the combination of rituximab plus lenalidomide is a useful combination to study in FL, MZL, and MCL, where no single standard of care is available.

The current study is a Phase 3b, multicenter, randomized, open-label study designed to compare the efficacy and safety of lenalidomide plus rituximab combination maintenance therapy (for 18 cycles) followed by optional lenalidomide single-agent maintenance (to progression) versus rituximab single-agent maintenance (for 18 cycles) after 12 cycles of induction therapy with lenalidomide plus rituximab in subjects with relapsed/refractory FL, transformed FL, MZL, or MCL. It is anticipated that with a longer duration of lenalidomide we will observe a longer duration

of response with minimal added toxicities. The multicenter nature of the study provides assurance that the results are likely to have general applicability.

Subjects are required to have measurable disease and to have frequent periodic disease assessments for an accurate assessment of PFS, the primary endpoint of this study. Because extranodal disease is common in MCL and MZL, the Cheson criteria (Cheson, 1999) will be modified to allow inclusion of sites of dominant extranodal disease as measurable disease, as has been previously used in a mantle cell lymphoma study (Fisher, 2006; Kane, 2007). The use of this established tool will ensure that data across centers are evaluated consistently and also allow for comparison to historical data. For assessment of MZL, endoscopy has been added to the efficacy assessment. In addition, in this clinical trial, these criteria exclude the use of PET scan, which is less established as an indicator of disease activity in indolent lymphoma compared to aggressive lymphoma.

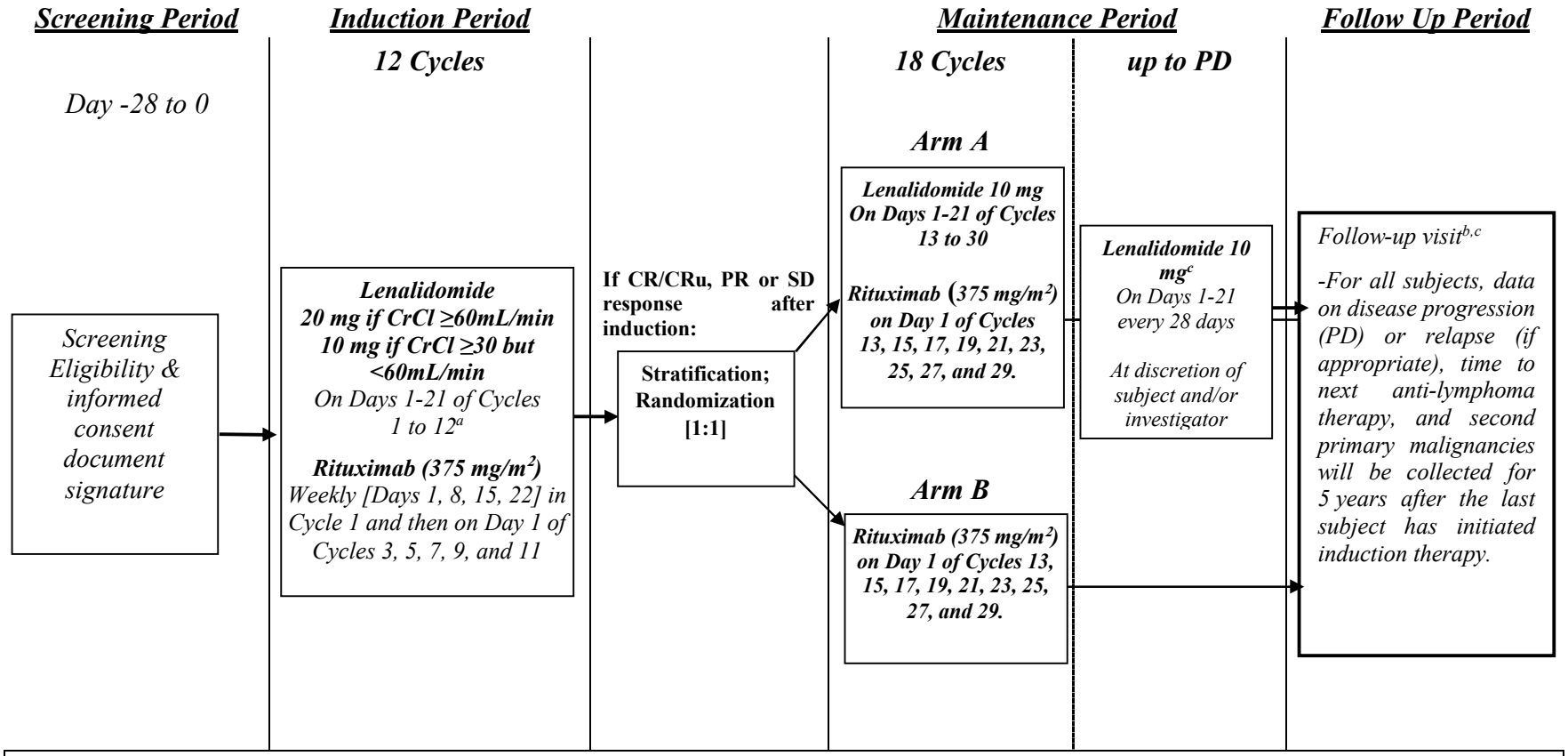
The primary endpoint of PFS is an accepted measure of clinical benefit.

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 version 3.0.

Monitoring for certain events (see Section 6.2 for details), including TFR, tumor lysis syndrome (TLS), and venous and arterial thromboembolic events (VTE and ATE) will be performed along with safety assessments routinely conducted in investigational studies of hematologic malignancies. Prophylaxis for thromboembolic events is strongly recommended for subjects who are at risk for thromboembolic events (TE). Thromboembolic events, TFR and TLS will be recorded as AEs.

Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to IP (study drug), occurring at any time for the duration of the study, from the time of signing the ICD for 5 years from the date the last subject initiates induction therapy.

Figure 1: Overall Study Design



[a] Treatment must begin no later than 1 week after completing enrollment in IVRS to receive induction therapy.

[b] All enrolled subjects are followed for disease progression using the same schedule described in Table 1. This includes subjects who discontinue the protocol-specified treatment or the study early for any reason without documented evidence of PD or relapse.

[c] Upon confirmation of 114 PFS events, subjects will be followed up for survival and SPM as detailed in the follow-up section. See Section 4.1.6.

4.3 Study Duration

The expected accrual duration is approximately 63 months. Subjects will receive protocol-specified treatment until relapse or progression of disease, withdrawal of consent or unacceptable toxicity. The study duration to events for primary analysis is estimated to be 105 months. Subjects will be followed for disease progression, survival, subsequent anti-lymphoma therapy and SPMs. Upon confirmation of 114 PFS events, subjects will be followed for survival and SPMs for 5 years after the last subject has initiated induction therapy. All subjects who will be on treatment upon reaching 5 years after the last subject has initiated induction therapy [redacted] will continue the treatment and will be followed up for safety purposes only.

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

5 TABLE OF EVENTS

Table 1: Schedule of Study Assessments

PROCEDURE[a]	Screening Period	Every Cycle Day 1 Induction & Maintenance Periods (± 3 days)	Induction Period								Maintenance Period	At 3 cycles (84 days after C1D1) (±2 weeks) At 6 cycles (168 days after C1D1)(±2 weeks) Every 6 cycles (168 days) (±2 weeks) up to 5 years then Annually (± 3 weeks)[b]	At Treatment Discontinuation/ Completion	Follow-up		[redacted]
			Cycle 1			Cycles 2 & 3	Cycles 3, 5, 7, 9 & 11	Cycles 5 & 9	Cycle 7	Cycle 10	Cycles 13, 15, 17, 19, 21, 23, 25, 27 & 29			If no PD then follow the CT scan assessment schedule[b]	[redacted]	
	Days -28 to -1	Up to PD for Arm A Or up to 30 cycles for Arm B	Day 1 (± 3 days)	Day 8 & 15 (± 1 day)	Day 22	Day 15 (± 1 day)	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)					
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Inclusion/Exclusion Criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographic Data	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphoma and Complete Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Central Nervous System Lymphoma Evaluation	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Creatinine Clearance (Cockcroft-Gault Estimation)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12-Lead Electrocardiogram	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HBV Screening[c]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Schedule of Study Assessments

PROCEDURE[a]	Screening Period	Every Cycle Day 1 Induction & Maintenance Periods (± 3 days)	Induction Period								Maintenance Period	At 3 cycles (84 days after C1D1) (±2 weeks) At 6 cycles (168 days after C1D1)(±2 weeks) Every 6 cycles (168 days) (±2 weeks) up to 5 years then Annually (± 3 weeks)[b]	At Treatment Discontinuation/ Completion	Follow-up		[redacted]
			Cycle 1			Cycles 2 & 3	Cycles 3, 5, 7, 9 & 11	Cycles 5 & 9	Cycle 7	Cycle 10	Cycles 13, 15, 17, 19, 21, 23, 25, 27 & 29			If no PD then follow the CT scan assessment schedule[b]	[redacted])	
	Days -28 to -1	Up to PD for Arm A Or up to 30 cycles for Arm B	Day 1 (± 3 days)	Day 8 & 15 (± 1 day)	Day 22	Day 15 (± 1 day)	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)					
Safety Assessments																
Adverse Events	From signing ICD and until 28 days after the last dose															
Assessment of Second Primary Malignancy[d]	From signing ICD and up to and including the Follow-up Period (5 years from last subject initiating induction treatment) [redacted]															
Pregnancy Test (FCBP Only)[e]	X	X	X	X	X	-	-	-	-	-	-	-	X[f]	-	-	-
Birth Control/ Lenalidomide Counseling	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Distribute Lenalidomide Counseling Sheet	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior/ Concomitant Medications/ Procedures/ Hospitalizations	From signing of ICD until 28 days after last dose of treatment															-
Physical Examination	X	X	-	-	-	-	-	-	-	-	-	-	X	-	-	-

Table 1: Schedule of Study Assessments

PROCEDURE[a]	Screening Period	Every Cycle Day 1 Induction & Maintenance Periods (± 3 days)	Induction Period								Maintenance Period	At 3 cycles (84 days after C1D1) (±2 weeks) At 6 cycles (168 days after C1D1)(±2 weeks) Every 6 cycles (168 days) (±2 weeks) up to 5 years then Annually (± 3 weeks)[b]	At Treatment Discontinuation/ Completion	Follow-up		[redacted]
			Cycle 1			Cycles 2 & 3	Cycles 3, 5, 7, 9 & 11	Cycles 5 & 9	Cycle 7	Cycle 10	Cycles 13, 15, 17, 19, 21, 23, 25, 27 & 29			If no PD then follow the CT scan assessment schedule[b]	[redacted]	
	Days -28 to -1	Up to PD for Arm A Or up to 30 cycles for Arm B	Day 1 (± 3 days)	Day 8 & 15 (± 1 day)	Day 22	Day 15 (± 1 day)	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)					
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
B Symptoms	X	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
Vitals Signs	X	X	-	-	-	-	-	-	-	-	-	-	X	-	-	-
Hematology Laboratory Tests[g]	X	X	-	X	-	X	-	-	-	-	-	-	X	-	-	-
Serum Chemistry Laboratory Tests[g]	X	X	-	X	-	X	-	-	-	-	-	-	X	-	-	-
Thyroid Stimulating Hormone[g,n] (TSH)	X	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
Tumor Flare and Tumor Lysis Assessments[h]	-	-	X	X	-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Schedule of Study Assessments

PROCEDURE[a]	Screening Period	Every Cycle Day 1 Induction & Maintenance Periods (± 3 days)	Induction Period								Maintenance Period	At 3 cycles (84 days after C1D1) (±2 weeks) At 6 cycles (168 days after C1D1)(±2 weeks) Every 6 cycles (168 days) (±2 weeks) up to 5 years then Annually (± 3 weeks)[b]	At Treatment Discontinuation/ Completion	Follow-up		[redacted]
			Cycle 1			Cycles 2 & 3	Cycles 3, 5, 7, 9 & 11	Cycles 5 & 9	Cycle 7	Cycle 10	Cycles 13, 15, 17, 19, 21, 23, 25, 27 & 29			If no PD then follow the CT scan assessment schedule[b]	[redacted]	
	Days -28 to -1	Up to PD for Arm A Or up to 30 cycles for Arm B	Day 1 (± 3 days)	Day 8 & 15 (± 1 day)	Day 22	Day 15 (± 1 day)	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)					
Efficacy Assessments																
CT with contrast or MRI of Neck, Chest, Abdomen and Pelvis	X	-	-	-	-	-	-	-	-	-	-	X[o]	-	X	-	-
Bone Marrow Biopsy[i]	X	Only if nodal CR and bone marrow involvement at baseline														
Endoscopy/Gastric Biopsy[j]	X[j]	Repeat twice within 3 months of CR/CRu by IWG criteria														
Response Assessment	-	-	-	-	-	-	-	-	-	-	-	X[o]	-	X	-	-
Subsequent Anti-Lymphoma Therapies	-	-	-	-	-	-	-	-	-	-	-	-	X[o]	-	X	-
[redacted]																
Survival	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X	X
Treatment																
Tumor lysis prophylaxis[l]	-	-	X	X	-	-	-	-	-	-	-	-	-	-	-	-

Table 1: Schedule of Study Assessments

PROCEDURE[a]	Screening Period	Every Cycle Day 1 Induction & Maintenance Periods (± 3 days)	Induction Period								Maintenance Period	At 3 cycles (84 days after C1D1) (±2 weeks) At 6 cycles (168 days after C1D1)(±2 weeks) Every 6 cycles (168 days) (±2 weeks) up to 5 years then Annually (± 3 weeks)[b]	At Treatment Discontinuation/ Completion	Follow-up		
			Cycle 1			Cycles 2 & 3	Cycles 3, 5, 7, 9 & 11	Cycles 5 & 9	Cycle 7	Cycle 10	Cycles 13, 15, 17, 19, 21, 23, 25, 27 & 29			If no PD then follow the CT scan assessment schedule[b]	[redacted]	[redacted]
	Days -28 to -1	Up to PD for Arm A Or up to 30 cycles for Arm B	Day 1 (± 3 days)	Day 8 & 15 (± 1 day)	Day 22	Day 15 (± 1 day)	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)					
[redacted]																
Administer Rituximab[m]	-	-	X	X	X	-	X	-	-	-	X	-	-	-	-	-
Study Drug Return/ Accountability	-	X	-	-	-	-	-	-	-	-	-	-	X	-	-	-

Arm A: Experimental arm; Arm B: Control arm; CR: Complete Response; CRF: Case Report Form; CT: Computed Tomography; C1D1: Cycle 1 Day 1; FCBP: Females of childbearing potential; HBV: Hepatitis B Virus; ICD: Informed Consent Document; MRI: Magnetic Resonance Imaging; MZL: Marginal Zone Lymphoma; PD: Progressive Disease; PR: Partial Response; SAE: Serious Adverse Event; IP: Investigational Product; IWG: International Working Group; SOC: Standard of Care

[a] See Section 6 for details on the procedures.

[b] Efficacy assessments to be performed until progression, relapse or initiation of new anti-lymphoma therapy. See Section 6.3 for details.

[c] Eligibility for the study is based on the local HBV tests including if performed as standard of care within 4 weeks prior to enrollment in IVRS to receive induction therapy.

[d] 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. 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 for 5 years from the date the last subject initiates induction treatment. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other seriousness criteria apply; these events must also be documented in the appropriate page(s) of the CRF and the 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-rays, CT scans, etc.).

[e] For females of childbearing potential only. All FCBP enrolled into this study must conform to all aspects of the lenalidomide Pregnancy Prevention Plan (standalone document). A local laboratory will be used for all pregnancy testing, including the Screening tests (see Section 6.2.3 and 7.2).

[f] All FCBP must have pregnancy tests at treatment discontinuation and at Day 28 following lenalidomide discontinuation. For FCBP with irregular menstrual cycles pregnancy tests will be conducted weekly during the 4 weeks of treatment, and then every 14 days through 28 days following the last dose of lenalidomide. Refer to Section 6.2.3.

[g] 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 (see Section 6.2.10). Hematology and serum chemistry labs should be done before administration of study drugs; when these are required on these visits per above table the allowed window periods will be as follow: Day 1 (-3 days) of every treatment cycle, Day 8 (-1 day) and Day 15 (-1 day).

[h] 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 if necessary and as instructed (see Section 9.3.1)

[i] Bone marrow biopsy is required at Screening (for staging). A bone marrow biopsy conducted as SOC within 24 weeks prior to enrollment in IVRS to receive induction therapy may be used for Screening. During the study bone marrow biopsy is required only if the subjects had positive bone marrow at Screening and has otherwise fulfilled the criteria for a nodal CR. See more details in Section 6.1.5.

[j] Only for subjects with MZL involving gastric area. Subjects will have a repeat gastric biopsy for histological evaluation if the subject has fulfilled the IWG criteria for response of at least a CR/CRu. See more details in Section 6.1.6.

[redacted]

[l] All subjects at risk for TLS should receive TLS prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of the first cycle or as clinically indicated. To monitor for TLS, 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. See more details in Section 9.3.1.

[m] See Section 8 for more details regarding treatment administration. Possible time windows mentioned do not concern treatment schedule. Initiation of induction treatment should begin no later than 1 week after completion of enrollment in IVRS to receive induction therapy

[n] Thyroid stimulating hormone will be assessed at Screening and end of induction treatment or treatment discontinuation and thereafter as clinically indicated during the maintenance treatment period.

[o] Upon confirmation of 114 PFS events, CT scans, [redacted], response assessment, and subsequent anti-lymphoma therapies will no longer be required to be completed.

6 PROCEDURES

Subjects will be screened for protocol eligibility during a period of no more than 28 days prior to enrollment in IVRS to receive induction therapy (the Screening period) as outlined in the Schedule of Study Assessments. Procedures conducted as standard of care may be used to meet the requirements of this study provided they meet the description and timeline specified in the protocol.

Cycle definition: defined in this study as lenalidomide Cycle; 21 days treatment + 7 days rest period = 28 days total.

6.1 Study Entry

6.1.1 Informed Consent Document

The subject must approve and sign the ICD prior to undergoing any study-related Screening assessments

6.1.2 Inclusion and Exclusion Criteria

The subject's eligibility (inclusion and exclusion criteria) must be evaluated during the Screening Period prior to enrollment in IVRS to receive induction therapy (see Section 7.2 and 7.3).

6.1.3 Demographic Data

The demographic data will include (but not be limited to) the subject's initials, date of birth, age, gender, and race/ethnic origin. The demographic profile will be recorded in the source documents and case report form (CRF).

6.1.4 Lymphoma and Complete Medical History

A medical history will be obtained by the investigator or qualified designee within 4 weeks prior to the first day of treatment. Medical history judged as relevant to the study and to the safety of the study subject will be recorded in the source documents and CRF.

Eligibility for FL grades 1-3b, transformed FL, MZL and MCL subjects will be based on local pathology review. For MCL confirmation of Cyclin D1 expression or the presence of the t(11;14) translocation is recommended. Diagnosis based on core biopsy is acceptable, but diagnosis based on fine needle aspiration is not considered acceptable pathologic data for entry into this study.

6.1.5 Bone Marrow Biopsy

Bone marrow biopsy is required at Screening (for staging). A recent bone marrow biopsy conducted within 24 weeks of Cycle 1 Day 1, is acceptable as the Screening biopsy. If no such recent bone marrow biopsy is available, then a repeat biopsy will be required prior to enrollment in IVRS to receive induction therapy. During the treatment period (induction or maintenance) of the study, a bone marrow biopsy is required only if the subject had positive bone marrow at Screening and has otherwise fulfilled the criteria for a nodal CR. The bone marrow procedure should be performed within 28 days after the criteria for radiological CR have otherwise been met. The biopsy may be unilateral or bilateral at the discretion of the investigator.

6.1.6 Endoscopy and Gastric Biopsy

Subjects with MZL involving the gastric area will undergo endoscopy as part of the response assessment. Histological evaluation for subjects with MZL involving the gastric area (for staging) based on endoscopy and gastric biopsy (from stomach, duodenum, and gastroesophageal junction and from any abnormal-appearing site) is required during Screening. A recent histological evaluation, conducted within 12 weeks prior to C1D1, is acceptable as the Screening assessment. If no such recent evaluation is available, then gastric repeat biopsy and histological evaluation will be required for subjects with MZL involving the gastric area prior to enrollment in IVRS to receive induction therapy.

Subjects with MZL involving the gastric area will have a repeat gastric biopsy for histological evaluation if the subject has fulfilled the IWG criteria for response of at least a CR/CRu. For subjects achieving radiological CR/CRu, a biopsy performed at two separate time points within 3 months after the criteria for CR/CRu were first met is required to confirm response. Histological evaluation of the gastric biopsy will be performed by the local pathologist. The Groupe d' Etude des Lymphomes de l' Adulte (GELA) grading system (Copie-Bergman, 2003; Copie-Bergman, 2012) is suggested to be used in the pathologic assessment.

6.1.7 Central Nervous System Lymphoma

Subjects with current or past Central Nervous System (CNS) lymphoma involvement are excluded from the study. Subjects with suspicion of CNS involvement must undergo neurologic evaluation and CT or MRI of brain and a lumbar puncture to exclude active CNS disease.

6.1.8 Lenalidomide Dosing - Creatinine Clearance (Cockcroft-Gault Estimation)

To determine the dose of lenalidomide on C1D1, the Cockcroft-Gault estimation of creatinine clearance (CrCl) will be assessed at Screening by the local laboratory utilizing actual body weight (Cockcroft, 1976; Luke, 1990; Griggs, 2012) and will be recorded in the source documents and CRF. See also Section 6.2.10.

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

6.1.9 12-Lead Electrocardiogram

12-lead electrocardiogram (ECG) is performed at Screening and as clinically indicated thereafter.

6.1.10 Hepatitis B

Hepatitis B Screening is required for all subjects and includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) and hepatitis B surface antibody (anti-HBs). See exclusion criterion # 6 (Section 7.3) for further details. Eligibility for the study is based on the local HBV tests including if performed as standard of care within 4 weeks prior to enrollment in IVRS to receive induction therapy.

6.2 Safety Assessments

Serial assessments of safety will be performed as outlined in the Schedule of Study Assessments (Table 1).

Time to histological transformation will be measured based on documentation of histological transformation as assessed by the investigator. The date of the histology/pathology report will be used as the date of transformation. In case of clinical suspicion of transformation, including rapid disease progression, unexpected changes in "B" symptoms or rapidly increasing lactate dehydrogenase (LDH), a biopsy should be performed. In this clinical trial, histological transformation will be considered disease progression.

Subjects who relapse or progress will continue to be followed for SPMs for 5 years from the date of the last subject initiates induction therapy.

6.2.1 Adverse Events

Adverse events will be assessed and hospitalizations recorded from the signing of the informed consent form up to 28 days after the last dose of treatment with the exception of Second Primary Malignancies, see Section 6.2.2 below.

6.2.2 Second Primary Malignancies

Second primary malignancies are new cancers that are diagnosed in patients following a prior diagnosis of a first cancer. For the MAGNIFY trial, the primary (first) cancer is follicular grades 1-3b, transformed FL, marginal zone, or mantle cell lymphoma. Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to IP (study drug), occurring at any time for the duration of the study, from the time of signing the ICD for 5 years from the date the last subject initiates induction therapy. [redacted]

6.2.3 Birth Control and Lenalidomide Counseling

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 all females of childbearing potential (FCBP)[1] two pregnancy tests must be performed prior to the first dose of study drug: one test during Screening period (10 to 14 days prior to the first dose of lenalidomide) and one test within 24 hours prior to the first dose of lenalidomide. See the Pregnancy Prevention Plan for more details (standalone document).

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted on Day 1 of every lenalidomide treatment Cycle. All subjects must also be counseled against sharing lenalidomide and donating blood during and within 28 days of discontinuing

[1] Female of child-bearing potential definition: a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

protocol-specified therapy. Pregnancy tests for all FCBP will be performed weekly during the first Cycle, every 28 days (Day 1 of every Cycle) during treatment, at study discontinuation, and at Day 28 following study drug discontinuation. Additionally, for FCBP with irregular menstrual cycles pregnancy tests will be conducted weekly during the first 4 weeks of treatment and then every 14 days through 28 days following the last dose of lenalidomide. See the Pregnancy Prevention Plan for more details.

6.2.4 Study Drug Return/Accountability

The reconciliation of capsules will be done at the beginning of each Cycle and at treatment discontinuation. See Sections 8.4, 8.5, and 8.6 for more details.

6.2.5 Prior and Concomitant Medications, Procedures and Hospitalizations

Relevant prior and concomitant medications, procedures and hospitalizations will be collected from signing of informed consent through 28 days after the last dose of investigational product, and will be recorded in the source documents.

6.2.6 Physical Examination

The subject must have a physical examination performed within 4 weeks prior to the first day of treatment. The physical examination assessments should be repeated at the beginning of each Cycle, at treatment discontinuation and at any additional times as deemed necessary by the investigator. Investigators are required to report any clinically significant abnormal findings as AEs.

6.2.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status (see Appendix C) will be measured within 2 weeks prior to the first day of treatment. ECOG status will also be measured at treatment discontinuation. Investigators are to report any clinically significant abnormal findings as AEs.

6.2.8 B Symptoms

The B symptom assessment is to be performed at Screening, at treatment discontinuation, and at any additional times as deemed necessary by the investigator.

B symptoms are fever (>38°C), night sweats, and weight loss greater than 10% within the prior 6 months.

6.2.9 Vital Signs

Vital signs including height (at Screening only), weight, blood pressure, pulse, and temperature will be measured at the beginning of each Cycle, at treatment discontinuation and at designated times thereafter. Investigators are required to report any clinically significant abnormal findings as AEs.

6.2.10 Clinical Laboratory Safety Tests

The local laboratory will perform hematology and chemistry testing of Screening and on-study subject blood samples. Their results will be the basis for safety endpoint calculations.

If Screening labs are drawn within 1 week before receipt of study drug on C1D1, they do not need to be repeated on C1D1.

Clinical laboratory safety tests will include hematology, serum chemistry, and thyroid stimulating hormone (TSH) assessment according to standard laboratory procedures.

The principal investigator (PI) or medically-qualified designee will review and assess all clinical laboratory data. The laboratory reports should be initialed and dated by the PI or medically qualified designee, and the clinical significance of any abnormal laboratory results should be indicated. Abnormal laboratory results may be repeated to rule out laboratory errors. Any clinically-significant abnormal laboratory result should be reported as an AE and should be followed to resolution (ie, it returns to baseline or becomes clinically insignificant).

Additional clinical safety laboratory evaluations should be performed if judged clinically appropriate by the investigator or medically qualified designee, or if the ongoing review of the data suggests that a more detailed assessment of clinical laboratory safety evaluations is warranted.

6.2.10.1 Hematology

Hematology laboratory tests will include hemoglobin, hematocrit, white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count. Any circulating abnormal cells (tumor cells) will also be recorded as the absolute count.

Hematology laboratory tests should be done before administration of study drugs; when these are required on these visits per Schedule of Study Assessments (Table 1), the allowed window periods will be Day 1 (-3 days) of every treatment cycle, Day 8 (-1 day) and Day 15 (-1 day). Hematology tests will be required during the Screening Visit and Day 1 of every treatment Cycle (induction and maintenance period), Days 8 and 15 of Cycle 1, Day 15 of Cycles 2 and 3, and at treatment discontinuation.

Complete blood count (CBC), ANC, ALC and platelet count will be recorded in the CRF.

6.2.10.2 Serum Chemistry

Serum chemistry will include total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT) or serum glutamic pyruvate transaminase (SGPT), sodium, potassium, chloride, blood urea nitrogen, creatinine, and LDH.

Serum chemistry laboratory tests should be done before administration of study drugs; when these are required on these visits per Schedule of Study Assessments (Table 1), the allowed window periods will be on Day 1 (-3 days) of every treatment cycle, Day 8 (-1 day) and Day 15 (-1 day). Serum chemistry tests will be required during Screening and Day 1 of every treatment Cycle (induction and maintenance period), Days 8 and 15 of Cycle 1, Day 15 of Cycles 2 and 3, and at treatment discontinuation.

Calcium, phosphorus, uric acid, potassium, creatinine, total bilirubin, AST, ALT and LDH will be recorded in the CRF.

6.2.10.3 Thyroid Stimulating Hormone

Thyroid stimulating hormone (TSH) will be assessed at Screening and end of induction treatment or treatment discontinuation and thereafter as clinically indicated during the maintenance treatment period. Results of TSH testing will be recorded in the CRF.

6.2.11 Assessments for Tumor Flare

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

Tumor flare reaction (TFR) is defined in the NCI-CTCAE version 3.0 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 non-Hodgkin lymphoma (NHL) (Witzig, 2009), TFR has also been reported at a lower rate in NHL patients 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 in subjects with CLL. Manifestations include 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 of lenalidomide and occurs within the first 2 to 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 to 2 weeks with or without intervention (Witzig, 2009).

The experience with tumor flare in Celgene-sponsored studies of single agent lenalidomide in NHL is summarized. Over 400 subjects with relapsed or refractory aggressive or indolent non-Hodgkin lymphoma have received lenalidomide in four Phase 2 clinical studies. These 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 non-Hodgkin lymphoma, 49 subjects with relapsed/refractory aggressive NHL, and 217 subjects with relapsed/refractory aggressive NHL, respectively. These protocols suggested that any subject who experienced TFR during the first 1 to 2 weeks of Cycle 1 may be treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDS). TFR occurred in 4 subjects in the NHL-001 study (Grade 1 [n = 1] and Grade 2 [n = 3]), in none in the NHL-002 study; and in 7 of 217 subjects in the NHL-003 study (Grade 1 [n = 2], Grade 2 [n = 2 and Grade 3 [n = 3]). In a recent study evaluating lenalidomide as single agent in subjects with MCL (n = 134) who relapsed or progressed after or were refractory to bortezomib, TFR was reported in 13 subjects (10%) (Goy, 2013).

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

It is important to note that the increased lymphadenopathy seen in TFR may mimic PD. 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 the 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.

6.2.12 Assessments for Tumor Lysis

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. Three 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 study), 49 subjects with relapsed/refractory aggressive NHL (NHL-002 study), and 217 subjects with relapsed/refractory aggressive NHL (NHL-003 study). All three studies suggested that subjects receive tumor lysis prophylaxis (allopurinol or equivalent) and be well hydrated during the first 7 days of lenalidomide administration in the first Cycle or as clinically indicated. Grade 1 TLS occurred in 1 of the 309 (0.3%) subjects receiving lenalidomide. There was one subject with findings consistent with laboratory evidence of TLS in the MCL-001 study, a Phase 2 clinical trial of single agent lenalidomide in subjects with MCL (Goy, 2013).

In an investigator-initiated study, a single-center, open-label Phase 2 study, Dutia et al evaluated the use of lenalidomide and rituximab in subjects with relapsed or refractory indolent B-cell NHL

(Dutia, 2010). Two of the first four 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 recommended that subjects at risk for TLS receive prophylaxis (allopurinol, rasburicase, or equivalent as per institutional guidelines) during the first week of the first Cycle or as clinically indicated (see Section 9.3.1 for more information).

Tumor lysis syndrome assessments are conducted in Cycle 1 on Days 1, 8 (± 1 day), and 15 (± 1 day), and when clinically indicated thereafter. 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 (if subject is at risk) as instructed (see Section 9.3.1 for more details).

Severity grading for TLS should follow the Cairo-Bishop Grading System for TLS (Appendix D) rather than using the CTCAE version 4.03.

6.2.13 Deep Vein Thrombosis

6.2.13.1 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 single-agent lenalidomide. A significantly increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) has been observed in patients with multiple myeloma who were treated with lenalidomide and dexamethasone therapy (Revlimid PI, 2014). Clinical data in multiple myeloma patients treated with lenalidomide suggests that concomitant administration of gluco-corticosteroids or erythropoietin can increase the thrombotic risk. Male gender and smoking history have also been reported to increase the risk of VTE in myeloma patients treated with lenalidomide (Leleu, 2011).

In the two pivotal randomized studies (MM-009 and MM-010) a significantly increased risk of DVT and PE was seen in subjects with multiple myeloma who were treated with REVLIMID® (lenalidomide) in combination with dexamethasone (Celgene, 2014). In these pivotal trials for REVLIMID® (lenalidomide) in subjects with multiple myeloma receiving lenalidomide plus dexamethasone, deep venous thrombosis and pulmonary embolism were reported in the lenalidomide plus dexamethasone arm at a rate of 7.4% and 3.7% of subjects respectively, compared to 3.1% 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 that thromboembolic events were significantly higher in subjects treated with lenalidomide/dexamethasone in the absence of prophylactic use of an anticoagulant ($p < 0.001$) (Dimopoulos, 2009). The effect of adding erythropoietin to lenalidomide/dexamethasone demonstrated a higher, but not statistically significant rate of thrombosis in the erythropoietin group, 18% versus 10% for the lenalidomide/dexamethasone group without the addition of erythropoietin ($p = 0.14$) (Weber, 2007). The ECOG trial (E4A03) evaluated lenalidomide 25 mg on Days 1 to 21 plus high-dose dexamethasone 40 mg on Days 1 to 4, 9 to 12, and 17 to 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, 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.

More recently, Palumbo et al. (Palumbo, 2012) published results from an international multi-center phase 3 pivotal trial in patients administered lenalidomide maintenance therapy following melphalan, prednisone, and lenalidomide induction therapy (MPR+R) versus. patients receiving MPR or MP induction therapy only. In this trial, the incidence of Grade 3 or 4 deep-vein thrombosis was 3% in the lenalidomide-containing induction treatment groups of the trial and 1% in the control group treated with melphalan-prednisone induction. During the maintenance phase of MPR-R, the incidence of new or worsened grade 3 or 4 adverse events was low (0 to 6%). Deep-vein thrombosis was reported in 2 patients (2%) in the MPR-R group and 1 (1%) in the MPR group;

6.2.13.2 Deep Vein Thrombosis in Non-Hodgkin Lymphoma

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

Venous thromboembolism including DVT and PE, has been reported in patients during treatment for NHL generally, 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 lymphoma (HG-NHL) 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.

In lenalidomide clinical trials, DVT and PE were reported in 7 (2.6%) and 6 (2.2%) of 266 subjects with relapsed or refractory aggressive NHL receiving lenalidomide in clinical studies NHL-002 and NHL-003 (Wiernik, 2008; Witzig, 2011) and in 5 (4%) and 3 (2%) of 134 subjects with relapsed or refractory MCL receiving lenalidomide in the clinical study MCL-001 (Goy, 2013). 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 was required for subjects considered to be high risk of developing DVT in NHL-003. In the recent CALGB study evaluating lenalidomide plus rituximab versus lenalidomide single agent therapy in relapsed FL subjects (N = 89), thrombosis was reported in 2 (4%) of 44 subjects in the lenalidomide plus rituximab arm versus 7 (16%) of 45 subjects in the lenalidomide arm (Leonard, 2012). In a study evaluating lenalidomide plus rituximab in relapse refractory MCL subjects (n = 44), three thromboembolic events were reported (2 [5%] grade 3; 1 [5%] Grade 4) after 379 Cycles of lenalidomide plus rituximab (Wang, 2012).

It cannot be excluded 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 strongly recommended that all subjects at risk receive anti-thrombotic prophylaxis, and all subjects will be closely monitored for VTE, see Section 9.1.2.

6.3 Efficacy Assessments

Radiological assessments for efficacy will be CT scan or MRI, to confirm the presence of measurable disease of > 1.5 cm in the transverse diameter at baseline. A CT is to be performed with contrast unless it is medically contraindicated. The regions to be imaged can be the neck, chest, and abdomen/pelvis, as well as any other regions clinically indicated for tumor imaging. The same imaging modality and regions for lesion evaluation at Screening must be consistently used throughout the study. CT/MRI scan performed for the purpose of standard of care may be used as the Screening CT scan if it is obtained within 8 weeks prior to C1D1.

All CT or MRI scan assessments will be determined from first dose date and will follow the counting of the dosing Cycles (ie, 1 cycle = 28 days). It is critical that the same modality used at Screening be used throughout the study for each subject. The scans must be performed:

- At 3 cycles after C1D1 (84 days ± 2 weeks)
- At 6 cycles after C1D1 (168 days ± 2 weeks)
- then every 6 cycles (168 days ± 2 weeks) for 5 years
- and annually (± 3 weeks) thereafter until disease progression, relapse, or initiation of new anti-lymphoma therapy
- After the confirmation of the 114 PFS events, no efficacy assessments will be conducted

A subject with positive bone marrow at Screening will have a repeat bone marrow biopsy to confirm radiological CR only if the subject has otherwise fulfilled the criteria for a nodal CR; this bone marrow biopsy should be performed within 28 days after the criteria for CR have otherwise been met.

In addition to CT/MRI scan to assess disease, subjects with MZL involving the gastric area will undergo endoscopy as part of the response assessment. Subjects will have a repeat gastric biopsy for histological evaluation if the subject has fulfilled the IWG criteria for response of at least a CR/CRu. Histological evaluation will be performed by local pathologies laboratories using the GELA grading system (Copie-Bergman, 2003; Copie-Bergman, 2012; see also Section 6.1.6).

All enrolled subjects are followed for PD or relapse using the schedule described in Table 1.This includes subjects who discontinue treatment for any reason without documented evidence of PD or relapse. Subjects who start a new anti-lymphoma therapy without evidence of PD or relapse will not be followed by radiological assessments.

Since the study endpoint is PFS based on CT, 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) and other assessments will be made according to a modification of the IWG 1999 criteria (Cheson, 1999), which are considered the primary method of response assessment. Scan results will be assessed by the Investigator or qualified site personnel. The modifications to the Cheson 1999 criteria are:

- Allow the inclusion of extranodal disease as measurable disease, as long as they fulfill all other requirements of measurable disease, including >1.5 cm in the longest transverse diameter.
- > 2.0 cm bone marrow biopsy length is not required if the biopsy sample is considered adequate for assessment by the investigator.
- Gastric MALT subjects are required to undergo an additional evaluation of endoscopy and gastric biopsy at 2 time points within 3 months of radiologic evaluation demonstrating CR/CRu.
- PET scan is not considered part of the response criteria.

A similar modification to include extranodal disease as a measurable disease has been used previously (Fisher, 2006; Kane, 2007). The additional assessments – clinical assessments, bone marrow biopsy assessments, and endoscopic assessments (including biopsy) – are considered confirmatory to the initial CT scan findings. Bone marrow assessments are considered in the response assessment only in subjects with bone marrow involvement in the baseline bone marrow biopsy. Endoscopic biopsy and evaluation of the biopsy findings are required for confirmation of response only in subjects with an investigator-assessed pathologic diagnosis of MZL involving the gastric area. 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.

Subjects who relapse or progress will continue to be followed for TTNLT and survival for 5 years from the date of the last subject initiating induction therapy.

6.3.1 Subsequent Anti-lymphoma Therapy

In the Follow-up Period, [redacted] for subsequent anti-lymphoma therapy. The date of first documented administration of a new anti-lymphoma treatment regimens following discontinuation from the study treatment will be recorded. After the confirmation of 114 PFS events, there will be no assessment of subsequent anti-lymphoma therapy.

[redacted]

7 STUDY POPULATION

Subjects must have an investigator-assessed diagnosis of Grade 1, 2,3a, 3b FL, transformed FL, MZL, or MCL Stage I to IV, must have been previously treated for their lymphoma, must be refractory or must have relapsed after their last treatment, must have at least one measurable nodal or extranodal lesion by CT or MRI scan, and must have adequate bone marrow function, liver function and renal function.

7.1 Number of Subjects and Sites

Approximately 500 subjects in the USA are planned to be enrolled in this study. Celgene Corporation will select approximately fifteen (15) sites within Germany. Subject enrollment will include approximately 50 subjects in Germany collectively.

7.2 Inclusion Criteria

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

1) Males and females ≥ 18 years old at the time of signing the informed consent document
2) Histologically confirmed FL (Grade 1, 2, 3a, or 3b), transformed FL, MZL, or MCL by WHO 2008 classification (Jaffe, 2009) as assessed by the investigator or local pathologist
3) Must have been previously treated with at least one prior treatment for lymphoma including radiotherapy, chemotherapy, immunotherapy, chemoimmunotherapy, or novel agent.
4) Must have documented relapsed, refractory or PD after last treatment
   a) Relapsed lymphoma: defined as subject who relapsed after initial response of CR to prior therapy
   b) Progressive lymphoma: defined as subject who progressed after initial response of PR or SD to the prior therapy
   c) Refractory lymphoma: defined as subjects who received therapy and who experienced a best response of PD
   d) Subjects with gastric MALT lymphoma and evidence of *H. pylori* infection must have documented non-response to antibiotic therapy as judged by a minimum follow-up of 12 months after successful *H. pylori* -eradication
   e) Subjects who are rituximab-refractory (defined as a subject who experienced a best response of PD or SD to treatment with rituximab or a rituximab-containing regimen OR a response (PR or CR) lasting fewer than 6 months following the last rituximab dose) are eligible
5) Bi-dimensionally measurable disease on cross sectional imaging by CT or MRI with at least one lesion > 1.5 cm in the transverse diameter, as defined by a modification of the IWG 1999 criteria (Cheson, 1999; see Section 6.3). Measurable disease cannot be previously irradiated
6) Must be in need of treatment for relapsed or refractory disease as assessed by the investigator
7) Performance status < 2 on the ECOG scale (Appendix C)

8) All females of childbearing potential (FCBP)[2] must:
   a) Have two negative pregnancy tests as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence3 from heterosexual contact
   b) Either commit to true abstinence[3] 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), and for 28 days after discontinuation of study therapy
9) Male subjects must:
   a) Must practice true abstinence[3] 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
10) 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 drug 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 study drug discontinuation
11) Understand and voluntarily sign an informed consent document prior to any study-related assessments/procedures being conducted
12) Able to adhere to the study visit schedule and other protocol requirements

7.3 Exclusion Criteria

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

1) Presence or history of CNS involvement by lymphoma
2) Any medical condition (other than the underlying lymphoma) that requires chronic steroid use
3) Subjects taking corticosteroids during the last 1 week prior to C1D1, unless administered at a dose equivalent to < 20 mg/day of prednisone (over this week)
4) Major surgery (excluding lymph node or bone marrow biopsy) within 28 days prior to signing informed consent

[2] See definition in 6.2.3.
[3] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. (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 Day 1 dosing or use of the following prior to Day 1 dosing:
   a) Antibody agents within 4 weeks
   b) Radioimmunotherapy within 3 months
6) Seropositive for or active viral infection with hepatitis B virus (HBV):
   - HBsAg positive
   - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA

     Note: Subjects who are HBsAg negative, anti-HBs positive, and/or anti-HBc positive, but viral DNA negative are eligible
   - Subjects who are seropositive because of HBV vaccination are eligible (HBV surface antibody positive, HBV core antibody negative, and HBV surface antigen negative)
7) Known seropositive for or active infection with hepatitis C virus (HCV), including positive HCV RNA
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 (rituximab)
11) Prior history of invasive malignancies, other than FL, transformed FL, MZL or MCL unless the subject has been free of the disease for ≥ 5 years. Exceptions include a history of previously treated:
   a) Localized non-melanoma skin cancer
   b) Carcinoma in situ of the cervix
   c) Carcinoma in situ of the breast
   d) Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)
12) Prior use of lenalidomide
13) Known allergy to thalidomide
14) Neuropathy > Grade 2
15) Subjects who are at a risk for a thromboembolic event and are not willing to take VTE prophylaxis
16) Any of the following laboratory abnormalities during Screening period:
   a) Absolute neutrophil count (ANC) < 1.5 x 109/L unless secondary to bone marrow involvement by lymphoma as demonstrated by recent bone marrow aspiration and bone marrow biopsy
   b) Platelet count <75 x 109/L unless secondary to bone marrow involvement by lymphoma as demonstrated by recent bone marrow aspiration and bone marrow biopsy
   c) Hemoglobin < 8.0 g/dL (5 mmol/L) unless secondary to bone marrow involvement by lymphoma as demonstrated by recent bone marrow aspiration and bone marrow biopsy
   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) Total bilirubin > 2.0 mg/dl (34 µmol/L) except in cases of Gilberts Syndrome and documented liver or pancreatic involvement by lymphoma
f) Creatinine clearance of < 30 mL/min

17) Uncontrolled intercurrent illness including, but not limited to:
a) Uncontrolled diabetes mellitus as assessed by the investigator
b) Chronic symptomatic congestive heart failure (Class III or IV of the New York Heart Association Classification for Heart Disease
c) Unstable angina pectoris, angioplasty, stenting, or myocardial infarctions within 6 months
d) Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia. Subjects with controlled atrial fibrillation that is asymptomatic are eligible.

18) Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form and participating in the study

19) Any condition including the presence of laboratory abnormalities, that places the subject at unacceptable risk if he/she were to participate in the study

20) Any condition that confounds the ability to interpret data from the study

21) Pregnant or lactating females

8 DESCRIPTION OF STUDY TREATMENTS

8.1 Description of Investigational Product(s)

Investigational products in this study are lenalidomide and rituximab.

Celgene Corporation will supply lenalidomide 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg capsules for oral administration. Subjects will receive treatment with lenalidomide for 21 days per Cycle.

Study drug will be packaged in bottles containing study capsules for days 1 - 21 of every 28 day Cycle.

Commercially available intravenous (IV) formulation of rituximab may be used.

In Germany, Celgene Corporation will supply both lenalidomide capsules and rituximab intravenous formulation as investigational products.

8.2 Treatment Administration and Schedule

Eligible subjects entering the Induction Treatment Phase will be enrolled using an Interactive Voice Response System (IVRS). Subjects entering the Maintenance Phase will be randomized using the IVRS into one of two arms (experimental or control) in a 1:1 ratio. Randomization will be stratified as described in Section 8.3. Subjects randomized under previous protocol (version 16 January 2014) who achieve a response of SD or better at the end of the Induction Treatment Period will remain in their originally assigned arm of maintenance therapy.

Study Treatments, please see Sections 8.2.1 and 8.2.2 for details

- Induction Period (12 Cycles)

  Lenalidomide 20 mg (10 mg if creatinine clearance ≥ 30 mL/min but < 60 mL/min) once daily on Days 1 to 21 of every 28-day Cycle for Cycles 1 to 12 **AND** rituximab 375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15, and 22) and Day 1 of every 28-day Cycle for Cycles 3, 5, 7, 9, and 11

  Followed by Maintenance Period

- **Arm A (Experimental arm)**: Lenalidomide + rituximab (Maintenance) followed by optional lenalidomide (Maintenance)
  - Maintenance Period (18 Cycles)

    Lenalidomide 10 mg once daily on Days 1 to 21 of every 28-day Cycle for Cycles 13 to 30 AND rituximab 375 mg/m2 on Day 1 of every 28-day Cycle for Cycles 13, 15, 17, 19, 21, 23, 25, 27, and 29

  Followed by

  - Optional Maintenance Period (up to PD)

    Lenalidomide 10 mg once daily on Days 1 to 21 of every 28-day Cycle up to PD. This treatment will be at the discretion of the subject and the investigator.

  VERSUS

- **Arm B (Control arm)**: Rituximab (Maintenance)
  - Maintenance Period (18 Cycles)

    Rituximab 375 mg/m2 on Day 1 of every 28-day Cycle for Cycles 13, 15, 17, 19, 21, 23, 25, 27, and 29

Induction treatment must begin no later than 1 week after enrollment in IVRS to receive induction therapy. The Treatment Period for each subject starts with first intake of study drug, which is defined as Day 1 of Cycle 1.

8.2.1 Lenalidomide Therapy

Lenalidomide dosing will be based on a subject's creatinine clearance calculated using the Cockcroft-Gault formula and actual body weight. This calculation will be performed at Screening by the local laboratory utilizing actual body weight.

- Subjects who have a creatinine clearance ≥ 60 mL/min will receive oral lenalidomide at a dose of **20 mg** once daily on Days 1 to 21 in each 28-day Cycle. A minimum 7-day rest period following the 21 days of dosing is mandatory regardless of the allowed visit windows.
- Subjects who have moderate renal insufficiency (creatinine clearance ≥ 30 mL/min but < 60 mL/min) will receive a lower starting dose of lenalidomide of **10 mg** once daily on Days 1 to 21 of the 28-day Cycle in Cycle 1 and in Cycle 2. A minimum 7-day rest period following the 21 days of dosing is mandatory regardless of allowed visit windows. 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.
- Subjects who have renal insufficiency (creatinine clearance < 30 mL/min) are to be excluded from the study.

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

Lenalidomide may be administered until disease progression; therefore, there is no need to "make up" a missed dose due to a transient toxicity. If a delay for toxicity occurs during planned treatment days, subjects should skip those days and either restart drug immediately after the toxicity resolves or finish the mandatory seven-day rest period, as appropriate. If a delay for toxicity extends the rest period beyond 7-days, the next dose of drug should begin a new Cycle.

8.2.2 Rituximab Therapy

The planned dose of rituximab is **375 mg/m^2** every week in Cycle 1 (Days 1, 8, 15, and 22) and on Day 1 of every other 28-day Cycle up to 30 Cycles (3, 5, … 29). Premedication should be administered (see Rituximab PI and Section 9.3.2). The infusion should be according to instructions in the package insert and institutional guideline.

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 information for further information on rituximab therapy including guidance on pregnancy restrictions.

8.2.3 Lenalidomide Therapy in Maintenance

The planned dose of lenalidomide during the Maintenance Therapy Period is **10 mg** once daily on Days 1 to 21 of a 28-day Cycle. A minimum 7-day rest period following the 21 days of dosing is mandatory regardless of allowed visit windows.

- Subjects who have undergone dose reduction for adverse events during the Induction Period (first 12 Cycles) and are receiving lenalidomide at a dose **less** than **10 mg** will continue at their current dose during maintenance. No dose increase will be permitted.

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 drug(s) causing the toxicity.

8.2.4.1 Overdose

Overdose as defined for this protocol, refers to lenalidomide and rituximab. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of these drugs assigned to a given subject, regardless of any associated adverse events or sequelae:

Per oral	any amount over the protocol-specified dose
Intravenous	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.

See Section 11.1 for the reporting of adverse events associated with overdose.

8.2.4.2 Dose Modification or Interruption for Lenalidomide

The dose of lenalidomide for each subject will be interrupted and modified following toxicity as described in Table 2. Refer to Table 3 and Table 4 (and Table 5 for the maintenance period) for dose reduction instructions for study drug; the dose may also be reduced for reasons in addition to those listed in Table 2 per investigator discretion. If a dose is reduced, re-escalation is not permitted unless discussed with Celgene Medical Monitor.

If a subject experiences an AE that requires a dose interruption, the subject cannot be re-started on study drug 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 [and Table 5 for the maintenance period] 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 for that next Cycle once the AE has resolved and the requirements detailed below have been met.

The new Cycle of treatment may begin on the scheduled Day 1 of the next Cycle once a 7-day rest period has occurred and if:

- 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).
- Lenalidomide-related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity.
- Any other lenalidomide-related AE not requiring discontinuation has resolved to ≤ Grade 2 severity.

If these conditions are not met on Day 1 of a new Cycle, the subject will be evaluated at least once every seven days and a new Cycle of study drug will not be initiated until the toxicity has resolved as described above. If a new Cycle is delayed for more than 28 consecutive days (counting begins following the mandatory 7-day rest period), the Medical Monitor must be notified. The treatment can be resumed according to the treating physician and could be discussed with the Medical Monitor.

The study assessments should remain in line with dosing days (the actual number of days that lenalidomide plus rituximab has been administered) but the tumor assessments will be determined from C1D1 and will follow the counting of the dosing Cycles, ie, 28-day cycles.

Table 2: Dose Modification for Lenalidomide

NCI CTCAE Toxicity Grade[a]	ACTION REQUIRED
Grade 3 neutrophil count decreased (neutropenia) (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 ≥ 38.5º 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 [50 x 10^9/L])	• Hold (interrupt dose) • Follow CBC weekly • If thrombocytopenia resolves to ≤ Grade 2 restart at next lower dose level

Table 2: Dose Modification for Lenalidomide

NCI CTCAE Toxicity Grade[a]	ACTION REQUIRED
Rash Grades 1-2	• Determine the causative study drug(s) • Start supportive measures[b] if Grade 2 • No dose adjustment
Grade 3 (Non-desquamating or non-blistering)	• Hold (interrupt dose) • Start supportive measuresb • Evaluate at least weekly • If rash resolves to ≤ Grade 1 restart at next lower dose
Grade 4[c]	• Discontinue lenalidomide • Dermatology evaluation • Consider supportive measuresb
Desquamating (blistering) rash Any Grade[c]	• Discontinue lenalidomide • Dermatology evaluation • Consider supportive measuresb
Stevens-Johnson Syndrome or Toxic epidermal necrolysis	• Discontinue lenalidomide • Dermatology evaluation
Allergic reaction or hypersensitivity Grade 2	• Determine the causative study drug(s) • Hold (interrupt) dose. Follow at least every seven days • When the toxicity resolves to ≤ Grade 1 restart at next lower dose level
Grades 3-4	• Discontinue lenalidomide
Constipation Grades 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
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.

Table 2: Dose Modification for Lenalidomide

NCI CTCAE Toxicity Grade[a]	ACTION REQUIRED
Tumor Flare Reaction (TFR)[a] Grades 1-2	• Continue lenalidomide, maintain dose level • At the investigator's discretion may initiate therapy with NSAIDs, limited duration corticosteroids, and/or narcotics
Grades 3-4	• Hold (interrupt dose) and initiate therapy with NSAIDs, corticosteroids, and/or narcotics • When symptoms resolve to ≤ Grade 1, restart at same dose level for the rest of the Cycle
Laboratory TLS or Grade 1 TLS	• Continue lenalidomide (maintain dose), or at the investigator's discretion, continue lenalidomide 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
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

Table 2: Dose Modification for Lenalidomide

NCI CTCAE Toxicity Grade[a]	ACTION REQUIRED
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 at the same dose • If hyperthyroidism confirmed and alternative etiologies eliminated, restart lenalidomide dosing at next lower dose
Liver Function[d]	
ALT Grade 2 (>3 - 5 x ULN) **and** Total bilirubin Grade 1 (> ULN - 1.5 x ULN)	• Continue study drug: re-test at next scheduled visit • No dose modification
ALT ≥ 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, perform weekly testing of liver functions during that Cycle and then decrease the dose by one level when recovered (returned to baseline)
Cairo-Bishop Toxicity Grade (see Appendix D)	
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

Notes: AE: Adverse Event; ALT: alanine aminotransferase; ASCO: American Society of Clinical Oncology ; CBC: Complete Blood Count; ESMO: European Society for Medical Oncology; G-CSF: Granulocyte Colony-Stimulating Factor; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; LLN: lower limit of normal; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID: non-steroidal anti-inflammatory drugs; PO: Per Oral; QAM: every morning; QPM: every evening; TFR: Tumor Flare Reaction; TLS: Tumor Lysis Syndrome; TSH: Thyroid stimulating hormone; ULN: upper limit of normal.

[a] AEs are Graded using the NCI CTCAE vrsion 4.03; however TFR will be graded using NCI CTCAE version 3.0. Severity grading for TLS should follow the Cairo-Bishop Grading System for TLS (Appendix D) (not CTCAE version 4.03).

[b] Suggested supportive measures - 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 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 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.

8.2.4.3 Dose Reduction Levels Based on Lenalidomide Starting Dose

The daily dose of lenalidomide 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.

Note, rituximab dosing should continue as per protocol even if lenalidomide has been discontinued due to toxicity.

Subjects who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase.

For subjects with a starting dose of 20 mg 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 (a decrement of 5 mg; refer to Table 3) at the next treatment Cycle if toxicity requiring dose modifications (as in Section 8.2.4.2) 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 (Days 1 to 21 of 28 days) in Cycle 1 and 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
- The daily oral dose of study drug may be reduced successively by one level in response to an event of toxicity as described in Table 2

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 unless discussed with medical monitor.

[b] Subjects who cannot tolerate Dose Level 4 are to be discontinued from the Treatment Period 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 Day Cycles
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 to 21 of each 28 day Cycle at the discretion of the treating physician from Cycle 3 onwards.

[a, b] Once the dose is escalated to 15 mg once daily for 21 days every 28 days, the 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 unless discussed with medical monitor.

[c, d] Subjects who cannot tolerate Dose Level 3 are to be discontinued from the Treatment period of the study.

8.2.4.4 Dose Reduction Levels Based on Lenalidomide Maintenance Starting Dose

The daily dose of lenalidomide in maintenance may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction from one Cycle to the next unless otherwise permitted after consultation with the medical monitor. No dose (re)escalation is permitted at any time.

Subjects who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase.

The daily oral dose of study drug shall be reduced by one level (refer to Table 5) at the next treatment Cycle if toxicity requiring dose modifications (as in Section 8.2.4.2; Table 2) has occurred during the previous treatment Cycle.

Table 5: Dose Reduction Steps for Adverse Events Related to Study Drug for Subjects Initiating Maintenance Treatment at 10 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)	**10 mg daily on Days 1-21, every 28 days**
Level 2[a]	5 mg daily on Days 1-21, every 28 days
Level 3[a]	2.5 mg daily on Days 1-21, every 28 days
Level 4[a, b]	2.5 mg every **other** day on Days 1-21, every 28 days

[a] Once a subject's dose has been reduced, no dose re-escalation will be permitted unless discussed with medical monitor.

[b] Subjects who cannot tolerate Dose Level 4 are to be discontinued from the Treatment Phase of the study.

8.2.4.5 Dose Adjustment for Rituximab

The dose of rituximab will be interrupted and modified according to the clinical practice of the investigator's institution, and in line with the approved prescribing information, including administration, warnings, precautions, contraindications, and adverse reactions, as applicable.

In case a dose is missed during the Cycle because of toxicity, it will not be rescheduled. In case of delay in the start of the next Cycle due to toxicity, rituximab of the next Cycle will be postponed until the AE has resolved, at which point the next Cycle is started.

8.3 Method of Treatment Assignment

Enrollment into the Induction Treatment Period will occur in the Screening Period, once all the required Screening procedures have been completed and subject meets all eligibility criteria, and all required data have been submitted to the IVRS/ Interactive Web Response System (IWRS) system. Upon completion of 12 cycles of induction therapy and achieving a response of PR or CR/CRu or having SD, the maintenance treatment will be randomly assigned using the IVRS. Subjects randomized under previous protocol (version 16 January 2014) who achieve a response of SD or better at the end of the Induction Treatment Period will remain in their originally assigned arm of maintenance therapy.

- Subjects will undergo randomization in a 1:1 ratio to either Arm A (maintenance therapy as rituximab plus lenalidomide followed by optional lenalidomide) or Arm B (maintenance therapy as rituximab). The randomization procedure will be accomplished by a validated interactive voice response system (IVRS/IWRS).
- Randomized subjects will be stratified by:
  - Histology (FL (grades 1-3b and transformed FL) versus MZL versus MCL)
  - Lines of anti-lymphoma therapy (≤ 2 vs. > 2 lines)
  - Age (< 65 vs. ≥ 65 years)

8.4 Packaging and Labeling

Lenalidomide will be packaged in bottles and each bottle will contain 21 capsules.

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

In Germany, rituximab intravenous formulation packaging and label will be provided as investigational product.

8.5 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 and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

8.6 Investigational Product Compliance

For the oral medication lenalidomide, 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, the reconciliation of capsules will be done at the beginning of each Cycle and at treatment discontinuation.

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 prescription and over-the-counter medications, treatments and therapies which are related to an adverse event or are clinically relevant from 28 days prior to the start of the study drug through the last dose of study drug must be recorded on the appropriate page of the CRF.

9.1.1 Tumor Flare Reaction 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 in 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. The decision by the investigator to take prophylactic measures should be made carefully after an assessment of an individual subject's underlying risk factors.

As reference information, for subjects receiving lenalidomide in open-label trials, it is strongly recommended that subjects with VTE risk receive either aspirin (70 – 325 mg PO 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 International Normalized Ratio [INR] of 2.0). 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

Growth factors (e.g., G-CSF, erythropoietin) 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 administered during the Screening Period to increase a subject's blood values in order to meet entry criteria and 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 or equivalent) is prohibited during the Treatment Phase. For subjects receiving systemic corticosteroids at doses above 20 mg/day (prednisone 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 or equivalent) are allowed for the treatment of TFR at any time, for rituximab cytokine release syndrome prophylaxis with each rituximab infusion on Cycle 1 Day 1, 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.

9.3 Required Concomitant Medications and Procedures

9.3.1 Tumor Lysis Syndrome Prophylaxis

All subjects at risk for TLS should receive TLS prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of the first Cycle or as clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for TLS, the subjects will have 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 per investigator discretion. Any subject contact that is made on Day 5 (± 1 day) should be documented in the subject's medical record, and any AEs that are discovered should be captured on the CRF. TLS will be assessed by the Cairo-Bishop Grading system (see Appendix D).

9.3.2 Rituximab Premedication

Premedication consisting of acetaminophen and an antihistamine should be administered before each rituximab infusion (see package insert). 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 and infusion rate should be applied as recommended by the manufacturer/current guidelines.

10 STATISTICAL ANALYSES

10.1 Overview

The objective of the statistical analyses is to compare the efficacy and safety of lenalidomide plus rituximab combination maintenance therapy (for 18 cycles) followed by optional lenalidomide single-agent maintenance (to progression) versus rituximab single-agent maintenance (for 18 cycles) after 12 cycles of induction therapy with lenalidomide plus rituximab in subjects with relapsed/refractory follicular lymphoma grades 1-3b, transformed follicular lymphoma, marginal zone lymphoma, or mantle cell lymphoma.

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

10.2 Study Population Definitions

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

Intent-to-treat (ITT) population: The ITT population is defined as all subjects who are randomized and have received at least one dose of maintenance therapy.

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

1) are randomized
2) have received at least one dose of maintenance therapy
3) have confirmed diagnosis of relapsed/refractory FL grades 1-3b, transformed FL, MZL, or MCL
4) have SD, PR or CR/CRu after completing induction therapy
5) have at least one tumor assessment for efficacy after beginning of maintenance therapy

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 drug, including induction therapy. The safety population will be used for all safety analyses. For safety analysis of the maintenance period, subjects will be analyzed according to the treatment that they actually received.

Induction Efficacy Population: The Induction Efficacy Population is defined as all subjects who meet all of the criteria for eligibility into the study. [redacted]

[redacted]

10.3 Sample Size and Power Considerations

The main objective of the study is to demonstrate the efficacy of lenalidomide plus rituximab maintenance therapy followed by the optional lenalidomide single-agent maintenance versus the rituximab single-agent maintenance. The primary endpoint is PFS, which is defined as the time from the first dose date of maintenance therapy to objective disease progression or death from any cause, whichever occurs first.

To fulfill the primary objective of the study, it must be shown that the experimental arm (Arm A) is superior to the control arm (Arm B) on the primary endpoint at a one-sided $\alpha = 0.025$ level. It is hypothesized that the median PFS from the first dose date of maintenance therapy is [redacted] in Arm A and [redacted] in Arm B for FL (grades 1-3b and transformed FL) and MZL subjects, and that the median PFS from the first dose date of maintenance therapy is [redacted] in Arm A and [redacted] in Arm B for MCL subjects (about 10% are MCL subjects) (corresponding to a hazard ratio of [redacted] for all histologies). The sponsor may make a determination to close entry to one or more histologies if enrollment is skewed or oversubscribed. For 80% power to detect this difference with a one-sided $\alpha = 0.025$, a total of 191 PFS events that happen after the first dose date of maintenance therapy would have been required.

Based on the rate of accrual anticipated in this study, and an annual dropout rate of 5%, it was planned to enroll a total of 500 subjects to the induction treatment phase. It was projected that approximately 314 subjects would have been randomized at a ratio of 1:1 into the two maintenance treatment arms based on an estimated response rate of the induction therapy (Wang, 2012; Leonard, 2012). It was expected that the 191 PFS events that occur after the first dose date of maintenance therapy would have been available in about 57 months from the first dose date of maintenance therapy, and the total study duration from the beginning of induction period would have been about 69 months.

[redacted]. The primary efficacy endpoint is planned now at 114 PFS events. The expected accrual duration for 500 subjects is approximately 63 months. The study duration to events for primary analysis is estimated to be 105 months. The duration of the entire study will be approximately 10 years (accrual period of approximately 5 years plus 5 years from last subject initiating induction therapy).

Assuming a hazard ratio (HR) of [redacted], the power is about 57.9%. If HR is 20% better than originally assumed, ie, HR = 0.533, the power would be 92%.

Sample size was calculated using the East® Version 6.5 software system (Cytel Inc., 675 Massachusetts Avenue, Cambridge, MA 02139, http://www.cytel.com).

10.4 Background and Demographic Characteristics

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

10.5 Subject Disposition

Subject disposition (analysis population allocation, randomization status, discontinuation of treatment, primary reason for early treatment discontinuation, discontinuation of study, and primary reason for early study discontinuation) will be summarized using frequency and percentage for all enrolled subjects. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6 Efficacy Analysis

All efficacy analyses will be performed on the ITT population. Efficacy analyses will also be performed on the mITT population as supportive evidence and to assess robustness of efficacy findings. Subjects will be analyzed according to randomized treatment group.

10.6.1 Primary Efficacy Endpoint

Progression-free Survival

The primary efficacy endpoint for the study is PFS, which is defined as the time from the first dose date of maintenance therapy to objective disease progression or death from any cause, whichever occurs first. The PFS events will be determined using a modification of the IWG 1999 criteria (Cheson, 1999).

Subjects who did not experience disease progression and who did not die before the clinical data cut-off date will be censored at the time of the last visit with adequate response assessment when the subjects were known not to have progressed. Subjects who received new anticancer therapy without objective disease progression will be censored at the date of the last radiological assessment prior to the new anticancer therapy.

The primary efficacy endpoint will be compared between the two treatment arms when 114 PFS events that happen after the first dose date of maintenance therapy are observed.

10.6.2 Secondary Efficacy Endpoint

Secondary efficacy endpoints will include OS, IOR, ORR, CRR, DOR, DOCR, TTNLT and TTHT.

Overall Survival

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

Overall survival information will be collected for 5 years from the date of the last subject initiating induction therapy. The additional OS data may be analyzed as supplementary information. No formal hypothesis testing will be performed post the final primary endpoint analysis.

Improvement of Response

Improvement of response is defined as the proportion of subjects who have improved their tumor response during the maintenance phase, that is, the proportion of subjects who are converted from PR at the end of induction period to CR/CRu as best response, and subjects who are converted from SD at the end of induction period to PR or better as best response during the maintenance phase.

Overall Response Rate

Overall response will be analyzed in two aspects. The overall response rate at the end of 18 cycles of maintenance therapy is defined as the proportion of subjects with a response of at least PR (including CR, Cru, and PR) by the end of 18 cycles of maintenance therapy and prior to any treatment change.

In addition, best ORR, defined as the proportion of subjects with a best response of at least PR (including CR, CRu and PR) after the first dose date of maintenance therapy and prior to any treatment change, will also be presented.

Complete Response Rate

Complete response will also be analyzed in two aspects. The complete response rate at the end of 18 cycles of maintenance therapy is defined as the proportion of subjects with a response of at least CRu (including CR and CRu) by the end of 18 cycles of maintenance therapy and prior to any treatment change.

In addition, best CRR, defined as the proportion of subjects with a best response of at least CRu (including CR and CRu) after the first dose date of maintenance therapy and prior to any treatment change, will also be presented.

Duration of Response

Duration of response is defined only for subjects who have achieved PR or better after the first dose date of maintenance therapy and prior to any treatment change. It is calculated as the time from the initial response (at least PR) after the first dose date of maintenance therapy and prior to treatment change to documented disease progression or death.

Subjects who have not progressed or died at the time of the clinical data cutoff date will be censored at the last assessment showing no progression. Subjects who change treatment without evidence of disease progression will be censored at the last assessment showing no progression prior to treatment change.

Duration of Complete Response

Duration of complete response is defined only for subjects who have achieved CR/CRu after the first dose date of maintenance therapy and prior to any treatment change. It is calculated as the

time from the initial response (at least CRu) after the first dose date of maintenance therapy and prior to treatment change to documented disease progression or death.

Subjects who have not progressed or died at the time of the clinical data cutoff date will be censored at the last assessment showing no progression. Subjects who change treatment without evidence of disease progression will be censored at the last assessment showing no progression prior to treatment change.

Time to Next Anti-lymphoma Treatment

Time to next anti-lymphoma treatment is defined as the time from the first dose date of maintenance therapy to the time of first documented administration of new anti-lymphoma therapy. Subjects without new treatment therapy will be censored at the last visit.

Time to Histological Transformation

Time to histological transformation is defined as the time from the first dose date of maintenance therapy to the time of histological transformation as measured based on documentation of histological transformation (as assessed by the investigator). In case of clinical suspicion of transformation, including rapid disease progression, unexpected changes in "B" symptoms or rapidly increasing LDH, a biopsy should be performed. In this clinical trial, histological transformation will be considered disease progression. This endpoint will not be calculated for subjects randomized with transformed Follicular Lymphoma (tFL).

[redacted]

10.6.4 Analysis Methods

Time-to-Event Endpoints

For the time-to-event endpoints, the Kaplan-Meier estimates of the survival function will be calculated and graphically presented. The stratified log-rank test will be performed to evaluate treatment efficacy. The experimental arm will be declared superior if the 2-sided p-value from the stratified log-rank test is less than or equal to the desired significance level in favor of the experimental arm. The un-stratified log-rank test will be performed as sensitivity analysis.

Hazard ratio with two-sided 95% confidence interval (CI) will be estimated using the Cox proportional hazards model.

Binary Endpoints

The binary endpoints such as IOR will be summarized in frequency and percentage. The stratified Cochran-Mantel-Haenszel (CMH) test will be performed to evaluate treatment efficacy. The un-stratified CMH test will be performed as sensitivity analysis.

10.7 Safety Analysis

Safety analyses will be based on all subjects in the safety population, and will be analyzed by the induction period, maintenance period, and follow-up period.

Study drug exposure will be summarized, including duration of study drug, total dose taken, and dose reductions.

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

AEs will be coded according to Medical Dictionary for Drug Regulatory Activities (MedDRA) and classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.03, except for tumor flare, which will be assessed using version 3.0). The incidence rates of AEs will be tabulated by system organ class and preferred term. The incidence of AEs will also be tabulated by severity within each system organ class and preferred term. The most severe grade of each preferred term for a subject will be utilized for summaries of AEs by NCI CTCAE grade.

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

AEs of interest include SPM, VTE, ATE, TLS, and TFR. All AEs with corresponding attributes will be displayed in a by-subject listing. Adverse events leading to death or to discontinuation from treatment, events classified as CTCAE Grade 3 or higher, suspected treatment-related events, and SAEs will also be displayed in separate by-subject listings.

Laboratory data will be summarized according to the CTCAE severity grade.

10.8 Interim Analysis

A formal interim analysis for futility only is planned to examine the overall response rate to induction therapy, which is defined as the proportion of subjects whose response at the end of induction period is at least PR (including CR, CRu and PR). It will be conducted with the first 50 efficacy evaluable subjects by the end of the Induction Period. Efficacy evaluable subjects are defined as subjects who have had the scheduled response assessment at 12 months, or progressed or died before the end of the Induction Treatment Period. If the lower limit of the 95% confidence interval for overall response rate during the induction period in these 50 subjects is less than 30% then the trial might be stopped for futility.

Since this interim analysis is only to evaluate the induction therapy, it has no impact on the number of events we need for the maintenance period, sample size, or alpha.

Considering the current PFS event rate and estimated timing of final analysis, one nonbinding interim analysis for patients in the maintenance phase is planned at 50% of information (95 PFS events) for both superiority and futility. The date of occurrence of the 95th PFS event will be used as data cut-off date for the analysis. This interim analysis will be conducted by an external independent statistician, while the study team will remain blinded.

The study may be stopped early for futility if the observed hazard ratio (HR) is > 1.154, based on Gamma (-8) family (Hwang, Shih, and DeCani, 1990), ie, in favor of the control arm, and/or if recommended by the DMC based on the safety profile of this combination regimen. The stopping boundary for superiority based on O'Brien Fleming Analog (Lan & DeMets, 1983) is hazard ratio ≤ 0.546, if the observed HR cross the superiority boundary in favor of the proposed treatment, the trial may stop and claim the superiority. To ensure the overall 1-sided type 1 error remains at 0.025, an appropriate amount of alpha will be spent for the interim analysis.

[redacted]

The DMC will review the efficacy and safety data from these analyses and communicate recommendations to the sponsor who may use the recommendations in a risk/benefit analysis.

10.9 Other Topics

Not applicable.

11 ADVERSE EVENTS

11.1 Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (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 adverse event should be reported as separate terms. See Section 8.2.4.1 for more details.

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

All AEs will be recorded by the investigator from the time the subject signs informed consent until 28 days after the last dose of IP and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (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. Note that 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).

11.2 Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

11.2.1 Seriousness

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

- Results in death;
- Is life-threatening (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 for 5 years from the date the last subject initiates induction therapy. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other seriousness 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 or an elective procedure for a pre-existing condition unrelated to the studied indication, which has not worsened from baseline.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

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

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

11.2.2 Severity / Intensity

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

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03). However, TFR will be graded using NCI CTCAE version 3.0. Severity grading for TLS should follow the Cairo-Bishop Grading System for TLS (Appendix D) rather than using the CTCAE v4.03.

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

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

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

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

11.2.3 Causality

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

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

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

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

11.2.4 Duration

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

11.2.5 Action Taken

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

11.2.6 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3 Abnormal Laboratory Values

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

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

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

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

11.4 Pregnancy

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

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, Celgene will follow up with the clinical investigator each trimester of pregnancy and for 1 year following the birth of the infant (if applicable). Please reference the pregnancy information consent (permission) forms for data collection for additional information.

11.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β human chorionic gonadotropin [βhCG] or a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The exposure of any pregnant female (e.g., caregiver or pharmacist) to lenalidomide, is also an immediately reportable event.

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

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

If the outcome of the pregnancy was abnormal (e.g., spontaneous abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the seriousness 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 6.2.2). 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

for 5 years from the date the last subject initiates induction therapy. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other seriousness 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.).

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

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

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

11.5.1 Safety Queries

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

11.6 Expedited Reporting of Adverse Events

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

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

Celgene or its authorized representative shall notify the investigator of the following information:

- 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.

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

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

Celgene Drug Safety Contact Information:

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

12 DISCONTINUATIONS

12.1 Treatment Discontinuation

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

- Adverse event(s)
- PD or relapse
- Subject withdrawal (subject no longer wants to receive study drug, but is willing to have additional data collected)
- Withdrawal of consent (both from treatment and study, including release of further subject data)
- Death
- Lost to follow-up
- Protocol violation
- Lack of efficacy
- The completion of study treatment (the completion of 30 Cycles for subjects in arm B) as per protocol

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

12.2 Study Discontinuation and Completion

The following events are considered sufficient reasons for discontinuing a subject from follow-up in the study:

- Screen failure
- Withdrawal of consent (including release of further subject data).
- Death
- Lost to follow-up
- Protocol violation
- Lack of efficacy

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

Once the 114 PFS events are confirmed, the follow-up period will continue for 5 years after the last subject has initiated induction therapy, and all subjects who are in the follow-up period will be deemed as completed and will be off boarded from the study [redacted].

13 EMERGENCY PROCEDURES

13.1 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/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.

13.2 Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

14 REGULATORY CONSIDERATIONS

14.1 Good Clinical Practice

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

14.2 Investigator Responsibilities

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

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

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

The investigator is responsible for documentation of every procedure and assessment required by this protocol in a source document to be maintained by the site. Some procedures or assessments required in this study may be considered standard of care. These must be captured in the source document as well.

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.

14.3 Subject Information and Informed Consent

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

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

amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the investigator's study files and a copy given to the study subject.

14.4 Confidentiality

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

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

14.5 Protocol Amendments

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

14.6 Institutional Review Board/Independent Ethics Committee Review and Approval

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

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

by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

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

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

14.7 Ongoing Information for Institutional Review Board / Ethics Committee

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

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

14.8 Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc.). At termination and investigator's discretion, subjects who had been receiving lenalidomide without unacceptable toxicities and have not met the criteria for withdrawal may continue to receive open-label lenalidomide provided by the Sponsor.

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

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

15 DATA HANDLING AND RECORDKEEPING

15.1 Data/Documents

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

15.2 Data Management

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

15.3 Record Retention

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

- Signed informed consent documents for all subjects.
- Subject identification code list, Screening log (if applicable), and enrollment log.
- Record of all communications between the investigator and the IRB/EC.
- Composition of the IRB/EC.
- Record of all communications between the investigator, Celgene, and their authorized representative(s).
- List of Sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures.
- 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.

16 QUALITY CONTROL AND QUALITY ASSURANCE

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

16.1 Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. 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 on-site 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.

16.2 Audits and Inspections

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

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

17 PUBLICATIONS

The results of this study 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.

18 REFERENCES

Ahmadi T, Chong EA, Gordon A, et al. Phase II trial of lenalidomide - rituximab +/- dexamethasone in relapsed or refractory indolent B-cell or mantle cell lymphomas resistant to rituximab [abstract]. Blood 2011;118:266.

AJCC Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven;1997:289-294.

Ansell SM, Witzig TE, Kurtin PJ, Sloan JA, Jelinek DF, Howell KG, et al. Phase 1 study of interleukin-12 in combination with rituximab in patients with B-cell non-Hodgkin lymphoma. Blood 2002; 99(1):67-74.

Arcaini L, Lucioni M, Boveri E, Paulli M. Nodal marginal zone lymphoma: current knowledge and future directions of an heterogeneous disease. Eur J Haematol. 2009;83(3):165-74.

Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782-91.

Baiocchi RA, Alinari L, Lustberg ME, Lin TS, Porcu P, Li X, et al. Phase 2 trial of rituximab and bortezomib in patients with relapsed or refractory mantle cell and follicular lymphoma. Cancer 2010;117(11):2442-51.

Bastion Y, Sebban C, Berger F, Felman P, Salles G, Dumontet C, et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. J Clin Oncol 1997;15:1587-94.

Bennett M, Schechter GP. Treatment of splenic marginal zone lymphoma: splenectomy versus rituximab. Semin Hematol. 2010;47(2):143-7.

Bertoni F, Coiffier B, Salles G, Stathis A, Traverse-Glehen A, Thieblemont C, et al. MALT lymphomas: pathogenesis can drive treatment. Oncology 2011;25(12):1134-47.

Boccadoro M, Cavallo F, Gay M, Di Raimondo F, Nagler A, Montefusco V et al. Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) plus lenalidomide maintenance or no maintenance in newly diagnosed multiple myeloma (MM) patients. [abstract]. ASCO, 2013; abstract 8509.

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127:3-11.

Cairo MS, Coiffier B, Reiter A, and Younes A. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. British J Haemat. 2010;149:578-86.

Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 2011;117(19):5019-32.

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003 (http://ctep.cancer.gov) Publish date: August 9, 2006.

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.03 (http://ctep.cancer.gov) Publish date: June 14, 2010.

Cartron G, Zhao-Yang L, Baudard M, Kanouni T, Rouillé V, Quittet P, et al. Granulocyte-macrophage colony-stimulating factor potentiates rituximab in patients with relapsed follicular lymphoma: results of a phase II study. J Clin Oncol. 2008; 26(16):2725-31.

Casulo C, Burack R, Friedberg J. Transformed follicular non-Hodgkin lymphoma. Blood 2014; 125(10): 40-7.

Revlimid [Package Insert]. Summit, NJ: Celgene Corp; 2015

[redacted]

Chanan-Khan AA, Cheson BD. Lenalidomide for the treatment of B-cell malignancies. J Clin Oncol 2008a; 26(9):1544-52.

Chanan-Khan AA, Whitworth A, Bangia N, Porter CW, Lee K. Lenalidomide-associated tumor flare reaction is manageable in patients with chronic lymphocytic leukemia. J Clin Oncol 2008b;26(29):4851-2.

Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkins lymphomas. J Clin Oncol 1999; 17(4):1244-53.

Cheson BD. Radioimmunotherapy of non-Hodgkin's lymphomas. Blood. 2003;101:391-8.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Coiffier B, Osamanov EA, Hong X, Scheliga A, Mayer J, Offner F, et al. Bortezomib plus rituximab versus rituximab alone in patients with relapsed, rituximab-naive or rituximab-sensitive follicular lymphoma: a randomized phase 3 trial. Lancet Oncol. 2011;12:773-84.

Copie-Bergman C, Gaulard P, Lavergne-Slove A, Brousse N, Fléjou JF, Dordonne K, et al. Proposal for a new histological grading system for post-treatment evaluation of gastric MALT lymphoma. Gut. 2003; 52:1656.

Copie-Bergman, C, Wotherspoon AC, Capella C, Motta T, Pedrinis E, Pileri SA, et al. Gela histological scoring system for post-treatment biopsies of patients with gastric MALT lymphoma is feasible and reliable in routine practice. Br J Haematol. 2012;160:47-52.

Corazzelli G, De Filippi R, Capobianco G, Frigeri F, DeRosa V, Laccarino G, et al. Tumor flare reactions and response to lenalidomide in patients with refractory classic Hodgkin lymphoma. Am J Hematol. 2010;85(1):87-90.

Czuczman MS, Leonard JP, Jung S, Johnson JL, Hsi ED, Byrd JC et al. Phase II trial of galiximab (anti-CD80 monoclonal antibody) plus rituximab (CALGB 50402): Follicular Lymphoma International Prognostic Index (FLIPI) score is predictive of upfront immunotherapy responsiveness. Annals of Oncol. 2012;23 (9):2356-62.

Czuczman MS, Vose JM, Witzig TE, Zinzani PL, Buckstein R, Polikoff J, et al. The differential effect of lenalidomide monotherapy in patients with relapsed or refractory transformed non-Hodgkin lymphoma of distinct histological origin. Br J Haematol. 2011;154(4):477-481.

Czuczman MS. Anti-CD80 monoclonal antibody: galiximab. Haematologica reports 2005;1(8):35-6.

Dave S, Wright G, Tan B, Rosewald R, Gascoyne RD, Chan WC, Fisher RI, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med. 2004;351:2159-69.

Davis TA, Grillo-Lopez AJ, White CA, McLaughlin P, Czuczman MS, Link BK, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. J Clin Oncol. 2000a; 18:3135-43.

Davis TA, Maloney DG, Grillo-López AJ, White CA, Williams ME, Weiner GJ, et al. Combination immunotherapy of relapsed or refractory low-Grade or follicular non-Hodgkin's lymphoma with rituximab and interferon-alpha-2a. Clin Cancer Res. 2000b; 6(7):2644-52.

Dimopoulos MA, Chen C, Spencer A, Niesvizky R, Attal M, Stadtmauer EA, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia. 2009;23(11):2147-52.

Dreyling M, Kluin-Nelemans HC, Beà S, Klapper W, Vogt N, Delfau-Larue MH, et al; European MCL Network. Update on the molecular pathogenesis and clinical treatment of mantle cell lymphoma: report of the 11th annual conference of the European Mantle Cell Lymphoma Network. Leuk Lymphoma. 2013b;54(4):699-707.

Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, et al. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann Oncol. 2013a;24(4):857-77.

Dutia M, DeRoock I, Chee K, O'Donnell R, Quirch C, Reed-Pease C, et al. Analysis of a Phase 2 study of lenalidomide and rituximab in relapsed or refractory non-Hodgkin's lymphoma [abstract]. Haematologica. 2010; 95(Suppl 2):118, Abstract # 0295.

Eve HE, Rule SA. Lenalidomide-induced tumour flare reaction in mantle cell lymphoma. Br J Haematol. 2010;151(4):410-2

Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol. 2009; 27(27):4555-62.

Fernàndez V, Hartmann E, Ott G, Campo E; Rosenwald A. Pathogenesis of mantle-cell lymphoma: all oncogenic roads lead to dysregulation of cell cycle and DNA damage response pathways. J Clin Oncol. 2005;23(26):6364-9.

Fisher RI, Bernstein SH, Kahl BS, Djulegovic B, Robertson MJ, de Vos S, et al, Mulicenter Phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2006; 24(30):4867-74

Forstpointner R, Dreyling M, Repp R, Hermann S, Hänel A, Metzner B, et al; German Low-Grade Lymphoma Study Group. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2004;104(10):3064–71.

Fowler N, Davis E, Rawal S, Nastoupil L, Hagemeister F, McLaughlin P, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol 2014;15(12):1311–8.

Fu K, Weisenburger DD, Greiner TC, Dave S, Wright G, Rosenwald A, et al. Cyclin D1-negative mantle cell lymphoma: a clincopathologic study based on gene expression profiling. Blood. 2005;106:4315-21.

Gaidarova S, Corral L, Glezer E, Schafer PH, Lopez-Girona A, et al. Treatment of MCL cells with combined rituximab and lenalidomide enhances NK-Mediated synapse formation and cell killing. [abstract]. ASH, 2009; abstract 1687.

Galustian, C, Labarthe MC, Barlett JB, Dalgleish AG. Thalidomide-derived immunomodulatory drugs as therapeutic agents. Expert Opin Biol Ther 2004;4(12):1963-70.

Ghielmini M, Vitolo U, Kimby E, Montoto S, Walewski J, Pfreundschuh M, et al; Panel Members of the 1st ESMO Consensus Conference on Malignant Lymphoma. ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol. 2013;24(3):561-76.

Gopal A, Kahl B, deVos S, Wagner-Johnston N, Schuster S, Jurczak W, et al. PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma. N Engl J Med 2014;370:1008-1018.

Gorgun G, Ramsay AG, Holderried TA, Zahrieh D, Le Dieu R, Liu F, et al. E(mu)-TCL1 mice represent a model for immunotherapeutic reversal of chronic lymphocytic leukemia-induced T-cell dysfunction. Proc Natl Acad Sci USA 2009;106(15):6250-5.

Goy A, Sinha R, Williams ME, Besisik SK, Drach J, Ramchandren R et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: Phase II MCL-001 (EMERGE) study. J Clin Oncol. 2013; 31: 3688-95.

Goy A. Are we improving the survival of patients with mantle cell lymphoma: if so, what is the explanation? Leuk Lymphoma. 2011;52(10):1828-30.

Goy A, Bernstein SH, Kahl BS, Dejulbegovic B, Robertson MJ, De Vos S et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann. of Oncol. 2009; 20:520-5.

Gribben JG. Implications of the tumor microenvironment on survival and disease response in follicular lymphoma. Current Opinion in Oncol. 2010;22(5):424-30.

Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, et al; American Society of Clinical Oncology. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2012;30(13):1553-61.

Habermann TM, Lossos IS, Justice G, Vose JM, Wiernik PH, McBride K, et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. Br J Haematol. 2009;145(3):344-9.

Harris NL, Swerdlow SH, Jaffe ES, et al. Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Thiele J et al (editors): WHO classification of tumours of haematopoietic and lymphoid tissues, Fourth Edition. Lyon: IARC: 2008:214-9.

Hernandez-Ilizaliturri FJ, Reddy N, Holkova B, Ottman E, Czuczman, MS. Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model. Clin Can Res. 2005;11(16):5984-92.

Higgins RA, Blankenship JE, Kinney MC. Application of immunohistochemistry in the diagnosis of non-Hodgkin and Hodgkin lymphoma. Arch Pathol Lab Med. 2008;132(3):441-61.

[redacted]

Isaacson PG, Chott A, Nakumura S, Müller-Hermelink HK et al. Extranodal marginal cell lymphoma of mucosa-associated tissue (MALT-lymphoma). In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Thiele J et al (editors). WHO classification of tumours of the haematopoietic and lymphoid tissues, Fourth Edition. Lyon: IARC: 2008:214-9.

Jaffe E. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program. 2009:523-31.

Kane RC, Dagher R, Farrell A, Ko CW, Sridhara R, Justice R, et al. Bortezomib for the treatment of mantle cell lymphoma. Clin Cancer Res. 2007;13(18 Pt 1):5291-4.

Kiesewetter B, Fridrik M, Willenbacher W, Willenbacher E, Greil R, Raderer M. A phase II trial of rituximab plus lenalidomide in patients with lymphoma of the mucosa associated lymphoid tissue (MALT-lymphoma): agmt (arbeits-gemeinschaft medikamentoese tumortherapie) MALT 2 study. 12th Triennial international conference on malignant lymphoma (ICML 2013): Abstract # 251.

Kiesewetter B, Troch M, Dolak W, Müllauer L, Lukas J, Zielinski CC, et al. A Phase II study of lenalidomide in patients with extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT lymphoma). Haematologica. 2012;98(3):353-6.

Komrokji RS, Uppal NP, Khorana AA, Lyman GH, Kaplan KL, Fisher RI, et al. Venous thromboembolism in patients with diffuse large B-cell lymphoma. Leukemia and lymphoma 2006; 47(6):1029-33.

Leleu X, Daley L, Rodon P, Hulin C, Dauriac C, Hacini H, et al. Final Analysis of MELISSE, a Large Multicentric Observational Study to Determine Risk Factors of Venous Thromboembolism in Patients with Multiple Myeloma Treated with Immunomodulator Drugs. ASH, 2011; Abstract # 1235.

Leonard J, Jung S, Johnson JL, Bartlett N, Blum KA, Cheson BD, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma. [abstract]. 2012 ASCO Annual Meeting. J Clin Oncol 2012;30(suppl); abstr 8000.

Leonard JP, Coleman M, Ketas J, Ashe M, Fiore JM, Furman RR, et al. Combination antibody therapy with epratuzumab and rituximab in relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol. 2005;23(22):5044-51.

Lopez-Girona A, Mendy D, Ito T, Miller K, Gandhi AK, Kang J, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. Leukemia 2012;26(11):2326-35

Lossos I, Gascoyne R. Transformation of Follicular Lymphoma. Best Pract Res Clin Haematol. 2011; 24(2):147–163

Luke DR, Halstenson CE, Opsahl JA, Matzke GR. Validity of creatinine clearance estimates in the assessment of renal function. Clin Pharmacol Ther 1990;48(5):503-8.

Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2013; 31: 2189-204.

Martin P, Jung S, Johnson J, Elstrom R, Bartlett N, Blum K et al. CALGB 50803 (ALLIANCE): A phase 2 trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma. 12th Triennial international conference on malignant lymphoma (ICML 2013): Abstract # 63.

Martinelli G, Schmitz SFH, Utiger U, Cerny T, Hess U, Bassi S, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol. 2010;28(29):4480-84.

Matutes E, Oscier D, Montalban C, Berger F, Callet-Bauchu E, Dogan A et al. Splenic marginal zone lymphoma proposals for a revision of diagnostic, staging and therapeutic criteria. Leukemia 2008;22(3):487-95.

McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-81.

McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16(8):2825-33.

Velcade [Package Insert]. Cambridge, MA: Millenium Pharmaceuticals Inc; 2014.

Mohren M, Markmann I, Jentsch-Ullrich K, Koenigsmann M, Lutze G, Franke A, et al. Increased risk of thromboembolism in patients with malignant lymphoma: a single-centre analysis. Br J Cancer 2005;92(8):1349-51.

Morin RD, Mendez-Lago M, Mungall AJ, Goya R, Mungall KL, Corbett RD, et al. Frequent mutation of histone modifying genes in Non-Hodgkin lymphoma. Nature 2011;476(7360):298-303.

Morschhauser F, Fowler NH, Feugier P, Bouabdallah R, Tilly H, Palomba ML, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med. 2018 Sep 6;379(10):934-47.

Munshi NC, Anderson KC. New Strategies in the Treatment of Multiple Myeloma. Clin Cancer Res. 2013. [Epub ahead of print]

NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Non-Hodgkins lymphomas. Version 1. 2015. Available from: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

NCT01122472: Study of Lenalidomide Maintenance Versus Placebo in Responding Elderly Patients With DLBCL and Treated With R-CHOP (REMARC). (www.ClinicalTrials.gov identifier: NCT01122472). Available from: http://clinicaltrials.gov/show/NCT01122472. Accessed April 18, 2013.

NCT01216683: Bendamustine Hydrochloride and Rituximab With or Without Bortezomib Followed by Rituximab With or Without Lenalidomide in Treating Patients With High-Risk Stage II, Stage III, or Stage IV Follicular Lymphoma (www. ClinicalTrials.gov identifier: NCT01216683). Available from: http://clinicaltrials.gov/show/NCT01216683. Accessed April 18, 2013.

NCT01415752: Rituximab, Bendamustine Hydrochloride, and Bortezomib Followed by Rituximab and Lenalidomide in Treating Older Patients With Previously Untreated Mantle Cell

Lymphoma. (www. ClinicalTrials.gov identifier: NCT01415752). Available from: http://clinicaltrials.gov/show/NCT01415752. Accessed April 18, 2013.

NCT01476787: Combined Rituximab and Lenalidomide Treatment for Untreated Patients With Follicular Lymphoma (RELEVANCE). (www. ClinicalTrials.gov identifier: NCT01476787). Available from: http://clinicaltrials.gov/show/NCT01476787. Accessed April 18, 2013.

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

Ottinger H, Belka C, Kozole G, Engelhard M, Meusers P, Paar D, et al: Deep venous thrombosis and pulmonary artery embolism in high-Grade non Hodgkin's lymphoma: Incidence, causes and prognostic relevance. Eur J Haematol 1995;54(3):186-94,1995.

Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012;366(19):1759-69.

Park LC, Woo SY, Kim S, Jeon H, Ko YH, Kim SJ, Kim WS. Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: results from a prospective cohort study with Asian population. Thromb Res. 2012;130(3):e6-12.

Imbruvica [Package Insert]. Sunnyvale, CA: Pharmacyclics Inc; 2015.

Piro LD, White CA, Grillo-Lopez AJ, Janakiraman N, Saven A, Beck TM, et al. Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low Grade or follicular non-Hodgkin's lymphoma. Annals of Oncol. 1999;10(6):655-61.

Rajkumar SV, Jacobus S, Callander N, Fonseca R, Vesole DH, Williams ME, et al: Eastern Cooperative Oncology Group. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010 Jan;11(1):29-37.

Rambaldi A, Lazzari M, Manzoni C, Carlotti E, Arcaini L, Baccarani M, et al. Monitoring of minimal residual disease after CHOP and rituximab in previously untreated patients with follicular lymphoma. Blood 2002;99(3):856-62.

Ramsay AG, Clear AJ, Fatah R, Gribben JG. Multiple inhibitory ligands induce impaired T-cell immunologic synapse function in chronic lymphocytic leukemia that can be blocked with lenalidomide: establishing a reversible immune evasion mechanism in human cancer. Blood 2012;120(7):1412-21.

Ramsay AG, Clear AJ, Kelly G, Fatah R, Matthews J, Macdougall F et al. B Follicular lymphoma cells induce T-cell immunologic synapse dysfunction that can be repaired with lenalidomide: implications for the tumor microenvironment and immunotherapy. Blood. 2009a;114(21):4713-20.

Ramsay AG, Gribben JG. Immune dysfunction in chronic lymphocytic leukemia T cells and lenalidomide as an immunomodulatory drug. Haematologica. 2009b;94(9):1198-202.

Ramsay AG, Johnson AJ, Lee AM, Gorgün G, Le Dieu R, Blum W, et al. Chronic lymphocytic leukemia T cells show impaired immunological synapse formation that can be reversed with an immunomodulating drug. J Clin Invest. 2008;118(7):2427-37.

Reddy N, Hernandez-Ilizaliturri FJ, Deeb G, Roth M, Vaughn M, Knight J, et al. Immunomodulatory drugs stimulate natural killer-cell function, alter cytokine production by dendritic cells, and inhibit angiogenesis enhancing the anti-tumour activity of rituximab in vivo.Br J Haematol. 2007;140(1):36-45.

Rituximab [package insert]. South San Fransisco, CA: Genentech Inc; 2014.

Robb-Smith AHT. U.S. National Cancer Institute working formulation of non-hodgkin's lymphomas for clinical use. The Lancet. 1982;320(8295):432-4.

Robinson KS, Williams ME, van der Jagt RH, Cohen P, Jerst JA, Tulpule A, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol, 2008;26(27):4473–9.

Ruan J, Martin P, Shah B, Schuster S, Smith S, Furman R, et al. Sustained Remission with the Combination Biologic Doublet of Lenalidomide Plus Rituximab As Initial Treatment for Mantle Cell Lymphoma: A Multi-Center Phase II Study Report. Blood 2014; 124, Abstracts, no. 625; ASH, 2014

Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-Grade non-Hodgkin's lymphoma. J Clin Oncol. 2005;23(15):3383–9.

Sacchi S, Federico M, Vitolo U, Boccomini C, Vallisa D, Baldini L, et al. Clinical activity and safety of combination immunotherapy with IFN-alpha 2a and Rituximab in patients with relapsed low Grade non-Hodgkin's lymphoma. Haematologica, 2001;86(9):951-8.

Salar A, Domingo-Domenech E, Estany C, Canales MA, Gallardo F, Servitje O, et al. Combination therapy with rituximab and intravenous or oral fludarabine in the first-line, systemic treatment of patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type. Cancer 2009;115(22):5210-7.

Salles GA. Clinical features, prognosis and treatment of follicular lymphoma. Hematology Am Soc Hematol Educ Program. 2007:216-25.

Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood. 2004;104(5):1258-65.

Stamatopoulos K, Kosmas C, Belessi C, Stavroyianni N, Kyriazopoulos P, Papadaki T, et al. Molecular insights into the immunopathogenesis of follicular lymphoma. Immunol Today. 2000;21(6):298-305.

Thieblemont C, Tilly H, Da Silva MG, Casasnovas RO, Fruchart C, Morschhauser F, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2017 Aug 1;35(22):2473-81.

Van Oers MH, Van Glabbeke M, Giurgea L, Klasa R, Marcus RE, Wolf M, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol. 2010;28(17):2853–8.

Vaidyanathan G, Czuczman M. Follicular lymphoma grade 3: Review and updates. Clin Lymphoma, Myeloma, & Leukemia 2014; 14(6): 431-5.

Wang M, Fayad L, Wagner-Bartak N, Zhang L, Hagemeister F, Neelapu SS, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a Phase 1/2 clinical trial. Lancet Oncol. 2012;13(7):716-23.

Wang M, Rule S, Martin P, Goy A, Auer R, Kahl B, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2013;369:507-16.

Wang M, Fowler N, Wagner-Bartak N, Feng L, Romaguera J, Neelapu S, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Leukemia 2013; 27: 1902–9.

Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al; Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357(21):2133-42.

Wiernik PH, Lossos IS, Tuscano JM, Justice G, Vose JM, Cole CE, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodkin's lymphoma. J Clin Oncol 2008; 26 (30):4952-7.

Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory, low-Grade follicular or transformed B-cell non-Hodgkin's lympohoma. J Clin Oncol 2002; 20(10):2453-63.

Witzig TE, Vose JM, Luigi Zinzani PL, Reeder CB, Buckstein R, Polikoff JA, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011;22(7):1622-7.

Witzig TE, Wiernik PH, Moore T, Reeder C, Cole C, Justice G, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's lymphoma. J Clin Oncol 2009;27(32):5404-09.

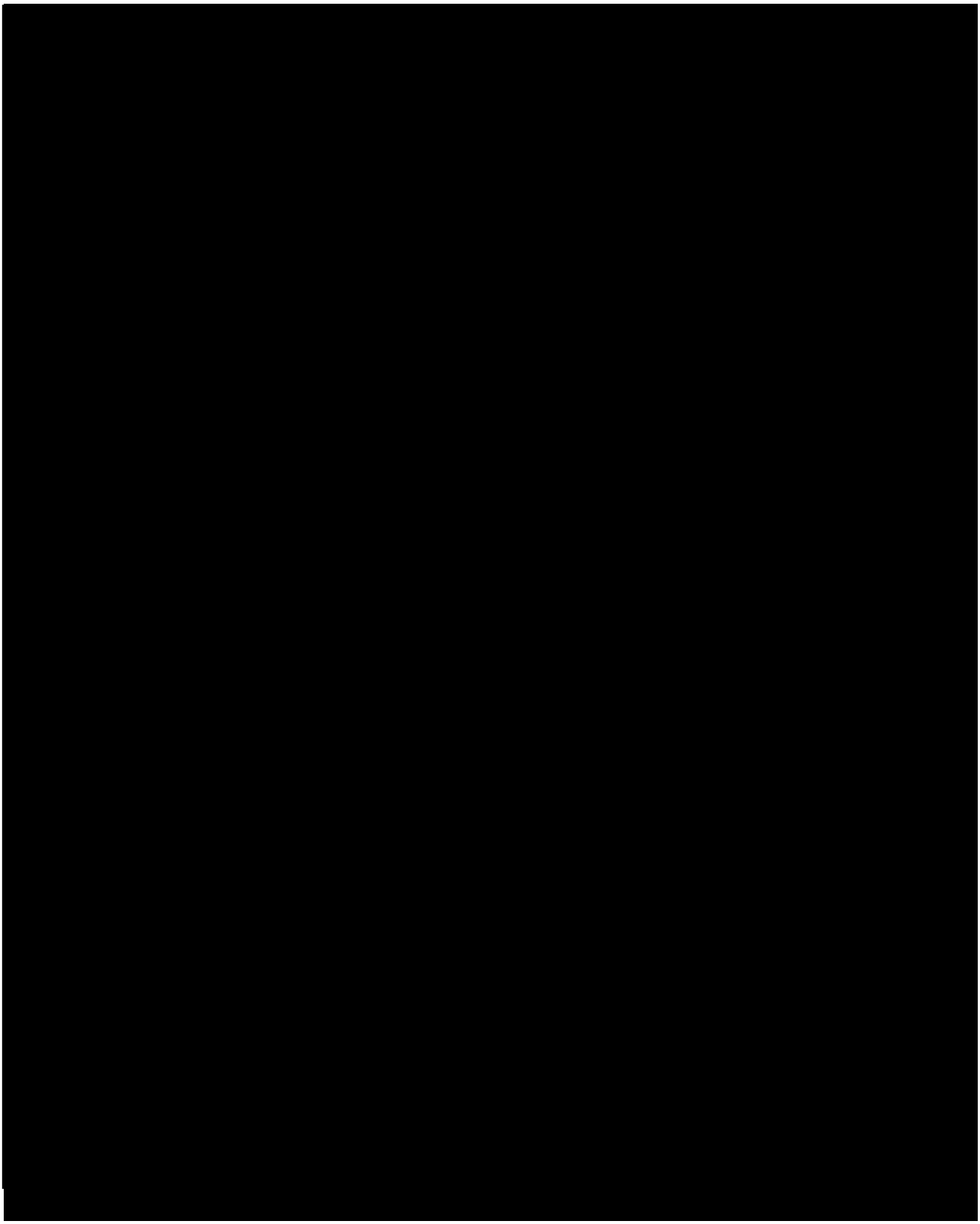
Wu L, Adams M, Carter T, Chen R, Muller G, Stirling D, et al. Lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. Clin Cancer Res. 2008;14(14):4650-7.

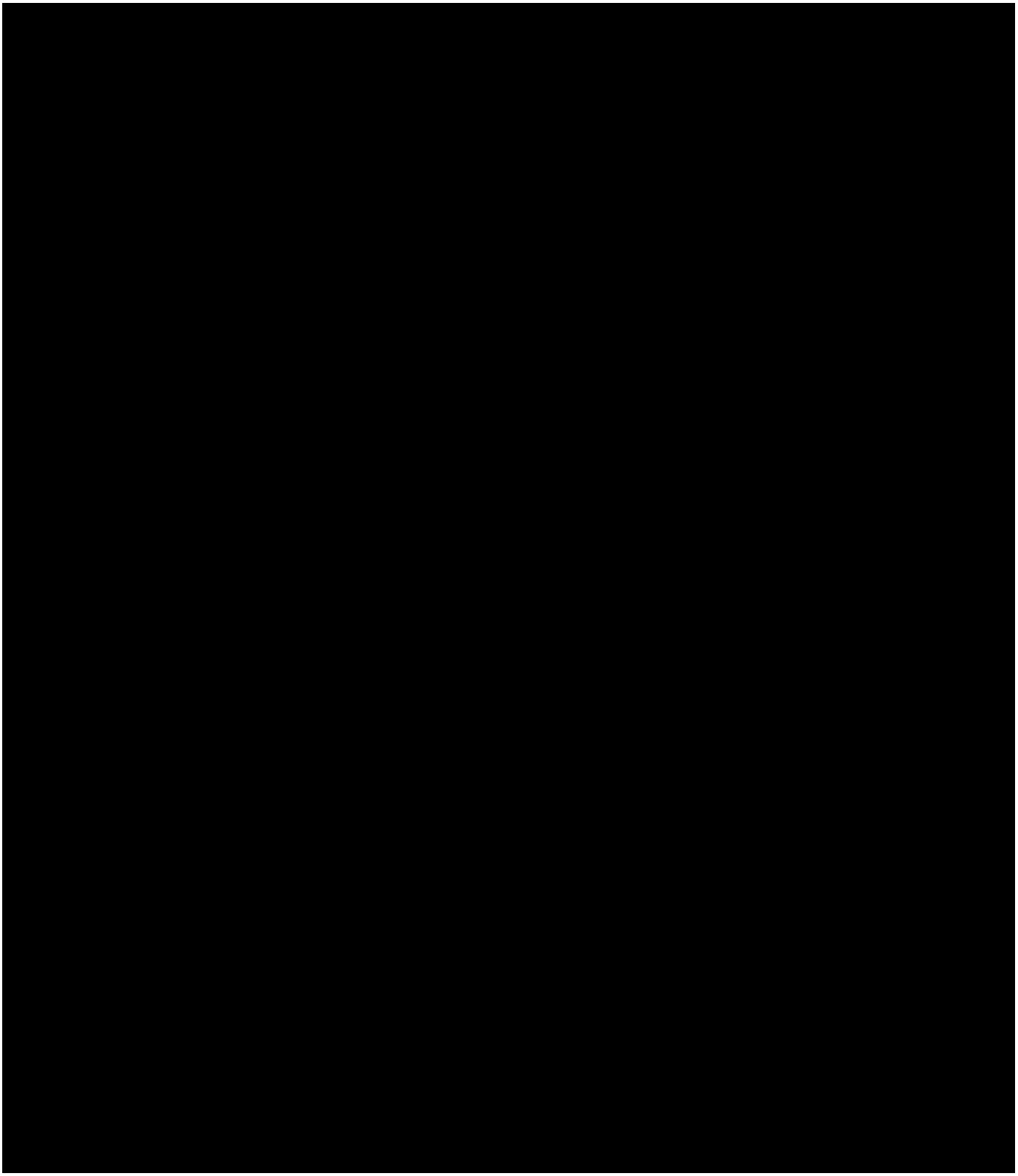
Zhang L, Qian Z, Cai Z, Sun L, Wang H, Bartlett JB, et al. Synergistic antitumor effects of lenalidomide and rituximab on mantle cell lymphoma in vitro and in vivo Am J Hematol 2009; 84(9):553-9.

Zhou X, Teegala S, Huen A, Ji Y, Fayad L, Hagemeister FB, et al. Incidence and risk factors of venous thromboembolic events in lymphoma. Am J Med. 2010;123(10):935-41.

19 APPENDICES

[redacted]





19.2 Appendix B: 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 (AJCC, 1997). Non Hodgkin's lymphoma.

19.3 Appendix C: 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

Source: Oken, 1982.

19.4 Appendix D: 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; TLS: Tumor Lysis Syndrome.

[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.

19.5 Appendix E: Response Criteria for NHL

19.5.1 Tumor Assessment by 1999 IWG Criteria for NHL

Table 6: Tumor Assessment by 1999 IWG Criteria

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
Cru	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
SD	Less than PR but is not PD nor relapsed disease			
Relapse or PD	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

Normal for lymph nodes is defined as follows:

Lymph nodes and nodal masses $\leq$ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy.

Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to $\leq$ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD)

Indeterminate bone marrow is defined by increased number or size of aggregates without cytological or architectural atypical

19.5.2 Additional Response Assessment in Gastric MALT subjects with Radiological Response of at Least a PR by 1999 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 6.1.6). The histological scoring will be based on the GELA histological scoring system (Table 7). Final response assessment in subjects with gastric MALT will incorporate the IWG criteria as well as the histological findings.

Table 7: 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)

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 investigations 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

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Considering the current progression free survival (PFS) event rate, which is slower than originally predicted (approximately 60 PFS events as of August 2020), the challenging follow-up of subjects in the context of the COVID-19 pandemic, and estimated timing of final analysis, one nonbinding interim analysis for patients in the maintenance phase is planned at 50% of information (95 PFS events) for both superiority and futility. This analysis will enhance formal benefit/risk assessment for subjects continuing on treatment. The date of occurrence of the 95th PFS event will be used as data cut-off date for the analysis. This interim analysis will be conducted by an external independent statistician, while the study team will remain blinded.

The study may be stopped early for futility if the observed hazard ratio (HR) is > 1.154, based on Gamma (-8) family (Hwang, Shih, and DeCani, 1990), ie, in favor of the control arm, and/or if recommended by the data monitoring committee (DMC) based on the safety profile of this combination regimen. The stopping boundary for superiority based on O'Brien Fleming Analog (Lan & DeMets, 1983) is hazard ratio ≤ 0.546, if the observed HR cross the superiority boundary in favor of the proposed treatment, the trial may stop and claim the superiority, reflecting a one-sided p-value < 0.002.

The stopping rule for superiority will occur if the observed hazard ratio HR is ≤ 0.54.

Revised Section: Section 10.8

Additional Updates

- Study team changes resulted in updates in the medical monitor and emergency contact information.

Revised Section: Medical Monitor / Emergency Contact Information.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Incorporation of information communicated per Protocol Addendum for Germany

A protocol addendum dated 22 Jun 2017 was issued to address aspects of the protocol that are adapted in order to comply with laws and drug regulations applicable in Germany. These changes are now incorporated in the current global protocol amendment.

- **Number of Subjects and Sites**

Celgene will select fifteen (15) sites within Germany. Subject enrollment of approximately 50 subjects is planned in Germany collectively from sites listed in the clinical trial application at submission to regulatory authorities.

Revised Section: Section 7.1

- **Description of Investigational Product(s)**

This is to clarify that for Germany, Celgene will supply both lenalidomide capsules and rituximab intravenous formulation as investigational products (IPs).

Revised Section: Section 8.1

- **Packaging and Labeling in Germany**

This is to clarify that for Germany, rituximab intravenous formulation packaging and label will be provided as an IP.

Revised Section: Section 8.4

Clarification of the Efficacy Assessments frequency

This is to clarify that schedule of tumor assessment would follow cycles rather than calendar months, to ensure that all subjects have a tumor assessment performed as required by protocol, prior to randomization. Additionally, clarification added that efficacy assessment should be performed until progression, relapse or initiation of new anti-lymphoma therapy.

Revised sections: Section 5 Table of Events, Section 6.3, Section 8.2

Clarification of the collection window for laboratory samples

The protocol now includes a clarification for the window for collection of hematology and serum chemistry samples as communicated to the sites in the administrative change letter dated 11 May 2018 as well as a site communication sent on 18 Jun 2018. This is in line with the update of the protocol in Germany following the request from the German health authority, BfArM on 23 Jul 2018.

Revised sections: Section 5 Table of Events, Section 6.2.

Update to clinical background information on lenalidomide

- Addition of results of the RELEVANCE and REMARC trials

Revised section: Section 1.6.1, Section 1.7, Section 18

Additional Updates

- Study team changes resulted in updates in the medical monitor and emergency contact information.

Revised Sections: Section medical monitor and emergency contact information.

- Minor editorial and formatting changes (eg, consistency of acronym use throughout the document per Celgene Style Guide, spelling, grammatical error corrections, etc.) were also made throughout the document.

Revised sections: Section 1.6, Section 1.7, Section 7.3

- Grading of tumor flare reaction and tumor lysis syndrome clarified

Revised sections: Section 6.2, Section 8.2

- Number of sites revised per current status for German sites

Revised sections: Section 7.1

- Description of IP updated

Revised section: Section 8.1

- Update of evaluation and reporting of adverse events per current guidelines

Revised section: Section 11

- Update of birth control and pregnancy language per Celgene standard language

Revised sections: Section 6.2, Section 11.4

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Modification of Randomization Timepoint

The primary purpose of this protocol amendment is to change the timing of randomization from prior to induction therapy to prior to maintenance therapy. This is due to feedback received from external experts in statistical analysis and institutional review boards regarding the statistical section of the previous protocol to ensure the validity of statistical comparison between two maintenance treatment groups.

Section 10.6 of the previous protocol defined the primary endpoint as PFS from randomization (prior to induction therapy) until PD/Death. However, since all patients receive the same induction therapy prior to maintenance therapy, comparing PFS from induction therapy between both arms is not suitable as a primary endpoint for the trial. Also, the intent to treat (ITT) population is defined as the primary population. This included all patients who did not proceed to maintenance therapy, yet the events occurring during induction therapy were not to be included in the primary endpoint analysis of the previous protocol.

Furthermore, since only patients achieving Partial Response or better at the end of the induction treatment were allowed to continue to maintenance, it is possible that the maintenance arms would not be balanced per randomization stratification factors in the previous protocol.

Changing the timing of randomization from prior to induction (as per previous protocol) to prior to maintenance allows for PFS from the timepoint of randomization to maintenance to be statistically viable as a primary endpoint.

It is important to note that the treatment used in the induction phase of the clinical trial remains experimental as it is not an approved regimen. As a result, data will continue to be collected on subjects during the induction phase of the trial in much the same manner as per the previous version of the protocol (Protocol Amendment1 16 Jan 2014). The change of randomization timepoint bring this study design in line with similar trials that seek to determine the treatment effect of a maintenance regimen in a patient population receiving a common induction regimen (eg., PRIMA trial published by Salles, et al., Lancet 2011, as referenced in the protocol).

Modification of Inclusion/Exclusion Criteria

One goal of this study is to gain experience with the lenalidomide plus rituximab regimen in subjects who represent the population seen in a range of clinical practice settings in the United States. Feedback from participating sites advised slight modifications to the inclusion/exclusion criteria to be more representative of this disease population. These modifications are as follows:

For the inclusion criteria:

- ECOG < 2 (previous protocol) will be changed to ECOG ≤ 2.
- Simplify prior treatment language to include a broader range of treatments (including novel agents)
- Allow inclusion of patients with grade 3b and transformed follicular lymphoma

For the exclusion criteria:

- Neuropathy > grade 1 (previous protocol) will be changed to Neuropathy > grade 2.
- 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. Carcinoma in situ of the breast, and incidental histological finding of prostate cancer (TNM stage of T1a or T1b) have been added as exceptions. These changes are to align this particular study with the rules agreed upon with Health authorities.

Lenalidomide monotherapy maintenance changed to optional

In the previous version of the protocol (Protocol Amendment 1 16 Jan 2014) patients were to continue lenalidomide single agent maintenance after completing 18 cycles of lenalidomide + rituximab maintenance with lenalidomide monotherapy maintenance until disease progression. Due to feedback from participating sites and their experience in treating patients with maintenance therapy, the protocol amendment will make this component of treatment optional at the discretion of the physician and/or patient.

Revision to Secondary Endpoints and Interim Analyses

As this trial is a maintenance trial, and patients randomized to the maintenance treatment period must have a minimum response of stable disease, it is important to analyze whether there is an improvement in response with prolonged maintenance treatment. As a result, Improvement of Response was added as a secondary endpoint.

Due to different durations of treatment in the maintenance phase, Time to Treatment Failure (TTF) may be biased as an endpoint. The control arm (Arm B) maintenance treatment is defined as 18 cycles with Rituximab whereas the experimental Arm A has the option to continue treatment with lenalidomide single agent until progression of disease. As a result, TTF has been removed as a secondary endpoint.

In the previous protocol (Protocol Amendment 1 16 Jan 2014), there were four planned interim analyses. This is now reduced to a single interim analysis for futility of the induction treatment regimen. [redacted]

These major changes as well as minor changes in language have been made throughout multiple sections of the protocol.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Addition of Overall Survival as a secondary endpoint.
- Changes in the pregnancy restriction language to reflect the Rituximab Prescribing information.

The amendment also includes several other minor clarifications and corrections:

- Changes to Schedule of activities including correction/deletion of footnotes, Deletion of certain procedures at specific timepoints:
    - Modification of frequency of QoL questionnaire to collect data required for this IIIb study.
    - Deletion of footnote re: ECOG status assessment timing.
    - Broadening window allowed for scans to allow them to be completed at scheduled visits.
- Statement added to Procedures section reflecting ability to use standard of care procedures to meet the requirements of the study if they meet the description and timeline specified in the protocol.
- Statements added to reflect data that will be collected in the CRF, Source Document and/or Adverse Event pages.
- Statement that local labs will be used for the study, and which lab results will be captured in the CRF.
- Correction of typographical errors, or grammar.
- Modification of the timepoints ECOG performance status will be assessed.
- Correction of numbers in statistical section .