DISCLOSURE

REDACTED PROTOCOL AMENDMENT 6

CC-5013-MCL-002

A PHASE 2, MULTICENTER, RANDOMIZED OPEN-LABEL STUDY TO DETERMINE THE EFFICACY OF LENALIDOMIDE (REVLIMID®) VERSUS INVESTIGATOR'S CHOICE IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

The information contained in the attached report is the property of Celgene and should not be shared or used for any purpose other than that for which it was provided.

Celgene is committed to providing information about its clinical trials to researchers and patients with the goal of furthering science and enhancing healthcare worldwide. Laws and regulations require, however, that Celgene protects patient privacy. The company may further have legal or contractual obligations not to disclose commercial or technical information provided by or related to certain partner companies or vendors.

The attached report is presented in its original format, but certain information has been redacted in order to comply with the aforementioned obligations or to protect Celgene's confidential commercial information. The redactions are based on the following principles:

- Redacted information has been replaced by grey space, maintaining original spacing and pagination.
- Any information that might allow the identification of individuals has been redacted for anonymization.
- Attachments to this report that contain confidential information are not made available. Such attachments include those that contain identifiable patient information, such as subject listings, narratives, and profiles. They also may contain confidential commercial information such as methodologies, and hypothesis generating and exploratory analyses.
- Cross-references to these attachments (such as links to subject listings in Section 16.2) are not redacted from the body of the report. However, the hyperlinks in the electronic document are no longer functional.
- Information about Celgene vendors and their services are redacted because many contracts prohibit disclosure of that information. Further, laws and regulations prevent us from disclosing certain information about our vendors or their services because it is protected by copyright.

Information about Celgene's redaction policies and the availability of additional data from this report may be found at http://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/.

A PHASE 2, MULTICENTER, RANDOMIZED OPEN-LABEL STUDY TO DETERMINE THE EFFICACY OF LENALIDOMIDE (REVLIMID®) VERSUS INVESTIGATOR'S CHOICE IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

The "SPRINT" trial

STUDY DRUG:	Lenalidomide
PROTOCOL NUMBER:	CC-5013-MCL-002
DATE	21 October 2008
Amendment # 1	21 April 2009
Amendment # 2	14 December 2009
Amendment # 3	29 April 2011
Amendment # 4	27 September 2011
Amendment # 5	22 March 2013
Amendment # 6	31 May 2018
EudraCT NUMBER	2008-003389-25

{See appended electronic signature page}

Signature of Celgene Therapeutic Area Head

Printed Name of Celgene Therapeutic Area Head

Date Signed _____

dd/mmm/yy

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	dd/mmm/yy

Printed Name of Site Principal Investigator and Title

Site Number_____

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, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations and local regulations governing the conduct of clinical studies.

1. STUDY CONTACT INFORMATION

Table 1: Celgene Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Responsible Clinical Research Physician / Medical Monitor		86 Morris Avenue Summit, NJ 07901 Phone : Mobile :
Lead Study Manager		Celgene R&D SARL Phone: Mobile :
International Drug Safety Contact for EU countries **For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines**	Clinical Trial Safety	Celgene International Sàrl Route de Perreux 1 2017- Boudry –Switzerland Phone: Fax:
Drug Safety Contact for ex-EU countries	Global Drug Safety (North America)	Celgene Global Drug Safety 86 Morris Avenue Summit, NJ 07901 Phone: Fax: Email:

Name of central laboratory(ies) and other medical and/or technical department(s) and /or institutions

2. SYNOPSIS

Name of Sponsor/Company: Celgene Corporation
Name of Investigational Product: Lenalidomide/CC-5013
Protocol Number: CC-5013-MCL-002
Protocol Title: A Phase 2, multicenter, Randomized open-Label study to determine the efficacy of lenalidomide (revlimid®) versus investigator's choice in patients with relapsed or refractory mantle cell lymphoma
Indication: Relapsed/refractory Mantle Cell Lymphoma (MCL)
Phase of development: Phase 2 Extended Access Phase
Study Duration: Patients will continue study treatment until disease progression, unacceptable toxicity, or voluntary treatment withdrawal. Patients will be followed for survival until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and complete response [CR] / complete response unconfirmed [CRu]) has been reached, or 4 years from last patient randomized, whichever comes later, at which time the study will end for subjects still on lenalidomide treatment in countries where lenalidomide is available post-trial in the commercial setting. These subjects will have a "discontinuation from treatment" visit at the end of their 7 day rest period from their last on-study treatment cycle. At this "discontinuation from treatment" visit commercial lenalidomide will be dispensed to the subject. Between this visit and 28 days after, if a patient experiences a SAE, this SAE will be reported via the standard post marketing process. A pregnancy test should be performed 28 days post treatment discontinuation visit. An Extended Access Phase will be made available for subjects on study treatment in countries where lenalidomide is only available under a clinical trial protocol as post-trial access. These subjects will have a "discontinuation from treatment" visit assessment prior to being transferred to the Extended Access Phase. The Extended Access Phase will end for ongoing subjects still on lenalidomide treatment as soon as lenalidomide can be accessed in the commercial setting. Guidance on the schedule of assessments for the Extended Access Phase is provided in Table 4. The clinical database will be locked after the last eligible subject has been transferred to post-trial access in the commercial setting or to the Extended Access Phase, whichever comes later. Clinical study data will no longer be collected on CRFs following the clinical database lock. A 28-day safety follow-up assessment will not be required either for subjects transferred to post-trial access in the commercial setting or transferred to the Extended Access Phase (after the clinical database lock). For subjects in the Extended Access Phase, SAE forms will be reported to Celgene Safety via the standard reporting process for SAEs (including second primary malignancies) in clinical trials and, drug accountability information will be reviewed periodically by the study monitor.

The End of Trial is defined as either the date of the last visit of the last subject to complete the Extended Access Phase or the date of receipt of the last data point from the last subject in the Extended Access Phase, whichever comes later.

Objectives:

Primary:

- To compare the progression free survival (PFS) of lenalidomide monotherapy versus investigator's choice single agent in patients with mantle cell lymphoma (MCL) who are refractory to their regimen or have relapsed once, twice or three times.

Secondary:

- To determine the overall response rate (ORR) of lenalidomide monotherapy or investigator's choice single agent in patients with relapsed or refractory MCL.
- To evaluate the safety of lenalidomide monotherapy or investigator's choice single agent in patients with relapsed or refractory MCL.
- To determine the time to progression, and overall survival of patients with relapsed or refractory MCL who have received treatment with lenalidomide or investigator's choice single agent.
- To investigate the health-related quality of life (QoL) of patients treated with lenalidomide or investigator's choice single agent treatment.

Protocol Amendment #4:

Study Endpoints:

Primary

- Progression free survival defined as the time from randomization to the first observation of disease progression or death due to any cause. If the patient has not progressed or died, PFS will be censored at the time of last completed assessment when the patient was known not to have progressed. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free.

Secondary

- Overall response rate (CR, CRu, and partial response [PR]) assessed by a modification of the International Workshop Response Criteria IWRC (Cheson, 1999).
- Duration of response
- Tumor control rate (Rates for CR, CRu, PR, and stable disease [SD])
- Time to progression
- Time to treatment failure
- Time to tumor response
- Overall survival (OS)
- Safety
- Quality of Life (EORTC QLQ-C30)

Background and Rationale:

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment (Armitage, 1993). Most (approximately 80-90%) of the NHLs are of B-cell origin and around 10-15% are of T-cell origin. The prognosis depends on the histologic type, stage, and treatment. Mantle cell lymphoma (MCL) is a distinct subtype within B-cell non-Hodgkin's lymphoma that is characterized by the t(11; 14)(q13; q32) chromosomal translocation subsequently leading to the overexpression of cyclin D1. This subtype accounts for approximately 5% of all newly diagnosed malignant lymphomas. Although morphologically similar to indolent lymphomas, the natural history of MCL is more aggressive than that of indolent lymphomas. CHOP chemotherapy, as well as more intensive chemotherapy regimens such as hyper-CVAD or autologous transplantation have been used, often in combination with anti-CD20 monoclonal antibody rituximab (Epner, 2007; Pan 2002). Other agents, such as fludarabine based regimens, cytarabine, gemcitabine are also used to treat MCL (Tobinai, 2006). However, MCL remains an incurable disease, and novel therapeutic strategies are needed. The increasing understanding of the MCL cell biology has led to the development of new therapeutic agents with antitumor activity that target crucial biological pathways, including cell cycle inhibitors (i.e. flavopiridol), mTOR inhibitors (i.e. temsirolimus, everolimus), proteasome inhibitors (bortezomib) and histone deacetylase inhibitors (Kouroukis, 2003; Goy, 2005; O'Connor, 2005; Hess 2009). The combination of these new therapeutic strategies with existing standard chemotherapy regimens, and better risk stratification of the patients may change the management and outcome of MCL patients (Jares, 2008). Lenalidomide is a member of immunomodulatory agents, IMiDs®, with potent immuno-stimulatory, anti-angiogenic and pro-apoptotic activities *in vitro*. It has been shown to have efficacy in another B-cell malignancy, multiple myeloma. Preliminary data is available on the activity of lenalidomide in relapsed or refractory MCL patients in two Celgene-sponsored clinical trials of lenalidomide in aggressive NHL, study CC-5013-NHL-002 and study CC-5013-NHL-003. In study CC-5013-NHL-002 of lenalidomide monotherapy in patients with

relapsed or refractory aggressive NHL (Wiernik, 2008), 15 of 49 patients had MCL. In these MCL patients lenalidomide therapy achieved an Overall Response Rate (ORR) of 53%. Three patients (20%) had a CR or unconfirmed CR, and 5 patients (33%) had a PR. The median duration of response was 13.7 months and median PFS was 5.6 months. The most common grade 4 adverse event was thrombocytopenia (13%) and the most common grade 3 adverse events were neutropenia (40%), leucopenia (27%), and thrombocytopenia (20%). (Habermann, 2009). In another ongoing study of lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL (CC-5013-NHL-003), 57 of 217 patients had MCL (Witzig, 2011). In the 57 MCL patients who were evaluable for response assessment, lenalidomide therapy led to an objective response rate of 42% (25/57). Median progression-free survival (PFS) was 5.7 months. Overall, the primary side effect of lenalidomide was reversible myelosuppression. Grades 3 or 4 neutropenia occurred in 41%, thrombocytopenia in 19%, anemia in 9.2%. Grade 3 and grade 4 febrile neutropenia occurred in only 2% of patients.

Based on these preliminary observations, the current study is being conducted to evaluate the activity and safety of lenalidomide in a larger population of patients with relapsed or refractory mantle cell lymphoma.

Study Design:

This is a multicenter, randomized, open-label, comparative controlled phase II study to determine the efficacy and safety of single agent lenalidomide over a concurrent control group treated with an investigator's choice single agent in patients with mantle cell lymphoma who are refractory to their regimen or have relapsed once, twice or three times (Figure 1). The study design aims to compare the PFS of lenalidomide therapy over a single agent of investigator's choice.

The investigator's choice in the control arm comprises the monotherapy treatment with one of the following: chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine. The investigator shall choose the single agent of choice in the control arm for each patient prior to randomization on to the study. Patients in the investigator's choice arm will have the option to switch to lenalidomide at time of progressive disease.

Patients will be stratified according to:

- Time since diagnosis (<3 years or ≥ 3 years)
- Time since last treatment (<6 months [refractory] or ≥ 6 months)
- Prior stem cell transplant (yes or no)

Treatment and clinical characteristics will be assessed at screening/baseline, but not used for stratification:

- Number of prior treatment lines (with description of treatment regimens, including first line treatment and stem cell transplant)
- MCL International Prognostic Index (MIPI) score at time of initial diagnosis, if available
- MIPI score at randomization

- Ki-67 index in the original pathology specimen at diagnosis, if available or at time of relapse
- Age and gender
- Absolute lymphocyte counts at baseline
- Time since last rituximab to cycle 1 day 1

The patients in the study will undergo three consecutive phases: Screening phase, Treatment phase, and Follow-up phase.

Screening phase:

Patients will be screened for protocol eligibility within 28 days prior to randomization as outlined in Table 2: Schedule of Study Assessments. Screening/baseline assessments will begin once the patient has accepted and signed the informed consent form. Complete blood count (CBC) and serum chemistry tests will be required within 7 days of first dose of study drug. Serology, for HBV (at least HBsAg, anti-HBs and anti-HBc) and for HCV will be required as screening assessment within 28 days of randomization in endemic areas. Eligibility for the study is based on the local assessments (CBC, chemistry and serology as well as the local results of the archival tumor / lymph node biopsy) done during the screening/baseline phase of the study.

Confirmation of mantle cell lymphoma diagnosis by the central pathology is not required before randomization or treatment start, but will be performed centrally at a later stage. Eligibility for the study is based on assessment of the local pathology results by the investigator. Diagnosis based on needle aspirations are not considered acceptable pathologic data for entry in this study.

The confirmation material submitted for Central Pathology Review must include a biopsy-proven mantle cell lymphoma specimen, including overexpression of cyclin D1 by immunohistochemistry. In patients whose tumors are negative for Cyclin D1 overexpression, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable.

Tumor / lymph node biopsy specimen, which may be archival slides from specimen obtained at the time of initial diagnosis, with representative stained slides supporting the diagnosis of mantle cell lymphoma (H&E or Giemsa staining and Cyclin D1 staining), must be sent as soon as possible to central pathology before randomization but at the latest 8 weeks after randomization. It is highly recommended to submit also the original paraffin block (called tumor block) which will be returned to the original institution. If the tumor block cannot be sent, 4-5 additional unstained slides must be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. Evidence of the translocation t(11;14)(q13:q32) by FISH can be submitted using the original slide or the corresponding confirming photographies. If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD10, CD20, CD23, BCL2, Ki-67.

Furthermore, it is highly recommended to perform an unilateral bone marrow biopsy at screening, and to send it to Central Pathology for review at the latest 8 weeks after randomization.

During the screening/baseline phase, the investigator must allocate one of the "investigator's choice" options to the patient prior to the randomization.

Treatment phase:

Once all eligibility criteria are met and baseline assessments completed, patients will be randomized 2:1 to receive lenalidomide monotherapy or the investigator's choice. The first treatment dose of the first cycle administered to the patient is called C1D1. Treatment should start as soon as possible after randomization, but maximum time between randomization and C1D1 is 4 days, once the patient has fulfilled the requirements of the Lenalidomide pregnancy prevention program (see Appendix 21.8). Patients will continue in the treatment phase until disease progression, unacceptable toxicity or voluntary treatment withdrawal. Toxicity will be assessed using the NCI CTCAE criteria version 3 and the dose of lenalidomide or the investigators choice single agent will be reduced accordingly (see Table 8 and Table 9 for dose reductions).

Serial assessments of safety and efficacy (CT scans with contrast /MRI with contrast every 56 days ± 7 days for the first 6 months and then every 90 days ± 15 days thereafter) will be performed as outlined in the Schedule of Study Assessments or as directed in the dose modification section. Patients may continue participation in the treatment phase of the study until disease progression or unacceptable toxicity or voluntary patient withdrawal from treatment, at which point, the patients will enter the follow-up phase.

Diagnostic imaging results (CT scan with contrast/MRI with contrast) will be reviewed locally and also sent for central review.

CT scans is the preferred procedure. If CT is contraindicated, MRI is acceptable. It is advised to stick to the same procedure for a given patient throughout the study.

Patients who withdraw consent for treatment will continue to be followed for safety, efficacy (disease progression), second primary malignancies, and for survival.

Prophylaxis for TLS and thromboembolism and assessment and management of tumor flare in patients assigned to receive lenalidomide:

Tumor flare and tumor lysis have been reported in patients with chronic lymphocytic leukemia treated with lenalidomide. Tumor flare and tumor lysis have also been noted in a smaller proportion of patients with non-Hodgkin's lymphoma treated with lenalidomide,

based on limited data. Patients in this study should be monitored for tumor flare and tumor lysis.

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is a well-known constellation of metabolic abnormalities resulting from spontaneous or treatment related tumor necrosis or fulminant apoptosis. The metabolic abnormalities include: hyperkalemia, hyperuricemia and hyperphosphatemia with secondary hypocalcaemia.

In patients with CLL, the onset of TLS is rapid, usually within 24 to 48 hours after the first dose but can also occur after the first week of treatment. The presence of known risk factors like bulky disease, moderate renal insufficiency, high ALC and high uric acid levels (> 8 mg/dL) prior to therapy increases the likelihood of TLS. Early identification of patients 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, 2004).

Patients in the lenalidomide arm in this study should receive tumor lysis prophylaxis (allopurinol or equivalent) and be well hydrated (orally) during the first 7 days of lenalidomide administration in the first cycle or as clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for tumor lysis syndrome and cytopenia(s), the patients will have a complete blood count (CBC) and chemistry drawn on Days 1, 2, 4, 8 and 15 of the first cycle and additionally as clinically indicated. TLS will be assessed by Cairo-Bishop Grading system. (See Appendix 21.6).

If a patient develops laboratory TLS (defined by the presence of two or more serum value abnormalities of uric acid, potassium, phosphorous or calcium) or ≥ Grade 1 TLS (defined by the presence of laboratory TLS and one or more of the following criteria: creatinine ≥ 1.5 x ULN, arrhythmia or seizures), appropriate medical management should be initiated according to the local standard of care in each institution with vigorous IV hydration (rasburicase treatment is considered appropriate if it is approved by the local Health Authority).

Tumor flare reaction

Tumor flare reaction (TFR) is defined as a sudden and tender increase in the size of the disease bearing sites, including the lymph nodes, spleen and or the liver often accompanied by low-grade fever, non-pruritic diffuse rash and in some cases increase in the peripheral blood lymphocyte counts. In CLL patients, the onset of tumor flare may be as early as within a few hours after the first dose and has a median duration of 14 days. This usually occurs only during the first cycle of treatment. Tumor flare will be recorded as an AE (graded using the NCI CTCAE criteria version 3) and not as progressive disease (PD) and will be treated symptomatically first with non-steroidal anti-inflammatory agents (NSAIDs). Narcotics or prednisone may be used at the investigator's discretion, to treat the tumor flare reaction.

Thromboembolism

All patients treated with lenalidomide regardless of prior thromboembolic history will receive prophylactic aspirin [ASA] (70 – 100 mg) daily unless contraindicated. If ASA is

contraindicated, use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the International normalized ratio (INR) in the range of 2-3 may be considered.

The choice of prophylactic agent(s), and also the interruption or discontinuation of such prophylaxis if needed, should be based on the local standard of care and the investigator's best judgement after careful consideration of the benefit versus the potential risk for the individual patient.

Cross over (for patients in the investigators choice Arm B only):

Patients in the investigator's choice arm B, who have documented progressive disease will have the option to receive single agent lenalidomide treatment. Patients will undergo baseline assessments as outlined in the schedule of assessments of Table 3 for Cycle 1 Day 1.

For patients in Arm B treatment with lenalidomide will start as soon as recovery from toxicities of prior treatments. The maximum duration between last day of last cycle of treatment in Arm B and first lenalidomide cycle is 10 weeks. Patients in cross-over treatment with lenalidomide will be assessed for safety, response evaluation, second primary malignancies, and overall survival follow-up. CT scans with contrast /MRI with contrast are recommended to be performed every 90 days (± 15 days) from the start of lenalidomide cross-over treatment until disease progression or treatment discontinuation for any other reason (i.e. toxicity) [Table 3]. Once a patient experiences disease progression or relapse or a patient has stopped treatment for other reasons the patient will enter the follow-up phase. In the follow-up phase for patients with progressive disease only assessments for safety (including second primary malignancies) and overall survival will be done. For patients who have entered the follow-up phase due to treatment discontinuation for other reasons additionally CT scans with contrast /MRI with contrast will be performed at pre-defined intervals and assessments for safety (including second primary malignancies) and overall survival will be done. Patients will be followed until either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time the study will end for ongoing subjects still on lenalidomide treatment in countries where lenalidomide is available post-trial in the commercial setting. Subjects on study treatment will be transferred to post-trial access in the commercial setting (wherever applicable). An Extended Access Phase will be made available for subjects on study treatment in countries where lenalidomide is only available under a clinical trial protocol as post-trial access. The Extended Access Phase will end for ongoing subjects as soon as lenalidomide can be accessed in the commercial setting.

Follow-up phase

Subjects withdrawn for any reason from the Extended Access Phase will not participate in a study follow-up phase. At their next visit 28 days later any SAEs experienced during this time window will be reported via the standard post-marketing process. Thereafter prescribers will be expected to follow the normal post-marketing SAE reporting requirements as applicable in their country

Once a patient experiences disease progression or relapse or a patient has stopped treatment for other reasons, the patient will enter the follow up phase.

- **All patients who discontinue** treatment in either study arm or cross-over treatment will undergo a safety follow-up visit 28 days after last dosing day for assessment of adverse events (including a physical examination), lenalidomide counseling and for a medically supervised pregnancy test for FCBP in Arm A and in cross over as specified in Appendix 21.8. Vital signs, CBC with differential, and serum chemistry are to be performed as clinically indicated. A 28-day safety follow-up assessment will not be required either for subjects transferred to post-trial access in the commercial setting or to the Extended Access Phase. These subjects will have a "discontinuation from treatment" visit at the end of their 7 day rest period from their last on-study treatment cycle. At this "discontinuation from treatment" visit commercial lenalidomide will be dispensed to the subject. Between this visit and 28 days after, if a patient experiences a SAE, this SAE will be reported via the standard post marketing process. A pregnancy test should be performed 28 days post treatment discontinuation visit.
- Patients who discontinue treatment **due to progressive disease or relapse:**
  - Should be followed by clinic visit or documented telephone contact every 90 days (± 15 days) for survival, second primary malignancies and for the first subsequent antilymphoma therapy (including the time of and best response to the first antilymphoma treatment regimen utilized after discontinuation from treatment in this study)
- Patients who discontinued treatment **due to reasons other than progressive disease or relapse:**
  - Clinic visits should occur every 56 days to assess disease status (physical exam) until disease progression or relapse
  - CT scan with contrast/MRI with contrast should occur every 56 days (± 7 days) until disease progression or relapse up to 6 months from the start of study drug then every 90 days ± 15 days thereafter.
  - After disease progression or relapse has occurred, patients should be followed by clinic visit or documented telephone contact every 90 days (± 15 days) for survival, second primary malignancies and for the first subsequent antilymphoma therapy (including the time of and best response to the first antilymphoma treatment regimen utilized after discontinuation from treatment in this study).
  - Patients in the follow-up phase who withdraw consent for efficacy (disease progression) follow-up will continue to be followed for second primary malignancies and for survival. A full consent withdrawal must be documented to disallow survival follow up.

The follow-up phase will continue until either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall

response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time the follow-up study phase will be closed.

Extended Access Phase:

Following the approval of Protocol Amendment #6 an Extended Access Phase will be made available for subjects on study treatment in countries where lenalidomide is only available under a clinical trial protocol as post-trial access.

These subjects will have a "discontinuation from treatment" visit assessment prior to being transferred to the Extended Access Phase.

Following the approval of Protocol Amendment #6, subjects on study treatment will be considered to have entered the study Extended Access Phase. Study visits and serial measurements of safety should continue to be performed as per guidance outlined in Table 4.

Subjects may remain on study until progressive disease or withdrawal for other reasons. Only serious adverse events (SAEs) including second primary malignancies (SPMs), and drug accountability record information will be collected and reported for these subjects. Follow-up survival data will no longer be collected by Celgene for these subjects.

The Extended Access Phase will end for ongoing subjects still on lenalidomide treatment as soon as lenalidomide can be accessed in the commercial setting.

Data Monitoring Committee

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study and efficacy for futility at a pre-defined time point. Specifics are outlined in the DMC charter. The first safety analysis will occur after the first 40 patients have received at least 2 cycles of treatment or have discontinued prior to completing 2 cycles. The second safety analysis as well as an efficacy analysis for futility will occur after 80 patients complete 2 cycles or withdraw before completing 2 cycles. A third safety analysis will occur after 120 patients complete 2 cycles or withdraw before completing 2 cycles. A fourth safety analysis will occur after 200 patients complete 2 cycles or withdraw before completing 2 cycles.

Independent External Pathological Review

An independent central pathologist will review the lymph node/tumor biopsy for retrospective confirmation of the diagnosis of mantle cell lymphoma.

The confirmation material submitted for Central Pathology Review must include a biopsy-proven mantle cell lymphoma specimen, including overexpression of cyclin D1 by immunohistochemistry. In patients whose tumors are negative for Cyclin D1 overexpression, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable.

Tumor / lymph node biopsy specimen, which may be archival slides from specimen obtained at the time of initial diagnosis, with representative stained slides supporting the diagnosis of mantle cell lymphoma (H&E or Giemsa staining and Cyclin D1 staining), must be sent as soon as possible to central pathology before randomization, but at the latest 8 weeks after randomization. It is highly recommended to submit also the original paraffin block (called tumor block) which will be returned to the original institution. If the tumor block cannot be

sent, 4-5 additional unstained slides must be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. Evidence of the translocation t(11;14)(q13:q32) by FISH can be submitted using the original slide or the corresponding confirming photographies. If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD10, CD23, CD20, BCL2, Ki-67.

Furthermore, it is highly recommended to perform an unilateral bone marrow biopsy at screening, and to send the tumor block to Central Pathology for review at the latest 8 weeks after randomization.

The central pathologist will also review any pathology specimens obtained as part of response assessment, including assessment of bone marrow biopsy required for response assessment of CR/CRu.

For further details, please refer to central pathology manual.

Independent Review Committee (IRC):

The IRC is composed of two external independent radiologists (with an additional radiologist adjudicator in the event of a tie) and a hemato/-oncologist. The IRC will perform a blinded, independent assessment of radiological response (including assessment of Stable Disease [SD] and Progressive Disease [PD]); review the tumor response data and the dates of disease progression for each patient. The data reviewed by the IRC will be used in the primary analysis and these assessments will be included in the Clinical Study Report.

– **Number of patients**: approximately 250 randomized patients

Study Population

Inclusion Criteria

- Patients with histologically proven mantle cell non-Hodgkin's lymphoma [MCL] {including overexpression of cyclin D1 by immunohistochemistry}. In patients whose tumors are negative for the cyclin D1 overexpression or translocation, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable.
- Patients who are refractory to their regimen or have relapsed once, twice or three times and who have documented progressive disease (Refractory to prior chemotherapy regimens is defined as not having reached a CR or PR to prior treatment)
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2
- Must be ≥18 years of age at the time of signing the informed consent form.

- Must have had at least one prior combination chemotherapy regimen with an alkylating agent, and comprising either an anthracycline and/or cytarabine and/or fludarabine (with or without rituximab)
- Prior stem cell transplant is allowed.
- Must be ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study
- Must have measurable disease on cross sectional imaging by CT (or MRI, if CT is contraindicated) that is at least 2 cm in the longest diameter and measurable in two perpendicular dimensions
- Must be able to adhere to the study visit schedule and other protocol requirements
- Life expectancy of greater than 3 months
- Females of childbearing potential (FCBP)† must:
  - Have two negative medically supervised pregnancy tests prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy (see specifics in Appendix 21.8). This applies even if the patient practices complete and continued sexual abstinence
  - Either commit to continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, highly effective contraception without interruption, at least 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for at least 28 days after discontinuation of study therapy (see specifics in Appendix 21.8)
- Male patients must:
  - Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy (see specifics in Appendix 21.8). Agree to not donate semen or sperm during study drug therapy and for at least 28 days after end of study drug therapy (see specifics in Appendix 21.8)
- All patients must:
  - Have an understanding that the study drug could have a potential teratogenic risk.
  - Agree to abstain from donating blood while taking study drug therapy and for at least 28 days after end of study drug therapy (See specifics in Appendix 21.8)
  - Agree not to share study medication with another person.
  - Agree to be counseled about pregnancy precautions and risks of fetal

† Definition found in appendices

exposure. (See specifics in Appendix 21.8)

Exclusion Criteria

- Diagnosis of lymphoma other than mantle cell lymphoma
- Prior history of malignancies, other than mantle cell lymphoma, unless the patient has been free of the disease for ≥ 5 years. Exceptions include the following:
  - Basal cell carcinoma of the skin
  - Squamous cell carcinoma of the skin
  - Carcinoma in situ of the cervix
  - Carcinoma in situ of the breast
  - Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)
- Transformed lymphoma
- Prior use of lenalidomide
- Patients who are candidates for autologous or allogeneic transplantation at the time of inclusion in the study
- Prior allogeneic transplantation with persistent donor hematopoiesis
- Prior radiotherapy within 4 weeks prior to randomization
- Active CNS lymphoma with the exception of those patients whose CNS lymphoma has been treated with chemotherapy, radiotherapy or surgery, have remained asymptomatic for 90 days (3 months) and demonstrate no CNS lymphoma as shown by lumbar puncture, CT/brain MRI are eligible. Patients with a history of CNS involvement or CNS symptoms will be required to have negative CSF cytology examination and a head CT during the screening period (known and active CNS or leptomeningeal involvement).
- Known seropositive for or active viral infection with human immunodeficiency virus (HIV)
- Known seropositive for or active viral infection with hepatitis B virus:
  - HBsAg positive.
  - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA.
  - Patients who are HBsAg negative and viral DNA negative are eligible.
  - Patients who had hepatitis B but have received an antiviral treatment and show no detectable viral DNA for 6 months are eligible.
  - Patients who are seropositive because of hepatitis B virus vaccine are eligible.
- Known seropositive for or active viral infection with hepatitis C virus
  - Patients who had hepatitis C but have received an antiviral treatment and show

no detectable viral RNA for 6 months are eligible.

- Patients who are not willing to take DVT prophylaxis, if they are at risk (see definition in Section 10.1.6)
- Patients should not be receiving corticosteroids 7 days prior to randomization, except for prednisone ≤ 10 mg/day or equivalent for purposes other than treating MCL
- Pregnant or lactating females
- Any of the additional following laboratory abnormalities:
  - Absolute neutrophil count (ANC) <1,500 cells/mm^3 (1.5 x 10^9/L)
  - Platelet count < 60,000/mm^3(60 x 10^9/L)
  - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) > 3.0 x upper limit of normal (ULN), except in patients with documented liver involvement by lymphoma
  - Serum total bilirubin > 1.5 x ULN, except in case of Gilbert's Syndrome and documented liver involvement by lymphoma.
  - Calculated creatinine clearance (Cockcroft-Gault formula) of < 30 mL/min
- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form.
- Participation in another clinical trial during the screening/baseline phase and treatment phase of the study.
- Any use of experimental drug during 4 weeks prior to randomization.

Investigational product, dosage and mode of administration [Arm A]:

- Patients, who have a creatinine clearance ≥ 60 mL/min, will receive oral lenalidomide that is initiated on Day [D] 1 of Cycle 1 at a dose of 25 mg [p.o.] once daily for 21 days (D1 – D21) in each 28 day cycle.
- Patients 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 for 21 days (D1 – D21) in Cycle 1 and Cycle 2. After Cycle 2, if the patient remains free of Grade 3 or Grade 4 toxicity, the dose will be increased to 15 mg once daily for 21 days (D1 – D21) in each 28 day cycle.

Treatment is to be continued until disease progression or unacceptable toxicity.

Study Drug Supplies:

Following the approval of Protocol Amendment #6, Celgene Corporation will supply 5 mg, 10 -mg, 20 mg, and 25 mg strengths in countries where lenalidomide is only available under a clinical trial protocol. No more than a 21-day supply of study drug will be dispensed at a time.

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Health care providers should consider wearing gloves when directly handling Revlimid (lenalidomide) capsules followed by standard hand washing.

Other recommended medications such as aspirin will be provided by the investigative site. Celgene will not provide these medications.

Patients in Arm B will receive investigator's choice single agent reference therapy. This includes:

Chlorambucil tablets 2 mg;

Rituximab 500 mg vials;

Cytarabine Injection Solution 100 mg/ml;

Gemcitabine 1g vial;

Fludarabine 10 mg film-coated tablets;

Fludarabine 25mg/ml Concentrate for Solution for Injection or Infusion:

Please refer to the prescribing information provided by Celgene **on all** of the above

For dosing of the investigators choice single agents, please refer to Table 3 based on published data and expert opinions.

Investigators should refer to the approved Summary of Product Characteristics (SPC), provided by Celgene, for the investigator's choice therapy for complete prescribing information including administration, warnings, precautions, contraindications, and adverse reactions and follow institutional procedures for the administration of the agents, where applicable. Paper prints will be provided in the Investigator's and Pharmacy binders.

The investigator's choice treatment will be provided by Celgene.

Assessments:

Efficacy:

- Date of documentation of disease progression
- Overall response rate (PR or better) as defined by a modification of the International Workshop Response Criteria (Cheson, 1999)
- Tumor control rate (CR, CRu, PR or SD)
- CT with contrast/MRI with contrast is performed at baseline then every 56 days (±7 days) after Day 1, Cycle 1 for the first 6 months and then every 90 days ± 15 days thereafter until documented progressive disease; or when clinically indicated

  To ensure comparability, baseline and on-study methods for response assessment must be performed using identical techniques.
- Bone marrow biopsy if the patient has met all other criteria for CR

- Physical Exam

Safety:

- AEs / SAEs severity is graded using NCI CTCAE criteria version 3.0
- Vital signs
- Clinical laboratory evaluations
- ECOG status
- Serum/urine beta-human chorionic gonadotropin (β-hCG) (FCBP only)
- Concomitant medications
- Hospitalizations
- 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 21.1.9). This includes any second primary malignancy, regardless of causal relationship to study drug (lenalidomide or Investigator Choice arm drugs), occurring at any time for the duration of the study, from the time of signing the Informed Consent Document (ICD) through follow-up for overall survival. The Follow-Up Phase involves patient contact every 90 days (± 15 days) until patient death or until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time the follow-up study phase will be closed. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents.
- Following the approval of Protocol Amendment #6, only SAE data (including SPMs) will continue to be collected and reported to Celgene on SAE CIOMs forms for subjects in the Extended Access Phase.

Statistical Analysis:

Sample Size:

The main objective of the study is to demonstrate the efficacy of lenalidomide over an investigator's choice single agent based on PFS. The primary analysis is to compare PFS between lenalidomide and investigator's choice monotherapy.

Protocol Amendment #4:

The third independent DMC meeting was held on July 22, 2011, in which the committee

members reviewed un-blinded both safety and efficacy data from 166 randomized patients. No safety concerns were noted. The DMC observed that the interim PFS in the control arm is different from the intial assumptions which were used to calculate the sample size described in Protocol Amendment #2.

The DMC therefore recommended increasing the sample size from 174 (number of patients randomized at the time of the DMC was held) to 250 patients and conducting the underpowered primary analysis one year after the last patient being randomized. This would allow a more reliable estimation of the treatment effect aiming at demonstrating a clinically meaningful improvement in PFS between the experimental arm and the control arm. In addition, the proposed timing for the analysis will allow a reasonable follow up for overall survival so full information on the clinical benefit of lenalidomide can be provided at the time of PFS analysis.

The type I error will be controlled with adequate methods and the details will be further described in the SAP.

Protocol Amendment #2

With a hazard ratio of 1.7, full information necessary for a one-sided log rank test with an overall alpha of 0.025, to have 80% power, will be achieved when approximately 128 patients have progressed or died (PFS).

Original Protocol

The sample size of this study was originally calculated to estimate the Overall Response Rate (ORR), which was the original objective of the study. Sample size calculation was based on the width of the 95% confidence interval around a certain point estimate for ORR that is considered significant clinical activity. Based on preliminary data, a response rate in the range of 30% to 40% was reasonably expected. A sample size equal to 100 allows us to construct a two sided 95% confidence interval with a width of 9% (one direction) for an expected proportion of 30%. The lower observed confidence interval limit would be about 21%, which was still considered clinically meaningful. This sample size allowed a width (one direction) of 9.6% for an expected proportion of 40% and 9.3% for an expected proportion of 35% (See Table 10).

Table 9 Confidence Intervals

	95% Two-Sided Confidence Intervals (N=100)		
Response rate	30%	35%	40%
CI[1]	0.214 – 0.400	0.257 – 0.452	0.303 – 0.503

[1] Exact confidence intervals based on the Clopper-Pearson method

Using a one group $\chi 2$ test with a 0.050 two-sided significance level a sample size of 100 patients will have 81% power to detect the difference between the Null hypothesis proportion of 20% and the alternative proportion of 32%. No formal sample size calculation will be done for the control arm. With a 2:1 ratio 50 patients are needed in the control arm. Assuming that 10% of patients will be lost to follow up, 167 patients were to be randomized.

Efficacy Analysis:

The *primary endpoint* is progression free survival (PFS). PFS is defined as the time from randomization until objective tumor progression or death for any reason. Patients who do not progress at the time of analysis will be censored. Progression will be determined according to the International Workshop Response Criteria (IWRC) (Cheson, 1999), as modified by Fisher et al 2006; Kane et al 2007 for target lesions will be used (see Section 21.5 and Table 8 for a detailed description of the modifications). The assessment will be reviewed by an independent review committee. The primary analysis will be done in the intent-to-treat (ITT) population for PFS, overall response rate, overall survival and secondary endpoints. All patients who have received at least one single treatment dose (C1D1) with centrally confirmed histology of mantle cell non-Hodgkin's lymphoma will be included in the sensitivity analysis. Sensitivity analyses will be conducted for the primary and secondary endpoints based on the Full Analysis Set (FAS), and the Per Protocol set (if the PPS population differs ≥10% in size from the FAS).

Further *secondary endpoints* include:

- Overall response rate (CR, CRu and PR)
- Duration of response: will be measured from the time of initial response (at least PR) until documented tumor progression or death. Patients who do not progress at the time of analysis will be censored. This analysis will be restricted to responder patients.
- Tumor control rate (Rates for CR, CRu, PR and stable disease [SD])
- Duration of stable disease: will be calculated as the time from the first evidence of stable disease to documented disease progression or documented response or death. Patients who do not progress or respond at the time of analysis will be censored. This analysis will be restricted to the subgroup of stable disease patients.
- Time to progression, (TTP) is defined as the time from randomization until objective tumor progression; TTP does not include deaths. Patients without progression at the time of analysis will be censored. Deaths due to progression of disease will be considered as an event.
- Time to tumor response (TTR) is defined as the time from randomization until confirmed response (CR, CRu, PR). Patients with SD or progression at the time of analysis will be censored.
- TTF is defined as the time from the first dose of study drug to discontinuation of treatment for any reason, including disease progression, treatment toxicity or death. Patients who are still on drug at the time of the analysis or complete the treatment according to the protocol will be censored.
- Overall survival: defined as the time from randomization until death from any cause. Patients alive or lost to follow up at the time of analysis will be censored.
- QoL (EORTC QLQ-C30)

- Safety

Efficacy analysis will be conducted one year after the last patient is randomized.

An update of the time to events endpoints and overall survival will be done at the end of the follow up. No adjustment for multiplicity will be applied.

All efficacy analysis will be conducted on intent to treat basis.

The Kaplan-Meier procedure will be used to characterize time to event endpoints and duration of response. Median times-to-event and their respective two-sided 95% confidence intervals will be provided for each of these variables. The stratified log-rank test will be used as the main analysis to compare treatment arms for time-to-event variables and an unstratified log-rank test will be used as supportive analysis. The Cox proportional hazards regression model will be used to assess the significance of stratification factors on treatment differences. Any demographic or baseline characteristics variables considered as strong predictive or prognostic factors will also be included as part of the formal statistical analysis plan. The MIPI score at randomization will be analyzed as a stratification factor.

Data will be analyzed and displayed per treatment group in a descriptive manner.

The probability of response rate will be estimated using the proportion of patients with responses with exact two-sided 95% confidence intervals.

The EORTC QLQ-C30 will be analyzed using change from baseline and percentage of change from baseline according to functional scores and the recommendations in the EORTC manual.

The response rate in the cross-over portion of patients in Arm B will be analyzed in a descriptive manner.

Interim analysis and DMC:

An independent Data Monitoring Committee will review the safety data and efficacy data for futility to assess benefit to risk considerations throughout the study.

Futility analysis will be conducted when approximately 80 patients complete 2 cycles or withdraw before completing 2 cycles (around 54 patients in the lenalidomide arm). Additional efficacy and safety data might be provided to the DMC members on request as outlined in the DMC charter.

DMC will conduct an analysis for futility on PFS and Overall response rate. No specific stopping rules will be given to the DMC for the PFS; the following rules might be used for overall response rate.

Based on a 95% CI approach, if the upper bound is below 20% in the lenalidomide arm, the DMC should recommend stopping the trial.

Frequency of response	Binomial Proportion P	Exact Lower CL, Binomial Proportion[1]	Exact Upper CL, Binomial Proportion[1]
1	1.8519	0.04687	9.8915
2	3.7037	0.45173	12.7472
3	5.5556	1.16068	15.3885
4	7.4074	2.05510	17.8933
5	9.2593	3.07528	20.3002
6	11.1111	4.18838	22.6313
7	12.9630	5.37430	24.9012
8	14.8148	6.61976	27.1198
9	16.6667	7.91544	29.2941
10	18.5185	9.25455	31.4297

[1]Exact confidence intervals based on the Clopper-Pearson method

Safety analysis:

Data from all patients who received at least one dose of study drug will be included in the safety analyses.

Adverse event severity will be classified using the NCI CTCAE criteria, version 3.0.

Adverse event frequency will be tabulated by body system, and MedDRA term.

In the by-patient analysis, a patient having the same event more than once will be counted only once. Adverse events will be summarized by worst NCI CTCAE grade. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, study-drug related events, and serious adverse events will be listed separately.

Second primary malignancies throughout the course of the study will be monitored as events of interest, and will be listed and be analyzed separately.

The probability of dose reduction will be estimated using the proportion of patients with dose reduction.

Laboratory data will be graded according to NCI CTCAE severity grade.

Extended Access Phase:

For the Extended Access Phase only SAE (including SPMs) data will be reported to Celgene drug safety. No statistical analysis is planned to be performed on this safety data.

Table 2: Schedule of Study Assessments for Arm A and Arm B patients (28 days = 1 cycle)

Procedure	Screening/ Baseline (-28 Days)	Every Cycle Day 1 ± 3 days[25]	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2-4 Day 15 ± 1 day	Every 56 days After Cycle 1 Day 1 ± 7 days for the first 6 months and then every 90 days ± 15 days thereafter	At Treatment Discontinuation	Follow-up for patients after PD[21]	Follow-up for non-PD patients[22]
Inclusion/exclusion criteria	X							
Complete medical history	X							
CNS Lymphoma Evaluation[1]	X							
MCL International Prognostic Index (MIPI)[2]	X							
Prior lymphoma therapy	X							
Creatinine Clearance (Cockcroft-Gault estimation)[3]	X							
12-Lead ECG[4]	X							
Lymph node or tumor biopsy specimen slides[5]	X							
Eastern Cooperative Oncology Group (ECOG) performance status	X	X				X		
Vital Signs[6]	X	X				X		
CBC with Differential[7]	X	X	X[9]	X		X		
Serum Chemistry[8]	X	X	X[9]	X		X		
Serology HBV, HCV in endemic areas	X							
Thyroid function test[18]	X							
Pregnancy Testing (FBCP only)	X[10]	X[11]				X[11]	X[11]	X[11]
Lenalidomide Counseling and distribute lenalidomide Information Sheet[12]	X	X					X[13]	X[13]
Assessment of Lymphoma-related Symptoms	X	X				X		
Adverse Events	X	X	X	X		X	X[14]	X[14]
Record Hospitalizations		X				X		
Assessment of Second Primary Malignancies[15]	X	X	X	X		X	X	X
Tumor Flare / Tumor lysis Assessment[16]			X[16]					
Concomitant medications/Procedures	X	X	X			X		
Physical examination[17]	X	X				X	X	X

Table 2: Schedule of Study Assessments for Arm A and Arm B patients (28 days = 1 cycle) (Continued)

Procedure	Screening/ Baseline (-28 Days)	Every Cycle Day 1 ± 3 days[25]	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2-4 Day 15	Every 56 days After Cycle 1 Day 1 ± 7 days for the first 6 months and then every 90 days ± 15 days thereafter	At Treatment Discontinuation	Follow-up for patients after PD[21]	Follow-up for non-PD patients[22]
CT with contrast (or MRI with contrast, if CT contraindicated) of neck, chest, abdomen and pelvis[19]	X[26]				X[19]			X[19]
Target and non-target lesion measurements[19]	X				X[19]			
Response assessment					X[19]			
Progression-Free Survival[20]					X[19]		X	X
Overall survival							X[21]	X[22]
Quality of Life	X[23]	X[23]				X[23]		
Bone Marrow Biopsy	X[24a]				X[24b]			
Dispense study drug[25]		X[25]						
Study drug return		X				X		

1 Patients with a history of CNS involvement or CNS symptoms will be required to have negative CSF cytology examination, and a head CT/brain MRI during the screening/baseline period.

2 MIPI: age, performance status, LDH, absolute leukocyte count, at time of diagnosis, if available.

3 Cockcroft-Gault estimation of creatinine clearance (CrCl): CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]); for females, the formula is multiplied by 0.85. Creatinine clearance should be determined utilizing actual body weight or ideal body weight, which ever is less (Cockcroft, 1976; Luke, 1990).

4 12-Lead ECG is performed at baseline and as clinically indicated thereafter.

5 Representative slides documenting the diagnosis (H&E or Giemsa staining) and supporting the diagnosis of MCL (Cyclin D1 immunostaining), shall be sent together with the tumor block to central pathology as soon as possible, preferably before randomization for confirmation of mantle cell lymphoma, but at the latest 8 weeks after randomization. In patients whose tumor is negative for Cyclin D1, evidence of overexpression of Cyclin D2 or D3 is acceptable. Additionally, slides supporting the translocation by FISH or corresponding confirming photographies shall be submitted at the same time, if available. It is also recommended to send for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD23, CD20, BCL2, Ki-67. In case the tumor block can not be sent, 4-5 additional, unstained slides must also be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

6 Vital signs include weight, height (only at screening), blood pressure, temperature, and pulse.

7 Complete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, MCV, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.

[8] Serum chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, sodium, potassium, blood urea nitrogen, creatinine and LDH).

[9] If screening/baseline assessment hematology, and chemistry labs are performed within 7 days before Cycle 1, Day 1, they do not need to be repeated on Cycle 1, Day 1.

[10] Only for patients in Arm A and patients in cross over: before starting study drug: Females of Childbearing Potential (FCBP) must confirm that they are using reliable methods of birth control, and must have two negative pregnancy tests prior to starting study drug: The first pregnancy test must be performed within 10-14 days prior to the start of study drug, and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative. All patients will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. (See specifics as described in Appendix 21.8).

[11] Only for patients in Arm A and patients in cross over: during the study participation and for 28 days following discontinuation from the study treatment: FCBP must agree to have two pregnancy tests (See specifics as described in Appendix 21.8). In addition to the required pregnancy testing, the investigator must confirm with FCBP that she is continuing to use reliable methods of birth control at each visit (See specifics as described in Appendix 21.8).

[12] Only for patients in Arm A and patients in cross over: all patients must be counseled about pregnancy precautions and risks of fetal exposure.

[13] Only for patients in Arm A and patients in cross over: after 28 days post-last dose of lenalidomide.

[14] Adverse events will be assessed 28 days post-last dose of treatment during follow-up.

[15] 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 21.1.9). This includes any second primary malignancy, regardless of causal relationship to study drug (lenalidomide or Investigator Choice arm drugs), occurring at any time for the duration of the study, from the time of signing the ICD through follow-up for overall survival. The Follow-Up Phase involves patient contact every 90 days (± 15 days) until patient death or until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time the follow-up study phase will be closed. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory pathology results, imaging results, etc.).

[16] Tumor flare / tumor lysis syndrome assessment, only for patients in Arm A, at **Cycle 1: Day 2, 4, 8, and 15**, and when clinically indicated thereafter.

[17] Physical examination including lymphadenopathy, hepatomegaly, and splenomegaly as clinically indicated. Physical examination on study should be done at baseline, Cycle 1 D1 and D15 and then Day 1 of every Cycle.

[18] Thyroid function tests (TSH, fT3, fT4) are performed at baseline/screening only and as clinically indicated.

[19] CT with contrast/MRI with contrast must be performed every 56 days (± 7 days) up to 6 months from the start of study drug then every 90 ±15 days thereafter, during the follow up phase for patients who have discontinued study treatment due to adverse events without evidence of progressive disease. CT scan with contrast /MRI with contrast does not need to be performed during follow-up for patients who discontinued due to disease progression or relapse.

[20] Progression free survival is assessed until progression of disease or until next lymphoma treatment is given, whichever comes first. Patients in the investigators choice Arm B have the option to receive lenalidomide at time of documented disease progression.

[21] Patients will be followed (clinic visit or documented telephone contact) for overall survival every 90 days (± 15 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later. At this time the follow-up study phase will be closed.

[22] Patients will be followed (clinic visit or documented telephone contact) for overall survival every 56 days (± 7 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later. At this time the study will end for ongoing subjects still on lenalidomide treatment in countries where lenalidomide can be accessed post-trial in the commercial setting. An Extended Access Phase will be made available for subjects on study treatment in countries where they can only access lenalidomide under a clinical trial protocol as post-trial access. These subjects will have a "discontinuation from treatment" visit assessment prior to being transferred to the Extended Access Phase. The Extended Access Phase will end for ongoing subjects as soon as lenalidomide can be accessed in the commercial setting. Follow-up survival data will no longer be collected by Celgene for these subjects.

[23] QoL will be assessed at screening/baseline after Cycle 2 [C3D1] (±7 days), after Cycle 4 [C5D1] (±7 days), after Cycle 6 [C7D1] (±7 days), after Cycle 8 [C9D1] (±7 days), and at treatment discontinuation (±7 days).

[24a] Unilateral bone marrow biopsy is highly recommended at screening that will be submitted to Central Pathology for review at the latest within 8 weeks after randomization.

[24b] Unilateral bone marrow biopsy during treatment is required only if the patient has otherwise fulfilled the criteria for CR. The bone marrow procedure should be performed 28 days after the criteria for CR have otherwise been met.

[25] Dispense study drug on Day 1 only of each treatment cycle. Cycle 1 should start as soon as possible after randomization, but maximum time between randomization and C1D1 is 4 days, once the patient has fulfilled the requirements of the Lenalidomide pregnancy prevention program. For lenalidomide, a minimum 7 day rest period is mandatory before starting each new treatment cycle regardless of allowed ± visit windows.

[27] If a CT scan or MRI was done within 28 days of the randomization, then the CT scan or MRI does not have to be repeated for the screening assessment.

Table 3: Schedule of study assessments for patients with cross-over on lenalidomide after progression in investigator's choice Arm B (28 days = 1 cycle) – No more than 10 weeks after last day of last cycle of treatment in Arm B

Procedure	Every Cycle Day 1 ± 3 days[13]	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2- 4 Day 15	Every 90 days After Cycle 1 Day 1 ± 15 days	At Treatment Discontinuation	Follow-up for patients after PD[11]	Follow-up for non-PD patients[12]
Eastern Cooperative Oncology Group (ECOG) performance status	X				X		
Vital Signs[1]	X				X		
CBC with differential[2]	X	X	X		X		
Serum Chemistry[3]	X	X	X		X		
Pregnancy Testing for FCBP[4]	X				X		
Lenalidomide Counseling and distribute lenalidomide Information Sheet [5]	X						
Distribute Lenalidomide counseling sheet[5]	X		X				
Dispense study drug[13]	X[13]						
Study drug return	X				X		
Adverse Events[6]	X	X	X		X		X[6]
Assessment of Second Primary Malignancies[7]	X	X	X	X	X	X	X
Tumor Flare /Tumor Lysis Assessment[8]		X					
Record Hospitalizations	X				X		
Concomitant medications/ Procedures	X	X	X		X		
CT with contrast (or MRI with contrast, if CT contraindicated) of neck, chest, abdomen and pelvis[9]				X			X[9]
Target and non-target lesion measurements				X			
Response assessment				X			
Progression-Free Survival[10]				X		X	X
Overall survival						X[11]	X[12]

[1] Vital signs include weight, blood pressure, temperature, and pulse.

[2] Complete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, MCV, white blood cell WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.

[3] Serum chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), sodium, potassium, blood urea nitrogen, creatinine and lactate dehydrogenase).

[4] During the study participation and for 28 days following discontinuation from the study treatment: FCBP must agree to have pregnancy tests (See specifics as described in Appendix 21.8). In addition to the required pregnancy testing, the investigator must confirm with FCBP that she is continuing to use reliable methods of birth control at each visit (See specifics as described in Appendix 21.8).

[5] All patients must be counseled about pregnancy precautions and risks of fetal exposure.

[6] Adverse events will be assessed 30 days post-last dose during follow-up.

[7] 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 21.1.9). This includes any second primary malignancy, regardless of causal relationship to study drug (lenalidomide or Investigator Choice arm drugs), occurring at any time for the duration of the study, from the time of signing the ICD through follow-up for overall survival. The Follow-Up Phase involves patient contact every 90 days (± 15 days) until patient death or until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time the follow-up study phase will be closed. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory pathology results, imaging results, etc.).

[8] Tumor flare/Tumor lysis assessment at Cycle 1: Day 2, 4, 8, and 15, and when clinically indicated.

[9] CT with contrast/ or MRI with contrast must be performed every 90 days (± 15 days) from the start of lenalidomide cross-over treatment, and during the follow up phase for patients who have discontinued treatment due to adverse events without evidence of progressive disease. CT scan with contrast /MRI with contrast does not need to be performed during follow-up for patients who discontinued due to disease progression or relapse.

[10] Progression Free Survival is assessed until progression of disease or until next lymphoma treatment is given, whichever comes first.

[11] Patients will be followed (clinic visit or documented telephone contact) for overall survival every 90 days (± 15 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later. At this time the follow-up study phase will be closed.

[12] Patients will be followed (clinic visit and CT scan/MRI) for overall survival every 90 days (± 15 days) from the start of lenalidomide cross-over treatment until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later. At this time the study will end for ongoing subjects still on lenalidomide treatment in countries where lenalidomide can be accessed post-trial in the commercial setting. An Extended Access Phase will be made available for subjects on study treatment in countries where they can only access lenalidomide under a clinical trial protocol as post-trial access. These subjects will have a "discontinuation from treatment" visit assessment prior to being transferred to the Extended Access Phase. The Extended Access Phase will end for ongoing subjects as soon as lenalidomide can be accessed in the commercial setting. Follow-up survival data will no longer be collected by Celgene for these subjects.

[13] Starting cross-over lenalidomide treatment after disease progression is extensively documented in Arm B should be as soon as toxicities of prior Arm B treatments have resolved and all inclusion/exclusion criteria are met, but not later than 10 weeks after last day of last Arm B treatment cycle and as soon as the patient has fulfilled the requirements of the Lenalidomide pregnancy prevention program. Once lenalidomide treatment is started, a minimum 7-day rest period is mandatory before starting each new treatment cycle regardless of allowed ± visit windows.

Table 4: Schedule of Study Assessments: Guidance for Extended Access Phase

Assessment	Day 1 of Each Cycle[a] Extended Access Phase (± 3 days)	Extended Access Phase Discontinuation (at day of discontinuation)
Informed consent[b]	**X** Prior to first cycle treatment	-
Lenalidomide counseling/distribute lenalidomide counseling sheet	**X**	**X**
Concomitant medication/therapies	**X** recorded in the subjects' records only	**X** recorded in the subjects' records only
Adverse events including assessment of second primary malignancies[c]	**SAEs only**	**SAEs only**
Study drug dispensation/return/accountability	**X**	**X**
CBC with differential[d]	**X** As per local practice	**X** As per local practice
Serum Chemistry[e]	**X** As per local practice	**X** As per local practice
All other safety labs	**X** As per local practice	**X** As per local practice
Pregnancy Testing (FBCP only)[f]	**X**	X **and** at 28 days post discontinuation treatment visit

ALT = alanine transaminase; AST = aspartate transaminase; FCBP = female of childbearing potential; SGOT = serum glutamic-oxaloacetic transaminase; SGPT= serum glutamic-pyruvic transaminase.

a. A cycle is equal to 28 days. If the administration of study drug has not been interrupted, the next cycle of therapy and assessments are to be given/done as in the Treatment Phase of the protocol.

b. Informed consent for the Extended Access Phase must be signed and dated by subjects in countries where they can only continue receiving lenalidomide under a clinical trial protocol.

c. Second primary malignancies (SPMs) will be monitored as events of interest and must be reported as serious adverse events. This includes any SPM, regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the informed consent up to and including the Extended Access Phase. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply. 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.).

d. According to local practice hematology tests should be performed for complete blood cell count (CBC) and will include red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count. This information will no longer be collected by Celgene on an eCRF, however the information will continue to be recorded in the subjects' medical records.

e. According to local practice serum chemistry tests should be performed (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), sodium,

potassium, blood urea nitrogen, creatinine and lactate dehydrogenase. This information will no longer be collected by Celgene on an eCRF, however the information will continue to be recorded in the subjects' medical records.

[f.] For FCBP with regular or no menses and on lenalidomide, pregnancy testing has to occur every 28 days after the first 4 weeks of therapy through 28 days following treatment discontinuation. For FBCP with irregular menses such testing must happen after the first four weeks of treatment though 28 days following treatment discontinuation.

3. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 5: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AE	Adverse event
ALC	Absolute lymphocyte count
ALT (SGPT)	Alanine transaminase (serum glutamic- pyruvic transaminase)
ANC	Absolute neutrophil count
APC	Activated protein C
AST (SGOT)	Aspartate transaminase (serum glutamic-oxaloacetic transaminase)
ASA	Acetylsalicylic acid
ß- HCG	Beta human chorionic gonadotropin
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete response
CrCl	Calculated creatinine clearance
CRu	Complete response unconfirmed
CRF	Case report form
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computerized Tomography
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
ECG	Electrocardiogram

Table 5: Abbreviations and Specialist Terms (Continued)

Abbreviation or specialist term	Explanation
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for Evaluation of Medicinal Products
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FCBP	Female of childbearing potential
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis B virus
HC	Health Canada
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD	Informed Consent Document
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IMiD®	Immunomodulatory drug
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent to treat
IUD	Intrauterine device

Table 5: Abbreviations and Specialist Terms (Continued)

Abbreviation or specialist term	Explanation
IUS	Intrauterine system
IWRC	International Workshop Response Criteria
LDH	Lactate dehydrogenase
MCL	Mantle cell lymphoma
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Drug Regulatory Activities
MIPI	MCL International Prognostic Index
MITT	Modified intent to treat
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NSAIDS	Non-steroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PPS	Per-protocol (Set)
PR	Partial response
PTT	Partial thromboplastin time
PT	Prothrombin Time
QoL	Quality of Life
RDC	Response Determination Committee
RBC	Red blood cell
R-CHOP	Rituximab -Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone
R-Hyper CVAD	Rituximab -Cyclophosphamide Vincristine, Adriamycin and Dexamethasone

Table 5: Abbreviations and Specialist Terms (Continued)

Abbreviation or specialist term	Explanation
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SPD	Sum of the products of the greatest diameter
TCR	Tumor control rate
TFR	Tumor flare reaction
TFT	Thyroid function tests
TLS	Tumor lysis syndrome
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TTF	Time-to-treatment failure
TTP	Time to progression
TTR	Time to tumor response
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WHO	World Health Organization
WMA	World Medical Association

5. INTRODUCTION

5.1. Mantle Cell Lymphoma

Mantle-cell lymphoma (MCL) 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 the cyclin D1 are associated with the landmark t (11;14)(q13;q32) chromosomal translocation (Fernandez, 2005). In rare cases, overexpression of other cyclin D members is seen (Fu, 2005). MCL accounts for approximately 5% of all lymphomas and usually affects predominantly 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 led to an improved ability to diagnose MCL and recognition that most cases had a clinical behavior similar to aggressive lymphomas. There is a subgroup of MCL that show an indolent clinical course, and recent gene profiling studies in the tumor tissue demonstrated a signature of 13 genes that were underexpressed in the indolent tumors when compared to the conventional disease. Notably, SOX11 was absent in indolent cases. This was further validated in an independent series of 112 MCL and lack of SOX11 was associated with increased overall survival (Fernandez, 2010). In addition, several histopathological, cytologic distinct subtypes have been identified, mainly based on the growth pattern and type of proliferation: the typical nodular or diffuse proliferation of atypical lymphoid cells, and the blastoid variant. The blastoid variant mimics acute lymphocytic and follows an aggressive course with a particularly poor prognosis (Schlette, 2001).

Recent efforts have been made to administer intensive chemotherapy including high-dose cytarabine based regimens with rituximab or autologous stem cell transplantation (ASCT) as the upfront therapy in younger patients with good performance status. Several randomized and non-randomized studies have provided evidence that intensive chemotherapy followed by ASCT may benefit patients aged younger than 65 years (de Guibert, 2006; Dreyling, 2005; Geisler, 2008). The reported 3 year overall survival rates range from 70 to75% and thus are above the reported historical median survival data of 3 years.

Unlike other lymphoma types, there is no clear agreement on the treatment to be used for front-line therapy. Most physicians have used rituximab-containing anthracycline-based chemotherapy regimens such as R-CHOP, or on high-dose cytarabine regimens such as R-Hyper CVAD or R-DHAP. Fludarabine-based regimens are also commonly used, however often in the relapsed setting, together with anthracyclines or alkylating agents. The European MCL network currently is conducting a randomized phase III trial comparing first line treatment of R-FC with R-CHOP.

In patients with mantle cell lymphoma who have relapsed after initial therapy including intensive chemotherapy or autologous transplantation, the prognosis is poor and there is no clear consensus on how such patients should be treated. One agent, the proteasome inhibitor Bortezomib has been approved in the US and other countries for the treatment of relapsed/refractory MCL (Fisher, 2006; Kane, 2007). In a single arm phase II study of 155 patients a response rate of 31% was achieved with duration of 9 months.

The main concern with MCL is that relapses occur eventually in most patients and despite initial responses, the remission durations are short. Thus, patients need repeated treatment in order to control the disease as long as possible. Other agents that have been demonstrated to display activity in a variety of B-cell lymphomas are commonly used in relapsed MCL patients. Fludarabine single agent induces response rates of 30 – 40% when used in the first-line setting and 63% when combined with cyclophosphamide (Foran, 1999; Cohen, 2001). Single agent therapy with fludarabine is being used in the relapsed setting once patients have received anthracyclines and cytarabine. (Zinzani, 2000; Tobinai, 2006). Gemcitabine as another nucleoside analogue has distinct antitumor activity in relapsed MCL (Dumontet, 2001). A single center study of 30 patients treated with gemcitabine and dexamethasone showed a response rate of 36% (Morschhauser, 2007). Single agent rituximab led to objective antitumor responses in 22% of the patients with MCL (Ghielmini, 2000). Chlorambucil as a backbone of the treatment of intermediate risk and indolent lymphomas is also used in MCL patients (Rai, 2000; Ardeshna, 2003). Single agent intermediate and high dose cytarabine (2 – 8 g total dose according to the *UK SPC, 2007* for Cytarabine) has shown activity in relapsed refractory non-Hodgkin's lymphoma when administered at doses of 4 – 8 g/m^2 in a 21 to 28 days cycle (Kantarjian, 1983).

However, options are limited for patients with relapsed mantle cell lymphoma and there is a clear need for novel innovative approaches. The increasing understanding of the MCL cell biology has led to the development of new therapeutic agents with antitumor activity that target crucial biological pathways, including cell cycle inhibitors [e.g. flavopiridol], mTOR inhibitors [temsirolimus (Hess, 2009), everolimus (Haritunians, 2007)] and histone deacetylase inhibitors. These new therapeutic approaches have been studied in patients previously treated with aggressive regimens (Kouroukis, 2003; Goy, 2005; O'Connor, 2005). The combination of these new therapeutic strategies and the correct stratification of the patients according to the risk may ultimately change the management and outcome of MCL patients (Jares, 2008).

5.2. Background and Rationale for Lenalidomide

Lenalidomide (REVLIMID® Celgene Corp., NJ, USA) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs. It offers potential benefit over the first commercially available IMiD® compound, thalidomide, in terms of both safety and efficacy in patients (Galustian, 2004). Thalidomide has been evaluated in 16 patients with relapsed/refractory mantle cell lymphoma patients for antitumor activity in combination with rituximab. Thirteen patients (81%) experienced objective response and the estimated 3 year survival ws 75% (Kaufmann, 2004). The key to the therapeutic potential of lenalidomide lies in the fact that it has multiple mechanisms of action, which act to produce anti-inflammatory, anti-angiogenic, and anti-tumor effects. These effects are thought to be contextual in that they depend on both the cell type and the triggering stimulus. To date, lenalidomide has been associated with TNF-α inhibitory, T-cell co-stimulatory, and anti-angiogenic effects (Galustian, 2004).

Lenalidomide is marketed in the United States, Canada and Argentina for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk Myelodysplastic Syndrome (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities and in combination with dexamethasone for patients with previously treated multiple myeloma. Lenalidomide is also approved and marketed in multiple

countries including the US and EU, 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 treatment for various hematological and oncologic indications. Studies have also been conducted in non-oncologic conditions including complex regional pain syndrome.

5.2.1. Preclinical studies with Lenalidomide

Lenalidomide displays antiproliferative effects against hematopoietic tumor cells, especially those of the B cell lineage, including mantle cell Lymphoma. A dose-dependent upregulation of the p21WAF-1 expression was observed in Namalwa lymphoma- cell line, and in U266- and LP-1 multiple myeloma cell lines (Verhelle, 2007). The p21WAF-1 upregulation correlated with increased binding to the cyclin dependent kinases CDK2, CDK4 and CDK6 complexes leading to decreased retinoblastoma protein phosphorylation and G1/G0 cell cycle arrest (Verhelle, 2007). These data suggest that the lenalidomide mechanism of action involves upregulation of p21WAF-1, which may be in part responsible for the antiproliferative activity observed against tumor cells.

The effect of lenalidomide on proliferation of mantle cell lymphoma, and on the expression of several important genes involved in cancer cell cycle, was examined by quantitative real-time polymerase chain reaction. As mentioned before, mantle cell lymphoma usually has a t(11;14) translocation, resulting in cyclin D1 overexpression**.** Results indicate that high baseline cyclin D1 and low p21 gene expression in MCL cell lines correlate with sensitivity to lenalidomide and may be predictive of a good clinical response to lenalidomide. In addition, monitoring of SPARC expression in MCL patients may enable early identification of patients who are responding to lenalidomide therapy. SPARC (osteonectin) is a gene coding for a matrix glycoprotein recently proposed to be a potential tumor suppressor and important for the inhibition of erythroid cell proliferation by lenalidomide. The level of constitutive cyclin D1 gene expression in MCL cell lines correlates with the order of sensitivity to lenalidomide. Conversely, the constitutive p21 gene expression is inversely proportional to lenalidomide sensitivity. Therefore, the baseline cyclin D1 to p21 gene expression *ratio* could be predictive of patient response to lenalidomide therapy. It was also found that lenalidomide markedly increases SPARC gene expression in NHL cells in a manner that correlates with the anti-proliferative activity of lenalidomide. The order of sensitivity to lenalidomide by various NHL cell lines is Namalwa (Burkitt's lymphoma)>Rec-1>Jeko-1>Granta-519>JVM-2 (all MCL)> DB (diffuse large B cell lymphoma). Thus SPARC gene induction may be a biomarker of NHL or MCL tumor response to lenalidomide (Zhang, 2007).

Lenalidomide also enhances T and NK cell stimulation, and augments NK cell-mediated hematopoietic tumor cell lysis, which may contribute to its clinical anti-tumor activity. In both freshly isolated T cells and in differentiated Th1 cells, lenalidomide enhanced T cell proliferation and augmented production of interleukin 2 (IL-2) and interferon γ (IFN-γ) following T cell receptor activation (Corral,1999; Schafer, 2003). Several pre-clinical studies show that the mechanism of lenalidomide comprises T cell activation and may involve induction of the Akt pathway and AP-1 transcriptional activity.

The effects of lenalidomide on NK and T cell activity have also been examined. Using NKT cells from healthy donors and multiple myeloma (MM) patients, *in vitro* treatment with

lenalidomide significantly enhanced NKT cell expansion in response to stimulation with dendritic cells presenting the NKT ligand α-galactosyl-ceramide. Lenalidomide markedly enhanced *in vitro* NK-cell mediated lysis of both MM cell lines and autologous patient MM cells. When the tumor cells were co-cultured with PBMC, lenalidomide enhanced the apoptosis of both K562 cells and Raji cells (Zhu, 2008), supporting an NK cell mediated lysis mechanism.

Thus there is direct antiproliferative activity of lenalidomide against hematopoietic tumor cells, especially those of the B cell lineage and including MCL, via upregulation of the tumor suppressor genes p21 and SPARC. Furthermore, the immunomodulatory effects of lenalidomide on T and NK cells, alone and in combination with antibodies such as rituximab, may enhance its anti-tumor activity in MCL patients.

Furthermore, recent preclinical studies suggest that lenalidomide may promote restoration of anti-tumor immunological effects in patients with certain hematological malignancies. It was reported that patients with CLL have a dysfunction of their T cells (Ramsay, 2008). When the dysfunction was studied using an *in vitro* system, in which the restoration of the immunologic synapse was taken as the functional assay, treatment of both the patient's T cells and the CLL cells was required for synapse formation. It was also reported that the impaired T cell immunological synapse formation was seen in both CD4 and CD8 T cells from follicular lymphoma (FL) patients compared to age-matched healthy donors (Ramsay, 2009). This defect was induced by tumor contact since T cell defects were induced in healthy T cells when they were co-cultured for 48 hr with allogeneic FL cells, but not with healthy allogeneic B cells. In co-culture with FL cells, previously healthy T cells showed suppressed recruitment of integrin LFA-1, Lck, Itk, Rab27A and filamin-A to the synapse in subsequent T cell: APC interactions. It was further demonstrated that the immune synapse defects were repaired in part by treatment of the cells with the immunomodulatory drug lenalidomide. Treatment of both FL B cells and autologous T cells with lenalidomide (0.5 μM for 24h) was required to enhance formation of the F-actin synapse and recruitment of tyrosine-phosphorylated protein and filamin-A irrespective of the presence of exogenous antigen.

Additionally, it was described that lenalidomide up-regulated the expression of genes involved in the immune response, such as co-stimulatory and antigen-presenting molecules (Gaidarova, 2008). Furthermore, lenalidomide treatment induced actin cytoskeleton reorganization and polarization of MCL cells as early as 30 min, prior to a detectable increase of CD1c expression and could be responsible for re-localization of CD1c protein to polarized sites at the plasma membrane. Lenalidomide had similar effects on γδT cells, inducing actin cytoskeleton dynamics and polarization within minutes in these cells. Lenalidomide enhanced the number of γδT-MCL immune synapses and the lytic activity of γδT cells against the tumor cells.

These laboratory observations of direct lenalidomide effects on tumor cells, in inducing the expression of potential tumor suppressor genes and proteins potentially involved in tumor cell recognition by T cells, as well as cellular lenalidomide effects on the host immune cells potentially to improve tumor cell recognition, serve as the scientific basis for the clinical approach described in the clinical trial protocol.

5.2.2. Clinical Studies of lenalidomide in Non-Hodgkin's Lymphoma

Three phase 2 studies of single-agent lenalidomide have been conducted in patients with relapsed/refractory NHL (CC-5013-NHL-001 in indolent NHL and CC-5013-NHL-002 and

NHL-003 in aggressive NHL). The dose/regimen used in these studies was 25 mg p.o. once daily for 21 days (D1 – D21) in 28 day cycle, for maximum of either 52 weeks (NHL-001 or NHL-002) or until disease progression (NHL-003). Patients with mantle cell lymphoma were included in NHL-002 and NHL-003.

In the two phase 2 clinical studies that include aggressive histologies (including MCL, DLBCL, transformed and FL grade 3), the overall response rate (ORR) was 35% in NHL-002 and 36% in NHL-003, respectively (Wiernik, 2008). In NHL002, fifteen of 49 patients had MCL with a median duration of disease of 5.1 years and a median of 4 prior treatments before enrollment. In these MCL patients an ORR of 53% was demonstrated. Three patients (20%) had a CR or unconfirmed CR, and 5 patients (33%) had a PR. The median duration of response was 13.7 months and median PFS was 5.6 months. The most common grade 4 adverse event was thrombocytopenia (13%) and the most common grade 3 adverse events were neutropenia (40%), leucopenia (27%), and thrombocytopenia (20%). (Habermann, 2009). In the second study (NHL-003) which was initiated in November 2006, 217 patients were enrolled. In the 57 MCL patients who were evaluable for response assessment, lenalidomide therapy led to an objective response rate of 42% (25/57). Median progression-free survival (PFS) was 5.7 months. Overall, the primary side effect of lenalidomide was reversible myelosuppression. Grades 3 or 4 neutropenia occurred in 41%, thrombocytopenia in 19%, anemia in 9.2%. Grade 3 and grade 4 febrile neutropenia occurred in only 2% of patients (Witzig, 2011).

5.2.3. Clinical Studies of Lenalidomide in Multiple Myeloma

Two pivotal multicenter, randomized, placebo-controlled studies comparing lenalidomide plus dexamethasone to dexamethasone in relapsed or refractory patients determined that combination therapy with lenalidomide and high-dose pulse dexamethasone is significantly more effective than high-dose pulse dexamethasone therapy alone as judged by time to progression (TTP), progression free survival (PFS), time to –treatment failure (TTF), and the proportion of patients who responded to therapy (MM-009 and MM-010) (Dimopoulos, 2007; Weber, 2007).. In both trials, superior response rates (61% vs. 19.9 % in MM-009 [$p < 0.001$] and 60.2% vs. 24% in MM-010 [$p < 0.001$]) and greater median times to progression (11.1 vs. 4.7 months in MM-009 [$p < 0.001$] and11.4 vs. 4.7 months in MM-010 [$p < 0.001$]) were achieved by patients who were treated with the combination of lenalidomide and dexamethasone compared to patients who received placebo plus dexamethasone. Moreover, patients in the lenalidomide plus dexamethasone treatment group had a significant survival advantage compared to the placebo plus dexamethasone group ($p < 0.001$ and $p = 0.03$ in MM-009 and MM-010, respectively).

5.2.4. Clinical Studies of Lenalidomide in Myelodysplastic syndromes

Lenalidomide has been investigated in patients with MDS in three phase 2 studies for the treatment of patients with transfusion-dependent anemia due to Low-or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. In MDS, lenalidomide was studied at the dose/regimen of 10 mg daily (CC-5013-MDS-002/CC-5013-MDS-003) until disease progression. Results from the CC-5013-MDS-003 study, in MDS with an associated del 5 (q31-33) cytogenetic abnormality, showed transfusion independence in 67 % of the patients. Median duration from the date when red blood cell (RBC) transfusion independence was first declared (the last day of the 56-day RBC transfusion-free period) to the date when an additional

transfusion was received after the 56-day transfusion-free period among responders was 44 weeks. Cytogenetic response was achieved in approximately 75 % of patients. Grade 3/4 neutropenia and thrombocytopenia are the most common AEs associated with the use of lenalidomide, but are manageable with dose reductions and/or interruptions (List, 2006).

5.2.5. Clinical Studies of Lenalidomide in Chronic Lymphocytic Leukemia

Lenalidomide monotherapy has been investigated in two investigator initiated trials (IIT) in patients with relapsed/refractory CLL (Chanan-Khan, 2006) (Chanan-Khan, 2007), (Ferrajoli, 2008). In one study patients with relapsed/refractory CLL were treated with lenalidomide at 25mg x 21 d q 28 days (Chanan-Khan, 2006) (Chanan-Khan, 2007). Results from this study showed an overall response rate of 53% with 18% of patients achieving a CR and 36% achieving a PR. The median PFS time is 19.4 months (1.2 – 38+ months). Fatigue (83%) and flare reaction (tender swelling of lymph nodes and/or rash) (58%) were the most common non-hematologic AEs reported. Other important AEs reported were tumor lysis syndrome (5%); Grade 3 and 4 thrombocytopenia (45%), and Grade 3 and 4 neutropenia (70%). Pulmonary embolism was reported in two patients (5%). In the second IIT study (Ferrajoli, 2008), continuous dosing of lenalidomide was investigated in patients with relapsed/refractory CLL. Lenalidomide was administered daily for 28 days of 28-day cycles until disease progression. An overall response rate of 32% was observed with 3 CR (7%), 1 nodular PR (2%), 10 PR (23%). Myelosuppression was the most common toxicity observed, 41% ≥ Grade 3 neutropenia and 16% Grade 3 thrombocytopenia.

6. STUDY OBJECTIVES

6.1. Primary Objective

- To compare the Progression Free Survival (PFS) of lenalidomide monotherapy versus investigator's choice single agent in patients with mantle cell lymphoma (MCL) who are refractory to their regimen or have relapsed once, twice or three times.

6.2. Secondary Objectives

- To determine the overall response rate (ORR) of lenalidomide monotherapy or investigator's choice single agent in patients with relapsed or refractory MCL.
- To evaluate the safety of lenalidomide monotherapy or investigator's choice single agent in patients with relapsed or refractory MCL.
- To determine the time to progression, and overall survival of patients with relapsed or refractory MCL who have received treatment with lenalidomide or of investigator's choice single agent.
- To investigate the health-related quality of life (QoL) of patients treated with lenalidomide or investigator's choice single agent treatment.

7. STUDY ENDPOINTS

7.1. Primary

- Progression free survival defined as the time from randomization to the first observation of disease progression or death due to any cause. If the patient has not progressed or died, PFS will be censored at the time of last completed assessment when the patient was known not to have progressed. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free.

7.2. Secondary

- Overall response rate (complete response [CR], complete response unconfirmed [CRu], and partial response [PR]) assessed by a modification of the International Workshop Response Criteria IWRC (Cheson, 1999)
- Duration of response
- Tumor control rate (Rates for CR, CRu, PR, and stable disease [SD])
- Time to progression
- Time to treatment failure
- Time to tumor response
- Overall survival (OS)
- Safety
- Quality of Life (EORTC QLQ-C30)

8. OVERALL STUDY DESIGN

8.1. Design Rationale

This study is designed to evaluate the efficacy and safety of lenalidomide therapy versus investigator's choice in patients with relapsed and refractory mantle cell lymphoma. The primary efficacy objective is based on PFS.

The multicenter nature of the study provides assurance that the results are likely to have general applicability. Patient eligibility criteria are consistent with those used in studies of this population. Patients are required to have measurable disease to facilitate the accurate assessment of response, the secondary efficacy endpoint. The International Workshop Response Criteria (IWRC) selected (Cheson, 1999) provides an international standard for the assessment of lymphoma. Minor modifications to the IWRC will be made to account for differences in the evaluation of response in mantle cell lymphoma, such as the evaluation of extranodal disease (Kane, 2007; Fisher, 2006). The use of this tool will ensure that data across centers are evaluated consistently. Safety will be assessed by evaluating AEs and laboratory data. Adverse event and abnormal laboratory value severity will be graded using version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Monitoring for tumor flare and tumor lysis syndrome will be performed along with safety measures that are routinely assessed in investigational studies of hematologic malignancies. Tumor flare reaction and tumor lysis syndrome will be recorded as AEs.

Extended Access Phase:

Following the approval of Protocol Amendment #6 an Extended Access Phase will be made available for subjects on study treatment in countries where lenalidomide is only available under a clinical trial protocol as post-trial access.

These subjects will have a "discontinuation from treatment" visit assessment prior to being transferred to the Extended Access Phase

Following the approval of Protocol Amendment #6, subjects on study treatment will be considered to have entered the study Extended Access Phase. Study visits and serial measurements of safety should continue to be performed as per guidance outlined in Table 4.

Subjects may remain on study until progressive disease or withdrawal for other reasons. Only serious adverse events (SAEs) including second primary malignancies (SPMs), and drug accountability record information will be collected and reported to Celgene for these subjects. Follow-up survival data will no longer be collected by Celgene for these subjects.

The Extended Access Phase will end for ongoing subjects still on lenalidomide treatment as soon as lenalidomide can be accessed in the commercial setting.

8.1.1. Dose Rationale

The dose selected (25 mg [p.o.] once daily for 21 days (D1 – D21) in each 28 day cycle) has shown activity in three studies in NHL utilizing lenalidomide and is also the approved dose schedule when used in combination with dexamethasone for patients with multiple myeloma who have been treated with at least one prior therapy.

8.1.2. Discussion of Study Design

This is a multicenter, randomized, open-label, comparative controlled phase II study to determine the efficacy and safety of single agent lenalidomide over a concurrent control group treated with an investigator's choice single agent in patients with mantle cell lymphoma who are refractory to their regimen or have relapsed once, twice or three times (Figure 1). The study aims to compare the PFS of lenalidomide therapy over a single agent of investigator's choice.

The investigator's choice in the control arm comprises the monotherapy treatment with one of the following: chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine. The investigator shall choose the single agent of choice in the control arm for each patient prior to randomization on to the study. Patients in the investigator's choice arm will have the option to switch to lenalidomide at time of progressive disease.

8.1.2.1. Stratification

Patients will be stratified according to:

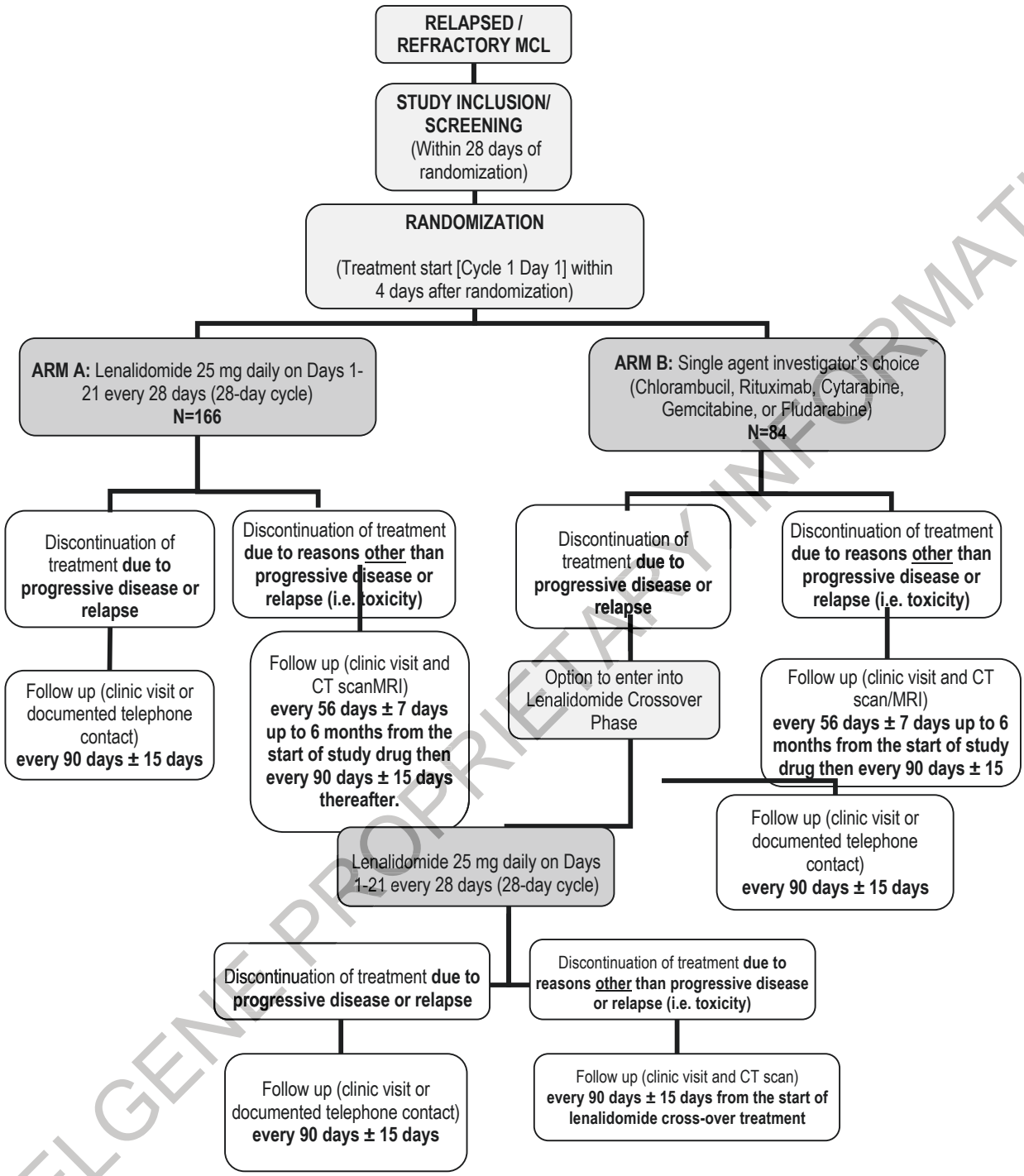
- Time since diagnosis (<3 years or ≥ 3 years)
- Time since last treatment (<6 months [refractory] or ≥ 6 months)
- Prior stem cell transplant (yes or no)

Treatment and clinical characteristics will be assessed at screening/baseline, but not used for stratification, and will be used within an exploratory analysis:

- Number of prior treatment lines (with description of treatment regimens, including first line treatment and stem cell transplant)
- MCL International Prognostic Index (MIPI) score at time of diagnosis, if available
- MIPI score at randomization
- Ki-67 index (as defined by Determann et al, 2008) in the original pathology specimen at diagnosis, if available, or at time of relapse
- Age and gender
- Absolute lymphocyte counts at baseline
- Time since last rituximab dose to cycle 1 day 1

This study will be conducted in three phases as shown below in Figure 1: Screening phase, Treatment phase, and Follow-up phase.

Figure 1: Overall Study Design



Following the approval of Protocol Amendment #6 an Extended Access Phase will be made available for subjects on study treatment in countries where lenalidomide is only available under a clinical trial protocol as post-trial access.

Screening Phase

Patients will be screened for protocol eligibility within 28 days prior to randomization as outlined in Table 2: Schedule of Study Assessments. Screening/baseline assessments will begin once the patient has accepted and signed the informed consent form. CBC and serum chemistry tests will be required within 7 days of first dose of study drug. Serology, for HBV (at least HBsAg, anti-HBs and anti-HBc) and for HCV will be required as screening assessment within 28 days of randomization in endemic areas. Eligibility for the study is based on the local assessments (CBC, chemistry and serology as well as the local results of the archival tumor / lymph node biopsy) done during the screening/baseline phase of the study.

Confirmation of mantle cell lymphoma diagnosis by the central pathology is not required before randomization or treatment start, but will be performed centrally at a later stage. Eligibility for the study is based on assessment of the local pathology results by the investigator. Diagnosis based on needle aspirations are not considered acceptable pathologic data for entry in this study.

The confirmation material submitted for Central Pathology Review must include a biopsy-proven mantle cell lymphoma specimen, including overexpression of cyclin D1 by immunohistochemistry. In patients whose tumors are negative for Cyclin D1 overexpression, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable.

Tumor / lymph node biopsy specimen, which may be archival slides from specimen obtained at the time of initial diagnosis, with representative stained slides supporting the diagnosis of mantle cell lymphoma (H&E or Giemsa staining and Cyclin D1 staining), must be sent as soon as possible to central pathology before randomization but at the latest 8 weeks after randomization. It is highly recommended to submit also the original paraffin block (called tumor block) which will be returned to the original institution. If the tumor block cannot be sent, 4-5 additional unstained slides must be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. Evidence of the translocation t(11;14)(q13:q32) by FISH can be submitted using the original slide or the corresponding confirming photographies. If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD23, CD20, BCL2, Ki-67.

Furthermore, it is highly recommended to perform an unilateral bone marrow biopsy at screening, and to send the tumor block to Central Pathology for review at the latest 8 weeks after randomization.

During the screening/baseline phase, the investigator must allocate one of the “investigator’s choice” options to the patient prior to the randomization.

8.1.2.2. Treatment Phase

Once all eligibility criteria are met and baseline assessments completed, patients will be randomized 2:1 to receive lenalidomide monotherapy or the investigator’s choice. The first treatment dose of the first cycle administered to the patient is called C1D1. Treatment should

start as soon as possible after randomization, but maximum time between randomization and C1D1 is 4 days, once the patient has fulfilled the requirements of the Lenalidomide pregnancy prevention program (see Section 21.7). Patients will continue in the treatment phase until disease progression, unacceptable toxicity or voluntary treatment withdrawal. Toxicity will be assessed using the NCI CTCAE criteria version 3 and the dose of lenalidomide or the investigators choice single agent will be reduced accordingly (see Table 8 and Table 9 for dose reductions).

Serial assessments of safety and efficacy (CT scans with contrast or MRI with contrast every 56 days ± 7 days for the first 6 months and then every 90 days thereafter) will be performed as outlined in the Schedule of Study Assessments or as directed in the dose modification section. Patients may continue participation in the treatment phase of the study until disease progression or unacceptable toxicity or voluntary patient withdrawal from treatment, at which point, the patients will enter the follow-up phase.

Diagnostic imaging results (CT scan with contrast or MRI with contrast, if CT scan is contraindicated) will be reviewed locally and also submitted for central review.

CT scans is the preferred procedure. If CT is contraindicated, MRI is acceptable. It is advised to stick to the same procedure for a given patient throughout the study.

Patients who withdraw consent for treatment will continue to be followed for safety, efficacy (disease progression), second primary malignancies, and for survival.

Cross over (for patients in the investigators choice Arm B only):

Patients in the investigator's choice Arm B, who have documented progressive disease will have the option to receive single agent lenalidomide treatment. Patients will undergo baseline assessments as outlined in the schedule of assessments of Table 3 for Cycle 1 Day 1.

Treatment with lenalidomide will start as soon as recovery from toxicities of prior treatments of Arm B have resolved and all inclusion/exclusion criteria are met (i.e. laboratory parameters), but no longer than 10 weeks after last day of last treatment cycle in Arm B.

Assessments during treatment with lenalidomide will be for safety, response evaluation, second primary malignancies, and overall survival follow-up. CT scans with contrast/MRI with contrast are recommended to be performed every 90 days (± 15 days) until disease progression or treatment discontinuation for any other reason (i.e. toxicity). Once a patient experiences disease progression or relapse or a patient has stopped treatment for other reasons the patient will enter the follow-up phase. In the follow-up phase for patients with progressive disease only assessments for safety (including second primary malignancies) and overall survival will be done. For patients who have entered the follow-up phase due to treatment discontinuation for other reasons additional CT scans with contrast /MRI with contrast will be performed at pre-defined intervals and assessments for safety (including second primary malignancies) and overall survival will be done. Patients will be followed until either 70% of the patients have died or the

median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time subjects on study treatment will be transferred to post-trial access in the commercial setting.

Follow-up Phase

Subjects withdrawn for any reason from the Extended Access Phase will not participate in a study follow-up phase. At their next visit 28 days later any SAEs experienced during this time window will be reported via the standard post-marketing process.

Once a patient experiences disease progression or relapse or a patient has stopped treatment for other reasons, the patient will enter the follow-up phase.

- All patients who discontinue treatment in either study arm or cross-over treatment will undergo a safety follow-up visit 28 days after last dosing day for assessment of adverse events (including via a physical examination), lenalidomide counseling and for a medically supervised pregnancy test for FCBP in Arm A and in cross over as specified in Section 21.7 . Vital signs, CBC with differential, and serum chemistry are to be performed as clinically indicated. A 28-day safety follow-up assessment will not be required either for subjects transferred to post-trial access in the commercial setting or to the Extended Access Phase. These subjects will have a "discontinuation from treatment" visit at the end of their 7 day rest period from their last on-study treatment cycle. At this "discontinuation from treatment" visit commercial lenalidomide will be dispensed to the subject. Between this visit and 28 days after, if a patient experiences a SAE, this SAE will be reported via the standard post marketing process. A pregnancy test should be performed 28 days post treatment discontinuation visit.
- Patients who discontinue treatment **due to progressive disease or relapse**:
  - Should be followed by clinic visit or documented telephone contact every 90 days (± 15 days) for survival, second primary malignancies and for the first subsequent antilymphoma therapy (including the time of and best response to the first antilymphoma treatment regimen utilized after discontinuation from treatment in this study).
- Patients who discontinued treatment **due to reasons other than progressive disease or relapse**:
  - Clinic visits should occur every 56 days to assess disease status (physical exam) until disease progression or relapse
  - CT scan with contrast/MRI with contrast should occur every 56 days (± 7 days) up to 6 months from the start of study drug then every 90 days ± 15 days thereafter until disease progression or relapse
  - After disease progression or relapse has occurred, patients should be followed by clinic visit or documented telephone contact every 90 days (± 15 days) for survival, second primary malignancies and for the first subsequent antilymphoma

therapy (including the time of and best response to the first antilymphoma treatment regimen utilized after discontinuation from treatment in this study).

– Patients in the follow-up phase who withdraw consent for efficacy (disease progression) follow-up will continue to be followed for second primary malignancies and for survival. A full consent withdrawal must be documented to disallow survival follow up.

The follow up phase will continue until either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time the follow-up study phase will be closed.

Extended Access Phase

Following the approval of Protocol Amendment #6 an Extended Access Phase will be made available for subjects on study treatment in countries where lenalidomide is only available under a clinical trial protocol as post-trial access.

These subjects will have a "discontinuation from treatment" visit assessment prior to being transferred to the Extended Access Phase

Following the approval of Protocol Amendment #6, subjects on study treatment will be considered to have entered the study Extended Access Phase. Study visits and serial measurements of safety should continue to be performed as per guidance outlined in Table 4.

Subjects may remain on study until progressive disease or withdrawal for other reasons. Only serious adverse events (SAEs) including second primary malignancies (SPMs), and drug accountability record information will be collected and reported for these subjects. Follow-up survival data will no longer be collected by Celgene for these subjects.

The Extended Access Phase will end for ongoing subjects still on lenalidomide treatment as soon as lenalidomide can be accessed in the commercial setting.

8.2. Assessment of Second Primary Malignancies

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 21.1.9). This includes any second primary malignancy, regardless of causal relationship to study drug (lenalidomide or Investigator Choice arm drugs), occurring at any time for the duration of the study, from the time of signing the ICD through follow-up for overall survival. The Follow-Up Phase involves patient contact every 90 days (± 15 days) until patient death or until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later. at which time the follow-up study phase will be closed.

Second primary malignancies (SPMs) will continue to be reported for subjects included in the Extended Access Phase.

8.3. Data Monitoring Committee

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study and efficacy for futility at a pre-defined time point. Specifics are outlined in the DMC charter. The first safety analysis will occur after the first 40 patients have received at least 2 cycles of treatment or have discontinued prior to completing 2 cycles. The second safety analysis as well as an efficacy analysis for futility will occur after 80 patients complete 2 cycles or withdraw before completing 2 cycles. A third safety analysis will occur after 120 patients complete 2 cycles or withdraw before completing 2 cycles. A fourth safety analysis will occur after 200 patients complete 2 cycles or withdraw before completing 2 cycles.

8.4. Independent External Pathological Review

An independent central pathologist will review the lymph node/tumor biopsy for retrospective confirmation of the diagnosis of mantle cell lymphoma.

The confirmation material submitted for Central Pathology Review must include a biopsy-proven mantle cell lymphoma specimen, including overexpression of cyclin D1 by immunohistochemistry. In patients whose tumors are negative for Cyclin D1 overexpression, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable.

Tumor / lymph node biopsy specimen, which may be archival slides from specimen obtained at the time of initial diagnosis, with representative stained slides supporting the diagnosis of mantle cell lymphoma (H&E or Giemsa staining and Cyclin D1 staining), must be sent as soon as possible to central pathology before randomization but at the latest 8 weeks after randomization. It is highly recommended to submit also the original paraffin block (called tumor block) which will be returned to the original institution. If the tumor block cannot be sent, 4-5 additional unstained slides must be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. Evidence of the translocation t(11;14)(q13:q32) by FISH can be submitted using the original slide or the corresponding confirming photographies. If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD20, CD23, BCL2, Ki-67.

Furthermore, it is highly recommended to perform an unilateral bone marrow biopsy at screening, and to send the tumor block to Central Pathology for review at the latest 8 weeks after randomization.

The central pathologist will also review any pathology specimens obtained as part of response assessment, including assessment of bone marrow biopsy required for response assessment of CR/CRu.

For further details, please refer to central pathology manual.

8.5. Independent Review Committee (IRC)

Diagnostic imaging results (CT with contrast /MRI with contrast) will be reviewed locally and also sent to IRC for central review. The IRC is composed of two external radiologists with an additional radiologist (adjudicator), in the event of a tie, and a hemato/-oncologist. The IRC will perform a blinded, independent assessment of radiological response (including assessment of SD and PD), review the tumor response data and the dates of disease progression for each patient.

All these data reviewed by the IRC will be used in the primary analysis and these assessments will be included in the Clinical Study Report.

For further details please refer to Central Radiology Manual.

9. STUDY POPULATION

9.1. Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Patients with histologically proven mantle cell non-Hodgkin's lymphoma [MCL] {including overexpression of cyclin D1 by immunohistochemistry}. In patients whose tumors are negative for the cyclin D1 overexpression or translocation, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable
1. Patients who are refractory to their regimen or have relapsed once, twice or three times and who have documented progressive disease. (Refractory to prior chemotherapy regimens is defined as not having reached a CR or PR to prior treatment)
2. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2
3. Must be ≥18 years of age at the time of signing the informed consent form
4. Must have had at least one prior combination chemotherapy regimen with an alkylating agent, and comprising either an anthracycline and/or cytarabine and/or fludarabine (with or without rituximab)
5. Prior stem cell transplant is allowed
6. Must be ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study
7. Must have measurable disease on cross sectional imaging by CT or MRI, if CT is contraindicated that is at least 2 cm in the longest diameter and measurable in two perpendicular dimensions
8. Must be able to adhere to the study visit schedule and other protocol requirements
9. Life expectancy of greater than 3 months
10. Females of childbearing potential (FCBP)[†] must:
    - Have two negative medically supervised pregnancy tests prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy (see specifics in Appendix 21.8). This applies even if the patient practices complete and continued sexual abstinence
    - Either commit to continued abstinence from heterosexual intercourse (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, highly effective contraception without interruption, at least 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for at least 28 days after discontinuation of study therapy (see specifics in Appendix 21.8).

[†]A FCBP is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (i.e., amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months)

11. Male patients must:
    - Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy (see specifics in Appendix 21.8).
    - Agree to not donate semen or sperm during study drug therapy and for at least 28 days after end of study drug therapy (see specifics in Appendix 21.8).
12. All patients must:
    - Have an understanding that the study drug could have a potential teratogenic risk
    - Agree to abstain from donating blood while taking study drug therapy and for at least 28 days after end of study drug therapy (see specifics in Appendix 21.8).
    - Agree not to share study medication with another person
    - Agree to be counseled about pregnancy precautions and risks of fetal exposure. See Appendix 21.8)

9.2. Patient Exclusion Criteria

1. Diagnosis of lymphoma other than mantle cell lymphoma
2. Prior history of malignancies, other than mantle cell lymphoma, unless the patient has been free of the disease for ≥ 5 years. Exceptions include the following:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin
    - Carcinoma in situ of the cervix
    - Carcinoma in situ of the breast
    - Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)
3. Transformed lymphoma
4. Prior use of lenalidomide
5. Prior radiotherapy within 4 weeks prior to randomization.
6. Patients who are candidates for autologous or allogeneic transplantation at the time of inclusion into the study.
7. Prior allogeneic transplantation with persistent donor hematopoiesis
8. Active CNS lymphoma with the exception of those patients whose CNS lymphoma has been treated with chemotherapy, radiotherapy or surgery, have remained asymptomatic for 90 days (3 months) and demonstrate no CNS lymphoma as shown by lumbar puncture, CT/brain MRI are eligible. Patients with a history of CNS involvement or CNS symptoms will be required to have negative CSF cytology examination and a head CT during the screening period (known and active CNS or leptomeningeal involvement)

9. Known seropositive for or active viral infection with human immunodeficiency virus (HIV)
10. Known seropositive for or active viral infection with hepatitis B virus:
    - HBsAg positive.
    - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA.
    - Patients who are HBsAg negative and viral DNA negative are eligible.
    - Patients who had hepatitis B but have received an antiviral treatment and show no detectable viral DNA for 6 months are eligible.
    - Patients who are seropositive because of hepatitis B virus vaccine are eligible.
11. Known seropositive for or active viral infection with hepatitis C virus (HCV)
    - Patients who had hepatitis C but have received an antiviral treatment and show no detectable viral RNA for 6 months are eligible.
12. Patients who are not willing to take DVT prophylaxis, if they are at risk (see definition in Section 10.1.6)
13. Patients should not be receiving corticosteroids 7 days prior to randomization, except for prednisone ≤ 10 mg/day or equivalent for purposes other than treating MCL
14. Pregnant or lactating females
15. Any of the additional laboratory abnormalities.
    - Absolute neutrophil count (ANC) < 1,500 cells/mm^3 (1.5 x 10^9/L)
    - Platelet count < 60,000/mm^3(60 x 10^9/L)
    - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) > 3.0 x upper limit of normal (ULN), except in patients with documented liver involvement by lymphoma
    - Serum total bilirubin > 1.5 x ULN, except in case of Gilbert's Syndrome and documented liver involvement by lymphoma.
    - Calculated creatinine clearance (Cockcroft – Gault formula) of <30 mL/min
16. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form
17. Participation in another clinical trial during the screening/baseline phase and treatment phase of the study
18. Any use of experimental drug during 4 weeks prior to randomization

10. DESCRIPTION OF TREATMENT

10.1. Treatment Assignments

The duration of a treatment cycle will be 28 days. The first dose of lenalidomide in cycle 1 defines day 1 of the treatment cycle, and each cycle thereafter will begin 29 days later.

The 28-day cycle length should be maintained throughout the entire treatment phase regardless of the dose interruptions and/or dose reductions.

10.1.1. Arm A

All patients who qualify for enrollment into the study will be randomized 2:1 to receive lenalidomide monotherapy (Arm A) or the investigator's choice (Arm B).

Patients in Arm A,

- Patients, who have a creatinine clearance ≥ 60 mL/min, will receive oral lenalidomide that is initiated on Day [D] 1 of Cycle 1 at a dose of **25 mg** p.o. once daily for 21 days (D1 – D21) in each 28 day cycle. A minimum 7 day rest period is mandatory before starting each new treatment cycle regardless of allowed ± **visit** windows.
- Patients 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 for 21 days (D1 – D21) in Cycle 1 and Cycle 2. A minimum 7 day rest period is mandatory before starting each new treatment cycle regardless of allowed ± visit windows. After Cycle 2, if the patient remains free of Grade 3 or Grade 4 toxicity, the dose will be increased to **15 mg** once daily for 21 days (D1 – D21) in each 28 day cycle.

Treatment is continued until disease progression or unacceptable toxicity.

10.1.2. Arm B

Patients in Arm B will receive investigator's choice single agent reference therapy. This includes:

Chlorambucil tablets 2 mg;

Rituximab 500 mg vials;

Cytarabine Injection Solution 100 mg/ml;

Gemcitabine 1g vial;

Fludarabine 10 mg film-coated tablets;

Fludarabine 25mg/ml Concentrate for Solution for Injection or Infusion

Please refer to the prescribing information provided by Celgene on all of the above

For dosing of the investigators choice single agents, please refer to Table 6 based on published data and expert opinions.

Investigators should refer to the approved Summary of Product Characteristics (SPC), provided by Celgene, for the investigator's choice therapy for complete prescribing information including administration, warnings, precautions, contraindications, and adverse reactions and follow institutional procedures for the administration of the agents, where applicable. Paper prints will be provided in the Investigator's and Pharmacy binders.

The investigator's choice treatment will be provided by Celgene.

Table 6: Overview of dosage of Investigator's choice drugs

Investigator's choice*	mg/m^2	Days	q days	max # cycles
Chlorambucil p.o. (Rai, 2000; Ardeshna, 2003)	40 (total monthly dose)	Split over 3-10 days	28	until PD or toxicity
Rituximab i.v. (Ghielmini, 2000)	375	1, 8, 15, 22	56#	until PD or toxicity
Cytarabine i.v. (Kantarjian, 1983; UK SPC)	1 -2 g/m^2 once or twice per day	1, 2	28	6
Gemcitabine i.v. (Dumontet, 2001)	1000	1, 8, 15	28	6
Fludarabine i.v. (Decaudin, 1998; Zinzani, 2000)	25	1-5	28	6
Fludarabine p.o. (Tobinai, 2006)	40	1-5	28	6

q days, repeated; y, years; i.v., intravenous; p.o., oral;
* Refer to the approved Summary of Product Characteristics (SPC), provided by Celgene for the investigator's choice therapy for complete prescribing information including administration, warnings, precautions, contraindications, and adverse reactions and follow institutional procedures for the administration of the agents, where applicable.
# Rituximab (single agent) is to be repeated every 56 days after Day 56 (given only on day 1 of every 56 days cycle). For the prevention of cytokine release syndrome associated with the treatment of Rituximab ≤ 125mg of methylprednisolone or equivalent are accepted on C1D1.

Patients in Arm B need to follow the scheduled visits as displayed in Table 2. For some drugs, additional visits may be needed.

10.1.3. Dose Modification or Interruption for Lenalidomide - Arm A

a) Dose modification

Patients will be evaluated for adverse events at each visit with the NCI CTCAE v3.0 used as a guide for the grading of severity. The dose of lenalidomide for each patient will be interrupted and modified following toxicity as described below.

Refer to Table 7 for instructions on dose modifications and Table 8 and Table 9 for dose reduction instructions for lenalidomide.

Table 7: Dose Modification for Lenalidomide

NCI CTCAE Toxicity Grade	Action Required
Sustained(≥ 7 days) Grade 3 neutropenia or ≥ Grade 3 associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• 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 at the discretion of the investigator
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000 cells/mm³ [50x10^9/L])	• Hold (interrupt dose) • Follow CBC weekly at least every seven days • If thrombocytopenia resolves to ≥ 60,000 cells/mm³ (60 x 10^9/L) restart at next lower dose level.
Desquamating (blistering) Rash ≥ Grade 3 or non-desquamating Rash Grade 4	• Discontinue lenalidomide study drug
Allergic reaction or hypersensitivity Grade 2 Grade 3-4	• Hold (interrupt dose). Follow at least every seven days • When the toxicity resolves to ≤ Grade 1 restart at next lower dose level • Discontinue lenalidomide study drug
Constipation Grade 1-2 ≥ Grade 3	• Initiate bowel regimen and maintain dose level • 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)
Newly developed ≥ Grade 3 peripheral neuropathy **(this applies only to those toxicities which begin or worsen while on study)**	• Hold (interrupt) dose • When the toxicity resolves to ≤ Grade 2 restart at next lower dose level

Table 7: Dose Modification for Lenalidomide (Continued)

NCI CTCAE Toxicity Grade	Action Required	
AST or ALT > 3 x ULN	Hold lenalidomide dosing; re-test at least weekly until AST or ALT < 2.5 x ULN or return to baseline	– Resume the same dose of lenalidomide if the event is considered NOT related to study drug treatment – Restart lenalidomide treatment at next lower dose level if the event is considered as related to drug treatment
Bilirubin > 3 x ULN*	Hold lenalidomide dosing; re-test at least weekly until bilirubin < 1.5 x ULN	– Resume the same dose of lenalidomide if the event is considered NOT related to study drug treatment – Restart lenalidomide treatment at next lower dose level if the event is considered as related to drug treatment
Tumor Flare Grade 3 or 4	• Interrupt lenalidomide therapy and initiate therapy with corticosteroids, NSAIDs and/or narcotics • Resume lenalidomide (decrease one dose level) when symptoms resolve to ≤ Grade 1	
TLS laboratory TLS and Grade 1 TLS	• Same dose of lenalidomide may be continued without interruption or dose reduction at the investigator's discretion. • Dose escalation to the next consecutive dose level is permitted when laboratory TLS is resolved and Grade 1 TLS is resolved to Grade 0.	
TLS ≥ Grade 2	• Interrupt lenalidomide therapy. • May resume lenalidomide when the TLS resolves to < Grade 1 (decrease one dose level) • If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following initiation of lenalidomide.	

Table 7: Dose Modification for Lenalidomide (Continued)

NCI CTCAE Toxicity Grade	Action Required
	• Re-escalation by one dose level at a time will be permitted after completion of one full cycle without laboratory TLS or ≥ Grade 1 TLS
Any other lenalidomide-related non-hematologic AE ≥ Grade 3 not requiring definitive treatment discontinuation	• Hold (interrupt lenalidomide dose). • When the AE resolves to ≤ Grade 2 restart at the same or at next lower dose level according to investigator's discretion

** For patients with Gilberts Syndrome or liver involvement by lymphoma, dose reductions should be made in consultation with the Celgene medical monitor*

If a patient experiences an AE that requires a dose interruption, the patient can not be re-started on study medication until the AE has resolved or reached acceptable grade described in Table 7. Once the AE has resolved, the patient may continue back on lenalidomide (at the dose level required in Table 7, and refer to Table 8 and Table 9 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 a cycle is delayed due to an AE the patient can re-start lenalidomide within a next cycle once a 7-day rest period has occurred and the requirements mentioned below have been met.

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

The next cycle of treatment may begin on the scheduled Day 1 if:

- The minimum 7 day rest period has elapsed following the last dose of study drug in the prior cycle (the rest period is mandatory regardless of allowed ± visit windows)
- The ANC is ≥ 1,000 cells/mm³ (1.0 X 10^9/L);
- The platelet count is ≥ 60,000 cells/mm³ (60 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 definitive treatment discontinuation has resolved to ≤ Grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the patient will be evaluated at least once every seven days and a new cycle of lenalidomide will not be initiated until the toxicity has resolved as described above.

If a new cycle is delayed for more than 28 days, the [redacted] Medical Monitor must be notified and treatment can be resumed according to the treating physicians' and [redacted] Medical

Monitors' clinical judgment. The Medical monitor may consult Celgene Clinical Research Physician for clinical judgment if appropriate.

If lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.

There will be no more than one dose reduction from one cycle to the next.

Once a dose reduction occurred, no re-escalation is permitted.

b) Dose reduction

The daily dose of lenalidomide may be reduced successively by one level from the starting dose of 25 mg p.o. once daily for 21 days (D1 – D21) in each 28 day cycle for patients with a creatinine clearance ≥ 60 mL/min (refer to dose reduction steps in Table 8) in case of severe toxicity.

Creatinine clearance (use Cockcroft – Gault formula) should be determined utilizing actual body weight or ideal body weight, which ever is less. For patients who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min], refer to dose reduction steps in Table 9.

Table 8: Dose reduction steps for Adverse Events related to Lenalidomide for patients initiating treatment at 25 mg daily on Days 1-21, every 28 days

Starting Dose	25 mg daily on Days 1-21, every 28 days
Level –1 Dose	20 mg daily on Days 1-21, every 28 days
Level –2 Dose	15 mg daily on Days 1-21, every 28 days
Level –3 Dose	10 mg daily on Days 1-21, every 28 days
Level –4 Dose	5 mg daily on Days 1-21, every 28 days
Level –5 Dose*	5 mg every other day between Days 1-21, every 28 days

*Once a patient's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate dose level 5 have to be discontinued from the Treatment Phase of the study.

Table 9: Dose reduction steps for Adverse Events related to Lenalidomide for patients initiating treatment at 10 mg daily on Days 1-21, every 28 days

Starting Dose	10 mg daily on Days 1-21, every 28 days
Level –1 Dose*	5 mg daily on Days 1-21, every 28 days
Level –2 Dose*	5 mg every other day between Days 1-21, every 28 days

*Once a patient's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate dose level -2 are to be discontinued from the Treatment Phase of the study.

10.1.4. Dose Modification or Interruption for Investigator's choice - Arm B

Patients will be evaluated for adverse events at each visit with the NCI CTCAE v3.0 used as a guide for the grading of severity. The dose of investigator's choice for each patient will be interrupted and modified according to the clinical practice of the investigators institution, where applicable and in line with the approved prescribing information provided by Celgene. Doses that were missed because of toxicity or any other reason will not be made up. Patients should continue with the next cycle when they are able.

10.1.5. Tumor Lysis and Tumor Flare - Lenalidomide

In a preliminary report of a study conducted with lenalidomide in relapsed/refractory chronic lymphocytic leukemia (CLL), some patients experienced tumor lysis syndrome, tumor flare reaction and occasionally cytopenias (neutropenia and thrombocytopenia) during the first week of Cycle 1 (Chanan-Khan, 2006; Moutouh-de Parseval, 2007; Andritsos, 2008; Eve, 2010). In some CLL patients, tumor flare and tumor lysis have been life-threatening and fatal. Among the NHL patients treated with lenalidomide in Celgene sponsored clinical trials in NHL patients (total number of NHL patients in database of approximately 250), four patients with tumor flares and one patient with tumor lysis have been reported. In addition, one patient with tumor flare and one patient with tumor lysis have been reported outside of clinical trials. Thus, in this study, patients should be monitored for tumor flare and tumor lysis.

Tumor lysis syndrome (TLS) can be defined as a 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.

The onset of TLS is rapid, usually within 24 to 48 hours after the first dose but can also occur after the first week of treatment. The presence of known risk factors like bulky disease, moderate renal insufficiency, high ALC and high uric acid levels (> 8 mg/dL) prior to therapy increases the likelihood of TLS. Early identification of patients 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, 2004).

Patients in the lenalidomide arm in this study should receive tumor lysis prophylaxis (allopurinol or equivalent) and be well hydrated (orally) during the first 7 days of lenalidomide administration in the first cycle or as clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for tumor lysis syndrome and cytopenia(s), the patients will have a (CBC) and chemistry drawn on Days 1, 2, 4, 8 and 15 of the first cycle and additionally as clinically indicated. TLS will be assessed by Cairo-Bishop Grading system (see Appendix 21.6).

If a patient develops laboratory TLS (defined by the presence of two or more serum value abnormalities of uric acid, potassium, phosphorous or calcium) or ≥ Grade 1 TLS (defined by the presence of laboratory TLS and one or more of the following criteria: creatinine ≥ 1.5 x ULN, arrhythmia or seizures), appropriate medical management should be initiated according to the local standard of care in each institution with vigorous IV hydration (rasburicase treatment is considered appropriate if it is approved by the local Health Authority).

Tumor flare reaction (TFR) is defined as a sudden and tender increase in the size of the disease bearing sites, including the lymph nodes, spleen and or the liver often accompanied by low-grade fever, non-pruritic diffuse rash and in some cases increase in the peripheral blood lymphocyte counts. The onset of tumor flare may be as early as within a couple of hours after the first dose and has a median duration of 14 days. This usually occurs only during the first cycle of treatment. Tumor flare will be recorded as an AE (graded using the NCI CTCAE criteria version 3) and not as progressive disease (PD) and will be treated symptomatically first with non-steroidal anti-inflammatory agents (NSAIDs). Narcotics or prednisone may be used at the investigator's discretion, to treat the tumor flare reaction.

10.1.6. Thromboembolism - Lenalidomide

All patients treated with lenalidomide regardless of prior thromboembolic history will receive prophylactic aspirin [ASA] (70 – 100 mg) daily unless contraindicated. If ASA is contraindicated, use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the International normalized ratio (INR) in the range of 2-3 may be considered.

The choice of prophylactic agent(s), and also the interruption or discontinuation of such prophylaxis if needed, should be based on the local standard of care and the investigator's best judgement after careful consideration of the benefit versus the potential risk for the individual patient.

10.1.7. Prior/Concomitant medications and other permitted concomitant therapies

Prior/Concomitant Medications

All medications (prescription, non-prescription and herbal), treatments and therapies taken from 30 days prior to the start of study drug through the last dose of study drug, must be recorded on the appropriate page of the electronic Case Report Form (eCRF). For subjects included in the Extension Access Phase information will no longer be collected on the eCRF. The investigator should ensure concomitant medications continue to be recorded in the subjects' medical records.

Other permitted concomitant therapies

Other therapies considered necessary for the patient's well being may be administered at the discretion of the Investigator.

Other recommended medications such as ASA, allopurinol, low molecular weight heparin, warfarin, analgesics, antihistamines, or other medications such as growth factors, and transfusions of red blood cells, platelets, or fresh frozen plasma given to assist in the management of complications associated with cancer or its therapy, will be provided by the investigative site, Celgene will not provide these medications.

Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically, but may be prescribed by the investigator for rescue from severe hematologic events, if it is thought to be appropriate. They should be used in accordance with the American Society of Clinical Oncology's (ASCO) and European Society for Medical Oncology (ESMO) guidelines, and recorded on concomitant medications CRF page.

10.1.8. Prohibited concomitant therapy

Concomitant use of other anti-cancer therapy while the patient is in the study is prohibited. Physiological doses of steroids (defined as ≤ 10 mg prednisone per day, or equivalent) are allowed during the study. Doses beyond 10 mg prednisone per day (or equivalent) are not allowed during the study or during the last 7 days of the screening period except for the treatment of tumor flare and for the prevention of cytokine release syndrome associated with the treatment of Rituximab on C1D1.

No investigational therapies or non-drug therapies shall be initiated while the patient is receiving lenalidomide.

Following the approval of Protocol Amendment #6, concomitant medications will no longer be collected and recorded in a specific CRF but should continue to be recorded in the subjects' medical records.

10.2. Discontinuation from Treatment

The following events are considered sufficient reasons for discontinuing a patient from study drug:

- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Disease Progression, disease relapse
- Patient partially withdraws consent (withdraws from treatment only).
- Patient is lost to follow-up
- Death
- Protocol violation

The reason for discontinuation should be recorded in the CRF and in the patient's medical records. Celgene is to be notified of all discontinuations from study drug.

Following the approval of the Protocol Amendment #6 reasons for discontinuation will no longer be recorded on a CRF, but they will be recorded in the subjects' medical records.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Supplier(s)

Celgene Corporation will supply oral lenalidomide capsules.

Celgene Corporation will provide commercial supplies of investigator choice therapies (see Table 6) and these therapies will be labeled appropriately as investigational material for the study. Celgene will not provide other recommended medications such as aspirin.

11.2. Dosage Form

Lenalidomide will be supplied as 5 mg, 10 mg, 20 mg and 25 mg capsules for oral administration.

The investigators choice therapies will be supplied as described in Table 6.

Following the approval of Protocol Amendment #6, Celgene Corporation will supply 5 mg, 10 - mg, 20 mg, and 25 mg strengths in countries where lenalidomide is only available under a clinical trial protocol. No more than a 21-day supply of study drug will be dispensed at a time.

11.3. Dosage Regimen

11.3.1. Lenalidomide

Lenalidomide will be supplied in bottles containing a 21 day supply. No more than a 28-day supply of study drug will be dispensed at a time. Treatment is to be continued as tolerated (see Section 10.1.3 Dose Moderation or Interruption) until disease progression or an unacceptable toxicity occurs.

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

Patients should be instructed to take the study drug at the same time each day.

11.3.2. Investigators Choice

The investigators choice therapies will be provided as commercial supply and in the dosages as described in Table 6.

11.4. Drug Dispensing Requirements

In investigational studies, lenalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of study patients. Once trained these healthcare staff will counsel study patients prior to study drug being dispensed to ensure that the study patient (FCBP & males) has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the study patient understands the risks associated with lenalidomide. This step will be documented by completing the Education and Counseling Guidance Document (Appendix 21.9), and no study drug will be dispensed until this step occurs. Counseling includes verification with the study patient that

required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet will be supplied as described in (Appendix 21.11).

11.5. Special Handling Instructions

Health care providers should consider wearing gloves when directly handling Revlimid (lenalidomide) capsules followed by standard hand washing. All patients should not extensively handle or open lenalidomide capsules and should maintain storage of capsules in the packaging until ingestion.

11.6. Treatment Compliance

Study personnel will review the dosing instructions with the patient prior to dispensing the study drug. The study drug bottle will be packaged with enough capsules for each 21-day treatment period. The patient will be instructed to return the study drug bottles, including any unused study drug to the site at the next visit. Patient compliance will be noted on the appropriate CRFs and source records based on a capsule count. To monitor treatment compliance, reconciliation of lenalidomide capsules will be done at each scheduled study visit. For subjects included in the Extension Access Phase drug accountability information will no longer be collected on eCRF. For subjects included in the Extended Access Phase, accountability of the study drug, including any drug lost or damaged, will be documented in the subjects' Drug Accountability and Dosing Record Sheets.The investigator should ensure concomitant medications continue reported in the subjects' medical record

11.7. Packaging and Labeling

The lenalidomide study drug will be packaged in bottles and each bottle will contain 21 capsules.

The label for study drug supplied by Celgene will bear Celgene's name and address, the protocol number, EudraCT number (as applicable), product name, dosage form and strength, medication identification/kit number, lot number, expiry date, dosing instructions, storage conditions, the quantity of study drug contained, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as needed or as applicable.

11.8. Receipt and Storage

The Investigator, or designee, is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug shipping order/packing slip.

The Investigator, or designee, will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene.

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

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

11.9. Record of Administration

Following the approval of Protocol Amendment #6 for subjects included in the Extended Access Phase, accurate recording of study drug administration will be made in the subjects' Drug

Accountability and Dosing Record Sheets. This information will reviewed by the study monitor at their site monitoring visits.

11.10. Accountability

An accurate accounting of the dispensing/return of study drug for each study patient 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 patient misses a dose, this information should be documented in the study patient's CRF and source documents.

Following the approval of Protocol Amendment #6 for subjects included in the Extended Access Phase, accountability of the study drug, including any drug lost or damaged, will be documented in the subjects' Drug Accountability and Dosing Record Sheets.

11.11. Handling and Disposal

Celgene will instruct the Investigator(s) on the return or destruction of unused study drug.

Following the approval of Protocol Amendment #6 for subjects included in the Extended Access Phase, accountability of the study drug, including any drug lost or damaged, will be documented in the subjects' Drug Accountability and Dosing Record Sheets.

12. ASSESSMENT OF EFFICACY

12.1. Assessments

The following efficacy assessments will be done at baseline and at scheduled intervals throughout the duration of the study as outlined in "Schedule of Study Assessments".

12.2. Methods and Timing of Efficacy Assessments

Response and progression will be evaluated using the international criteria proposed by the Modified International Workshop Response Criteria (IWRC) (Cheson, 1999; as modified in Kane, 2007; Fisher, 2006) for target and non-target lesions.

Date of documentation of disease progression

The date of documentation of disease progression will be the date of confirmation of disease progression whether on clinical or radiographic grounds.

CT scan/MRI

CT with contrast or alternatively MRI with contrast, if CT is contraindicated, is performed at baseline then every 56 days (±7 days) after Day 1, Cycle 1 for the first 6 months and then every 90 days ± 15 days thereafter until documented progressive disease; or when clinically indicated.

To ensure comparability, baseline and on-study methods for response assessment must be performed using identical techniques.

Any suspicion of progressive disease and eventually leading to additional investigations (e.g. colonoscopy) must be complemented by a re-staging procedure using CT scan (or MRI).

Bone Marrow Biopsy

Unilateral bone marrow biopsy during treatment is required only if patients has otherwise fulfilled the criteria for CR. The bone marrow procedure should be performed 28 days after the criteria for CR have otherwise been met.

Physical Examination and ECOG

All patients will be examined for ECOG status (Appendix 21.3), and receive a physical exam including lymphadenopathy, hepatomegaly and splenomegaly as described in Table 2 and as clinically indicated.

Progression-free survival/Overall Survival

All patients will be followed for progression-free survival and for overall survival after progression every 90 days. Cause of death, disease progression and lymphoma therapies are to be recorded in the CRF and the patient's medical record. Once patients have been discontinued from study drug, they will be followed for progression of disease (if applicable), lymphoma treatments, second primary malignancies and death. Patients will be followed until death or until either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time the study will end for

subjects still on lenalidomide treatment in countries where lenalidomide is available post-trial in the commercial setting.

Following the approval of Protocol Amendment #6 an Extended Access Phase will be made available for subjects on study treatment in countries where lenalidomide is only available under a clinical trial protocol as post-trial access.

Subjects in the Extended Access Phase may remain on study until progressive disease or withdrawal for other reasons. Only serious adverse events (SAEs) including second primary malignancies (SPMs), and drug accountability record information will be collected and reported for these subjects. Follow-up survival data will no longer be collected by Celgene for these subjects.

Patients who withdraw consent for treatment will continue to be followed for safety, efficacy (disease progression), second primary malignancies and for survival. Patients in the follow-up phase who withdraw consent for efficacy (disease progression) follow-up will continue to be followed for second primary malignancies and for survival. A full consent withdrawal must be documented to disallow follow up for second primary malignancies and for survival.

13. ASSESSMENT OF SAFETY

13.1. Assessments

- AEs/SAEs severity is graded using NCI CTCAE Version 3.0 (see Appendix 21.1)
- ECOG Performance Status
- Vital signs: Blood pressure, pulse, weight and height (screening only).
- Clinical laboratory evaluations:
  i. Hematology Labs: Red blood cell (RBC) count, hemoglobin, hematocrit, MCV, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.
  ii. Chemistry Labs: Sodium, potassium, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (AST/SGOT), alanine transaminase (ALT/SGPT), lactate dehydrogenase (LDH) and uric acid.
- Serum/urine beta-human chorionic gonadotropin (β-hCG) (FCBP only)
- Concomitant medications
- Hospitalizations
- 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 21.1.9). This includes any second primary malignancy, regardless of causal relationship to study drug (lenalidomide or Investigator Choice arm drugs), occurring at any time for the duration of the study, from the time of signing the ICD through follow-up for overall survival. The Follow-Up Phase involves patient contact every 90 days (± 15 days) until patient death or until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later, at which time the follow-up study phase will be closed.
- 12- lead ECG
- Assessment of Lymphoma-related Symptoms
- Calculated creatinine clearance (Cockcroft-Gault formula)
- Tumor Flare/Lysis Assessments (only for patients in Arm A and patients in cross over)
- FCBP should be monitored during the course of the study and after the end of study therapy to (only for patients in Arm A and patients in cross over):
  – Ensure that pregnancy tests are performed during the course of the study and after end of study therapy and are negative (See specifics as described in Appendix 21.8).

  - Ensure the study patient continues to practice abstinence or remains on adequate contraception (See specifics as described in Appendix 21.8).
  - If a FCBP becomes pregnant, treatment should be stopped and the study patient referred to the appropriate physician.
- Male study patients should be monitored during the course of the study and after the end of study therapy to:
  - Ensure they continue to use a condom during sexual contact with a FCBP
  - If a female partner of a male study patient becomes pregnant she should be referred to the appropriate physician.

13.2. Methods and Timing of Safety Assessments

Serial measurements of safety will be performed at baseline and at scheduled intervals throughout the duration of the study as outlined in "Schedule of Study Assessments (see Table 2)" as well as for patients in the investigators choice Arm B who are crossing over to lenalidomide therapy (see Table 3). All scheduled visits will have a ± 3 day window unless otherwise stated. The site's local laboratory will perform laboratory testing.

13.3. Recording and Reporting of Adverse Events

The recording and reporting of adverse events is described in Appendix 21.1.

For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines.

Extended Access Phase

Following the approval of Protocol Amendment #6, only serious adverse event reports will continue to be sent by the investigator to Celgene Safety. The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to Celgene Drug Safety by facsimile or e-mail. An initial written report (prepared by the Investigator(s) using the SAE Report Form provided by Celgene) is to be faxed or e-mailed to Celgene Drug Safety. The immediate reporting process and timelines apply also to reporting second primary malignancies (see Appendix 21.1.2).

Non-serious adverse events will no longer be collected on a CRF by Celgene, but should be recorded by the investigator in the subjects' medical records.

Post-trial Access in the commercial setting

Prescribers will be expected to follow the normal post-marketing reporting requirements as applicable in their country.

15. STATISTICAL ANALYSES

The objective of the statistical analyses will be to investigate the efficacy and safety of lenalidomide monotherapy in patients with relapse or refractory mantle cell lymphoma.

Following the approval of Protocol Amendment #6 and closure of the clinical database, no efficacy or safety analyses will be performed for the subjects in the Extended Access Phase.

15.1. Study Population Definitions

The primary efficacy analyses will be performed on the Intent-to-Treat Population (ITT) for the primary and secondary endpoints. Sensitivity analyses will be conducted for the primary and secondary endpoints based on the Full Analysis Set (FAS), and the Per Protocol set (if the PPS population differs ≥10% in size from the FAS).

The safety analyses will be conducted on the treated set.

15.1.1. Intent-to-Treat Population (ITT)

All randomized patients.

15.1.2. Treated Set

All enrolled patients who receive at least one dose of study drug.

15.1.3. Full Analysis Set (FAS)

The population will include all randomized patients that have received at least one single treatment dose (C1D1) with centrally confirmed histology of mantle cell lymphoma as well as documented progression at entry.

15.1.4. As Treated population

The As Treated population analysis set is defined as all randomized patients who receive at least two cycles of treatment regardless of the treatment arm.

This population will be used for exploratory analysis only, for the following endpoints: PFS, ORR and OS.

15.1.5. Per-protocol Set (PPS)

Per-protocol population is defined as all MCL randomized subjects who have met eligibility criteria, who received at least one dose of study treatment and who had at least one valid post baseline response assessment without any major protocol violation.

If the FAS population and the PPS population differ <10% in size no analysis will be conducted on the PPS population but if the PPS population differs ≥10% in size from the FAS, the sensitivity analysis on the primary endpoint will be conducted on the PPS population.

15.1.6. Subgroup analysis

Subgroup analyses will be conducted in an exploratory manner for the following endpoints PFS, ORR and OS in the following subgroups:

- Time since diagnosis (<3 years or ≥ 3 years)
- Time since last treatment (<6 months [refractory] or ≥ 6 months)
- Prior stem cell transplant (yes or no)
- Age (< 65, ≥ 65) and gender
- MCL International Prognostic Index (MIPI) score at initial time of diagnosis
- MIPI score at randomization
- Ki-67 index (as defined by Determann, 2008) labeling in the original pathology specimen at diagnosis, if available at time or at time of relapse
- Absolute lymphocyte count at baseline (< 800/mm^3 or ≥ 800/mm^3)
- Time since last rituximab to cycle 1 day 1 (< 230 days or ≥ 230 days)
- Number of prior treatment lines (with description of treatment regimens, including first line treatment and stem cell transplant) (1 vs >1), (<2 vs ≥2), (<3 vs ≥3)
- Number of relapses (1 vs > 1 relapses), (<2 vs ≥2 relapses), (<3 vs ≥3 relapses)

In addition other potential subgroups or prognostic factors may be used as exploratory analyses, to be further detailed in the statistical analysis plan.

15.2. Efficacy Evaluation

15.2.1. Primary Efficacy Endpoints

Progression-free survival (PFS)

PFS is defined as the time from randomization to the first observation of disease progression or death due to any cause. If the patient has not progressed or died, PFS will be censored at the time of last completed assessment when the patient was known not to have progressed. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free (see table below).

Censoring Rules for Time to event (Progression and/or Death) Endpoints

Situation	Date of Progression or Censoring	Situation Outcome
No baseline assessments	Randomization	Censored
Progression documented	First adequate assessment determined by central review	Progressed

No progression	Date of last adequate assessment with evidence of no progression	Censored
Study discontinuation for reasons other than disease progression or death	Date of last adequate assessment with evidence of no progression	Censored
New anti-lymphoma /non-protocol treatment started prior to progression	Date of last adequate assessment with evidence of no progression prior to the start of new anti-lymphoma treatment	Censored
Death before first PD assessment while on study	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after an extended lost-to-follow-up time (two or more missed assessments)	Date of last adequate assessment with evidence of no progression	Censored

As additional robustness checks of the primary endpoint and censoring definition, the time to event analysis will be repeated for the ITT population using the following modified methods of PFS:

a) Using the investigator assessment instead the IRC central review

b) Considering progression or death under a new anti-lymphoma treatment as an event

c) Considering death or progression after an extended lost-to-follow-up time (two or more missed assessments) as an event

d) One using the earliest progression date either in investigator set or IRC set.

Efficacy analysis will be conducted one year after the last patient is randomized.

15.2.2. Secondary Endpoints

Overall Response

The primary response rate will include best response of Complete Response (CR), Complete Response unconfirmed (CRu), or Partial Response (PR). The Modified International Workshop Response Criteria (IWRC) (Cheson, 1999) will be used and response assessed by CT scan with contrast /MRI with contrast every 56 days (± 7 days) for the first 6 months and then every 90 days ± 15 days thereafter.

Patients who discontinue before any post-randomization efficacy assessments will be considered non-responders.

Duration of Response

Duration of response will be measured from the time of initial response (at least PR) until documented tumor progression or death. Patients who do not progress at the time of analysis will be censored at the last assessment date that the patient is known to be progression-free. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free.

This analysis will be restricted to the subgroup of responding patients.

Tumor control rate

Rates for Complete Response (CR) / Complete Response unconfirmed (CRu), Partial response (PR) / and Stable Disease (SD)

Complete response/ Complete response unconfirmed /Partial response/Stable disease will be determined using the Modified International Workshop Response Criteria (IWRC) (Cheson, 1999; Kane, 2007; Fisher, 2006).

Duration of Stable Disease

Stable disease is defined as less than a PR but is not progressive disease or relapsed disease.

Duration of stable disease will be calculated as the time from the first evidence of stable disease to documented disease progression or documented response or death. Patients who do not progress or respond at the time of analysis will be censored at the last assessment date that the patient is known to be progression-free. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free.

This analysis will be restricted to the subgroup of stable disease patients.

Time to progression (TTP)

TTP will be defined as the time from randomization until objective tumor progression; TTP will not include deaths. Patients without progression at the time of analysis will be censored at the last assessment date that the patient is known to be progression-free. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free. Deaths due to progression of disease will be considered as an event.

Time to treatment failure (TTF)

TTF is defined as the time from the first dose of study drug to discontinuation of treatment for any reason, including disease progression, treatment toxicity or death. Patients who will be on drug or complete the treatment according to the protocol will be censored at the last date of drug intake.

Time to tumor response (TTR)

Time to tumor response (TTR) will be defined as the time from randomization until initial response (CR, CRu, PR) if it has been confirmed. Patients with progression at the time of analysis will be censored at the first assessment date that the patient is known to have

progressed. Patients with SD at the time of analysis will be censored at the last assessment date that the patient is known to be progression-free.

Overall Survival (OS)

Overall survival will be defined as the time from randomization until death from any cause. Patients alive or lost to follow up at the time of analysis will be censored at the last date the patient was known to be alive.

Quality of Life

Background:

Health-related quality of life (QoL) is recognized to be an important element in the treatment of cancer patients. Over the last two decades, there has been an major progress in the development of robust validated tools to measure the QoL of cancer patients being used both before and during cancer treatments. QoL studies are becoming routinely used in the overall setting of clinical studies in oncology.

Several QoL tools have been developed and validated; Two of the most widely used ones are the EORTC QLQ-C30 measure (Aaronson, 1993) as well as the functional assessment of cancer therapy (FACT-G). Of these two measures, the most frequently used and cited is the EORTC QLQ-C30 which has been most widely used in Europe (Bottomley, 2006; Fallowfield, 2002; Garret, 2002; Taphoorn, 2005). Meanwhile, they are recognized tools both by European and American regulatory authorities and the EORTC tool has been translated into over 70 languages, making it a valuable tool for international studies (Cull, 2002)

Rationale and objective:

QoL is important in relapsed and refractory MCL patients because cure is virtually not achievable and survival is poor. Therefore, the tolerability of a palliative intended treatment becomes even more important to maintain patients QoL as long as possible.

Commonly, patients with relapsed or refractory MCL often present with constitutional symptoms, such as asthenia, fatigue, weight loss and B-symptoms (including fever and night sweats).

The EORTC QLQ-C30 measure will be used in this study, given it is robust and will address the key issues in these patients. The expectations are that lenalidomide may improve the global health status score as well as the physical functional score. The fatigue item could be worse initially under lenalidomide, but may improve mid and long term in responding patients due to tumor control in relation to the control arm with expected shorter response duration.

The primary QoL objective is therefore to determine the impact of lenalidomide on overall health/QoL. The H_0 hypothesis will be tested that there is no difference in both arms during and after the treatment.

A secondary QoL objective is to evaluate the effect of the treatment of various symptoms and functioning scales, with the two key ones being physical functional and fatigue.

QoL instrument: EORTC QLQ-C30 (see attachment Appendix 21.12)

The version 3.0 of the EORTC QLQ-C30 is a 30-item scale. The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items.

FUNCTIONAL SCALES (16 questions)	SYMPTOM SCALES (6 questions)	SINGLE ITEMS (6 questions)	GLOBAL QUALITY OF LIFE (2 questions)
Physical	Fatigue	Constipation	Global QoL
Role	Pain	Diarrhoea	
Cognitive	Nausea/vomiting	Sleep	
Emotional		Dyspnoea	
Social		Appetite	
		Financial	

All of the scales and single-item measures range in score from 0 to 100. A higher scale score represents a higher level of well being and better ability of daily functioning. A 10 point change in the scoring is considered to be meaningful change in quality of life (Osoba, 1998).

Thus a high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatic problems.

Data collection and timing

Questionnaires must be filled out by the patient at 6 pre-specified time points (see below and Table 2) when the patient comes for a scheduled visit. They will be handed out by a nurse or the treating physician/investigator, and ideally are collected again soon after the patient has filled it out.

Patients will be asked to complete the questionnaire as completely and accurate as possible. The average time to complete the questionnaire is around 10-15 minutes. The reasons for not completing the questionnaire will be recorded

Quality of life will be assessed at 6 time points (refer to Table 2)

- at screening/baseline (within 7 days prior to randomization),
- after cycle 2 (C3D1)
- after cycle 4 (C5D1),
- after cycle 6 (C7D1),
- after cycle 8 (C9D1),
- and at time of discontinuation from treatment

A ± 7 days time window will be allowed.

Compliance & Missing data

During the study compliance will be investigated at each time point. Compliance rate will be descriptively compared between the 2 arms.

In the case that a patient still on study has not filled in the questionnaire, no more than ± 7 days delay is accepted.

The rate of compliance will be assessed after 40, 80, 120 and 200 patients enrolled.

Missing data will be reported as recommended in the EORTC scoring manual (Fayers, 2001).

- *Scales scores:* If at least 50% of the items have been answered, the scale scores will be calculated according to the standard equations given on the manual (any items with missing values will be ignored). In other cases, scores will be set to missing
- *Single-item measures*: the score will be set to missing

Statistical considerations

No calculation in terms of sample size will be performed based on changes in QoL.

In the absence of more specific hypothesis, the global score will be used as the primary QoL outcome and physical functional score and fatigue item will be used as secondary outcomes.

Expectations are that the global score and the physical functional score are improved by lenalidomide. The fatigue item may be worse initially under lenalidomide, but improve in mid and long term in responding patients due to tumor control compared to control arm with shorter response duration.

A difference of 10 points between the two arms is considered as clinically significant (Osoba, 1998).

15.2.3. Analysis Methods

All efficacy analyses will be conducted on intent to treat basis.

All efficacy analyses will be repeated on the Full Analysis Set (FAS) as sensitivity analysis for the primary endpoint.

The primary analysis for PFS to be performed on the ITT and FAS populations will be conducted one year after the last patient is randomized.

The Kaplan-Meier procedure will be used to characterize time to event endpoints (*e.g.*, PFS, TTP, TTR, OS) and duration of response. Median times-to-event and their respective two-sided 95% confidence intervals will be provided for each of these variables.

The stratified log-rank test will be used as the main analysis to compare treatment arms for time-to-event variables and an unstratified log-rank test will be used as supportive analysis. The Cox proportional hazards regression model will be used to assess the significance of stratification factors on treatment differences. Any demographic or baseline characteristics variables considered as strong predictive or prognostic factors will also be included as part of the formal statistical analysis plan.

Patients who drop out of the study without being evaluated for will be counted as non-responders. Responses from patients after they receive other anti-cancer treatments will be counted as non responder.

Secondary endpoints will be analyzed at the time of the primary analysis of response. An update of the time to events endpoints and overall survival will be done at the end of the follow up. No adjustment for multiplicity will be applied.

The probability of response rates will be estimated using the proportion of patients with responses with exact two-sided 95% confidence intervals.

The EORTC QLQ-C30 will be analyzed using change from baseline and percentage of change from baseline according to the functional scores and the recommendations in the EORTC scoring manual.

The EORTC Reference Data Manual (Scott, 2008) will also be used to descriptively check comparability between patients in our trial and with other comparable populations. The response rate in the cross-over portion of patients in Arm B will be analyzed in a descriptive manner.

15.3. Background and Demographic Characteristics

Summary statistics (mean, standard deviation, median, minimum and maximum) will be provided for those variables measured on a continuous scale. The frequency distribution (n %) will be provided for those variables measured on a nominal scale.

15.4. Study Drug

Dosage statistics (mean, median, standard deviation and range) will be provided. Timing and reasons for dose adjustments will be summarized.

15.5. Concomitant Therapy

By-patient listings will be provided for all concomitant medications and therapies taken during the trial. They will be coded and categorized by the WHO drug coding system and frequency summaries provided.

15.6. Safety Evaluation

Data from the treated population will be included in the safety analyses.

Adverse event severity will be classified using the NCI CTCAE criteria, version 3.0.

Adverse event frequency will be tabulated by body system, and MedDRA term.

In the by-patient analysis, a patient having the same event more than once will be counted only once. Adverse events will be summarized by worst NCI CTCAE grade. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, study-drug related events, and serious adverse events will be listed separately.

Second primary malignancies throughout the course of the study will be monitored as events of interest, and will be listed and be analyzed separately.

The probability of dose reduction will be estimated using the proportion of patients with dose reduction.

Laboratory data will be graded according to NCI CTCAE severity grade.

The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by baseline status.

Vital signs, ECGs and ECOG Performance Status will be summarized as appropriate.

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

15.7. Interim Analyses

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study and efficacy for futility at a pre-defined time point. Specifics are outlined in the DMC charter. Summaries of safety information will be prepared for Data Monitoring Committee (DMC) review. The first safety analysis will occur after the first 40 patients have received at least 2 cycles of treatment or have discontinued prior to completing 2 cycles. The second safety analysis as well as an efficacy analysis for futility will occur after 80 patients complete 2 cycles or withdraw before completing 2 cycles (around 54 patients in the lenalidomide arm). A third safety analysis will occur after 120 patients complete 2 cycles or withdraw before completing 2 cycles. A fourth safety analysis will occur after 200 patients complete 2 cycles or withdraw before completing 2 cycles. Additional efficacy and safety data might be provided to the DMC members on request as outlined in the DMC charter.

DMC will conduct an analysis for futility on PFS and Overall response rate. No specific stopping rules will be given to the DMC for the PFS, the following rules might be used for overall response rate.

Based on a 95% CI approach, if the upper bound is below 20% in the lenalidomide arm, the DMC should recommend stopping the trial.

Frequency of response	Binomial Proportion P	Exact Lower CL, Binomial Proportion[1]	Exact Upper CL, Binomial Proportion[1]
1	1.8519	0.04687	9.8915
2	3.7037	0.45173	12.7472
3	5.5556	1.16068	15.3885
4	7.4074	2.05510	17.8933
5	9.2593	3.07528	20.3002
6	11.1111	4.18838	22.6313
7	12.9630	5.37430	24.9012
8	14.8148	6.61976	27.1198
9	16.6667	7.91544	29.2941
10	18.5185	9.25455	31.4297

[1] Exact confidence intervals based on the Clopper-Pearson method

The third DMC recommended an increase of sample size. An adjustment of the alpha level for the final analysis is needed. The type I error will be controlled with adequate methods and details will be further described in the SAP.

15.8. Sample Size and Power Considerations

The main objective of the study is to demonstrate the efficacy of lenalidomide over an investigator's choice single agent based on PFS. The primary analysis is to compare PFS between lenalidomide and investigator's choice monotherapy.

Protocol Amendment #4:

The third independent DMC meeting was held on July 22, 2011, in which the committee members reviewed un-blinded both safety and efficacy data from 166 randomized patients. No safety concerns were noted. The DMC observed that the interim PFS in the control arm is different from the intial assumptions which were used to calculate the sample size described in Protocol Amendment #2.

The DMC therefore recommended increasing the sample size from 174 (number of patients randomized at the time of the DMC was held) to 250 patients and conducting the underpowered primary analysis one year after the last patient being randomized. This would allow a more reliable estimation of the treatment effect aiming at demonstrating a clinically meaningful improvement in PFS between the experimental arm and the control arm. In addition the proposed timing for the analysis will allow a reasonable follow up for overall survival so full information on the clinical benefit of lenalidomide can be provided at the time of PFS analysis.

The type I error will be controlled with adequate methods and the details will be further described in the SAP.

Protocol Amendment #2

With a hazard ratio of 1.7, full information necessary for a one-sided log rank test with an overall alpha of 0.025, to have 80% power, will be achieved when approximately 128 patients have progressed or died (PFS).

Original Protocol

The sample size of this study was originally calculated to estimate the Overall Response Rate (ORR), which was the original objective of the study. Sample size calculation was based on the width of the 95% confidence interval around a certain point estimate for ORR that is considered significant clinical activity. Based on preliminary data, a response rate in the range of 30% to 40% was reasonably expected. A sample size equal to 100 allows us to construct a two sided 95% confidence interval with a width of 9% (one direction) for an expected proportion of 30%. The lower observed confidence interval limit would be about 21%, which was still considered clinically meaningful. This sample size allowed a width (one direction) of 9.6% for an expected proportion of 40% and 9.3% for an expected proportion of 35% (See Table 10).

Table 10: Confidence Intervals

	95% Two-Sided Confidence Intervals (N=100)		
Response rate	30%	35%	40%
CI[1]	0.214 – 0.400	0.257 – 0.452	0.303 – 0.503

[1] Exact confidence intervals based on the Clopper-Pearson method

Using a one group $\chi 2$ test with a 0.050 two-sided significance level a sample size of 100 patients will have 81% power to detect the difference between the Null hypothesis proportion of 20% and the alternative proportion of 32%. No formal sample size calculation will be done for the control arm. With a 2:1 ratio 50 patients are needed in the control arm. Assuming that 10% of patients will be lost to follow up, 167 patients were to be randomized.

15.9. Other Topics

Exploratory Analyses:

Any subgroup analysis will be conducted on exploratory data.

Statistical tests will be performed to compare the two treatment arms only for exploratory purpose for the secondary endpoints.

Exploratory analysis will be conducted also on the As Treated population for the following endpoints: PFS, ORR and OS.

In order to evaluate the effect of cross over on overall survival a Mantel-Byar approach will be used. The estimation of the control arm without cross over and the mixed arm (Lenalidomide arm and cross over patients) will be estimated. A weighted logrank test or wilcoxon test will be used to take into account the cross over effect (Anderson, 1983; Klein, 1997; Colett, 2003)

Multivariate models will be used to identify those baseline and prognostic factors (e.g. absolute leukocyte count, time from diagnosis, number of prior therapies and any other variables suggested in the literature prior to the analysis) most predictive of response (Colett, 1991).

Mann-Whitney tests for simple comparison and longitudinal data modeling techniques (i.e. Proc mixed in SAS) for the QOL score. Details will be given in the statistical analysis plan.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. Monitoring

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

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

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. From time to time, representatives of this unit will conduct audits of clinical research activities in accordance with Celgene Standard Operating Procedures (SOPs) to evaluate compliance with Good Clinical Practice (GCP) guidelines and regulations.

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

16.3. Investigator(s) Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice and in the US Code of Federal Regulations. Celgene or a representative will contact and select all principal investigators or co-investigators who in turn will select their staff. The investigator must give the monitor access to relevant records to confirm the above.

The Investigator(s) is responsible for keeping a record of all patients who sign an Informed Consent Form and are screened for entry into the study. For those patients who fail screening the reason(s) for exclusion must be recorded in the patient's source documents and on the Screening Log provided by Celgene.

No procedure/assessment/measurement/test other than those outlined here, or in the schedule of study assessments, is to be performed without the prior written approval of Celgene, or unless deemed by the investigator(s) as necessary for the patient's medical care. Investigator(s) and/or authorized designee(s) must enter study data onto CRFs supplied by Celgene. The data on the CRF will be recorded in an anonymous manner to protect the patient's identity by using a unique identifier that will prevent personal identifiable information.

The Investigator(s), or a designated member of the Investigators' staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the patient's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The CRFs must be completed as soon as possible after the patient's visit but no later than prior to each monitoring visit and be made available to the Celgene representative(s) so that the accuracy and completeness may be checked.

Following the approval of Protocol Amendment #6 and closure of the clinical database, clinical study data will no longer be collected on CRFs by the investigator in the Expanded Access Phase. The investigator will be required to complete the subjects' Drug Accountability and Dosing Record Sheet at each subject visit, as well as to verify and assure appropriate filing in study files, and in subjects' medical records

17. REGULATORY CONSIDERATIONS

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

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (see Appendix 21.2). The review of this protocol by the IRB/IEC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Patients and Part 56 Institutional Review Boards. Before implementing this study, the protocol, the proposed informed consent form and other information to patients, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Celgene before the study initiation. The names and occupations of the chairman and the members of the IRB/IEC must be supplied to Celgene.

The Investigator(s) will be responsible for preparing documents for submission to the relevant IRB/IEC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

A copy of the IRB/IEC approval for the protocol and the Informed Consent is to be provided to Celgene. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

The Investigator(s) is responsible for notifying the IRB/IEC of any serious deviations from the protocol, or anything else that may involve added risk to patients.

Any advertisements used to recruit patients for the study must be reviewed and approved by Celgene and the IRB/IEC prior to use.

17.2. Protocol Amendments

Any amendment to this protocol that seems appropriate, as the study progresses (e.g. affects safety or efficacy) will be agreed upon between the coordinating and/or principal investigator(s) and the Celgene study physician. Amendments will be submitted to the IRB/IEC for written approval before the implementation of the amended version. The written signed approval from the IRB/IEC should refer specifically to the investigator(s) and to the protocol number and title and mention any amendment numbers that are applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

17.3. Informed Consent

The Investigator(s) must obtain informed consent of a patient or his/her designee prior to any study related procedures as per Good Clinical Practices (GCP) as set forth in the 21 CFR Parts 50 and 56 and ICH guidelines.

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

17.4. Patient Confidentiality

Celgene affirms the patient's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator(s) to permit Celgene's representatives and, when necessary, representatives of the FDA or other 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 patient's statement of informed consent, it is the responsibility of the Investigator(s) to obtain such permission in writing from the appropriate individual.

18. DATA HANDLING AND RECORDKEEPING

18.1. Data/Documents

The investigator(s) must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents, original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; patient files) and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, and filed and retained.

18.2. Data Management

Data will be entered into the clinical database per SOPs unless internal processes will be done by Data Management of Celgene, in this case Celgene SOPs will be used. 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.

Extended Access Phase

Following the approval of Protocol Amendment #6, CRF pages will no longer be completed. At each visit, the study monitor will be required to verify and assure appropriate filing in study files of the subjects' Drug accountability and Dosing Record Sheets and verify the information therein with the source records of the subject. The study monitor will record changes in the subjects' Drug Accountability and Dosing Record Sheet in their visit report.

18.3. Retention of Records

The Investigator must maintain records of all study documents and supporting information relating to the conduct of the study in accordance with ICH GCP and applicable local regulatory requirements. This documentation includes, but is not limited to, protocols, case report forms, advertising for study patient participation, adverse event reports, study patient source data, correspondence with health authorities and IRBs/IECs, informed consent documents, Investigator curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. Study patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice specified below. The study monitor or designee must be consulted if the Investigator wishes to assign the study files to someone else, remove them to another location or is unable to retain them for a specified period. The monitor will inform the Investigator of the dates for retention. 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.

For studies conducted in the United States under a US IND, the Investigator must retain the study records for a minimum of 2 years after a marketing application for the indication is

approved or for 2 years after the IND is withdrawn. If no application is filed, or if the application is not approved for the indication, the records are to be retained for two years after the investigation (i.e., the IND) is discontinued, and FDA is notified of that fact. For IND studies conducted outside the US, the Investigator must retain study records for the time period described above or according to local laws or requirements, whichever is longer. For studies not conducted under the US IND, the Investigator records must be retained until at least 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 investigational product. These documents should be retained for a longer period if required by other applicable regulatory requirements.

19. PREMATURE DISCONTINUATION OF THE STUDY

19.1. Single Site

The responsible clinical Investigator as well as Celgene has the right to discontinue a single site at any time during the study for reasonable medical or administrative reasons. Possible reasons for termination of the study could be, but are not limited to:

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

19.2. Study as a Whole

Celgene reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would have to be documented adequately with reasons being stated, and information would be issued according to local requirements (e.g., IRB/IEC, regulatory authorities, etc.).

20. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Natl Cancer Inst 1993; 85:365-376.

Armitage JO. Treatment of non-Hodgkin's lymphoma. *N Engl J Med.* 1993; 328(14):1023-30.

Andritsos L, Johnson AJ, Lozanski G, et al. Doses of Lenalidomide Are Associated With Unacceptable Toxicity Including Life Threatening Tumor Flare in Patients With Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2008; 26(15):2519-2525.

Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables *J Clin Oncol*. 2008; 26(24):3913-5.

Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response *J Clin Oncol.* 1983; 1(11):710-19.

Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan KA, Marcus RE, Jelliffe A, Vaughan G, Hudson , Linch DC; British National Lymphoma Investigation. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet.* 2003 Aug 16; 362(9383):516-22.

Bottomley A, Gaafa R, Manegold C, Burgers S, Coens C, et al. Short-term treatment-related symptoms and quality of life: results from an international randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an EORTC Lung-Cancer Group and National Cancer Institute, Canada, Intergroup Study. *J Clin Oncol.* 2006; 24(9):1435-42.

Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. *Biometrics*. 1982; 38(1): 29-41.

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification.*Br J Haematol*. 2004 Oct; 127 (1):3-11

Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia : results of a phase II study. *J Clin Oncol*. 2006 Dec 1; 24(34):5343-9.

Chanan-Khan A, Miller KC, Whitworth A, et al. Clinical activity of lenalidomide in relapsed or refractory chronic lymphocytic leukemia (CLL) patients: updated results of a phase II clinical trial. *Leuk Lymphoma.* 2007; 48 (suppl 1): S166.

Cheson B, Horning S, Coiffier B, Shipp M, Fisher R, Connors J, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphoma. *J Clin Oncol*.1999; 17: 1244-53.

Collett, D. *Modelling Binary Data.* 1991; London: Chapman & Hall.

Collett, D. *Modelling Survival Data in Medical Research Second Edition.* 2003; London: Chapman & Hall.

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

Cohen BJ, Moskowitz, Straus D, Noy A, Hedrick E, Zelenetz A. Cyclophosphamide/Fludarabine is active in the treatment of mantle cell lymphoma. *Leuk Lymph.* 2001; 42(5):1015-1022.

Clopper C, Pearson S. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 26: 404-413, 1934.

Corral L, Hasslet P, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thaliodimide analogues that are potent inhibitors of TNF-α. *J Immunol.* 1999; 163: 380-386.

Cull A, Sprangers MAG, Bjordal K, Aaronson NK, West K, Bottomley A. Guidelines for translating EORTC Questionnaires. Brussels, Belgium, Quality of Life Study Group Publications, EORTC Publications, 2002

Czuczman MS, Reeder CB, Polikoff J, et al. International Study of Lenalidomide in Relapsed/Refractory Aggressive Non-Hodgkin s Lymphoma). *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 8509)

Damaj G., Lefere F, Delaure R, Varet B, Furman R, Hermine O. Thalidomide therapy induces response in relapsed mantle cell lymphoma. *Leukemia*. 2003; 17(9):1914-1915.

Decaudin D, Bosq J, Tertian G, Nedellec G, Bennaceur A, Venuat AM, Bayle C, Carde P, Bendahmane B, Hayat M, Munck JN. Phase II trial of fludarabine monophosphate in patients with mantle-cell lymphomas. *J Clin Oncol.* 1998 Feb;16(2):579-83.

Determann O, Hoster E, Ott G, Wolfram Bernd H, Loddenkemper C, Leo Hansmann M, Barth TE, Unterhalt M, Hiddemann W, Dreyling M, Klapper W; European Mantle Cell Lymphoma Network and the German Low Grade Lymphoma Study Group.Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. *Blood*. 2008 Feb 15; 111(4):2385-7.

Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma . *New Engl J Med.* Nov 2007; 357:2123-2132

Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloblative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: results of a prospective randomized trial of the European MCL network. *Blood.* 2005; 105(7):2677-2684.

Dumontet C, Morschhauser F, Solal-Celigny P, Bouafia F, Bourgeois E, Thieblemont C, Leleu X, Hequet O, Salles G, Coiffier B. Gemcitabine as a single agent in the treatment of relapsed or refractory low-grade non-Hodgkin's lymphoma. *Br J Haematol.* 2001 Jun;113(3):772-8.

Epner EM, Unger J, Miller T, Rimzsa L, Spier C, Leblanc M. A multi center trial of hyper CVAD + Rituxan in patients with newly diagnosed mantle cell lymphoma. *Blood* (ASH Annual Meeting Abstracts), Nov 2007; 110**:**387

Eve HE, and Rule SAJ. Lenalidomide-induced tumour flare reaction in mantle cell lymphoma. *Br J Haematol.* Nov 2010 151: 410–412.

Fallowfield L, Gagnon D, Zagari M, Cella D, Bresnahan B, et al. Multivariate regression analyses of data from a randomised, double-blind, placebo-controlled study confirm quality of life benefit of epoetin alfa in patients receiving non-platinum chemotherapy. *Br J Cancer.* 2002; 87(12):1341-53.

Fayers P, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual (ed 3). Brussels, Belgium, EORTC Publications, 2001

Fernandez V, Hartmann E, Ott G, Campo E, Rosenwald . 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): 6364-6369.

Fernandez V, Serrano S, Jares P, Campo E. Genomic and Gene Expression Profiling Defines Indolent Forms of Mantle Cell Lymphoma. *Cancer Res.* 2010 Feb 15; 70 (4):1408-1418.

Ferrajoli A, Lee BN, Schlette EJ, O'Brien SM, Gao H, Wen S, Wierda WG, Estrov Z, Faderl S, Cohen EN, Li C, Reuben JM, Keating MJ. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. *Blood.* 2008 Jun 1; 111(11):5291-7.

Fisher RI, Bernstein SH, Kahl BS, et al. Mulicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol*. 2006; 24(30):4867-4874.

Foran JM, Rohatiner AS, Coiffier B, et al. Multicenter phase II study of Fludarabine phosphate for patients with newly diagnosed lymphoplasmacytoid lymphoma, Waldenstroms macroglobulinema, and mantle cell lymphoma. *J Clin Oncol.* 1999;17(2):546-553.

Fu K, Weisenburger DD, Greiner TC, et al. Cyclin D1-negative mantle cell lymphoma: a clincopathologic study based on gene expression profiling. *Blood.* 2005; 106:4315-4321

Gaidarova S, Corral LG, Gleizer E, Young D, Brady H, Bennett B, Lopez-Girona A. Lenalidomide enhances anti-tumor effect of γδ T cells against mantle cell lymphoma. *Blood.* 2008; 112:906, abstr 2616.

Galustian, C, Labarthe MC, Barlett JB, Dalgleish AG. Thalidomide-derived immunomodulatory drugs as therapeutic agents. *Expert Opin Biol Ther*. 2004; 4(12): 1963-1970.

Garret A, Schmedit L, Mackintosh A, Fitzpatrick. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ*.2002; 324:1417-1419.

Geisler CH, Kolstad A, Laurell A, Andersen NS, Pedersen LB, Jerkeman M, Eriksson M, Nordström M, Kimby E, Boesen AM, Kuittinen O, Lauritzsen GF, Nilsson-Ehle H, Ralfkiaer E, Akerman M, Ehinger M, Sundström C, Langholm R, Delabie J, Karjalainen-Lindsberg ML, Brown P, Elonen E; Nordic Lymphoma Group. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood.* 2008 Oct 1;112(7):2687-93. [Epub 2008 Jul 14].

Ghielmini M, Schmitz SF, Bürki K, Pichert G, Betticher DC, Stupp R, Wernli M, Lohri A, Schmitter D, Bertoni F, Cerny T. The effect of Rituximab on patients with follicular and mantle-cell lymphoma. Swiss Group for Clinical Cancer Research (SAKK). *Ann Oncol.* 2000; 11 Suppl 1:123-6.

Goy A, Younes A, McLaughlin P, Pro B, Romaguera JE, Hagemeister F, Fayad L, Dang NH, Samaniego F, Wang M, Broglio K, Samuels B, Gilles F, Sarris AH, Hart S, Trehu E, Schenkein D, Cabanillas F, Rodriguez AM. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2005 Feb 1;23(4):667-75. [Epub 2004 Dec 21].

de Guibert S, Jaccard A, Bernard M, Turlure P, Bordessoule D, Lamy T. Rituximab and DHAP followed by intensive therapy with autologous stem cell transplantation as first line therapy for mantle cell lymphoma. *Hematologica*. 2006; 91:425-426.

Habermann TM, Lossos IS, Justice G, Vose JM, Wiernik PH, McBride K, Wride K, Ervin-Haynes A, Takeshita K, Pietronigro D, Zeldis JB, Tuscano JM. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma.Br J Haematol. Feb 2009, (Epub ahead of print).

Haritunians T, Mori A, O'kelly J, Luong QT, Giles FJ, Koeffler HP. Antiproliferative activity of RAD001(everolimus) as a single agent and combined with other agents in mantle cell lymphoma. *Leukemia.* 2007; 21:333-339.

Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, Laurell A, Offner F, Strahs A, Berkenblit A, Hanushevsky O, Clancy J, Hewes B, Moore L, and Coiffier B. Phase III Study to Evaluate Temsirolimus Compared With Investigator's Choice Therapy for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma. *J Clin Oncol.* 2009; 27:3822-3829.

Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. 2008; 111: 558-565

Jares P, Campo E. Advances in understanding of mantle cell lymphoma. *J Haematology.* 2008 Apr 10. [Epub ahead of print]

Kane R, Dagher R, Farrell A, Ko C, Sridhara R, Justice R, Pazdur R. Bortezomib for the Treatment of Mantle Cell Lymphoma. *Clin Cancer Res*. 2007; 13(18): 5291-5294.

Kantarjian H, Barlogie B, Plunkett W, Velasquez W, McLaughlin P, Riggs S, Cabanillas F. High-dose cytosine arabinoside in non-Hodgkin's lymphoma. *J Clin Oncol.* 1983 Nov;1(11):689-94.

Kaufmann H, Raderer M, Wohrer S, et al. Antitumor activity of rituximab plus thalidomide in patients with relapsed/refractory mantle cell lymphoma. *Blood*. 2004; 104:2269-2271.

Klein J.P, Moeschberger ML. *Survival Analysis: Techniques for Censored and Truncated Data,* 1997; New York: Springer-Verlag.

Kouroukis CT, Belch A, Crump M, et al. Flovopiridol in untreated or relapsed mantle cell lymphoma: Results of a phase II study of the national cancer institute of Canada clinical trials group. *J Clin Oncol*. 2003; 21:1740-1745.

List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med.* 2006 Oct 5;355(14):1456-65.

Luke DR, Halstenson CE, Opsahl JA, Matzke GR. Validity of creatinine clearance estimates in the assessment of renal function. *Clin Pharmacol Ther.* 1990; 48: 503-508.

Morschhauser F, Depil S, Jourdan E, Wetterwald M, Bouabdallah R, Marit G, Solal-Céligny P, Sebban C, Coiffier B, Chouaki N, Bauters F, Dumontet C. Phase II study of gemcitabine-dexamethasone with or without cisplatin in relapsed or refractory mantle cell lymphoma. *Ann Oncol.* 2007 Feb;18(2):370-5. http://annonc.oxfordjournals.org/cgi/content/abstract/mdm463v1. Accessed 16 January 2008.

Moutouh-de Parseval LA, Weiss L, DeLap RJ, Knight RD, Zeldis JB.Tumor lysis syndrome/tumor flare reaction in lenalidomide-treated chronic lymphocytic leukemia.*J Clin Oncol.* 2007 Nov 1; 25(31):5047.

Miller KC, Czuczman MS, DiMiceli L, et al. Antileukemic effects of novel immunomodulatory agent lenalidomide with or without rituximab in patients with relapsed or refractory chronic lymphocytic leukemia: encouraging preliminary results of an ongoing Phase II clinical study .*J Clin Oncol*, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 6557

O' Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor Bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol.* 2005; 23: 676-684.

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol.* 1998; 16(1):139-44

Pan D, Moskowitz CH, Zelenetz AD, Straus D, Kewalaramani T, Noy A, et al. Rituximab for Aggressive Non-Hodgkin's Lymphomas Relapsing After or Refractory to Autologous Stem Cell Transplantation. *The Cancer Journal.* 2002; 8(5): 371-376.

Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med.* 2000;343:1750–1757.

Ramsay AG, Johnson AJ, Lee AM, Gorgun G, Le Dieu R, Blum W, Byrd JC, Gribben JG. Chronic Lymphocyctic Leukemia T cells Show Impaired Immunological Synapse Formation That can be Reversed with an Immunomudulation drug. *J. Clin. Invest.* 2008 July 1; 118(7): 22427-2437.

Ramsay AG, Clear AJ, Kelly G et al. Follicular lymphoma cells induce T-cell immunologic synapse dysfunction that can be repaired with lenalidomide: implications for the tumor microenvironment and immunotherapy. *Blood*. 2009; 114, (21) 4713-4720.

Schafer PH, Gandhi AK, Loveland MA, et al. Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. *J Pharmacol Exp Ther*. 2003; 305(3):1222-1232.

Schlette E, Lai R, Onciu M, Doherty D, Bueso-Ramos C, Medeiros LJ. *The US and Canadian academy of pathology, Inc*. 2001; 14(11):1133-1140.

Scott NW, Fayers PM, Aaronson NK, Bottomley A, Graeff de G, Groenvold et al. EORTC QLQ-C30 Reference Values. EORTC Quality of Life Group, EORTC publications 2008.

Taphoorn M, Stupp R, Coens C, Osoba D, Kortmann R, et al. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. *Lancet Oncol.* 2005; 6(12):937-44.

Tobinai K, Watanabe T, Ogura M, Morishima Y, et al. Phase II study of oral fludarabine phosphate in relapsed indolent B-Cell non-Hodgkins lymphoma. *J Clin Oncol*. 2006; 24(1):174-180.

UK SPC, UK Summary of Product Characteristics for Cytarabine Injection Solution 100mg/ml dated 26th April 2007 (Mayne Pharma plc).

Verhelle D, Corral LG, Wong K, et al. Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34+ progenitor cells. *Cancer Res.* 2007; 67(2):746-755.

Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America. *New Engl J Med.* Nov 2007. 357:2123-2132

Wiernik P, Lossos I, Tuscano J, Justice G, Vose J, et al. Lenalidomide Monotherapy in Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma. *J Clin Oncol.* 2008 Jul 7.

Witzig TE, Geyer SM, Ghobrial I, Inwards DJ, Fonseca R, Kurtin P, et al. Phase II Trial of Single-Agent Temsirolimus (CCI-779) for Relapsed Mantle Cell Lymphoma. *J Clin Oncol*. 2000; 23 (23): 5347-5356.

Witzig TE, Reeder CB, Polikoff J, et al. Initial Results from an International Study in Relapsed/Refractory Aggressive Non-Hodgkin s Lymphoma to Confirm the Activity, Safety and Criteria for Predicting Response to Lenalidomide Monotherapy. *Blood* (ASH Annual Meeting Abstracts), Nov 2007; 110: 2572.

Witzig TE, Vose JM., Zinzani PL, Reeder CB, Buckstein R, Polikoff J, Bouabdallah R, Haioun C, Tilly H, Guo P, Pietronigro D, Ervin-Haynes AL and Czuczman MS. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol*; 12 Jan 2011 [Epub ahead of print]

Zhang LH, Schafer PH, Muller G, Stirling DI, Bartlett JB. Lenalidomide displays direct anti-Hodgkin's Lymphoma (NHL) activity in association with enhanced SPARC expression but independent of its ability to strongly inhibit NHL cell VEGF production *in vitro*. Blood (ASH Annual Meeting Abstracts), Nov 2007; 110: 3473.

Zinzani PL, Magagnoli M, Moretti L, De Renzo A, Battista R, Zaccaria A, Guardigni L, Mazza P, Marra R, Ronconi F, Lauta VM, Bendandi M, Gherlinzoni F, Gentilini P, Ciccone F, Cellini C, Stefoni V, Ricciuti F, Gobbi M, Tura S. Randomized trial of fludarabine versus fludarabine and idarubicin as frontline treatment in patients with indolent or mantle-cell lymphoma. *J Clin Oncol.* 2000 Feb; 18(4):773-9.

Zhu D, Corral LG, Fleming YW, Stein B. Immunomodulatory drugs Revlimid® (lenalidomide) and CC-4047 induce apoptosis of both hematological and solid tumor cells through NK cell activation. *Cancer Immunol Immunother.* 2008 Apr 8. [Epub ahead of print].

21. APPENDICES

21.1. Adverse Event

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a patient 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 patient's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that is presented prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition this should be considered as an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form 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.

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

All AEs will be recorded by the Investigator(s) from time of signed informed consent through the end (see Table 3 and Appendix 21.1.9) of the designated follow-up period. AEs will be recorded on the AE page of the CRF and in the patient'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.

Following the approval of Protocol Amendment #6, only serious adverse event data (including second primary malignancies) on SAE forms will continue to be sent by the investigator to Celgene.

Non-serious adverse events will no longer be collected on a CRF by Celgene, but should be recorded in the subjects' medical records and reviewed by the study monitor.

21.1.1. Abnormal laboratory values defined as adverse events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.
- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention.
- Is judged by the Investigator(s) to be of significant clinical importance.

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 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.

21.1.2. Serious adverse event

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the patient is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the patient'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 patient 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.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

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

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

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 Appendix 21.1.9). This includes any second primary malignancy, regardless of causal relationship to study drug (lenalidomide or Investigator Choice arm drugs), occurring at any time for the duration of the study, from the time of signing the ICD through follow-up for overall survival. The Follow-Up Phase involves patient contact every 90 days (± 15 days) until patient death or until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the

second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory pathology results, imaging results, etc.).

21.1.3. Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The severity of AEs will be graded based upon the patient's symptoms according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 3.0) (http://ctep.cancer.gov/reporting/ctc.html). The AEs will be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Grade 4 = Life Threatening

Grade 5 = Death

21.1.4. Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

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

21.1.5. Duration

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

21.1.6. Action Taken

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

21.1.7. Outcome

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

21.1.8. Monitoring and reporting of adverse events

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

Following the approval of Protocol Amendment #6, only serious adverse event data (including second primary malignancies) on SAE forms will continue to be sent by the investigator to Celgene.

Non-serious adverse events will no longer be collected on a CRF by Celgene, but will be recorded in the subjects' medical records.

21.1.9. Immediate reporting of serious adverse events

Any AE that meets the criterion for any SAE requires the completion of an SAE Report Form in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study drug, that occur during the study, those made known to the Investigator(s) within 30 days after a patient's last dose of study drug, any second primary malignancies occurring at any time for the duration of the study through follow-up for overall survival, and those made known to the investigator(s) at anytime that are suspected of being related to study drug.

The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to Celgene Drug Safety by facsimile. An initial written report (prepared by the Investigator(s) using the SAE Report Form provided by Celgene) is to be faxed to Celgene Drug Safety. The immediate reporting process and timelines apply also to reporting second primary malignancies (see Appendix 21.1.2).

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

The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all SAE information, including correspondence with Celgene and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the patient's participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

21.1.10. Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient or the female partner of a male patient occurring while the patient is on study drug, or within 30 days of the patient's last dose of study drug, are considered immediately reportable events. Immediate is defined as within 24 hours of the study site's knowledge of the event. Study drug is to be discontinued immediately and the patient instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile using the SAE Report Form.

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

The Investigator(s) will follow the female patient until completion of the pregnancy, and must notify Celgene Drug Safety of the outcome of the pregnancy as a follow-up to the initial SAE report. Infant follow-up will occur for one year following birth in a FCBP who was treated with lenalidomide.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (i.e., report the event to Celgene Drug Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, Celgene Drug Safety should be advised by facsimile within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to Celgene Drug Safety by facsimile within 24 hours of the Investigators' knowledge of the event.

If the female is found not to be pregnant, any determination regarding the patient's continued participation in the study will be determined by the Investigator(s) and the Celgene Medical Monitor.

21.1.11. 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.

21.1.12. 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 and for chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine based on the UK SPCs.

For countries within the European Union, Celgene will report in an expedited manner to Regulatory Agencies and Ethics Committees concerned, adverse events in accordance with the

Detailed Guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3) and also in accordance with country specific requirements.

Celgene shall notify the Investigator of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, i.e., suspected unexpected serious adverse reaction (SUSAR). Note that such cases from blinded studies will be unblinded for reporting purposes.
- Any finding from tests in laboratory animals suggests a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.

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

The Investigator must keep copies of all pertinent safety information, including correspondence with Celgene and the IRB/IEC, on file (see Section 18.3 for records retention information).

For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines

21.2. Declaration of Helsinki

Initiated: 1964 17.C

Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964 and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the EMA General Assembly, Tokyo 2004

21.2.1. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human patients**.** Medical research involving human patients includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human patients.
5. In medical research on human patients, considerations related to the well being of the human patient should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human patients is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is patient to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be patient to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human patients in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human patients set forth in this Declaration.

21.2.2. Basic Principles for All Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human patient.
11. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human patients should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for patients.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human patients should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human patient must always rest with a medically qualified person and never rest on the patient of the research, even though the patient has given consent.
16. Every medical research project involving human patients should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the patient or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human patients unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human patients should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the patient. This is especially important when the human patients are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The patients must be volunteers and informed participants in the research project.
21. The right of research patients to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the patient, the confidentiality of the patient's information and to minimize the impact of the study on the patient's physical and mental integrity and on the personality of the patient.
22. In any research on human beings, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The patient should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the patient has understood the information, the physician should then obtain the patient's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the patient is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research patient who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a patient deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research patients with a condition that renders them unable

to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

21.2.3. Additional Principles for Medical Research Combined with Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research patients.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, reestablishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

[1] Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review. 6.10.2002

[2] Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trail access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements rot other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review. 9.10.2004

21.3. ECOG Performance Status Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 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

21.4. MCL International Prognostic Index (MIPI) score (Hoster, 2008)

Points	Age, y	ECOG	LDH ULN	WBC, 10^9/L
0	<50	0-1	<0.67	< 6.700
1	50-59	-	0.67 – 0.99	6.700-9.999
2	60-69	2-4	1 – 1.49	10.000 – 14.999
3	≥70	-	≥1.5	≥15.000

Low risk	0 – 3 points
Intermediate risk	4 -5 points
High risk	6 – 11 points

21.5. Modified International Workshop Response Criteria (Cheson, 1999)

Modifications will be applied (Fisher, 2006; Kane, 2007) to the Cheson criteria in order to alleviate the increased potential for variability of results in small nodes and to account for the common manifestation of MCL as extranodal disease, where sites of dominant extranodal disease (Target Lesions) can be included in the assessment of the sum of the perpendicular diameters of measurable lesions

Complete Response (CR):

- Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., lactate dehydrogenase [LDH]) definitely assignable to NHL.
- All lymph nodes and nodal masses must have regressed to normal size (≤ 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 ≤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).
- The spleen, if considered to be enlarged before therapy on the basis of CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determinations of splenic volume or splenic index by CT scan are cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging technique should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
- If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (≥ 20mm biopsy length in aggregate). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time. These studies should only be incorporated into trials examining important research questions.

Complete Response Unconfirmed (CRu): Those patients who fulfill the criteria for CR above but with one or more of the following features:

- A residual lymph node mass and extranodal target lesion greater than 1.5 cm in greatest transverse diameter that has regressed by more that 75% in the SPD. Individual nodes and extranodal target lesions that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
- Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

Partial Response (PR)

- ≥50% decrease in SPD of the six largest dominant nodes or nodal masses and extranodal measurable target lesions (including hepatic lesions), which together with nodal lesions must decrease by ≥ 50% from baseline in their SPD). These nodes or masses should be selected according to the following features:
- Clearly measurable in at least two perpendicular dimensions
- From as disparate regions of the body as possible
- Include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- No increase in the size of other nodes, liver, or spleen
- In addition to splenic and hepatic nodules, involvement of other organs is permitted to be considered measurable target lesions
- Bone marrow assessment is irrelevant for determination of PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified on the report, e.g. large-cell lymphoma or low-grade lymphoma (i.e., small, lymphocytic small cleaved or mixed small and large cells)
- No new sites of disease

Stable disease (SD): Stable disease is defined as less than a PR (see above) but is not progressive disease or relapsed disease (see below)

Relapsed disease in CR or CRu patients

- Appearance of any new lesions or increase by ≥ 50% in the size of previously involved sites
- ≥50% increase in greatest diameter of any previously identified node or measurable extranodal disease greater than 1 cm in its short axis or in the SPD of more than one mode

Progressive disease (PD) in PR patients or nonresponders

- ≥50 % increase from nadir in the SPD of any previously identified abnormal node or measurable nodal or extranodal disease for PRs or nonresponders
- Unequivocal progression of extranodal lesions, non-target lesions and the spleen and/or liver
- Appearance of any new lesion, with GD > 15mm if nodes, during or at the end of therapy

Table 11: Summary of Modified Response Criteria

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow	Extranodal (i.e. spleen, liver)
CR	Normal	Normal	Normal	Normal	Normal
Cru	Normal	Normal	Normal	Indeterminate	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate	>75% decrease
PR	Normal	Normal	Normal	Positive	Normal
	Normal	≥50% decrease	≥50% decrease	Irrelevant	≥50% decrease
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant	≥50% decrease
Relapse/PD	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance	New or increased

21.6. Cairo-Bishop Grading System for tumor lysis syndrome (TLS)

Grade	LTLS	Creatinine	Cardiac arrhythmia	Seizure
0	-	≤1.5 x ULN	None	None
I	+	1.5 x ULN	Intervention not indicated	None
II	+	>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
III	+	>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
IV	+	>6.0 x ULN	Life-threatening	Seizures of any kind are prolonged, repetitive or difficult to control
V	+	Death*	Death*	Death*

LTLS, local tumor lysis syndrome; ULN, upper limit of normal; ADL, activities of daily living.
* Probably or definitely attributable to clinical TLS.

21.7. Lenalidomide Pregnancy Prevention Plan for Subjects in Clinical Trials

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 21.8) provides the following information:
   - Potential risks to the fetus associated with lenalidomide exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
   - Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP
2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 21.9 and Section 21.10 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Lenalidomide Information Sheet (Section 21.11) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

21.8. Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

21.8.1. Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

21.8.1.1. Definition of Females of Childbearing Potential

A FCBP is 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).

21.8.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

21.8.2. Counseling

21.8.2.1. Females of Childbearing Potential

For a FCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 21.8.4) and in the Informed Consent
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

21.8.2.2. Females Not of Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

21.8.2.3. Males

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

21.8.3. Contraception

21.8.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not

recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

[Please note, the above highlighted text is applicable for protocols with dexamethasone-containing lenalidomide regimens.]

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

21.8.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

21.8.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

21.8.5. Pregnancy Precautions for Lenalidomide Use

21.8.5.1. Before Starting Lenalidomide

21.8.5.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed

within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

21.8.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

21.8.5.2. During and After Study Participation

21.8.5.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every
- 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every
- 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the
- Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

21.8.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

21.8.5.3. Additional Precautions

- Subjects should be instructed to never give lenalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

21.9. Lenalidomide Education and Counseling Guidance Document for Female Subjects

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) 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 during the preceding 24 consecutive months)
- ☐ NOT FCBP

21.9.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).
     - ☐ One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
       - Examples of highly effective methods:
         - Intrauterine device (IUD)
         - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
         - Tubal ligation

- Partner's vasectomy

- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.
- If the subject missed a period or has unusual menstrual bleeding.
- When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

21.9.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: ___ / ___ / ___ (dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

21.10. Lenalidomide Education and Counseling Guidance Document for Male Subjects

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: ___ / ___ / ___ (dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

21.11. Lenalidomide Information Sheet

For subjects enrolled in clinical research studies

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

   If you are a female who is able to become pregnant:

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during breaks (dose interruptions) of lenalidomide
     - for at least 28 days after the last dose of lenalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of lenalidomide
     - 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking lenalidomide if you become pregnant while taking lenalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide**

– The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

A small amount of lenalidomide is found in human semen. The risk to an unborn baby in females whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - During breaks (dose interruptions) of lenalidomide
  - For at least 28 days after the last dose of lenalidomide
- **Male subjects should not donate sperm or semen** while taking lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **Do not break, chew, or open lenalidomide capsules at any point.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

21.12. EORTC QLQ-C30 Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): |_|_|_|_|_|_|_|_|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Celgene Signing Page

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

UserName:
Title:
Date: Thursday, 31 May 2018, 12:37 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

This protocol is being amended to address the study treatment needs of subjects in countries where subjects can only receive lenalidomide treatment under a clinical trial protocol as post-trial access following the final lock of the clinical trial database.

Following approval of Amendment 6 and the closure of the clinical database, only serious adverse events and drug administration data will be collected by Celgene.

Amendment 6 will apply to 2 ongoing study subjects in Russia.

Significant changes included in this amendment are summarized below:

- Study Treatment Allocation Procedure (IMS Drug Ordering System (IDOS) will replace Interactive Voice Recognition System (IVRS)), and removal of all Central Laboratory Contacts.

Updated section: Section 1

- Extended Access Phase added

Updated sections: Synopsis, Table 2 footnotes, Table 3 footnotes, new Table 4, Section 8.1, Section 8.1.2.2, Section 8.2, Figure 1 footnote, Section 11.9, Section 11.11, Section 12.2, Section 13.3, Section 15, Section 16.3, Section 18.2.

- Case report form (CRF) pages no longer need to be completed following closure of the clinical database

Updated sections: Synopsis, new Table 4, Section 8.1, Section 10.1.7, Section 10.1.8, Section 10.2, Section 11.9, Section 11.11, Section 11.6, Section 13.3, Section 16.3, Section 18.2, Appendix 21.1, Appendix 21.1.8.

- Added Table 4 Schedule of Study Assessment: Guidance for Extended Access Phase
- Clarified collection of overall survival data

Updated sections; Synopsis, Table 2 footnotes, Table 3 footnotes, Section 8.1, Section 8.1.2.2, Section 12.2.

- Reporting of serious adverse events (SAEs) (including [second primary malignancies]SPMs) information to Celgene

Updated sections: Synopsis, new Table 4, Section 8.1, Section 8.1.2.2, Section 8.2, Section 12.2, Section 13.3, Appendix 21.1, Appendix 21.1.8.

- Included the statement in the case of pregnancies “Infant follow-up will occur for one year following birth in a FCBP who was treated with lenalidomide.”

Section 21.1.10

- Clarified collection of drug accountability information.

Updated sections: Synopsis, new Table 4, Section 8.1, Section 8.1.2.2, Section 10.1.8, Section 10.2, Section 11.9, Section 11.11, Section 12.2, Section 16.3, Section 18.2.

- Closure of study Follow-up phase

Updated sections: Synopsis, Table 2 footnotes, Table 3 footnotes, Section 8.1.2.2, Section 12.2.

- Access to lenalidomide in the commercial setting and ending of the study.

Updated sections: Synopsis, Table 2 footnotes, Table 3 footnotes, Section 8.1, Section 8.1.2.2, Section 13.3.

- Update of the Lenalidomide Pregnancy Prevention Program in Clinical Trials

Updated Sections: new Appendix 21.7, new Appendix 21.8, new Appendix 21.9, Section 21.10, Section 21.11.

The amendment also includes other clarifications and corrections:

- Coordinating Principal Investigator role discontinued
- Change to Safety Contact Information for non European Union (EU) countries
- Change to the Medical Monitor and Study Manager

Updated Section: Section 1

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- ***The amendment updates the study team contact information due to changes in personnel.***
  - This is noted in Protocol section 1 (Table 1; and Name of central laboratory(ies) and other medical and/or technical department(s) and/or institutions).
- ***The amendment modifies the requirement for thromboembolic prophylaxis (Synopsis: Thromboembolism; and Protocol section 10.1.6).***
  - This modification was implemented following a DMC recommendation for implementing mandatory prophylaxis for all study patients on lenalidomide after the DMC observed an increase in thromboembolic events in the lenalidomide arm compared to the control arm, and that a number of the patients with thromboembolic events were not receiving anti-thromboembolic prophylaxis.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- ***The amendment updates the Global Drug Safety address due to relocation.***
  - This is noted in Protocol section 1: Table 1.
-
- ***The amendment adds MIPI score at randomization to the list of treatment and clinical characteristics at screening/baseline, also to be analyzed as a stratification factor, and also to the list for subgroup analysis in the Synopsis (Study design and Efficacy Analysis) and in Protocol sections 8.1.2.1 and 15.1.6).***
  - This addition was implemented following recommendation from the third DMC for analysis according to MIPI at randomization, after the DMC observed an imbalance in terms of risk factors between the study arms which was not mitigated by the stratification factors.
- ***The amendment adds a fourth safety analysis to occur after 200 patients complete 2 cycles or withdraw before completing 2 cycles (Synopsis: Data Monitoring Committee; and Protocol sections 8.3 and 15.7).***
  - This addition was implemented to ensure ongoing safety monitoring with sample size increase to 250 pts.
- ***The amendment increases the sample size to 250 patients (Synopsis: Number of patients; Protocol: Figure 1).***
  - This sample size increase was implemented following recommendation from the third DMC to allow a more reliable estimation of potential PFS differences between the study arms after the DMC observed that the outcome in the control arm of the study was different from the initial assumptions used to calculate the sample size.
- ***The amendment modifies the duration of prior malignancy-free history (Synopsis: Exclusion Criteria; and Protocol section 9.2).***
  - This modification was implemented as requested by health authorities to reduce the risk of second primary malignancy (SPM) in patients treated with lenalidomide.
- ***The amendment updates the safety wording on second primary malignancies in the Synopsis (Safety, footnote 15 to Table 2, footnote 7 to Table 3) and Protocol sections 8.2, 13.1 and 21.1.2.***
  - This is the current SPM language according to the updated protocol template safety wording.

- ***The amendment increases the sample size to 250 patients and modifies the Efficacy analysis (Synopsis: Statistical Analysis; and Protocol sections 15.2.1, 15.2.3, 15.7, and 15.8).***

  These changes were implemented following recommendations from the third study DMC:

  - To allow a more reliable estimation of potential PFS differences between the study arms after the DMC observed that the outcome in the control arm of the study was different from the initial assumptions used to calculate the sample size;
  - Sub-populations and sub-groups are added to the analyses to evaluate potential correlation between safety and efficacy outcomes based on baseline characteristics or response to treatment in different patient populations; and
  - For analysis according to MIPI at randomization after the DMC observed an imbalance in risk factors between the study arms which was not mitigated by the stratification factors.

- ***The amendment adds sub-populations and sub-groups to the study analyses (Synopsis: Table 4; and Protocol sections 15.1and 15.9).***

  - Sub-populations and sub-groups are added to the analyses to evaluate potential correlation between safety and efficacy outcomes based on baseline characteristics or response to treatment in different patient populations.

- ***The amendment further clarifies and aligns the follow-up requirements for second primary malignancies in the Synopsis (Cross over) and Protocol sections 8.1.2.3 and 8.1.2.4.***

  - Further clarification and protocol wording alignment of the SPM follow-up requirements.

- ***The amendment adds a fourth EORTC QoL compliance assessment to occur after 200 patients complete 2 cycles or withdraw before completing 2 cycles (Protocol section 15.2.2).***

  - This addition was implemented to ensure ongoing monitoring of EORTC QoL compliance with sample size increase to 250 pts.

- ***The amendment updates the safety language according to the updated protocol template safety wording in Protocol section 21.1.***

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- ***The amendment updates the study team contact information due to changes in personnel and addresses.***
  - This is noted in Protocol section 1 (Table 1; and Name of central laboratory(ies) and other medical and/or technical department(s) and/or institutions).
- ***The amendment further clarifies the consent withdrawal requirements, and the difference between treatment discontinuation and study discontinuation aligning the wording used throughout the protocol.***
  - The consent withdrawal updates are located in the Synopsis (Treatment phase, Follow-up phase) and in Protocol sections 8.1.2.3, 8.1.2.4, 10.2, and 12.2. The treatment discontinuation updates are located in the Synopsis (Study duration, Treatment phase, Follow-up phase), the footnotes to Tables 2 & 3, and in Protocol sections 8.1.2.3, 8.1.2.4, , 21.8.1, and 21.8.2.
- ***The amendment adds the requirement that second primary malignancies be treated as SAEs and reported throughout the study duration including from the time of signing the Informed Consent Document (ICD) through follow-up for overall survival. The Follow-Up Phase involves patient contact every 90 days (± 15 days) until patient death or until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later.***
  - Recently there have been reports of second primary malignancies in clinical studies with lenalidomide. As it is unclear whether lenalidomide increases the risk of second primary malignancies, Celgene is asking that all subjects in all study treatment arms be followed to confirm if a diagnosis of a second primary malignancy has occurred.
  - In order to monitor and thoroughly evaluate all second primary malignancies that occur in subjects receiving any study medication, the protocol is being amended to require that second primary malignancies are assessed at every study visit and reported as serious adverse events at any time during the study – from the time of signing the Informed Consent Document (ICD) through follow-up for overall survival. The Follow-Up Phase involves patient contact every 90 days (± 15 days) until patient death or until either 70% of the patients have died, or the median follow-up in responding patients is > 2 years, or the median duration of response (overall response and CR/CRu) has been reached, or four years from last patient randomized, whichever comes later.
  - The related additions are located in the Synopsis (Study duration, Treatment phase, Follow-up phase, Safety Assessments, Safety analysis), Table 2 & footnotes, Table 3 & footnotes, Table 4 by adding Informed Consent Document (ICD), and in Protocol sections 8.1.2.3, 8.1.2.4, 8.2, 12.2, 13.1, 15.6, 21.1.2, and 21.1.6.

- ***The amendment aligns the wording used throughout the protocol for the study target population (the Synopsis: Primary Objective wording, Study design, and Inclusion criteria; and in Protocol sections 6.1, 8.1.2, and 9.1)***
  - The aligned wording specifies patients with mantle cell lymphoma (MCL) who are refractory to their regimen or have relapsed once, twice or three times.
- ***The amendment aligns the wording used throughout the protocol for naming the response assessment criteria (the Synopsis: Secondary endpoints, Efficacy assessments and Efficacy analysis; and in Protocol sections 7.2, 8.1, 12.2, 15.2.2, and 21.5).***
  - The aligned wording specifies the naming of the response assessment criteria as International Workshop Response Criteria (IWRC)
- ***The amendment clarifies start of treatment and tumor response assessments in the cross-over portion of the study (the Synopsis: Cross-over; Table 3 footnotes; Figure 1; and Protocol section 8.1.2.3).***
  - The clarification specifies that for the cross over patients the reference point for the imaging tumor assessment schedule is the start of lenalidomide cross-over treatment;
  - Another clarification specifies that the baseline assessments are outlined in the schedule of assessments (Table 3) for Cycle 1 Day 1.
- ***The amendment clarifies the timing and requirements for the safety follow-up visit 28 days after last dosing (the Synopsis: Follow-up phase; and Protocol section 8.1.2.4).***
  - The clarification summarizes in one paragraph the requirements and assessments for the safety follow-up visit 28 days after last dosing day in either study arm or cross-over treatment.
- ***The amendment aligns the accessibility options to the Summaries of Product Characteristics for the investigator's choice agents by removing the hyperlinks to their Internet locations (where previously available) and keeping only providing these by Celgene (the Synopsis: Study Drug Supplies; and Protocol section 10.1.2).***
- ***The amendment updates the analysis methods adding the stratified log-rank test for the main comparison; changing unstratified log-rank test to be used as supportive analysis; and adding that any demographic or baseline characteristics variables considered as strong predictive or prognostic factors will also be included as part of the formal statistical analysis plan (the Synopsis - Efficacy analysis; and Protocol section 15.2.3).***
  - The stratified log-rank test will be used as main analysis to take into account the stratification factors or any baseline characteristic affecting the outcome.

- ***The amendment further clarifies the interim analysis specifics by adding that additional efficacy and safety data might be provided to the DMC members on request as outlined in the DMC charter (the Synopsis - Efficacy analysis; and Protocol section 15.7).***
- ***The amendment clarifies the required minimal rest period in Arm A and cross-over treatment (Footnotes to Tables 2 and 3; and Protocol sections 10.1.1, and 10.1.3).***
  - The clarification specifies that for lenalidomide, a minimum 7 day rest period is mandatory before starting each new treatment cycle, therefore this period must be adhered to regardless of allowed ± visit windows.
- ***The amendment updates the dose modifications and interruptions for lenalidomide (Table 6 and Table 8).***
  - Action required is added for any other lenalidomide-related AE not requiring treatment discontinuation.
  - The 10mg every other day dose decrease step is removed due to safety considerations. This dose has been shown to be similar to the 5mg every day dose and switching from the first to the second dosing step will not constitute a dose decrease.
- ***The amendment aligns the requirements on prior/concomitant medication in terms of data collection and prohibited steroid therapy (Protocol sections 10.1.7 and 10.1.8).***
  - The requirements on prior/concomitant medications in terms of data collection are placed in one aligned paragraph in the appropriate protocol section.
  - The requirement on steroids at doses beyond 10mg prednisone per day is aligned throughout the protocol.

[redacted]

- ***The amendment specifies that other potential subgroups or prognostic factors may be used as exploratory analyses, to be further detailed in the statistical analysis plan (Protocol Section 15.1.4).***
- ***The amendment updates literature publications and references (the Synopsis: Background and rationale; and Protocol sections 5.1, 5.2.2, 10.1.5, and 20).***
  - Ten publications listed in the protocol text are added to the Reference section (previously missing); two publication references are updated in the amendment narrative and accordingly – in the Reference section (final publications now available); two new publication references are added to the amendment narrative and accordingly – to the Reference section (Eve E. 2010, Fernandez V. 2010); five corrections are made in references due to mistakes in author name or year.

SUMMARY OF CHANGES
TO PROTOCOL CC-5013-MCL-002

A PHASE 2, MULTICENTER, RANDOMIZED OPEN-LABEL STUDY TO DETERMINE THE EFFICACY OF LENALIDOMIDE (REVLIMID®) VERSUS INVESTIGATOR'S CHOICE IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

THE "SPRINT" TRIAL

PROTOCOL:	**CC-5013-MCL-002**
AMENDMENT #:	**2**
DATE:	**14 December 2009**

1. The amendment updates the Study Personnel. This is noted in Study Contact Information Table 1.

Current Language:

Global Study Manager		Celgene International Route de Perreux 1 2017 Boudry – Switzerland Phone : Fax : Email : Mobile Phone :
Responsible Clinical Research Physician		Celgene International Route de Perreux 1 2017 Boudry – Switzerland Phone : Fax : Email : Mobile Phone :
International Drug Safety Contact for EU countries **For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines**	Clinical Trial Safety	Celgene International Sàrl Route de Perreux 1 2017- Boudry Neuchatel Switzerland Tel: Fax:

Amended Language:

Lead ~~Global~~ Study Manager		Celgene International Route de Perreux 1 2017 Boudry – Switzerland Phone : Fax : Email : Mobile Phone :

Responsible Clinical Research Physician		Celgene International Route de Perreux 1 2017 Boudry – Switzerland **Phone :** **Fax :** Email : Mobile Phone :
International Drug Safety Contact for EU countries **For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines**	Clinical Trial Safety	Celgene International Sàrl Route de Perreux 1 2017- Boudry Neuchatel Switzerland Tel: Fax:

Reason for Change and addition:

Phone number and fax number have changed due to a move in new premises.

2. The amendment updates the name of central laboratory(ies) and other medical and/or technical department(s) and/or institutions.

Current Language:

Amended language:

Reason for Change: change of study personnel.

3. The amendment updates the objectives noted in the Synopsis and in section 6 of the protocol.

Current Language:

Objectives:

Primary:

- To determine the tumor response of lenalidomide monotherapy or single agent of investigator's choice in patients with mantle cell lymphoma (MCL) who have relapsed after or are refractory to at least 1 and up to 3 prior chemotherapy regimens.

Secondary:

- To evaluate the safety of lenalidomide monotherapy or single agent of investigator's choice in patients with relapsed or refractory MCL.
- To determine the time to progression, progression-free survival and overall survival of patients with relapsed or refractory MCL who have received treatment with lenalidomide or single agent of investigator's choice.
- To investigate the health-related quality of life (QoL) of patients treated with lenalidomide or investigator's choice single agent treatment.

Amended language:

Objectives:

Primary:

- ~~To determine the tumor response of lenalidomide monotherapy or single agent of investigator's choice in patients with mantle cell lymphoma (MCL) who have relapsed after or are refractory to at least 1 and up to 3 prior chemotherapy regimens.~~
- **To compare the progression free survival (PFS) of lenalidomide monotherapy versus investigator's choice single agent in patients with mantle cell lymphoma (MCL) who have relapsed after or are refractory to at least 1 and up to 3 prior chemotherapy regimens.**

Secondary:

- **To determine the overall response rate (ORR) of lenalidomide monotherapy or investigator's choice single agent in patients with relapsed or refractory MCL.**

- To evaluate the safety of lenalidomide monotherapy or ~~single agent of investigator's choice~~ investigator's choice **single agent** in patients with relapsed or refractory MCL.
- To determine the time to progression~~, progression-free survival~~ and overall survival of patients with relapsed or refractory MCL who have received treatment with lenalidomide or ~~single agent of~~ investigator's choice **single agent**.
- To investigate the health-related quality of life (QoL) of patients treated with lenalidomide or investigator's choice single agent treatment.

.

Reason for Change:

The primary objective has been changed from "determine the ORR" to "compare the PFS", since PFS is considered to be a more clinically relevant efficacy endpoint in this indication also with regard to using the study for registration.

"Determine the ORR" has moved from primary to secondary objectives.

4. The amendment updates the Study Endpoints noted in the Synopsis and in sections 7.1 and 7.2 of the protocol.

Current Language:

Study Endpoints:

Primary

- Overall response rate (complete response [CR], complete response unconfirmed [CRu], and partial response [PR]) assessed by a modification of the International Lymphoma Workshop Criteria IWRC] (Cheson, 1999) [hereafter modified 1999 IWRC].

Secondary

- Duration of response
- Progression-free survival
- Tumor control rate (Rates for CR, CRu, PR, and stable disease [SD])
- Time to progression
- Time to treatment failure

- Time to tumor response
- Overall survival (OS)
- Safety
- Quality of Life (EORTC QLQ-C30)

Amended language:

Study Endpoints:

Primary

- ~~Overall response rate (complete response [CR], complete response unconfirmed [CRu], and partial response [PR]) assessed by a modification of the International Lymphoma Workshop Criteria IWRC] (Cheson, 1999) [hereafter modified 1999 IWRC].~~
- **Progression free survival defined as the time from randomization to the first observation of disease progression or death due to any cause. If the patient has not progressed or died, PFS will be censored at the time of last completed assessment when the patient was known not to have progressed. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free.**

Secondary

- **Overall response rate (complete response [CR], complete response unconfirmed [CRu], and partial response [PR]) assessed by a modification of the International Lymphoma Workshop Criteria IWRC] (Cheson, 1999) [hereafter modified 1999 IWRC].**
- Duration of response
- ~~Progression-free survival~~
- Tumor control rate (Rates for CR, CRu, PR, and stable disease [SD])
- Time to progression
- Time to treatment failure
- Time to tumor response
- Overall survival (OS)
- Safety
- Quality of Life (EORTC QLQ-C30)

Reason for Change:

The primary endpoint has been changed from ORR to PFS, since it is considered to be a more clinically relevant efficacy endpoint in this indication also with regard to using the study for registration.

5. **The amendment updates the Background and Rationale. This is noted in the Synopsis (Background and Rationale).**

Current Language:

… The increasing understanding of the MCL cell biology has led to the development of new therapeutic agents with antitumor activity that target crucial biological pathways, including cell cycle inhibitors (i.e. flavopiridol), mTOR inhibitors (i.e. temsirolimus, everolimus), proteasome inhibitors (bortezomib, Velcade®) and histone deacetylase inhibitors (Kouroukis, 2003; Goy, 2005; O'Connor, 2005)…

… In another ongoing study of lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL (CC-5013-NHL-003), 53 of 203 patients had MCL (Zinzani, 2008). In the 39 MCL patients who were evaluable for response assessment, lenalidomide therapy led to an objective response rate of 41% with 5 CRs and 11 PRs . The most common grade 3 or 4 adverse events were neutropenia (51%) and thrombocytopenia (25%), anemia (13%), fatigue (10%) and febrile neutropenia (10%) (Zinzani, 2008).

Based on these preliminary observations, the current study is being conducted to evaluate the activity and safety of lenalidomide in a larger population of patients with relapsed or refractory mantle cell lymphoma.

Amended language:

… The increasing understanding of the MCL cell biology has led to the development of new therapeutic agents with antitumor activity that target crucial biological pathways, including cell cycle inhibitors (i.e. flavopiridol), mTOR inhibitors (i.e. temsirolimus, everolimus), proteasome inhibitors (bortezomib, Velcade®) and histone deacetylase inhibitors (Kouroukis, 2003; Goy, 2005; O'Connor, 2005, **Hess 2009**)…

… In another ongoing study of lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL (CC-5013-NHL-003), ~~53 of 203~~ **57 of 217** patients had MCL (Witzig, 2009). In the ~~53~~ **57** MCL patients who were evaluable for response assessment, lenalidomide therapy led to an objective response rate of ~~41% with 5 CRs and 11 PRs . The most common grade 3 or 4 adverse events were neutropenia (51%) and thrombocytopenia (25%), anemia (13%), fatigue (10%) and febrile neutropenia (10%) (Zinzani, 2008).~~ **42% (25/57). Median progression-free survival (PFS) was 5.7 months. Overall, the primary side effect of lenalidomide was reversible myelosuppression. Grades 3 or 4 neutropenia occurred in 41%, thrombocytopenia in 19%, anemia in 9%, and leucopenia in 7% of patients.** Based on these preliminary observations, the current study is being conducted to evaluate the activity and safety of lenalidomide in a larger population of patients with relapsed or refractory mantle cell lymphoma.

Reason for Change: literature update

6. **The amendment updates the Study Design. This is noted in the Synopsis and in section 8.1.2.**

Current Language:

This is a randomized, open-label, non comparative controlled phase II study to determine the efficacy and safety of single agent lenalidomide with a concurrent control group treated with an investigator's choice single agent in patients with mantle cell lymphoma who have relapsed after or are refractory to at least 1 and up to 3 prior lines of therapy. This study designs aims to determine the tumor response of

lenalidomide therapy or single agent of investigator's choice. This is a multicenter study. The investigator's choice in the control arm comprises the monotherapy treatment with one of the following: chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine. The investigator shall choose the single agent of choice in the control arm for each patient prior to randomization on to the study. Patients in the investigator's choice arm will have the option to switch to lenalidomide at time of progressive disease.

Amended language:

This is a **multicenter**, randomized, open-label, ~~non-~~comparative controlled phase II study to determine the efficacy and safety of single agent lenalidomide ~~with~~ **over** a concurrent control group treated with an investigator's choice single agent in patients with mantle cell lymphoma who have relapsed after or are refractory to at least 1 and up to 3 prior lines of therapy (Figure 1). ~~This~~ **The** study ~~designs~~ **aims** ~~to determine the tumor response~~ **to compare the PFS** of lenalidomide therapy ~~or~~ **over a** single agent of investigator's choice.

~~This is a multicenter study.~~ The investigator's choice in the control arm comprises the monotherapy treatment with one of the following: chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine. The investigator shall choose the single agent of choice in the control arm for each patient prior to randomization on to the study. Patients in the investigator's choice arm will have the option to switch to lenalidomide at time of progressive disease.

Reason for Change: design updated according to the new primary endpoint (PFS). See also the rationale for points #3 and #4.

7. The amendment updates the Screening phase. This is noted in the Synopsis and in section 8.1.2.2.

Current Language:

… Screening/baseline assessments will begin once the patient has approved and signed the informed consent form. Complete blood count (CBC) and serum chemistry tests will be required within 7 days of first dose of study drug. Eligibility for the study is based on the local assessments (CBC and chemistry as well as the local results of the archival tumor / lymph node biopsy) done during the screening/baseline phase of the study…

…. It is highly recommended to submit also the original paraffin block (called tumor block)…

…Evidence of the translocation t(11;14)(q13:q32) by FISH should be submitted using the original slide or the corresponding confirming photographies. The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD20, CD23, BCL2…

Amended language:

… Screening/baseline assessments will begin once the patient has ~~approved~~ **accepted** and signed the informed consent form. Complete blood count (CBC) and serum chemistry tests will be required within 7 days of first dose of study drug. **Serology, for HBV (at least HBsAg, anti-HBs and anti-HBc) and for HCV will be required as screening assessment within 28 days of randomization in endemic areas**. Eligibility for the study is based on the local assessments (CBC ~~and~~ ,chemistry **and serology** as well as the local results of the archival tumor / lymph node biopsy) done during the screening/baseline phase of the study…

… It is highly recommended to submit also the original paraffin block (called tumor block) **which will be returned to the original institution…**

… **The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis.** Evidence of the translocation t(11;14)(q13:q32) by FISH ~~should~~ **can** be submitted using the original slide or the corresponding confirming photographies. ~~The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis.~~ If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD20, CD23, BCL2, **Ki-67**.

Reason for Change:

The wording has been moved from "approved" to "accepted" since more appropriate.

Serological status for HIV, HBV and HCV has to be checked for each patient at baseline, as part of medical history and also to check also against the study exclusion criteria about previous or ongoing infection for HIV, HBV and HCV. See also point#14.

It is reminded that archival tumor specimens will be returned to the local pathologist.

The sentence for FISH slide has been reworded to emphasize it is an optional procedure.

Ki-67 immunostaining has been added as part of our stratification factor.

8. The amendment updates the Treatment phase. This is noted in the Synopsis and in section 8.1.2.3 of the protocol.

Current Language:

Once all eligibility criteria are met and baseline assessments completed, patients will be randomized 2:1 to receive lenalidomide monotherapy or the investigator's choice. The treatment phase will start with Day 1 of the first treatment dose of the first cycle, day 1 (C1D1) administered to the patient. Treatment should start as soon as possible after randomization, but maximum time between randomization and C1D1 is 4 days, once the patient has fulfilled the requirements of the Lenalidomide pregnancy prevention program (see Appendices 21.7 and 21.8). Patients will continue in the treatment phase until disease progression, unacceptable toxicity or voluntary withdrawal. Toxicity will be assessed using the NCI CTCAE criteria version 3 and the dose of lenalidomide or the investigators choice single agent will be reduced accordingly (Table 7 and Table 8 for dose reductions)…

Serial assessments of safety and efficacy (CT scans /MRI every 56 days ± 7 days for the first 6 months and then every 90 days ± 15 days thereafter) will be performed as outlined in the Schedule of Study Assessments or as directed in the dose modification section. Patients may continue participation in the treatment phase of the study until disease progression or unacceptable toxicity or voluntary patient withdrawal, at which point, the patients will enter the follow-up phase.

Diagnostic imaging results (CT scan /MRI) will be reviewed locally and also sent for central review.

… **Cross over (for patients in the investigators choice Arm B only)**:

…CT scans /MRI are recommended to be performed every 90 days (± 15 days) until disease progression or treatment discontinuation for any other reason (i.e. toxicity) [Amended language ***(highlighted in yellow)***

Table]…

Amended language:

Once all eligibility criteria are met and baseline assessments completed, patients will be randomized 2:1 to receive lenalidomide monotherapy or the investigator's choice. ~~The treatment phase **for each patient** will start **on study** Day 1 of the first treatment dose of the first cycle, day 1 (C1 D1) administered to the patient.~~ The first treatment dose of the first cycle **administered to the patient is called** C1D1. Treatment should start as soon as possible after randomization, but maximum time between randomization and C1D1 is 4 days, once the patient has fulfilled the requirements of the Lenalidomide pregnancy prevention program (see Appendices 21.7 and 21.8). Patients will continue in the treatment phase until disease progression, unacceptable toxicity or voluntary withdrawal. Toxicity will be assessed using the NCI CTCAE criteria version 3 and the dose of lenalidomide or the investigators choice single agent will be reduced accordingly (Table 7 and Table 8 for dose reductions)…

Serial assessments of safety and efficacy (CT scans **with contrast** /MRI **with contrast** every 56 days ± 7 days for the first 6 months and then every 90 days ± 15 days thereafter) will be performed as outlined in the Schedule of Study Assessments or as directed in the dose modification section. Patients may continue participation in the treatment phase of the study until disease progression or unacceptable toxicity or voluntary patient withdrawal, at which point, the patients will enter the follow-up phase.

Diagnostic imaging results (CT scan **with contrast** /MRI **with contrast**) will be reviewed locally and also sent for central review.

CT scans is the preferred procedure. If CT is contraindicated, MRI is acceptable. It is advised to stick to the same procedure for a given patient throughout the study.

… **Cross over (for patients in the investigators choice Arm B only)**:

… CT scans **with contrast** /MRI **with contrast** are recommended to be performed every 90 days (± 15 days) until disease progression or treatment discontinuation for any other reason (i.e. toxicity) [Amended language ***(highlighted in yellow)***

Table]…

Reason for Change:

The definition of C1D1 has been reworded for a better understanding.

For consistency purposes the term contrast has been added to CT-scan and MRI within all the protocol.

The CT scans is referred as the preferred imaging method to be used first. MRI is acceptable if CT scan is contraindicated.

9. The amendment updates the Follow-up Phase. This is noted in the Synopsis and section 8.1.2.3 of the protocol

Current Language:

- Patients who discontinued treatment **due to reasons other than progressive or relapse**:
    - Clinic visits should occur every 56 days to assess disease status (physical exam) until disease progression or relapse
    - CT scan/MRI should occur every 56 days (± 7 days) until disease progression or relapse up to 6 months from the start of study drug then every 90 days ± 15 days thereafter.

Amended language:

- Patients who discontinued treatment **due to reasons other than progressive or relapse**:
    - Clinic visits should occur every 56 days to assess disease status (physical exam) until disease progression or relapse
    - CT scan **with contrast**/MRI **with contrast** should occur every 56 days (± 7 days) until disease progression or relapse up to 6 months from the start of study drug then every 90 days ± 15 days thereafter.

Reason for Change:

For consistency purposes the term contrast has been added to CT-scan and MRI within all the protocol.

10. The amendment updates the Data Monitoring Committee. This is noted in the Synopsis and in section 8.2 of the protocol.

Current Language:

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study and efficacy for futility at a pre-defined time point. Specifics are outlined in the DMC charter. The first safety analysis will occur after the first 40 patients have received at least 3 cycles of treatment or have discontinued prior to completing 3 cycles. The second safety analysis as well as an efficacy analysis for futility will occur after 80 patients complete 3 cycles or withdraw before completing 3 cycles. A third safety analysis will occur after 120 patients complete 3 cycles or withdraw before completing 3 cycles.

Amended language:

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study and efficacy for futility at a pre-defined time point. Specifics are outlined in the DMC charter. The first safety analysis will occur after the first 40 patients have received at least 2 cycles of treatment or have discontinued prior to completing 2 cycles. The second safety analysis as well as an efficacy analysis

for futility will occur after 80 patients complete 2 cycles or withdraw before completing 2 cycles. A third safety analysis will occur after 120 patients complete 2 cycles or withdraw before completing 2 cycles.

Reason for Change:

For the DMC review, the number of cycles to be received or to be discontinued has been changed from 3 cycles to 2 cycles since the imaging assessments are planned after cycle 2 and after cycle 4 for the first 6 months. There is no plan to perform CT-scan or MRI after cycle 3.

11. The amendment updates the Independent External Pathological Review. This is noted in the Synopsis and in section 8.3 of the protocol.

Current Language:

It is highly recommended to submit also the original paraffin block (called tumor block). If the tumor block cannot be sent, 4-5 additional unstained slides must be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

Evidence of the translocation t(11;14)(q13:q32) by FISH should be submitted using the original slide or the corresponding confirming photographies. The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD23, CD20, BCL2…

Amended language:

It is highly recommended to submit also the original paraffin block (called tumor block) **which will be returned to the original institution**. If the tumor block cannot be sent, 4-5 additional unstained slides must be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. Evidence of the translocation t(11;14)(q13:q32) by FISH ~~should~~ **can** be submitted using the original slide or the corresponding confirming photographies. ~~The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis.~~ If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD23, CD20, BCL2, **Ki-67…**

Reason for Change:

It is highlighted that local pathology specimens that are sent to central pathologist laboratory will be sent back to the investigators' sites after central review.

The optional FISH slides have been re-worded for further clarify.

Ki-67 has been added as part of our stratification factor.

12. The amendment updates the Number of Patients. This is noted in the Synopsis.

Current Language:

Number of patients: 150 patients (100 in Arm A, 50 in Arm B)

Amended language:

Number of patients: ~~150 patients (100 in Arm A, 50 in Arm B)~~ **approximately 167 randomized patients**

Reason for Change: to provide with a more accurate expected sample size.

13. The amendment updates the Study Population Inclusion Criteria. This is noted in the Synopsis and in section 9.1 of the protocol.

Current Language:

… Patients who have progressed, relapsed after or are refractory to at least one, and up to three prior chemotherapy regimens, and who have documented progressive disease (Refractory to prior chemotherapy regimens is defined as not having reached a CR or PR to prior treatment)…

… Must have measurable disease on cross sectional imaging by CT/MRI that is at least 2 cm in the longest diameter and measurable in two perpendicular dimensions…

Amended language:

… Patients ~~and who have progressed, relapsed after or are refractory to at least one, and up to three prior chemotherapy regimens,~~ **who are refractory to their regimen or have relapsed once or up to three times** and who have documented progressive disease (Refractory to prior chemotherapy regimens is defined as not having reached a CR or PR to prior treatment)…

… Must have measurable disease on cross sectional imaging by CT~~/MRI~~ **(or MRI, if CT is contraindicated)** that is at least 2 cm in the longest diameter and measurable in two perpendicular dimensions…

Reason for Change:

Eligibility criterion about prior lines of treatment has been changed and is not only limited to prior chemotherapy (e.g immunotherapy can be considered as prior treatment line).

The preferred imaging method is CT scan. The inclusion criterion has been updated accordingly. See also rationale for point #8.

14. The amendment updates the Study Population Exclusion Criteria. This is noted in the Synopsis and in section 9.2 of the protocol.

Current Language:

- Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible
- Patients who are not willing to take DVT prophylaxis
- Patients should not be receiving corticosteroids except for prednisone ≤ 10 mg/day or equivalent for purposes other than treating MCL
- Any of the additional following laboratory abnormalities:
  - Absolute neutrophil count (ANC) <1,500 cells/mm^3 (1.5 x 10^9/L)
  - Platelet count < 60,000/mm^3(60 x 10^9/L)

- Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 5.0 x upper limit of normal (ULN).
- Serum total bilirubin > 2.0 mg/dL (34 µmol/L), except in case of hemolytic anemia
- Calculated creatinine clearance (Cockcroft-Gault formula) of < 30 mL/min

Amended language:

- Known seropositive for or active viral infection with human immunodeficiency virus (HIV)
- Known seropositive for or active viral infection with hepatitis B virus:
  - **HBsAg positive.**
  - **HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA.**
  - **Patients who are HBsAg negative and viral DNA negative are eligible.**
  - **Patients who had hepatitis B but have received an antiviral treatment and show no detectable viral DNA for 6 months are eligible.**
  - **Patients who are seropositive because of hepatitis B virus vaccine are eligible.**
- Known seropositive for or active viral infection with hepatitis C virus
  - **Patients who had hepatitis C but have received an antiviral treatment and show no detectable viral RNA for 6 months are eligible.**
- **Patients who are not** willing to take DVT prophylaxis, **if they are at risk (see definition in section 10.1.6)**
- Patients should not be receiving corticosteroids **7 days prior to randomization**, except for prednisone ≤ 10 mg/day or equivalent for purposes other than treating MCL
- Any of the additional following laboratory abnormalities:
  - Absolute neutrophil count (ANC) <1,500 cells/mm^3 (1.5 x 10^9/L)
  - Platelet count < 60,000/mm^3(60 x 10^9/L)
  - ~~Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 5.0 x upper limit of normal (ULN).~~
  - **Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) > 3.0 x upper limit of normal (ULN), except in patients with documented liver involvement by lymphoma**
  - ~~Serum total bilirubin > 2.0 mg/dL (34 µmol/L), except in case of hemolytic anemia~~
  - **Serum total bilirubin > 1.5 x ULN, except in case of Gilbert's Syndrome and documented liver involvement by lymphoma.**
  - Calculated creatinine clearance (Cockcroft-Gault formula) of < 30 mL/min

Reason for Change:

Exclusion criteria relative to previous or ongoing infection for HIV, HBV and HCV has been better defined for clarity purposes.

DVT prophylaxis is not mandatory for all the patients, only those at risk, as defined in section 10.1.6 of the protocol, that's why the criterion has been updated.

Exclusion criteria amended to reflect a mandatory 7 day washout period for prior corticotherapy.

The upper limit of abnormal liver values has been updated in accordance with Table 6 (modification of lenalidomide doses). In the current protocol a slight and not clinically relevant increase in AST/ALT could mean the patient was no longer eligible to participate.

15. The amendment updates the Study Drug Supplies. This is noted in the Synopsis and in section 11.5 of the protocol.

Current Language:

FCBP should not handle or administer lenalidomide unless they are wearing gloves…

Amended language:

~~FCBP should not handle or administer lenalidomide unless they are wearing gloves.~~ **Health care providers should consider wearing gloves when directly handling Revlimid (lenalidomide) capsules followed by standard hand washing…**

Reason for Change: recommendations for study drug handling are updated to reflect general clinical practice.

16. The amendment updates the Assessments Efficacy. This is noted in the Synopsis (Assessments Efficacy).

Current Language:

- Overall response rate (PR or better) as defined by a modification of the International Workshop Lymphoma Response Criteria (Cheson, 1999) [hereafter modified IWRC criteria]
- Date of documentation of disease progression
- CT with contrast/MRI is performed at baseline then every 56 days (±7 days) after Day 1, Cycle 1 for the first 6 months and then every 90 days ± 15 days thereafter until documented…

Amended language:

- **Date of documentation of disease progression**
- Overall response rate (PR or better) as defined by a modification of the International Workshop Lymphoma Response Criteria (Cheson, 1999) [hereafter modified IWRC criteria]
- **Tumor control rate (CR, CRu, PR or SD)**

- CT with contrast/MRI **with contrast** is performed at baseline then every 56 days (±7 days) after Day 1, Cycle 1 for the first 6 months and then every 90 days ± 15 days thereafter until documented…

Reason for Change:

Date of documentation of disease progression has been moved in first bullet point to reflect the change on primary objective and endpoint (PFS).

Tumor control rate inadvertently omitted from current protocol.

For consistency purposes the term contrast has been added to CT-scan and MRI within all the protocol.

17. The amendment updates the Statistical Analysis: Sample Size. This is noted in the Synopsis and in section 15.8 of the protocol.

Current Language:

The main objective of the study is to estimate the Overall Response Rate (ORR).

Sample size calculation is based on the width of the 95% confidence interval around a certain point estimate for ORR that is considered significant clinical activity…

… Using a one group $\chi 2$ test with a 0.050 two-sided significance level a sample size of 100 patients will have 81% power to detect the difference between the Null hypothesis proportion of 20% and the alternative proportion of 32%

As the study is a non comparative study no formal sample size calculation will be done for the control arm. With a 2:1 ratio 50 patients are needed in the control arm.

Amended language:

The main objective of the study is ~~to estimate the Overall Response Rate (ORR).~~ **to demonstrate the efficacy of lenalidomide over an investigator's choice single agent based on PFS.**

The primary analysis is to compare PFS between lenalidomide and investigator's choice monotherapy. For the primary efficacy variable PFS, a hazard ratio (HR) of 1.7 leading to an improvement in median PFS from 2.5 months for the control arm to at least 4.25 months for lenalidomide is considered clinically relevant.

These assumptions are supported by recent data published in relapsed refractory MCL.

With a hazard ratio of 1.7, full information necessary for a one-sided log rank test with an overall alpha of 0.025 to have 80% power, will be achieved when approximately 128 patients have progressed or died.

The sample size initially was calculated to estimate the Overall Response Rate (ORR), however it remains adequate to estimate PFS.

Sample size calculation is based on the width of the 95% confidence interval around a certain point estimate for ORR that is considered significant clinical activity…

…Using a one group $\chi 2$ test with a 0.050 two-sided significance level a sample size of 100 patients will have 81% power to detect the difference between the Null hypothesis proportion of 20% and the alternative proportion of 32%.

No formal sample size calculation will be done for the control arm. With a 2:1 ratio 50 patients are needed in the control arm.

Assuming that 10% of patients will be lost to follow up, 167 patients will be randomized.

~~As the study is a non comparative study no formal sample size calculation will be done for the control arm. With a 2:1 ratio 50 patients are needed in the control arm.~~

Reason for Change:

Statistical section updated according to primary objective/endpoint changes.

Precision about expected randomized patients and percentage of lost to follow-up, information inadvertently omitted from current protocol.

18. The amendment updates the Efficacy analysis. This is noted in the Synopsis of the protocol.

Current Language:

The *primary endpoint* is overall response rate (CR, CRu and PR). The International Workshop Lymphoma Response Criteria (IWRC) (Cheson, 1999), as modified by Fisher et al 2006; Kane et al 2007 for target lesions will be used (see Section 21.5 and Table 7 for a detailed description of the modifications). The assessment will be reviewed by an independent review committee. The primary analysis will be done in the intent-to-treat (ITT) population for overall response rate, progression-free-survival, and overall survival. All patients who have received at least one single treatment dose (C1D1) with centrally confirmed histology of mantle cell non-Hodgkin's lymphoma will be included in the sensitivity analysis.

Further *secondary endpoints* include:

- Duration of response: will be measured from the time of initial response (at least PR) until documented tumor progression or death. Patients who do not progress at the time of analysis will be censored. This analysis will be restricted to responder patients.
- Progression-free survival: defined as the time from randomization until objective tumor progression or death for any reasons. Patients who do not progress at the time of analysis will be censored….

… Efficacy analysis will be conducted when all patients have completed at least 6 months of treatment or discontinued before completing 6 months.

An update of the time to events endpoints and overall survival will be done at the end of the follow up. No adjustment for multiplicity is needed as it is a non comparative study.

All efficacy analysis will be conducted on intent to treat basis…

Amended language:

The *primary endpoint* is ~~overall response rate (CR, CRu and PR).~~ **progression free survival (PFS). PFS is defined as the time from randomization until objective tumor progression or death for any reason. Patients who do not progress at the time of analysis will be censored. Progression will be determined according to** the International Workshop Lymphoma Response Criteria (IWRC) (Cheson, 1999), as modified by Fisher et al 2006; Kane et al 2007 for target lesions will be used (see Section 21.5 and Table 7 for a detailed description of the modifications). The assessment will be reviewed by an

independent review committee. The primary analysis will be done in the intent-to-treat (ITT) population for **PFS**, overall response rate, progression-free-survival, ~~and~~ overall survival **and secondary endpoints**. All patients who have received at least one single treatment dose (C1D1) with centrally confirmed histology of mantle cell non-Hodgkin's lymphoma will be included in the sensitivity analysis.

Further *secondary endpoints* include:

- **Overall response rate (CR, CRu and PR)**
- Duration of response: will be measured from the time of initial response (at least PR) until documented tumor progression or death. Patients who do not progress at the time of analysis will be censored. This analysis will be restricted to responder patients.
- ~~Progression-free survival: defined as the time from randomization until objective tumor progression or death for any reasons. Patients who do not progress at the time of analysis will be censored.~~

… Efficacy analysis will be conducted when ~~all patients have completed at least 6 months of treatment or discontinued before completing 6 months.~~ **128 deaths or progressions have occurred.**

An update of the time to events endpoints and overall survival will be done at the end of the follow up. No adjustment for multiplicity ~~is needed as it is a non comparative study.~~ **will be applied**.

All efficacy analysis will be conducted on intent to treat basis.

The Kaplan-Meier procedure will be used to characterize time to event endpoints and duration of response. Median times-to-event and their respective two-sided 95% confidence intervals will be provided for each of these variables. An unstratified log-rank test will be used to compare treatment arms for time-to-event variables. The Cox proportional hazards regression model will be used to assess the significance of stratification factors on treatment differences.

~~The Kaplan-Meier procedure will be used to characterize time to event endpoints and duration of response. Median times-to-event and their respective two-sided 95% confidence intervals will be provided for each of these variables.~~

Reason for Change: statistical section updated according to primary objective/endpoint changes.

19. The amendment updates the Interim analysis and DMC. This is noted in the Synopsis and in section 15.7 of the protocol.

Current Language:

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study and efficacy for futility at a pre-defined time point. Specifics are outlined in the DMC charter. Summaries of safety information will be prepared for Data Monitoring Committee (DMC) review. The first safety analysis will occur after the first 40 patients have received at least 3 cycles of treatment or have discontinued prior to completing 3 cycles. The second safety analysis as well as an efficacy analysis for futility will occur after 80 patients complete 3 cycles or withdraw before completing 3 cycles. A third safety analysis will occur after 120 patients complete 3 cycles or withdraw before completing 3 cycles.

Futility analysis will be conducted when approximately 80 patients complete 3 cycles or with draw before completing 3 cycles (around 54 patients in the Rev arm).

Based on a 95%CI approach, if the upper bound is below than 20% in the Lenalidomide arm, the DMC should recommend stopping the trial.

Amended language:

An independent external Data Monitoring Committee (DMC) will review ongoing safety data throughout the study and efficacy for futility at a pre-defined time point. Specifics are outlined in the DMC charter. Summaries of safety information will be prepared for Data Monitoring Committee (DMC) review. The first safety analysis will occur after the first 40 patients have received at least ~~3~~ **2** cycles of treatment or have discontinued prior to completing ~~3~~ **2** cycles. The second safety analysis as well as an efficacy analysis for futility will occur after 80 patients complete ~~3~~ **2** cycles or withdraw before completing ~~3~~ **2** cycles. A third safety analysis will occur after 120 patients complete ~~3~~ **2** cycles or withdraw before completing ~~3~~ **2** cycles.

Futility analysis will be conducted when approximately 80 patients complete ~~3~~ **2** cycles or with draw before completing ~~3~~ **2** cycles (around 54 patients in the ~~Rev~~ **lenalidomide** arm).

DMC will conduct an analysis for futility on PFS and Overall response rate. No specific stopping rules will be given to the DMC for the PFS, the following rules might be used for overall response rate.

Based on a 95%CI approach, if the upper bound is below 20% in the lenalidomide arm, the DMC should recommend stopping the trial.

Reason for Change:

Statistical section updated according to primary objective/endpoint changes.

Number of cycles has been reduced to 2 cycles to fit with imaging assessments (see section 10).

20. **The amendment updates the Schedule of Study Assessments. This is noted in the Synopsis (Schedule of Study Assessments) Table 2.**

Amended language (highlighted in yellow)

Table 2: Schedule of Study Assessments for Arm A and Arm B patients (28 days = 1 cycle)

Procedure	Screening/ Baseline (-28 Days)	Every Cycle Day 1 ± 3 days	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2-4 Day 15 ± 1 day	Every 56 days After Cycle 1 Day 1 ± 7 days for the first 6 months and then every 90 days ± 15 days thereafter	At Treatment Discontinuation	Follow-up for patients after PD[20]	Follow-up for non-PD patients[21]
Inclusion/exclusion criteria	X							
Complete medical history	X							
CNS Lymphoma Evaluation[1]	X							
MCL International Prognostic Index (MIPI)[2]	X							
Prior lymphoma therapy	X							
Creatinine Clearance (Cockcroft-Gault estimation)[3]	X							
12-Lead ECG[4]	X							
Lymph node or tumor biopsy specimen slides[5]	X							
Eastern Cooperative Oncology Group (ECOG) performance status	X	X				X		
Vital Signs[6]	X	X				X		
CBC with Differential[7]	X	X	X[9]	X[9]		X		
Serum Chemistry[8]	X	X	X[9]	X[9]		X		
Serology HBV, HCV in endemic areas	X							
Thyroid function test[17]	X							
Pregnancy Testing (FBCP only)	X[10]	X[11]				X[11]	X[11]	X[11]
Lenalidomide Counseling and distribute lenalidomide Information Sheet[12]	X	X					X[13]	X[13]
Assessment of Lymphoma-related Symptoms	X	X				X		
Adverse Events	X	X	X	X		X	X[14]	X[14]
Record Hospitalizations		X				X		
Tumor Flare / Tumor lysis Assessment[15]			X[15]					
Concomitant medications/Procedures	X	X	X			X		

Procedure	Screening/ Baseline (-28 Days)	Every Cycle Day 1 ± 3 days	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2-4 Day 15 ± 1 day	Every 56 days After Cycle 1 Day 1 ± 7 days for the first 6 months and then every 90 days ± 15 days thereafter	At Treatment Discontinuation	Follow-up for patients after PD[20]	Follow-up for non-PD patients[21]
Physical examination[16]	X	X				X	X	X
CT with contrast **(or** MRI with contrast **if CT contraindicated)** of neck, chest, abdomen and pelvis[18]	X[26]				X[18]			X[18]
Target and non-target lesion measurements[18]	X				X[18]			
Response assessment					X[18]			
Progression-Free Survival[19]					X[18]		X	X

[5] Representative slides documenting the diagnosis (H&E or Giemsa staining) and supporting the diagnosis of MCL (Cyclin D1 immunostaining), shall be sent together with the tumor block to central pathology as soon as possible, preferably before randomization for confirmation of mantle cell lymphoma, but at the latest 8 weeks after randomization. In patients whose tumor is negative for Cyclin D1, evidence of overexpression of Cyclin D2 or D3 is acceptable. Additionally, slides supporting the translocation by FISH or corresponding confirming photographies shall be submitted at the same time, if available. It is also recommended to send for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD23, CD20, BCL2, **Ki-67**. In case the tumor block can not be sent, 4-5 additional, unstained slides must also be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

[10] **Only for patients in Arm A and patients in cross over: before** starting study drug: Females of Childbearing Potential (FCBP) must confirm that they are using reliable methods of birth control, and must have two negative pregnancy tests prior to starting study drug: The first pregnancy test must be performed within 10-14 days prior to the start of study drug, and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative. All patients will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. (See specifics as described in Appendices 21.7 and 21.8).

[11] **Only for patients in Arm A and patients in cross over: during** the study participation and for 28 days following discontinuation from the study: FCBP must agree to have two pregnancy tests (See specifics as described in Appendices 21.7 and 21.8). In addition to the required pregnancy testing, the investigator must confirm with FCBP that she is continuing to use reliable methods of birth control at each visit (See specifics as described in Appendices 21.7 and 21.8).

[12] **Only for patients in Arm A and patients in cross over: all patients** must be counseled about pregnancy precautions and risks of fetal exposure.

[13] **Only for patients in Arm A and patients in cross over: after 28** days post-last dose of lenalidomide.

[18] CT with contrast/MRI **with contrast** must be performed every 56 days (± 7 days) up to 6 months from the start of study drug then every 90 ±15 days thereafter, during the follow up phase for patients who have discontinued study due to adverse events without evidence of progressive disease. CT scan **with contrast** /MRI **with contrast** does not need to be performed during follow-up for patients who discontinued due to disease progression or relapse.

[26] If a CT scan or MRI was done within 28 days of the ~~first dose of study medication~~ **randomization**, then the CT scan or MRI does not have to be repeated for the screening assessment.

Reason for Change:

Changes in Table 2 reflect changes done within the protocol.

A window of 1 day has been added to give more flexibility for the visits at D15 of cycle 2, cycle 3 and cycle 4.

Monitoring of FBCP is only applicable to patients receiving lenalidomide (Arm A and cross over).

21. **The amendment updates the Schedule of Study Assessments for patients with cross-over. This is noted in the Synopsis (Schedule of Study Assessments) Table 3**

Amended language (highlighted in yellow)

Table 3: Schedule of study assessments for patients with cross-over on lenalidomide after progression in investigator's choice Arm B (28 days = 1 cycle) – No more than 10 weeks after last day of last cycle of treatment in Arm B

Procedure	Every Cycle Day 1 ± 3 days	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2- 4 Day 15	Every 90 days After Cycle 1 Day 1 ± 15 days	At Treatment Discontinuation	Follow-up for patients after PD[10]	Follow-up for non-PD patients[11]
Eastern Cooperative Oncology Group (ECOG) performance status	X				X		
Vital Signs[1]	X				X		
CBC with differential[2]	X	X	X		X		
Serum Chemistry[3]	X	X	X		X		
Pregnancy Testing for FCBP[4]	X				X		
~~Birth control / Lenalidomide Counseling~~ [5] **Lenalidomide Counseling and distribute lenalidomide Information Sheet**	X						
Distribute Lenalidomide counseling sheet[5]	X		X				
Dispense study drug	X						
Study drug return	X				X		
Adverse Events[6]	X	X	X		X		X[6]
Tumor Flare /Tumor Lysis Assessment[7]		X					
Record Hospitalizations	X				X		
Concomitant medications/ Procedures	X	X	X		X		
CT with contrast **(or** MRI with contrast, **if CT contraindicated)** of neck, chest, abdomen and pelvis				X			X[8]
Target and non-target lesion measurements				X			
Response assessment				X			
Progression-Free Survival[9]				X		X	X

Procedure	Every Cycle Day 1 ± 3 days	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2- 4 Day 15	Every 90 days After Cycle 1 Day 1 ± 15 days	At Treatment Discontinuation	Follow-up for patients after PD[10]	Follow-up for non-PD patients[11]
Overall survival						X[10]	X[11]

[8]CT with contrast/ or MRI **with contrast** is recommended 90 days (± 15 days) during the follow up phase for patients who have discontinued treatment due to adverse events without evidence of progressive disease. CT scan **with contrast** /MRI **with contrast** does not need to be performed during follow-up for patients who discontinued due to disease progression or relapse.

Reason for Change:

Changes in Table 3 have been done to be more consistent with Table 2.

22. The amendment updates the list of Abbreviations and Specialist Terms. This is noted in the protocol (Abbreviations and Specialist Terms) Table 4.

Current Language:

CT	Computerized Axial Tomography

Amended language:

CT	Computerized ~~Axial~~ Tomography
HR	**Hazard Ratio**
MRI	**Magnetic Resonance Imaging**

Reason for Change: HR and MRI were added since new (HR) or missing (MRI) in the previous protocol. The abbreviation of CT was revised to fit more with the appropriate terminology.

23. The amendment updates Mantel Cell Lymphoma. This is noted in the protocol in section 5.1.

Current Language:

However, options are limited for patients with relapsed mantle cell lymphoma and there is a clear need for novel innovative approaches. The increasing understanding of the MCL cell biology has led to the development of new therapeutic agents with antitumor activity that target crucial biological pathways, including cell cycle inhibitors [e.g. flavopiridol], mTOR inhibitors [temsirolimus (Witzig, 2005), everolimus (Haritunians, 2007)] and histone deacetylase inhibitors. These new therapeutic approaches have been studied in patients previously treated with aggressive regimens (Kouroukis, 2003; Goy, 2005; O'Connor, 2005). The combination of these new therapeutic strategies and the correct stratification of the patients according to the risk may ultimately change the management and outcome of MCL patients (Jares, 2008).

Amended language:

However, options are limited for patients with relapsed mantle cell lymphoma and there is a clear need for novel innovative approaches. The increasing understanding of the MCL cell biology has led to the development of new therapeutic agents with antitumor activity that target crucial biological pathways, including cell cycle inhibitors [e.g. flavopiridol], mTOR inhibitors [temsirolimus ~~(Witzig, 2005)~~ **(Hess, 2009)**, everolimus (Haritunians, 2007)] and histone deacetylase inhibitors. These new therapeutic approaches have been studied in patients previously treated with aggressive regimens (Kouroukis, 2003; Goy, 2005; O'Connor, 2005). The combination of these new therapeutic strategies and the correct stratification of the patients according to the risk may ultimately change the management and outcome of MCL patients (Jares, 2008).

Reason for Change: literature update.

24. The amendment updates Clinical Studies of lenalidomide in Non-Hodgkin's Lymphoma. This is noted in the protocol in section 5.2.2.

Current Language:

… In the second study (NHL-003) which was initiated in November 2006, 53 of 218 patients enrolled had MCL. As of March 1, 2008, 39 MCL patients were evaluable for response assessment (Zinzani, 2008). The median age was 66 (33–82) years. The median time from diagnosis to start of lenalidomide treatment was 3.4 (0.4–9) years. These patients had received a median of 3 (1–8) prior treatments, and 23% (9/39) of patients had received prior bortezomib treatment. The ORR to lenalidomide was 41% (16/39), including 13% (5/39) complete responses (CR/unconfirmed CR), and 28% (11/39) partial responses. Ten (26%) patients had stable disease. The most common grade 3 or 4 adverse events were neutropenia (51%) and thrombocytopenia (25%), anemia (13%), fatigue (10%) and febrile neutropenia (10%) (Zinzani, 2008).

Amended language:

… In the second study (NHL-003) which was initiated in November 2006, ~~53 of 218 patients enrolled had MCL. As of March 1, 2008, 39 MCL patients were evaluable for response assessment (Zinzani, 2008). The median age was 66 (33–82) years. The median time from diagnosis to start of lenalidomide treatment was 3.4 (0.4–9) years. These patients had received a median of 3 (1–8) prior treatments, and 23% (9/39) of patients had received prior bortezomib treatment. The ORR to lenalidomide was 41% (16/39), including 13% (5/39) complete responses (CR/unconfirmed CR), and 28% (11/39) partial responses. Ten (26%) patients had stable disease. The most common grade 3 or 4 adverse events were neutropenia (51%) and thrombocytopenia (25%), anemia (13%), fatigue (10%) and febrile neutropenia (10%) (Zinzani, 2008).~~ **217 patients were enrolled. In the 57 MCL patients who were evaluable for response assessment, lenalidomide therapy led to an objective response rate of 42% (25/57). Median progression-free survival (PFS) was 5.7 months. Overall, the primary side effect of lenalidomide was reversible myelosuppression. Grades 3 or 4 neutropenia occurred in 41%, thrombocytopenia in 19%, anemia in 9%, and leucopenia in 7% of patients. (Witzig 2009)**

Reason for Change: literature update.

25. The amendment updates Design Rationale. This is noted in the protocol in section 8.1

8.1. Design Rationale

Current Language:

This study is designed to investigate the efficacy and safety of lenalidomide therapy in patients with relapsed and refractory mantle cell lymphoma. The multicenter nature of the study provides assurance that the results are likely to have general applicability. Patient eligibility criteria are consistent with those used in studies of this population. Patients are required to have measurable disease to facilitate the accurate assessment of response, the primary efficacy endpoint.

Amended language:

This study is designed to ~~investigate~~ **evaluate** the efficacy and safety of lenalidomide therapy **versus investigator's choice** in patients with relapsed and refractory mantle cell lymphoma. **The primary efficacy objective is based on PFS.**

The multicenter nature of the study provides assurance that the results are likely to have general applicability. Patient eligibility criteria are consistent with those used in studies of this population. Patients are required to have measurable disease to facilitate the accurate assessment of response, the ~~primary~~ **secondary** efficacy endpoint.

Reason for Changes: design updated according to the new primary endpoint (PFS). See also the rationale for points #3 and #4.

26. The amendment updates Cross over (for patients in the investigators choice Arm B only). This is noted in the protocol in section 8.1.2.3.

Current Language:

Treatment with lenalidomide will start as soon as recovery from toxicities of prior treatments of Arm B have resolved and all inclusion/exclusion criteria are met (i.e. laboratory parameters), but no longer than 10 weeks after day 1 of last treatment cycle in Arm B.

Amended language:

Treatment with lenalidomide will start as soon as recovery from toxicities of prior treatments of Arm B have resolved and all inclusion/exclusion criteria are met (i.e. laboratory parameters), but no longer than 10 weeks after ~~day 1~~ **last day** of last treatment cycle in Arm B.

Reason for Change: typing error corrected so text in line with table 3: cross over to Arm A (lenalidomide) must be calculated from the last day of last cycle in Arm B (investigator's choice).

27. The amendment updates Follow-up Phase. This is noted in the protocol in section 8.1.2.4.

Current Language:

…. The follow up phase will continue until either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

Number of patients: approximately 150 patients (100 in Arm A, 50 in Arm B).

Amended language:

…. The follow up phase will continue until either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

~~Number of patients: approximately 150 patients (100 in Arm A, 50 in Arm B).~~

Reason for Change:

The sentence about the number of patients has been deleted since not appropriate in this section.

28. The amendment updates Independent Review Committee (IRC). This is noted in the protocol in section 8.4.

Current Language:

The IRC is composed of two external radiologists (with an additional radiologist (adjudicator) in the event of a tie), and a hemato/-oncologist. The IRC will perform a blinded, independent assessment of radiological response (including assessment of SD and PD), review the tumor response data and the dates of disease progression for each patient. These data reviewed by the IRC will be used in the primary analysis and these assessments will be included in the Clinical Study Report. For further details please refer to Central Radiology Manual.

Amended language:

Diagnostic imaging results (CT with contrast/MRI with contrast) will be reviewed locally and also sent to IRC for central review. The IRC is composed of two external radiologists with an additional radiologist (adjudicator), in the event of a tie, and a hemato/-oncologist. The IRC will perform a blinded, independent assessment of radiological response (including assessment of SD and PD), review the tumor response data and the dates of disease progression for each patient.

All these data reviewed by the IRC will be used in the primary analysis and these assessments will be included in the Clinical Study Report.

For further details please refer to Central Radiology Manual.

Reason for Change: it is reminded that local radiological assessments have to be done, independently of the central independent review.

29. The amendment updates Overview of dosage of Investigator's choice drugs. This is noted in the protocol in section 10.1.2 under Table 5

Current Language:

[#] Rituximab (single agent) is to be repeated every 56 days after Day 56 (given only on day 1 of every 56 days cycle). For the prevention of cytokine release syndrome associated with the treatment of Rituximab ≧ 125mg of methylprednisolone or equivalent are accepted on C1D1

Amended language:

[#] Rituximab (single agent) is to be repeated every 56 days after Day 56 (given only on day 1 of every 56 days cycle). For the prevention of cytokine release syndrome associated with the treatment of Rituximab ≤ 125mg of methylprednisolone or equivalent are accepted on C1D1.

Patients in Arm B need to follow the scheduled visits as displayed in Table 2. For some drugs, additional visits may be needed.

Reason for Change:

Correction of a typing error for the sign relative to maximum authorized dose of methylprednisolone.

For Arm B, it is clarified that additional visits, for example for Rituximab administered every 56 days: additional visits maybe done in between to follow the safety.

30. The amendment updates Dosage Modification for Lenalidomide. This is noted in the protocol in section 10.1.3 Table 6.

Amended language (highlighted in yellow)

Table 6: Dosage Modification for Lenalidomide

NCI CTCAE Toxicity Grade	Action Required
Allergic reaction or hypersensitivity Grade 2 Grade 3-4	• Hold (interrupt dose). Follow at least every seven days • When the toxicity resolves to ≤ Grade 1 restart at next lower dose level • Discontinue lenalidomide study drug
Constipation Grade 1-2 ≥ Grade 3	• Initiate bowel regimen and maintain dose level • 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)
Newly developed ≥ Grade 3 peripheral neuropathy **(this applies only to those toxicities which begin or worsen while on study)**	• Hold (interrupt) dose • When the toxicity resolves to ≤ Grade 2 restart at next lower dose level

~~ALT > 3 and ≤ 5x ULN and Total bilirubin ≤ 1.5 x ULN~~ **AST or ALT > 3 x ULN**	**Hold lenalidomide dosing; re-test at least weekly until AST or ALT < 2.5 x ULN or return to baseline**	**- Resume the same dose of lenalidomide if the event is considered NOT related to study drug treatment** **- Restart lenalidomide treatment at next lower dose level if the event is considered as related to drug treatment**
~~ALT > 3 and ≤ 5 x ULN and Total bilirubin > 1.5 x ULN~~ **Bilirubin > 3 x ULN***	**Hold lenalidomide dosing; re-test at least weekly until bilirubin < 1.5 x ULN**	**– Resume the same dose of lenalidomide if the event is considered NOT related to study drug treatment** **– Restart lenalidomide treatment at next lower dose level if the event is considered as related to drug treatment**
~~ALT > 5 x ULN or Total bilirubin > 1.5 x ULN~~ **Tumor Flare** **Grade 3 or 4**	**– Interrupt lenalidomide therapy and initiate therapy with corticosteroids, NSAIDs and/or narcotics** **– Resume lenalidomide (decrease one dose level) when symptoms resolve to ≤ Grade 1**	
TLS **laboratory TLS and Grade 1 TLS**	**– Same dose of lenalidomide may be continued without interruption or dose reduction at the investigator's discretion.** **– Dose escalation to the next consecutive dose level is permitted when laboratory TLS is resolved and Grade 1 TLS is resolved to Grade 0.**	
TLS ≥ Grade 2	**– Interrupt lenalidomide therapy.** **– May resume lenalidomide when the TLS resolves to < Grade 1 (decrease one dose level)** **– If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following initiation of lenalidomide.** **– Re-escalation by one dose level at a time will be permitted after completion of one full cycle without laboratory TLS or ≥ Grade 1 TLS**	

~~Alanine Transaminase (ALT) > 5 x ULN~~		

**** For patients with Gilberts Syndrome or liver involvement by lymphoma, dose reductions should be made in consultation with the Celgene medical monitor***

Reason for Change: The dose modification table is modified to make it easier to follow and in order to cover all the possible situations.

31. The amendment updates Dose Modification or Interruption for Investigator's choice - Arm B. This is noted in the protocol in section 10.1.4

Current Language:

Patients will be evaluated for adverse events at each visit with the NCI CTCAE v3.0 used as a guide for the grading of severity. The dose of investigator's choice for each patient will be interrupted and modified according to the clinical practice of the investigators institution, where applicable and in line with the approved prescribing information provided by Celgene.

Amended language:

Patients will be evaluated for adverse events at each visit with the NCI CTCAE v3.0 used as a guide for the grading of severity. The dose of investigator's choice for each patient will be interrupted and modified according to the clinical practice of the investigators institution, where applicable and in line with the approved prescribing information provided by Celgene. **Doses that were missed because of toxicity or any other reason will not be made up. Patients should continue with the next cycle when they are able.**

Reason for Change: Clarification of guidance for toxicity management.

32. The amendment updates Methods and Timing of Efficacy Assessments. This is noted in the protocol in section 12.2.

Current Language:

CT scan/MRI

CT with contrast or alternatively MRI, is performed at baseline then every 56 days (±7 days) after Day 1, Cycle 1 for the first 6 months and then every 90 days ± 15 days thereafter until documented progressive disease, or when clinically indicated.

To ensure comparability, baseline and on-study methods for response assessment must be performed using identical techniques.

Amended language:

CT scan/MRI

CT with contrast or alternatively MRI **with contrast**, **if CT is contraindicated**, is performed at baseline then every 56 days (±7 days) after Day 1, Cycle 1 for the first 6 months and then every 90 days ± 15 days thereafter until documented progressive disease; or when clinically indicated.

To ensure comparability, baseline and on-study methods for response assessment must be performed using identical techniques.

Any suspicion of progressive disease and eventually leading to additional investigations (e.g. colonoscopy) must be complemented by a re-staging procedure using CT scan (or MRI).

Reason for Change:

"If CT is contraindicated" has been added to fit with the recommendation to have CT as preferred imaging method (see also point #8).

For consistency purposes the term contrast has been added to CT-scan and MRI within all the protocol.

The last paragraph about suspicion of progression has been moved from section 13.1 to section 12.2, since it is more appropriate to have this explanation here.

33. The amendment updates Assessments. This is noted in the protocol in section 13.1.

Current Language:

- AEs/SAEs severity is graded using NCI CTCAE Version 3.0 (see Appendix 21.1)

Any suspicion of progressive disease and eventually leading to additional investigations (e.g. colonoscopy) must be complemented by a re-staging procedure using CT scan (or MRI)…

- Tumor Flare/Lysis Assessments
- FCBP should be monitored during the course of the study and after the end of study therapy to:

Amended language:

- AEs/SAEs severity is graded using NCI CTCAE Version 3.0 (see Appendix 21.1)

~~***Any suspicion of progressive disease and eventually leading to additional investigations (e.g. colonoscopy) must be complemented by a re-staging procedure using CT scan (or MRI)***…~~

- Tumor Flare/Lysis Assessments **(only in Arm A patients and patients in cross over)**
- FCBP should be monitored during the course of the study and after the end of study therapy to **(only in Arm A patients and patients in cross over):**

Reason for Change:

The paragraph about suspicion of progression has been moved from section 13.1 to section 12.2, since it is more appropriate to have this explanation in section 12.2.

Recommendations for TFR/TLS and monitoring of FCBP are only applicable for patients who receive lenalidomide.

35. The amendment updates Primary Efficacy Endpoints. This is noted in the protocol in section 15.2.1.

Current Language:

The primary response rate will include best response of Complete Response (CR), Complete Response unconfirmed (CRu), or Partial Response (PR). The Modified International Workshop Lymphoma Response Criteria (IWRC) (Cheson, 1999) will be used and response assessed by CT scan/MRI every 56 days (± 7 days) for the first 6 months and then every 90 days ± 15 days thereafter.

Primary analysis will be conducted on the blinded central independent review assessment. The investigator assessment will be used as sensitivity analysis.

Patients who discontinue before any post-randomization efficacy assessments will be considered non-responders.

Efficacy analysis will be conducted when all patients have completed at least 6 months of treatment or discontinued before completing 6 months.

Amended language:

Progression-free survival (PFS)

PFS is defined as the time from randomization to the first observation of disease progression or death due to any cause. If the patient has not progressed or died, PFS will be censored at the time of last completed assessment when the patient was known not to have progressed. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free (see table below).

Censoring Rules for Time to event (Progression and/or Death) Endpoints

Situation	Date of Progression or Censoring	Situation Outcome
No baseline assessments	Randomization	Censored

Progression documented	**First adequate assessment determined by central review**	**Progressed**
No progression	**Date of last adequate assessment with evidence of no progression**	**Censored**
Study discontinuation for reasons other than disease progression or death	**Date of last adequate assessment with evidence of no progression**	**Censored**
New anti-lymphoma /non-protocol treatment started prior to progression	**Date of last adequate assessment with evidence of no progression prior to the start of new anti-lymphoma treatment**	**Censored**
Death before first PD assessment while on study	**Date of death**	**Progressed**
Death between adequate assessment visits	**Date of death**	**Progressed**
Death or progression after an extended lost-to-follow-up time (two or more missed assessments)	**Date of last adequate assessment with evidence of no progression**	**Censored**

As additional robustness checks of the primary endpoint and censoring definition, the time to event analysis will be repeated for the ITT population using the following modified methods of PFS:

a) Using the investigator assessment instead the IRC central review

b) Considering progression or death under a new anti-lymphoma treatment as an event

c) Considering death or progression after an extended lost-to-follow-up time (two or more missed assessments) as an event

d) One using the earliest progression date either in investigator set or IRC set.

~~The primary response rate will include best response of Complete Response (CR), Complete Response unconfirmed (CRu), or Partial Response (PR). The Modified International Workshop Lymphoma Response Criteria (IWRC) (Cheson, 1999) will be used and response assessed by CT scan/MRI every 56 days (± 7 days) for the first 6 months and then every 90 days ± 15 days thereafter.~~

~~Primary analysis will be conducted on the blinded central independent review assessment. The investigator assessment will be used as sensitivity analysis.~~

~~Patients who discontinue before any post-randomization efficacy assessments will be considered non-responders.~~

Efficacy analysis will be conducted when ~~all patients have completed at least 6 months of treatment or discontinued before completing 6 months.~~ **128 deaths or progressions have occurred.**

Reason for Change: statistical section update according to PFS as primary endpoint.

36. The amendment updates Secondary Endpoints. This is noted in the protocol in section 15.2.2.

Current Language:

… Progression-free survival (PFS)

PFS is the time from randomization to the first observation of disease progression or death due to any cause. If the patient has not progressed or died, PFS will be censored at the time of last follow-up when the patient was known not to have progressed. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free…

Amended language:

Overall Response

The primary response rate will include best response of Complete Response (CR), Complete Response unconfirmed (CRu), or Partial Response (PR). The Modified International Workshop Lymphoma Response Criteria (IWRC) (Cheson, 1999) will be used and response assessed by CT scan with contrast/MRI with contrast every 56 days (± 7 days) for the first 6 months and then every 90 days ± 15 days thereafter.

Patients who discontinue before any post-randomization efficacy assessments will be considered non-responders.

~~Progression-free survival (PFS)~~

~~PFS is the time from randomization to the first observation of disease progression or death due to any cause. If the patient has not progressed or died, PFS will be censored at the time of last follow-up when the patient was known not to have progressed. Patients who will receive a new treatment without documented progression will be censored at the last assessment date that the patient is known to be progression-free.~~

Reason for Change: statistical section update according to PFS as primary endpoint and ORR moved to secondary endpoints.

37. The amendment updates Analysis Methods. This is noted in the protocol in section 15.2.3

Current Language:

All efficacy analyses will be conducted on intent to treat basis.

All efficacy analyses will be repeated on the Full Analysis Set (FAS) as sensitivity analysis for the primary endpoint and the duration of response.

The study is non comparative; data will be analyzed and displayed per treatment group in a descriptive manner.

The primary analyses for response will be performed on the ITT and FAS populations after all patient have completed 6 months of treatment or discontinued before completing 6 months. Patients who drop out of the study without being evaluated for will be counted as non-responders. Responses from patients after they receive other anti-cancer treatments will be counted as non responder.

Duration of response will be analyzed with the same populations as the primary endpoint.

Secondary endpoints will be analyzed at the time of the primary analysis of response. An update of the time to events endpoints and overall survival will be done at the end of the follow up. No adjustment for multiplicity is needed as it is a non comparative study.

The probability of response rates will be estimated using the proportion of patients with responses with exact two-sided 95% confidence intervals.

The Kaplan-Meier procedure will be used to characterize time to event endpoints (*e.g.*, PFS, TTP, TTR, OS) and duration of response. Median times-to-event and their respective two-sided 95% confidence intervals will be provided for each of these variables.

The EORTC QLQ-C30 will be analyzed using change from baseline and percentage of change from baseline according to the functional scores (pg.17) and the recommendations in the EORTC scoring manual. Statistical tests could be performed on an exploratory manner as described in section 15.9.

The EORTC Reference Data Manual (Scott, 2008) will also be used to descriptively check comparability between patients in our trial and with other comparable populations. The response rate in the cross-over portion of patients in Arm B will be analyzed in a descriptive manner.

Amended language:

All efficacy analyses will be conducted on intent to treat basis.

All efficacy analyses will be repeated on the Full Analysis Set (FAS) as sensitivity analysis for the primary endpoint ~~and the duration of response~~.

~~The study is non comparative; data will be analyzed and displayed per treatment group in a descriptive manner.~~

The primary analysis for ~~response~~ **PFS** will be performed on the ITT and FAS populations ~~after all patient have completed 6 months of treatment or discontinued before completing 6 months Patients who drop out of the study without being evaluated for will be counted as non-responders. Responses from patients after they receive other anti-cancer treatments will be counted as non responder.~~a**fter 128 deaths or progression have occurred.**

~~Duration of response will be analyzed with the same populations as the primary endpoint.~~

The Kaplan-Meier procedure will be used to characterize time to event endpoints (*e.g.*, PFS, TTP, TTR, OS) and duration of response. Median times-to-event and their respective two-sided 95% confidence intervals will be provided for each of these variables.

An unstratified log-rank test will be used to compare treatment arms for time-to-event variables. The Cox proportional hazards regression model will be used to assess the significance of stratification factors on treatment differences.

Patients who drop out of the study without being evaluated for will be counted as non-responders. Responses from patients after they receive other anti-cancer treatments will be counted as non responder.

Secondary endpoints will be analyzed at the time of the primary analysis of response. An update of the time to events endpoints and overall survival will be done at the end of the follow up. No adjustment for multiplicity will ~~is needed as it is a non comparative study~~ **be applied**.

The probability of response rates will be estimated using the proportion of patients with responses with exact two-sided 95% confidence intervals.

The EORTC QLQ-C30 will be analyzed using change from baseline and percentage of change from baseline according to the functional scores ~~(pg.17)~~ and the recommendations in the EORTC scoring manual. Statistical tests could be performed on an exploratory manner as described in section 15.9.

The EORTC Reference Data Manual (Scott, 2008) will also be used to descriptively check comparability between patients in our trial and with other comparable populations. The response rate in the cross-over portion of patients in Arm B will be analyzed in a descriptive manner.

Reason for Change:

Statistical section update according to PFS as primary endpoint and ORR moved to secondary endpoints.

Deletion of a page reference, useless since there is the appropriate cross reference section.

38. The amendment updates Interim Analyses. This is noted in the protocol in section 15.7

Current Language:

… Futility analysis will be conducted when approximately 80 patients complete 3 cycles or withdraw before completing 3 cycles (around 54 patients in the Rev arm).

Based on a 95%CI approach, if the upper bound is below than 20% in the rev arm, the DMC should recommend stopping the trial…

Amended language:

… Futility analysis will be conducted when approximately 80 patients complete 3 cycles or withdraw before completing 3 cycles (around 54 patients in the lenalidomide arm).

DMC will conduct an analysis for futility on PFS and Overall response rate. No specific stopping rules will be given to the DMC for the PFS; the following rules might be used for overall response rate.

Based on a 95% CI approach, if the upper bound is below ~~than~~ 20% in the lenalidomide arm, the DMC should recommend stopping the trial…

Reason for Change: DMC reviews extended to PFS and ORR.

39. The amendment updates Sample Size and Power Considerations. This is noted in the protocol in section 15.8.

Current Language:

The main objective of the study is to estimate the Overall Response Rate (ORR).

Sample size calculation is based on the width of the 95% confidence interval around a certain point estimate for ORR that is considered significant clinical activity.

Based on preliminary data it could reasonably expect a response rate in the range of 30% to 40%...

… As the study is a non comparative study no formal sample size calculation will be done for the control arm. With a 2:1 ratio 50 patients are needed in the control arm.

Amended language:

The main objective of the study changed to ~~estimate the Overall Response Rate (ORR)~~ **demonstrate the efficacy of lenalidomide over a single agent of investigator's choice based on PFS.**

The primary analysis for the study is to compare PFS between lenalidomide and a single agent of investigator's choice. For the primary efficacy variable PFS, a hazard ratio (HR) of 1.7 leading to an improvement in median PFS from 2.5 months for the control arm to at least 4.25 months for lenalidomide is considered clinically relevant.

These assumptions are supported by recent data published in relapsed refractory MCL.

With a hazard ratio of 1.7, full information necessary for a one-sided log rank test with an overall alpha of 0.025, to have 80% power, will be achieved when approximately 128 patients have progressed or died (PFS).

The sample size initially was calculated to estimate the Overall Response Rate (ORR).

Sample size calculation is based on the width of the 95% confidence interval around a certain point estimate for ORR that is considered significant clinical activity.

Based on preliminary data, a response rate in the range of 30% to 40% can reasonably be expected…

… ~~As the study is a non comparative study no formal sample size calculation will be done for the control arm.~~

No formal sample size calculation will be done for the control arm. With a 2:1 ratio 50 patients are needed in the control arm.

Assuming that 10% of patients will be lost to follow up, 167 patients will be randomized.

Reason for Change:

Statistical hypotheses revised in accordance with PFS as primary objective.

Precision about expected randomized patients and percentage of lost to follow-up, information inadvertently omitted from current protocol.

40. The amendment updates Other Topics. This is noted in the protocol in section 15.9.

Current Language:

Statistical tests will be performed to compare the two groups only for exploratory purpose.

Amended language:

Statistical tests will be performed to compare the two groups only for exploratory purpose **for the secondary endpoints.**

Reason for Change: "secondary endpoints were added to reflect the change in the nature of the study (non comparative to comparative).

41. The amendment updates Data Management. This is noted in the protocol in section 18.2.

Current Language:

Data will be 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.

Amended language:

Data will be entered into the clinical database per ~~Celgene~~ SOPs **unless internal processes will be done by Data Management of Celgene, in this case Celgene SOPs will be used.**

Reason for Change: clarification made regarding the SOPs used, taking into account that is the external vendor for different services, including data management.

42. The amendment updates References. This is noted in the protocol in section 20.

Current Language

Zinzani PL, Witzig TE, Vose JM, et al. Efficay and Safety of Lenalidomide Oral Montherapy in patients with Relapsed or Refractory mantle-Cell Lymphoma: Results of an international Study . *Blood* (ASH Annual Meeting Abstract); Nov. 2008; 112: 262.

Amended language:

~~Zinzani PL, Witzig TE, Vose JM, et al. Efficay and Safety of Lenalidomide Oral Montherapy in patients with Relapsed or Refractory mantle-Cell Lymphoma: Results of an international Study . *Blood* (ASH Annual Meeting Abstract); Nov. 2008; 112: 262.~~

Witzig TE, Vose JM., Zinzani PL, Reeder CB, Buckstein R, Polikoff J, Guo P, Pietronigro D, Ervin-Haynes A and Czuczman MS (ASH Annual Meeting Abstract); Nov. 2009; Abstract # 1676

Added language:

Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, Laurell A, Offner F, Strahs A, Berkenblit A, Hanushevsky O, Clancy J, Hewes B, Moore L, and Coiffier B. Phase III Study to Evaluate Temsirolimus Compared With Investigator's Choice Therapy for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma. J Clin Oncol 2009; 27:3822-3829.

Reason for Change: literature update.

43. Appendices.

Added Appendix: 21.9: EORTC QLQ-C30 Questionnaire

***Reason for addition*:** missing document

SUMMARY OF CHANGES
TO PROTOCOL CC-5013-MCL-002

A PHASE 2, MULTICENTER, RANDOMIZED OPEN-LABEL STUDY TO DETERMINE THE EFFICACY OF LENALIDOMIDE (REVLIMID®) VERSUS INVESTIGATOR'S CHOICE IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

THE "SPRINT" TRIAL

PROTOCOL:	**CC-5013-MCL-002**
AMENDMENT #:	**1**
DATE:	**21 April 2009**

1. The amendment updates the Study Personnel. This is noted in the Study Contact Information Table 1.

Current Language

Role in Study	Name	Address and Telephone Number
Global Study Manager		Celgene International Route de Perreux 1 2017 Boudry - Switzerland Phone: Fax: Email: Mobile Phone :
Responsible Clinical Research Physician		Celgene International Route de Perreux 1 2017 Boudry - Switzerland Phone: Fax: Email: Mobile Phone :
International Drug Safety Contact **(See Appendix 21.1 for local affiliate contact information)**	Clinical Trial Safety	Celgene International Sarl Route de Perreux 1 2017 Boudry - Switzerland Phone: Fax: Email:
24-Hour emergency contact		Tel : If not available : 24 hours call center Tel :

Added Language:

Role in Study: Responsible Clinical Research Physician

Name:

Address and Telephone Number:

Celgene International
Route de Perreux 1
2017 Boudry – Switzerland
Phone :
Fax :

Email :

Mobile Phone :

Amended Language:

International Drug Safety Contact

For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines

24-Hour Emergency Contact

If not available:

24 hours call center Tel :

Added language

Drug Safety Contact for ex-EU countries	Global Drug Safety (North America)	Celgene International 86 Morris Avenue Summit, New Jersey 07901 Phone: Fax: Email:

Reason for Chang and addition:

Change in personnel.

North America drug safety contact has been added for ex-EU countries like Israel.

2. The amendment updates the name of central laboratory(ies) and other medical and/or technical department(s) and /or institutions

Current Language:

Amended Language:

Interactive Voice Response System (IVRS)

Reason for Change:

To clarify roles, responsibilities and localization of different laboratories / medical / technical department(s).

4. The amendment updated the Background and rationale. This is noted in the synopsis (Background and Rationale).

Current Language:

Background and Rationale

…. In study CC-5013-NHL-002 of lenalidomide monotherapy in patients with relapse aggressive NHL, 15 of 49 patients had MCL (Wiernik, 2007; Wiernik, 2008). Lenalidomide therapy led to 1 complete response (CR), 1 complete response unconfirmed (CRu) and 6 partial responses (PR) in these patients with MCL (Tuscano, 2007). Four of 5 patients with a prior stem cell transplant responded. In another ongoing study of lenalidomide monotherapy in patients with relapsed or refractory NHL (CC-5013-NHL-003), 28 of 89 evaluable patients had MCL (Czuczman, 2008). Lenalidomide therapy led to an objective response rate of 36% in patients with MCL. In the 2 phase II clinical studies (NHL-002 and NHL-003), the most common grade 3/4 adverse events were neutropenia (21%) and thrombocytopenia (15%) (Habermann, 2008)…

Amended Language:

Background and Rationale

…. In study CC-5013-NHL-002 of lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL (Wiernik 2008), 15 of 49 patients had MCL. In these MCL patients lenalidomide therapy achieved an Overall Response Rate (ORR) of 53%. Three patients (20%) had a CR or unconfirmed CR, and 5 patients (33%) had a PR. The median duration of response was 13.7 months and median PFS was 5.6 months. The most common grade 4 adverse event was thrombocytopenia (13%) and the most common grade 3 adverse events were neutropenia (40%), leucopenia (27%), and thrombocytopenia (20%). (Habermann, 2009). In another ongoing study of lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL (CC-5013-NHL-003), 53 of 203 patients had MCL (Zinzani, 2008). In the 39 MCL patients who were evaluable for response assessment, lenalidomide therapy led to an objective response rate of 41% with 5 CRs and 11 PRs. The most common grade 3 or 4 adverse events were neutropenia (51%) and thrombocytopenia (25%), anemia (13%), fatigue (10%) and febrile neutropenia (10%) (Zinzani, 2008)....

Reason for Change:

Updated data available.

5. The amendment updated Screening Phase. This is noted in synopsis (Screening Phase) and in sections 8.1.2.2 of the protocol

Current Language:

Patients will be screened for protocol eligibility within 28 days prior to randomization as outlined in Table 2: Schedule of Study Assessments. Screening/baseline assessments will begin once the patient has approved and signed the informed consent form. CBC and serum chemistry tests will be required within 7 days of first dose of study drug. Eligibility for the study is based on the local assessments (CBC and chemistry as well as the local results of the tumor / lymph node biopsy and bone marrow specimens [if applicable]) done during the screening/baseline phase of the study.

Diagnosis of mantle cell lymphoma by local pathological review must be completed prior to randomization. The confirmation must include a biopsy-proven mantle cell lymphoma, including overexpression of cyclin D1 by immunohistochemistry or t(11;14)(q13:q32) by FISH. In patients whose tumors are negative for the cyclin D1 gene translocation, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable. Tumor / lymph node biopsy specimen, which may be archival slides from specimen obtained at the time of initial diagnosis, with representative stained slides supporting the diagnosis of MCL (Cyclin D1 staining or FISH slide), must be sent to central pathology before randomization for confirmation of mantle cell lymphoma; in parallel, 4-5 unstained slides must also be submitted. If such specimen slides are not available for submission, then a re-biopsy is required…

Amended Language:

Patients will be screened for protocol eligibility within 28 days prior to randomization as outlined in Table 2: Schedule of Study Assessments. Screening/baseline assessments will begin once the patient has approved and signed the informed consent form. Complete blood count (CBC) and serum chemistry tests will be required within 7 days of first dose of study drug. Eligibility for the study is based on the local assessments (CBC and chemistry as well as the local results of the archival tumor / lymph node biopsy) done during the screening/baseline phase of the study.

Confirmation of mantle cell lymphoma diagnosis by the central pathology is not required before randomization or treatment start, but will be performed centrally at a later stage. Eligibility for the study

is based on assessment of the local pathology results by the investigator. Diagnosis based on needle aspirations are not considered acceptable pathologic data for entry in this study.

The confirmation material submitted for Central Pathology Review must include a biopsy-proven mantle cell lymphoma specimen, including overexpression of cyclin D1 by immunohistochemistry. In patients whose tumors are negative for Cyclin D1 overexpression, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable.

Tumor / lymph node biopsy specimen, which may be archival slides from specimen obtained at the time of initial diagnosis, with representative stained slides supporting the diagnosis of mantle cell lymphoma (H&E or Giemsa staining and Cyclin D1 staining), must be sent as soon as possible to central pathology before randomization but at the latest 8 weeks after randomization. It is highly recommended to submit also the original paraffin block (called tumor block). If the tumor block cannot be sent, 4-5 additional unstained slides must be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

Evidence of the translocation t(11;14)(q13:q32) by FISH should be submitted using the original slide or the corresponding confirming photographies. The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. If available, it is also recommended to send, for central pathology review, slides containing immunostaining for CD3, CD5, CD10, CD20, CD23, BCL2.

Furthermore, it is highly recommended to perform an unilateral bone marrow biopsy at screening, and to send the tumor block to Central Pathology for review at the latest 8 weeks after randomization.

During the screening/baseline phase, the investigator must allocate one of the "investigator's choice" options to the patient prior to the randomization.

Reason for Change:

Clarification of specimens required for central pathology to confirm diagnosis of MCL at screening. Bone marrow biopsy at screening is highly recommended to:

- confirm MCL diagnosis, to exclude any lymphoma transformations
- confirm or infirm MCL bone marrow infiltration
- justify and explain a thrombocytopenia in screened patients
-

It also clarifies deadlines for shipment of these specimens from Investigators' sites to Central Pathology Laboratory.

6. The amendment updated Treatment Phase noted in synopsis, table 2 (foot note 25), Figure 1, and section 8.1.2.3 of the protocol

Current language:

> Treatment should start as soon as possible after randomization, but maximum time between randomization and C1 D1 is 14 days…

Amended language:

Treatment should start as soon as possible after randomization, but maximum time between randomization and C1 D1 is **4 days**, once the patients has fulfilled the requirements of the Lenalidomid pregnancy prevention program (see Appendices 21.7 and 21.8)…

Reason for change:

To optimize start of treatment, since shipment of study drugs for Arm B is initiated at screening visit, and not at randomization.

7. The amendment updated Treatment Phase noted in synopsis, and section 8.1.2.3 and of the protocol

Current Language:

Amended Language:

Reason for change:

8. The amendment updated the prophylaxis of tumor lysis syndrome noted in synopsis and in section 10.1.5 of the protocol

Current Language:

The Patients in the lenalidomide arm in this study should receive tumor lysis prophylaxis (allopurinol or equivalent) and be well hydrated (orally) during the first 7 days of lenalidomide administration in the first cycle or as clinically indicated. Hydration levels should be adjusted according to age and clinical status. To monitor for tumor lysis syndrome and cytopenia(s), the patients will have a complete blood count (CBC) and chemistry drawn on Days 1, 2, 4, 8 and 15 of the first cycle and additionally as clinically indicated. TLS will be assessed by Cairo-Bishop Grading system. (See Appendix 21.6).

Added Language:

If a patient develops laboratory TLS (defined by the presence of two or more serum value abnormalities of uric acid, potassium, phosphorous or calcium) or ≥ Grade 1 TLS (defined by the presence of laboratory TLS and one or more of the following criteria: creatinine ≥ 1.5 x ULN, arrhythmia or seizures), appropriate medical management should be initiated according to the local standard of care in each

institution with vigorous IV hydration (rasburicase treatment is considered appropriate if it is approved by the local Health Authority).

Reason for Change:

To provide guidance on proper medical management for Tumor Lysis Syndrome.

9. The amendment updated prophylaxis for thromboembolism noted in synopsis (treatment phase), section 10.1.6 of the protocol

Current language:

Patients in the lenalidomide arm will receive prophylactic aspirin [acetyl salicylic acid, ASA]] (70 – 100 mg) daily unless contraindicated. Patients who are at high risk for a thromboembolic event, such as history of a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history, or patients in whom ASA is contraindicated, or according to the discretion of the investigator, the use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the INR in the range of 2-3 may be considered.

Amended language:

Patients at high risk for a thromboembolic event (high risk is defined for example as a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history) will receive prophylactic aspirin [ASA] (70 – 100 mg) daily unless contraindicated. If ASA is contraindicated, use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the International normalized ratio (INR) in the range of 2-3 may be considered.

Reason for change:

To limit prophylaxis to patients with high risk for thromboembolic event.

10. The amendment added precision on the initiation of cross over treatment. This is noted in the synopsis, table 3 and section 8.1.2.3 of the protocol (Cross over for patients in the investigators choice Arm B only)

Current language:

For patients in Arm B treatment with lenalidomide will start as soon as recovery from toxicities of prior treatments. Treatment with lenalidomide will be for safety, response evaluation, and overall survival follow-up.

Added Language:

For patients in Arm B treatment ….. **The maximum duration between last day of last cycle of treatment in Arm B and first lenalidomide cycle is 10 weeks** …. Treatment with lenalidomide …

Reason for Change:

To extend duration of cross over treatment from Arm B to lenalidomide treatment, allowing patients to recover from toxicities of Arm B study drug.

11. The amendment updated sections relative to Independent External Pathological Review. This is noted in the synopsis, table 2 (foot note 6) and section 8.3 of the protocol

Current language:

Archival pathology slides of lymph node/tumor biopsy specimen obtained at the time of initial diagnosis and supporting the diagnosis of MCL must be sent to central pathology for confirmation of mantle cell lymphoma. If such archival specimen slides are not available for submission, then a re-biopsy is required prior to randomization. An independent central pathologist will review the lymph node/tumor biopsy as well as any available bone marrow biopsy and aspirate or other pathology slides for retrospective confirmation of the diagnosis of mantle cell lymphoma. The investigative site must submit lymph node/tumor biopsy slides and any available bone marrow biopsy and aspirate slides and other pathology slides as part of the screening phase to allow for a histological review as well as molecular evidence (FISH) of cyclin D1 gene translocation t(11;14)(q13;q32). In patients whose tumors are negative for the cyclin D1 translocation or in whom fluorescence in situ hybridization (FISH) data is not available, pathology specimen demonstrating overexpression of any one of cyclin D1, cyclin D2 or D3 by immunohistochemistry will be acceptable. The pathologist will also review any pathology specimens obtained as part of response assessment, including assessment of bone marrow aspirate and biopsy required for response assessment of CR/CRu.

Amended language:

An independent central pathologist will review the lymph node/tumor biopsy for retrospective confirmation of the diagnosis of mantle cell lymphoma.

The confirmation material submitted for Central Pathology Review must include a biopsy-proven mantle cell lymphoma specimen, including overexpression of cyclin D1 by immunohistochemistry. In patients whose tumors are negative for Cyclin D1 overexpression, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable.

Tumor / lymph node biopsy specimen, which may be archival slides from specimen obtained at the time of initial diagnosis, with representative stained slides supporting the diagnosis of mantle cell lymphoma (H&E or Giemsa staining and Cyclin D1 staining), must be sent as soon as possible to central pathology before randomization but at the latest 8 weeks after randomization. It is highly recommended to submit also the original paraffin block (called tumor block). If the tumor block cannot be sent, 4-5 additional unstained slides must be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

Evidence of the translocation t(11;14)(q13:q32) by FISH should be submitted using the original slide or the corresponding confirming photographies. The translocation t(11;14)(q13:q32) by FISH is optional and is not sufficient as sole proof for diagnosis. If available, it is also recommended to send, , for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD20, CD23, BCL2.

Furthermore, it is highly recommended to perform an unilateral bone marrow biopsy at screening, and to send the tumor block to Central Pathology for review at the latest 8 weeks after randomization.

For further details, please refer to central pathology manual.

Reason for change:

To clarify specimen required to central pathologist for confirmation of MCL diagnosis,

12. The amendment added Appendix 21.8 "Lenalidomide Pregnancy Risk Minimisation Plan (ex-EU territories)". This is noted in the synopsis (Inclusion Criteria), in table 2 (foot note 12) and sections 9.1 / 11.4 / 13.1 of the protocol

Reason for addition:

This appendix includes Lenalidomide Pregnancy Risk Minimisation Plan specific to North America which also applies to newly added Israelian sites.

13. The amendment updated Study Population Inclusion Criteria. This is noted in the synopsis and in the protocol section 9.1.

Current Language:

- Patients with histologically proven mantle cell non-Hodgkin's lymphoma [MCL] {including overexpression of cyclin D1 by immunohistochemistry or t(11;14)(q13;q32) translocation by FISH analysis}. In patients whose tumors are negative for the cyclin D1 overexpression or translocation, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable…
- …Females of childbearing potential (FCBP) must:
  - Have a negative medically supervised pregnancy test prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy (see specifics in Appendices 21.7 and 21.8). This applies even if the patient practices complete and continued sexual abstinence
- …Male patients must:
  - Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy (see specifics in Appendices 21.7 and 21.8)
  - Agree to not donate semen during study drug therapy and for a period after end of study drug therapy (see specifics in Appendices 21.7 and 21.8)
- All patients must:
  - Have an understanding that the study drug could have a potential teratogenic risk.
  - Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy (See specifics in Appendices 21.7 and 21.8)
  - Agree not to share study medication with another person.
  - Agree to be counseled about pregnancy precautions and risks of fetal exposure. See specifics in Appendices21.7 and 21.8)…

Amended Language:

- Patients with histologically proven mantle cell non-Hodgkin's lymphoma [MCL] {including overexpression of cyclin D1 by immunohistochemistry}. In patients whose tumors are negative for the cyclin D1 overexpression or translocation, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable…
- …Females of childbearing potential (FCBP) must:
  - Have **two** negative medically supervised pregnancy **tests** prior to starting of study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy (see specifics in Appendices 21.7 and 21.8). This applies even if the patient practices complete and continued sexual abstinence
  - …Male patients must:
    - Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy (see specifics in Appendices 21.7 and 21.8)
    - Agree to not donate semen **or sperm** during study drug therapy **and for 28 days after end of study drug therapy** (see specifics in Appendices 21.7 and 21.8)
  - All patients must:
    - Have an understanding that the study drug could have a potential teratogenic risk.
    - Agree to abstain from donating blood while taking study drug therapy and **for 28 days after end of study drug therapy** (See specifics in Appendices 21.7 and 21.8)
    - Agree not to share study medication with another person.
- Agree to be counseled about pregnancy precautions and risks of fetal exposure. See specifics in Appendices 21.7 and 21.8)…

Reason for change:

- **FISH analysis becomes optional** and not mandatory, since it is not sufficient as sole proof for MCL diagnosis.

- Consistency between protocol and synopsis to have **2 pregnancy tests** before starting treatment.

- Precision of the 28 days wash out period required for blood, semen or sperm donation to fit with lenalidomide RMP language.

14. The amendment updated Study Population Exclusion Criteria. This is noted in the synopsis and in the protocol section 9.2.

Current

Patients should not be given continuous corticosteroids except prednisone (or equivalent) for the treatment of tumor flare. In addition, prednisone or equivalent up to 10 mg for purposes other than treatment of lymphoma is allowed.

Amended

Patients should not be receiving corticosteroids except for prednisone ≤ 10 mg/day or equivalent for purposes other than treating MCL.

Added Language:

a. Prior radiotherapy within 4 weeks prior to randomization.

b. Any use of experimental drug during 4 weeks prior to randomization.

Reason for addition/change:

Criteria added on possibility to enroll patients who received prior radiotherapy or prior experimental therapy. To clarify permitted concomitant corticotherpay.

15. The amendment updated Investigator's choice therapy. This is noted in the synopsis and in the protocol section 10.1.2.

Current language:

- Chlorambucil
- Rituximab
- Cytarabine
- Gemcitabine
- Fludarabine

Amended language:

Chlorambucil tablets 2 mg:
http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=2474

http://emc.medicines.org.uk/

Rituximab 500 mg vials:
http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=2570

Cytarabine Injection Solution 100 mg/ml:
http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=8266

Gemcitabine 1g vial :
http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=596

Fludarabine 10 mg film-coated tablets :
http://emc.medicines.org.uk/emc/assets/c/html/displayDocPrinterFriendly.asp?documentid=4240

Fludarabine 25mg/ml Concentrate for Solution for Injection or Infusion:
Please refer to the prescribing information provided by Celgene

Added Language:

Paper prints will be provided in the Investigator's and Pharmacy binders.

Reason for addition/change:

To provide Investigators/Pharmacists with websites links of 5 drugs of Arm B, and paper copies of SPC.

16. The amendment updated Table 2 and Table 3 (Schedule of Assessments)

Current language:

Table 2: Schedule of Study Assessments

Procedure	Screening/ Baseline (-28 Days)	Cycle 1 Day 1, 2, 4, 8, 15	Every Cycle Day 1 ± 3 days	Cycles 2-4 Day 15	Every 56 days After Cycle 1 Day 1 ± 7 days for the first 6 months and then every 90 days	At Treatment Discontinuation	Follow-up for patients after PD[21]	Follow-up for non-PD patients[22]
Inclusion/exclusion criteria	X							
Complete medical history	X							
CNS Lymphoma Evaluation[1]	X							
MCL International Prognostic Index (MIPI)[2]	X							
Prior lymphoma therapy	X							
Creatinine Clearance (Cockcroft-Gault estimation)[3]	X							
Coagulation Tests[4]	X							
12-Lead ECG[5]	X							
Lymph node or tumor biopsy specimen slides[6]	X							
Eastern Cooperative Oncology Group (ECOG) performance status	X		X			X		
Vital Signs[7]	X		X			X		
CBC with Differential[8]	X	X[10]	X	X		X		
Serum Chemistry[9]	X	X[10]	X	X		X		
Thyroid function test[18]	X							
Pregnancy Testing (FBCP only)	X[11]		X[12]			X[12]	X[12]	X[12]
Birth control / Lenalidomide Counseling[13]	X					X[13]	X[14]	X[14]
Distribute Lenalidomide Counseling Sheet[13]	X		X[13]			X[14]		
Assessment of Lymphoma-related Symptoms	X		X			X		
Adverse Events	X	X	X	X		X	X[15]	X[15]
Record Hospitalizations			X			X		
Tumor Flare / Tumor lysis Assessment		X[16]						
Concomitant medications/Procedures	X	X	X			X		
Physical examination[17]	X		X			X	X	X

CT/MRI of neck, chest, abdomen and pelvis[19]	X[28]				X[19]			X[19]
Target and non-target lesion measurements[19]	X				X[19]			
Response assessment					X[19]			
Progression-Free Survival[20]					X[19]		X	X
Overall survival							X[21]	X[22]
Quality of Life	X[23]			X[23]		X[23]		
Bone Marrow Aspirate and Biopsy[24]					X[24]			
Dispense study drug[25]			X					
Study drug return			X			X		

[1]Patients with a history of CNS involvement or CNS symptoms will be required to have negative CSF cytology examination, and a head CT/brain MRI during the screening/baseline period.

[2]MIPI: age, performance status, LDH, absolute leukocyte count, at time of diagnosis, if available.

[3]Cockcroft-Gault estimation of creatinine clearance (CrCl): CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]); for females, the formula is multiplied by 0.85. Creatinine clearance should be determined utilizing actual body weight or ideal body weight, which ever is less (Cockcroft, 1976, Luke, 1990).

[4]Coagulation Tests include: Prothrombin Time (PT), Partial Prothrombin Time (PTT), APC resistance, von Willebrand Factor.

[5] 12-Lead ECG is performed at baseline and as clinically indicated thereafter.

[6] Diagnosis of mantle cell lymphoma by local pathological review must be completed prior to randomization. The confirmation must include a biopsy-proven mantle cell lymphoma, including overexpression of cyclin D1 by immunohistochemistry or t(11;14)(q13:q32) by FISH. In patients whose tumors are negative for the cyclin D1 gene translocation, evidence of overexpression of cyclin D2 or D3 by immunohistochemistry will be acceptable. Tumor / lymph node biopsy slides, which may be archival slides from specimen obtained at the time of initial diagnosis, with representative stained slides supporting the diagnosis of MCL (Cyclin D1 staining or FISH slide), must be submitted to central pathology before randomization for confirmation of mantle cell lymphoma. In parallel, 4-5 unstained slides must also be submitted. If such slides are not available for submission, then a re-biopsy is required.

[7]Vital signs include weight, height (only at screening), blood pressure, temperature, and pulse.

[8]Complete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, MCV, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.

[9]Serum chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, sodium, potassium, chloride, blood urea nitrogen, creatinine and LDH).

[10]If screening/baseline assessment hematology, and chemistry labs are performed within 7 days before Cycle 1, Day 1, they do not need to be repeated on Cycle 1, Day 1.

[11] Before starting study drug: Females of Childbearing Potential (FCBP) must confirm that she is using reliable methods of birth control, and must have two negative pregnancy tests prior to starting study drug: The first pregnancy test must be performed within 10-14 days prior to the start of study drug, and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative. All patients will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. (See specifics as described in Appendix 21.7 and 21.8).

[12]During the study participation and for 28 days following discontinuation from the study: FCBP must agree to have pregnancy tests (See specifics as described in Appendix 21.7 and 21.8). In addition to the required pregnancy testing, the investigator

must confirm with FCBP that she is continuing to use reliable methods of birth control at each visit (See specifics as described in Appendix 21.7 and 21.8).

[13]All patients must be counseled about pregnancy precautions and risks of fetal exposure.

[14]After 28 days post-last dose of lenalidomide.

[15]Adverse events will be assessed 28 days post-last dose of treatment during follow-up.

[16]Tumor flare / tumor lysis syndrome assessment at **Cycle 1: Day 2, 4, 8, and 15**, and when clinically indicated thereafter.

[17]Physical examination including lymphadenopathy, hepatomegaly, and splenomegaly as clinically indicated. Physical examination on study should be done at baseline, Cycle 1 D1 and D15 and then Day 1 of every Cycle.

[18]Thyroid function tests (TSH, fT3, fT4) are performed at baseline/screening only and as clinically indicated.

[19]CT with contrast/MRI must be performed every 56 days (± 7 days) up to 6 months from the start of study drug then every 90 ±15 days thereafter. during the follow up phase for patients who have discontinued study due to adverse events without evidence of progressive disease. CT scan/MRI does not need to be performed during follow-up for patients who discontinued due to disease progression or relapse.

[20]Progression Free Survival is assessed until progression of disease or until next lymphoma treatment is given, whichever comes first. Patients in the investigators choice Arm B have the option to receive lenalidomide at time of documented disease progression.

[21]Patients will be followed (clinic visit or documented telephone contact) for overall survival every 90 days (± 15 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

[22]Patients will be followed (clinic visit or documented telephone contact) for overall survival every 56 days (± 7 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

[23]QoL will be assessed at screening/baseline after Cycle 2 (C3D1) and after Cycle 4 [C5D1] (±7 days), and at treatment discontinuation (±7 days).

[24]Bone marrow aspirate and unilateral biopsy during treatment is required only if the patient has otherwise fulfilled the criteria for CR. The bone marrow procedure should be performed 28 days after the criteria for CR have otherwise been met.

[25] Dispense study drug on Day 1 only.

[28] If a CT scan or MRI was done within 14 days of the first dose of study medication, then the CT scan or MRI does not have to be repeated for the screening assessment.

Table 3: Schedule of study assessments for patients with cross-over on lenalidomide after progression in investigator's choice Arm B

Procedure	Cycle 1 Day 1, 2, 4, 8, 15	Every Cycle Day 1 ± 3 days	Cycles 2- 4 Day 15	Every 90 days After Cycle 1 Day 1	At Treatment Discontinuation	Follow-up for patients after PD[11]	Follow-up for non-PD[12]
Eastern Cooperative Oncology Group (ECOG) performance status		X			X		
Vital Signs[1]		X			X		
CBC with differential[2]	X	X	X		X		
Serum Chemistry[3]	X	X	X		X		
Pregnancy Testing for FCBP[4]		X			X		
Birth control / Lenalidomide Counseling [5]		X					
Distribute Lenalidomide counseling sheet[5]		X	X				
Adverse Events[6]	X	X	X		X		X[6]
Tumor Flare /Tumor Lysis Assessment[7]	X						
Record Hospitalizations		X			X		
Concomitant medications/ Procedures	X	X	X		X		
CT/MRI of neck, chest, abdomen and pelvis				X			X[8]
Target and non-target lesion measurements				X			
Response assessment				X			
Progression-Free Survival[9]				X		X	X
Overall survival						X[10]	X[11]

[1]Vital signs include weight, blood pressure, temperature, and pulse.
[2] Complete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, MCV, white blood cell WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.
[3]Serum chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), sodium, potassium, chloride, blood urea nitrogen, creatinine and lactate dehydrogenase).
[4] During the study participation and for 28 days following discontinuation from the study: FCBP must agree to have pregnancy tests (See specifics as described in Appendix 21.7 and 21.8) In addition to the required pregnancy testing, the investigator must confirm with FCBP that she is continuing to use reliable methods of birth control at each visit (See specifics as described in Appendix 21.7 and 21.8).
[5]All patients must be counseled about pregnancy precautions and risks of fetal exposure.
[6]Adverse events will be assessed 30 days post-last dose during follow-up.
[7]Tumor flare/Tumor lysis assessment at Cycle 1: Day 2, 4, 8, and 15, and when clinically indicated.

[8]CT with contrast/ or MRI is recommended 90 days (± 15 days) during the follow up phase for patients who have discontinued treatment due to adverse events without evidence of progressive disease. CT scan/MRI does not need to be performed during follow-up for patients who discontinued due to disease progression or relapse.

[9]Progression Free Survival is assessed until progression of disease or until next lymphoma treatment is given, whichever comes first.

[10]Patients will be followed (clinic visit or documented telephone contact) for overall survival every 90 days (± 15 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

[11]Patients will be followed (clinic visit and CT scan/MRI) for overall survival every 90 days (± 15 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

Amended language (highlighted in yellow):

Table 2: Schedule of Study Assessments (28 days = 1 cycle)

Procedure	Screening/ Baseline (-28days)	Every Cycle Day 1 ± 3 days	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2-4 Day 15	Every 56 days After Cycle 1 Day 1 ± 7 days for the first 6 months and	At Treatment Discontinuation	Follow-up for patients after PD[20]	Follow-up for non-PD patients[21]
Inclusion/exclusion criteria	X							
Complete medical history	X							
CNS Lymphoma Evaluation[1]	X							
MCL International Prognostic Index (MIPI)[2]	X							
Prior lymphoma therapy	X							
Creatinine Clearance (Cockcroft-Gault estimation)[3]	X							
12-Lead ECG[4]	X							
Lymph node or tumor biopsy specimen slides[5]	X							
Eastern Cooperative Oncology Group (ECOG) performance status	X	X				X		
Vital Signs[6]	X	X				X		
CBC with Differential[7]	X	X	X[9]	X		X		
Serum Chemistry[8]	X	X	X[9]	X		X		
Thyroid function test[17]	X							
Pregnancy Testing (FBCP only)	X[10]	X[11]				X[11]	X[11]	X[11]
Lenalidomide Counseling and distribute lenalidomide Information Sheet[12]	X	X					X[13]	X[13]
Assessment of Lymphoma-related Symptoms	X	X				X		
Adverse Events	X	X	X	X		X	X[14]	X[14]
Record Hospitalizations		X				X		
Tumor Flare / Tumor lysis Assessment[15]			X[15]					

Procedure	Screening/ Baseline (-28days)	Every Cycle Day 1 ± 3 days	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2-4 Day 15	Every 56 days After Cycle 1 Day 1 ± 7 days for the first 6 months and	At Treatment Discontinuation	Follow-up for patients after PD[20]	Follow-up for non - PD patients[21]
Concomitant medications/Procedures	X	X	X			X		
Physical examination[16]	X	X				X	X	X
CT/MRI of neck, chest, abdomen and pelvis[18]	X[27]				X[18]			X[18]
Target and non-target lesion measurements[18]	X				X[18]			
Response assessment					X[18]			
Progression-Free Survival[19]					X[18]		X	X
Overall survival							X[20]	X[21]
Quality of Life	X[22]	X[22]				X[22]		
Bone Marrow Biopsy	X[23a]				X[23b]			
Dispense study drug[25]		X[24]						
Study drug return		X				X		

[1]Patients with a history of CNS involvement or CNS symptoms will be required to have negative CSF cytology examination, and a head CT/brain MRI during the screening/baseline period.

[2]MIPI: age, performance status, LDH, absolute leukocyte count, at time of diagnosis, if available.

[3]Cockcroft-Gault estimation of creatinine clearance (CrCl): CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]); for females, the formula is multiplied by 0.85. Creatinine clearance should be determined utilizing actual body weight or ideal body weight, which ever is less (Cockcroft, 1976, Luke, 1990).

[4] 12-Lead ECG is performed at baseline and as clinically indicated thereafter.

[5] Representative slides documenting (H&E or Giemsa staining) and supporting the diagnosis of MCL (Cyclin D1 immunostaining), shall be sent together with the tumor block to central pathology as soon as possible, preferably before randomization for confirmation of mantle cell lymphoma, but at the latest 8 weeks after randomization. In patients whose tumor is negative for Cyclin D1, evidence of overexpression of Cyclin D2 or D3 is acceptable. Additionally, slides supporting the translocation by FISH or corresponding confirming photographies shall be submitted at the same time, if available. It is also recommended to send for central pathology review, slides containing immunostaining for CD3, CD5, CD 10, CD20, CD23, BCL2. In case the tumor block can not be sent, 4-5 additional, unstained slides must also be submitted. If such archival tissue is not available for submission, then a re-biopsy is required.

[6]Vital signs include weight, height (only at screening), blood pressure, temperature, and pulse.

[7]Complete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, MCV, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.

[8]Serum chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, sodium, potassium, blood urea nitrogen, creatinine and LDH).

[9]If screening/baseline assessment hematology, and chemistry labs are performed within 7 days before Cycle 1, Day 1, they do not need to be repeated on Cycle 1, Day 1.

[10] Before starting study drug: Females of Childbearing Potential (FCBP) must confirm that she is using reliable methods of birth control, and must have two negative pregnancy tests prior to starting study drug: The first pregnancy test must be performed within 10-14 days prior to the start of study drug, and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative. All patients will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. (See specifics as described in Appendices 21.7 and 21.8).

[11]During the study participation and for 28 days following discontinuation from the study: FCBP must agree to have two pregnancy tests (See specifics as described in Appendices 21.7 and 21.8). In addition to the required pregnancy testing, the investigator must confirm with FCBP that she is continuing to use reliable methods of birth control at each visit (See specifics as described in Appendices 21.7 and 21.8).

[12]All patients must be counseled about pregnancy precautions and risks of fetal exposure.

[13]After 28 days post-last dose of lenalidomide.

[14]Adverse events will be assessed 28 days post-last dose of treatment during follow-up.

[15]Tumor flare / tumor lysis syndrome assessment, only for patients in Arm A, at **Cycle 1: Day 2, 4, 8, and 15**, and when clinically indicated thereafter.

[16]Physical examination including lymphadenopathy, hepatomegaly, and splenomegaly as clinically indicated. Physical examination on study should be done at baseline, Cycle 1 D1 and D15 and then Day 1 of every Cycle.

[17]Thyroid function tests (TSH, fT3, fT4) are performed at baseline/screening only and as clinically indicated.

[18]CT with contrast/MRI must be performed every 56 days (± 7 days) up to 6 months from the start of study drug then every 90 ±15 days thereafter. during the follow up phase for patients who have discontinued study due to adverse events without evidence of progressive disease. CT scan/MRI does not need to be performed during follow-up for patients who discontinued due to disease progression or relapse.

[19]Progression Free Survival is assessed until progression of disease or until next lymphoma treatment is given, whichever comes first. Patients in the investigators choice Arm B have the option to receive lenalidomide at time of documented disease progression.

[20]Patients will be followed (clinic visit or documented telephone contact) for overall survival every 90 days (± 15 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

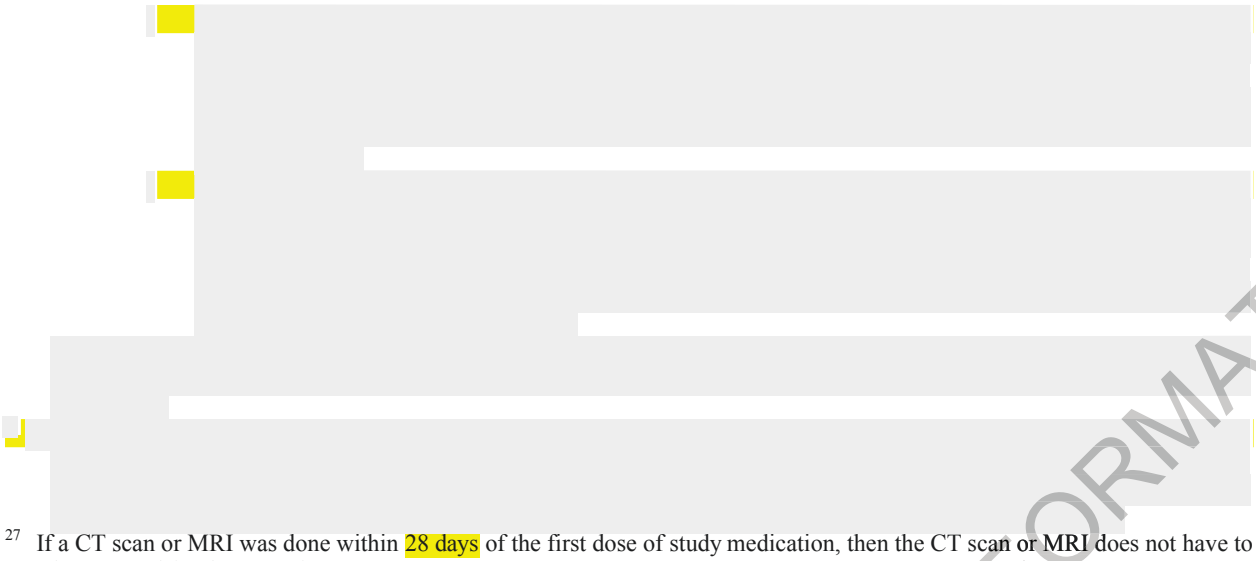
[21]Patients will be followed (clinic visit or documented telephone contact) for overall survival every 56 days (± 7 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

[22]QoL will be assessed at screening/baseline after Cycle 2 [C3D1] (±7 days), after Cycle 4 [C5D1] (±7 days), after Cycle 6 [C7D1] (±7 days), after Cycle 8 [C9D1] (±7 days), and at treatment discontinuation (±7 days).

[23a] Unilateral bone marrow biopsy is highly recommended at screening that will be submitted to Central Pathology for review at the latest within 8 weeks after randomization.

[23b] Unilateral bone marrow biopsy during treatment is required only if the patient has otherwise fulfilled the criteria for CR. The bone marrow procedure should be performed 28 days after the criteria for CR have otherwise been met.

[24] Dispense study drug on Day 1 only. Cycle 1 should start as soon as possible after randomization, but maximum time between randomization and C1 D1 is 4 days, once the patient has fulfilled the requirements of the Lenalidomide pregnancy prevention program.



[27] If a CT scan or MRI was done within 28 days of the first dose of study medication, then the CT scan or MRI does not have to be repeated for the screening assessment.

Table 3: Schedule of study assessments for patients with cross-over on lenalidomide after progression in investigator's choice Arm B (28 days = 1 cycle) – No more than 10 weeks after last day of last cycle of treatment in Arm B

Procedure	Every Cycle Day 1 ± 3 days	Cycle 1 Day 1, 2, 4, 8, 15	Cycles 2- 4 Day 15	Every 90 days After Cycle 1 Day 1	At Treatment Discontinuation	Follow-up for patients after PD[10]	Follow-up for non-PD[11]
Eastern Cooperative Oncology Group (ECOG) performance status	X				X		
Vital Signs[1]	X				X		
CBC with differential[2]	X	X	X		X		
Serum Chemistry[3]	X	X	X		X		
Pregnancy Testing for FCBP[4]	X				X		
Birth control / Lenalidomide Counseling [5]	X						
Distribute Lenalidomide counseling sheet[5]	X		X				
Adverse Events[6]	X	X	X		X		X[6]
Tumor Flare /Tumor Lysis Assessment[7]		X					
Record Hospitalizations	X				X		
Concomitant medications/ Procedures	X	X	X		X		
CT/MRI of neck, chest, abdomen and pelvis				X			X[8]
Target and non-target lesion measurements				X			
Response assessment				X			
Progression-Free Survival[9]				X		X	X
Overall survival						X[10]	X[11]

[1]Vital signs include weight, blood pressure, temperature, and pulse.
[2] Complete blood cell count (CBC) will include red blood cell count (RBC), hemoglobin, hematocrit, MCV, white blood cell WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count.
[3]Serum chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), sodium, potassium, blood urea nitrogen, creatinine and lactate dehydrogenase).
[4] During the study participation and for 28 days following discontinuation from the study: FCBP must agree to have pregnancy tests (See specifics as described in Appendices 21.7 and 21.8) In addition to the required pregnancy testing, the investigator

must confirm with FCBP that she is continuing to use reliable methods of birth control at each visit (See specifics as described in Appendices 21.7 and 21.8).

[5]All patients must be counseled about pregnancy precautions and risks of fetal exposure.

[6]Adverse events will be assessed 30 days post-last dose during follow-up.

[7]Tumor flare/Tumor lysis assessment at Cycle 1: Day 2, 4, 8, and 15, and when clinically indicated.

[8]CT with contrast/ or MRI is recommended 90 days (± 15 days) during the follow up phase for patients who have discontinued treatment due to adverse events without evidence of progressive disease. CT scan/MRI does not need to be performed during follow-up for patients who discontinued due to disease progression or relapse.

[9]Progression Free Survival is assessed until progression of disease or until next lymphoma treatment is given, whichever comes first.

[10]Patients will be followed (clinic visit or documented telephone contact) for overall survival every 90 days (± 15 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

[11]Patients will be followed (clinic visit and CT scan/MRI) for overall survival every 90 days (± 15 days) until death or either 70% of the patients have died or the median follow-up in responding patients is > 2 years or the median duration of response (overall response and CR/CRu) has been reached, which ever comes later, at which time the study will be terminated.

Reason for addition/change:

Major changes are the reflect of changes described in the present amendment (synospsis and protocol body). Coagulation tests and chloride tests have been suppressed since there is no central laboratory for biology, comparability of results from a laboratory to another would be difficult.

17. The amendment updated Table 4 of the protocol

Deletion of FFPE abbreviation

Addition of FL abbreviation for Follicular Lymphoma

18. The amendment updated section 5.2.1 of the protocol

Added language:

Furthermore, recent preclinical studies suggest that lenalidomide may promote restoration of anti-tumor immunological effects in patients with certain hematological malignancies. It was reported that patients with CLL have a dysfunction of their T cells (Ramsay et al, 2008). When the dysfunction was studied using an in vitro system, in which the restoration of the immunologic synapse was taken as the functional assay, treatment of both the patient's T cells and the CLL cells was required for synapse formation. It was also reported that the impaired T cell immunological synapse formation was seen in both CD4 and CD8 Tcells from follicular lymphoma (FL) patients compared to age-matched healthy donors (Ramsay et al, 2008). This defect was induced by tumor contact since T cell defects were induced in healthy T cells when they were co-cultured for 48 hr with allogeneic FL cells, but not with healthy allogeneic B cells. In co-culture with FL cells, previously healthy T cells showed suppressed recruitment of integrin LFA-1, Lck, Itk, Rab27A and filamin-A to the synapse in subsequent T cell: APC interactions. It was further demonstrated that the immune synapse defects were repaired in part by treatment of the cells with the immunomodulatory drug lenalidomide. Treatment of both FL B cells and autologous T cells with lenalidomide (1 μM for 24h) was required to enhance formation of the F-actin synapse and recruitment of tyrosine-phosphorylated protein and filamin-A irrespective of the presence of exogenous antigen.

Additionally, it was described that lenalidomide up-regulated the expression of genes involved in the immune response, such as co-stimulatory and antigen-presenting molecules (Gaidarova et al, 2008). Furthermore, lenalidomide treatment induced actin cytoskeleton reorganization and polarization of MCL cells as early as 30 min, prior to a detectable increase of CD1c expression and could be responsible for re-localization of CD1c protein to polarized sites at the plasma membrane. Lenalidomide had similar effects on γδ T cells, inducing actin cytoskeleton dynamics and polarization within minutes in these cells. Lenalidomide enhanced the number of γδT-MCL immune synapses and the lytic activity of γδT cells against the tumor cells.

These laboratory observations of direct lenalidomide effects on tumor cells, in inducing the expression of potential tumor suppressor genes and proteins potentially involved in tumor cell recognition by T cells, as well as cellular lenalidomide effects on the host immune cells potentially to improve tumor cell recognition, serve as the scientific basis for the clinical approach described in the clinical trial protocol.

Reason for addition:

Update on new preclinical data.

19. The amendment updated section 5.2.2 of the protocol

Current language:

Lenalidomide is an immunomodulatory agent with potent immuno-stimulatory, anti-angiogenic and pro-apoptotic activities in vitro. In addition, a related immunomodulatory agent, thalidomide, has been reported to have activity in mantle cell lymphoma when used as monotherapy and in combination with rituximab (Damaj, 2003; Kaufmann, 2004). In a recent study (study CC-5013-NHL-002) of lenalidomide monotherapy (25 mg p.o. once daily on days 1-21 of each 28-day cycle) in patients with relapsed aggressive NHL, 15 of 49 patients had MCL (Wiernik, 2007). Lenalidomide therapy led to 1 complete response (CR), 1 complete response unconfirmed (CRu) and 6 partial responses (PR) in these patients with MCL (Tuscano, 2007). Four of 5 patients with a prior stem cell transplant, and two of five patients who received prior bortezomib responded. In this study, the most common grade 4 adverse events were neutropenia (13%) and thrombocytopenia (13%). In another ongoing study of lenalidomide monotherapy (25 mg p.o. once daily on Days 1-21 of each 28-day cycle) in patients with relapsed or refractory NHL (CC-5013-NHL-003), 22 out of 89 patients had MCL (Czuczman, 2008). Lenalidomide therapy led to an objective response rate of 36% in these patients with MCL. In 2 phase II clinical studies (NHL-002 and NHL-003), the most common grade 3/4 AEs were neutropenia (21%) and thrombocytopenia (15%) (Habermann, 2008). Based on these preliminary observations, the current study is being conducted to evaluate the efficacy and safety of lenalidomide in patients with mantle cell lymphoma.

Amended language:

Three phase 2 studies of single-agent lenalidomide have been conducted in patients with relapsed/refractory NHL (CC-5013-NHL-001 in indolent NHL and CC-5013-NHL-002 and NHL-003 in aggressive NHL). The dose/regimen used in these studies was 25 mg p.o. once daily for 21 days (D1 – D21) in 28 day cycle, of either 52 weeks (NHL-001 or NHL-002) or until disease progression (NHL-003). Patients with mantle cell lymphoma were included in NHL-002 and NHL-003.

In the two phase 2 clinical studies that include aggressive histologies (including MCL, DLBCL, transformed and FL grade 3), the overall response rate (ORR) was 35% in NHL-002 and 36% in NHL-003, respectively (Wiernik, 2008). In NHL002, fifteen of 49 patients had MCL with a median duration of

disease of 5.1 years and a median of 4 prior treatments before enrollment In these MCL patients an ORR of 53% was demonstrated. Three patients (20%) had a CR or unconfirmed CR, and 5 patients (33%) had a PR. The median duration of response was 13.7 months and median PFS was 5.6 months. The most common grade 4 adverse event was thrombocytopenia (13%) and the most common grade 3 adverse events were neutropenia (40%), leucopenia (27%), and thrombocytopenia (20%). (Habermann, 2009). In the second study (NHL-003) which was initiated in November 2006, 53 of 218 patients enrolled had MCL. As of March 1, 2008, 39 MCL patients were evaluable for response assessment (Zinzani, 2008). The median age was 66 (33–82) years. The median time from diagnosis to start of lenalidomide treatment was 3.4 (0.4–9) years. These patients had received a median of 3 (1–8) prior treatments, and 23% (9/39) of patients had received prior bortezomib treatment. The ORR to lenalidomide was 41% (16/39), including 13% (5/39) complete responses (CR/unconfirmed CR), and 28% (11/39) partial responses. Ten (26%) patients had stable disease. The most common grade 3 or 4 adverse events were neutropenia (51%) and thrombocytopenia (25%), anemia (13%), fatigue (10%) and febrile neutropenia (10%) (Zinzani, 2008).

Reason for change:

Update on new data available

20. The amendment updated section 5.2.3 of the protocol

Deleted language:

MM-009 was conducted in North America and MM-010 was conducted in Europe, Israel, and Australia. In each study patients were randomized to receive lenalidomide and dexamethasone or placebo plus dexamethasone until the development of disease progression. Lenalidomide 25 mg or placebo once daily was given on days 1-21 of each 28-day cycle. Dexamethasone 40 mg/day was administered on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles and then on days 1-4 of each 28-day cycle thereafter.

Reason for addition:

Update on new data available.

21. The amendment updated section 5.2.4 of the protocol

Current language:

Lenalidomide has been investigated in patients with MDS in three Phase 2 studies. Results from all three studies indicate that lenalidomide is a safe and effective treatment for patients with low- or intermediate-1-risk MDS as well as in MDS with an associated del 5 (q31-33) cytogenetic abnormality. Results from the CC-5013-MDS-003 study, in MDS with an associated del 5 (q31-33) cytogenetic abnormality, showed transfusion independence in 67 % of the patients. Median duration from the date when red blood cell (RBC) transfusion independence was first declared (the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among responders was 44 weeks. Cytogenetic response was achieved in approximately 75 % of patients with complete cytogenetic response noted in more than 50 % of the cytogenetic responders. Grade 3/4 neutropenia and thrombocytopenia are the most common AEs associated with the use of lenalidomide, but are manageable with dose reductions and/or interruptions (List, 2006).

Amended language:

Lenalidomide has been investigated in patients with MDS in three phase 2 studies for the treatment of patients with transfusion-dependent anemia due to Low-or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. In MDS, lenalidomide was studied at the dose/regimen of 10 mg daily (CC-5013-MDS-002/CC-5013-MDS-003) until disease progression. Results from the CC-5013-MDS-003 study, in MDS with an associated del 5 (q31-33) cytogenetic abnormality, showed transfusion independence in 67 % of the patients. Median duration from the date when red blood cell (RBC) transfusion independence was first declared (the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among responders was 44 weeks. Cytogenetic response was achieved in approximately 75 % of patients. Grade 3/4 neutropenia and thrombocytopenia are the most common AEs associated with the use of lenalidomide, but are manageable with dose reductions and/or interruptions (List, 2006).

Reason for addition:

Update on new data available.

22. The amendment added a new section 5.2.5

5.2.5 Clinical Studies of Lenalidomide in Chronic Lymphocytic Leukemia

Lenalidomide monotherapy has been investigated in two investigator initiated trials (IIT) in patients with relapsed/refractory CLL (Chanan-Khan, 2006) (Chanan-Khan, 2007), (Ferrajoli, 2008). In one study patients with relapsed/refractory CLL were treated with lenalidomide at 25mg x 21 d q 28 days (Chanan-Khan, 2006) (Chanan-Khan, 2007). Results from this study showed an overall response rate of 53% with 18% of patients achieving a CR and 36% achieving a PR. The median PFS time is 19.4 months (1.2 – 38+ months). Fatigue (83%) and flare reaction (tender swelling of lymph nodes and/or rash) (58%) were the most common non-hematologic AEs reported. Other important AEs reported were tumor lysis syndrome (5%); Grade 3 and 4 thrombocytopenia (45%), and Grade 3 and 4 neutropenia (70%). Pulmonary embolism was reported in two patients (5%). In the second IIT study (Ferrajoli, 2008), continuous dosing of lenalidomide was investigated in patients with relapsed/refractory CLL. Lenalidomide was administered daily for 28 days of 28-day cycles until disease progression. An overall response rate of 32% was observed with 3 CR (7%), 1 nodular PR (2%), 10 PR (23%). Myelosuppression was the most common toxicity observed, 41% ≧ Grade 3 neutropenia and 16% Grade 3 thrombocytopenia.

23. The amendment updated section 10.1 of the protocol

Added language:

The duration of a treatment cycle will be 28 days. The first dose of lenalidomide in cycle 1 defines day 1 of the treatment cycle, and each cycle thereafter will begin 29 days later.

The 28-day cycle length should be maintained throughout the entire treatment phase regardless of the dose interruptions and/or dose reductions.

Reason for addition:

Clarification of cycle duration (28 days) regardless of the dose interruptions and/or dose reductions.

24. The amendment updated foot notes of table 5 noted in 10.1.2 of the protocol

Current language

Refer to the approved Summary of Product Characteristics (SPC), provided by Celgene, for the investigator's choice therapy for complete prescribing information including administration, warnings, precautions, contraindications, and adverse reactions and follow institutional procedures for the administration of the agents, where applicable.

Rituximab (single agent) is to be repeated every 56 days after Day 56 (given only on day 1 of every 56 days cycle).

Added language

Refer to the approved Summary of Product Characteristics (SPC), provided by Celgene **or reference links provided above in section 10.1.2.,** for the investigator's choice therapy for complete prescribing information including administration, warnings, precautions, contraindications, and adverse reactions and follow institutional procedures for the administration of the agents, where applicable.

Rituximab (single agent) is to be repeated every 56 days after Day 56 (given only on day 1 of every 56 days cycle). **For the prevention of cytokine release syndrome associated with the treatment of Rituximab ≥ 125mg of methylprednisolone or equivalent are accepted on C1D1**

Reason for change

To define permitted concomitant corticotherapy for patients receiving Rituximab.

25. The amendment updated table 6 noted in section 10.1.3 of the protocol

Added language:

NCI CTCAE Toxicity Grade	**Action Required**
Newly developed ≥ Grade 3 peripheral neuropathy **(this applies only to those toxicities which begin or worsen while on study)**	• Hold (interrupt) dose • When the toxicity resolves to ≤ Grade 2 restart at next lower dose level

(Alanine Transaminase) ALT > 5 x ULN	Exclude from study, unless the patient has documented liver metastases	N/A
ALT > 3 and ≤ 5x ULN and Total bilirubin ≤ 1.5 x ULN	Continue dosing; test at next scheduled visit	N/A
ALT > 3 and ≤ 5 x ULN and Total bilirubin > 1.5 x ULN	Hold lenalidomide dosing; re-test weekly until ALT and total bilirubin return to baseline	Resume the same dose of lenalidomide if recovery from the event is ≤ 14 days. If recovery is prolonged beyond 14 days, then the lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. If the values do not return to baseline within 28 days, the medical monitor must be notified.
ALT > 5 x ULN or Total bilirubin > 1.5 x ULN	Hold lenalidomide dosing; re-test weekly until ALT and total bilirubin return to baseline	Resume the same dose of lenalidomide if recovery from the event is ≤ 14 days. If recovery is prolonged beyond 14 days, then the lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. If the values do not return to baseline within 28 days, the medical monitor must be notified.

Added language after table 6

If a patient experiences an AE that requires a dose interruption, the patient can not be re-started on study medication until the AE has resolved or reached acceptable grade described in table 6. Once the AE has resolved, the patient may continue back on lenalidomide (at the dose level required in Table 6, and refer to tables 7 and 8 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 a cycle is delayed due to an AE the patient can re-start lenalidomide within a next cycle once a 7-day rest period has occurred and the requirements mentioned below have been met.

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

Reason for addition:

To consider lenalidomide dose adjustment in case of neurological and liver toxicities.

To clarify lenalidomide dose adjustment/interruption from a cycle to another, in case of AE.

26. The amendment updated section 10.1.7 of the protocol

Added language:

Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically, but may be prescribed by the investigator for rescue from severe hematologic events, if it is thought to be appropriate. They should be used in accordance with the American Society of Clinical Oncology's (ASCO) and European Society for Medical Oncology (ESMO) guidelines, and recorded on concomitant medications CRF page.

Reason for addition:

In case of hematologic events, to precise use of growth factors authorization within the study.

27. The amendment updated section 10.1.8 of the protocol

Current language:

Doses beyond 10 mg per day are not allowed during the study or during the 28-day screening period except for the treatment of tumor flare…

Amended language:

Doses beyond 10 mg per day are not allowed during the study or during the 28-day screening period except for the treatment of tumor flare **and for the prevention of cytokine release syndrome associated with the treatment of Rituximab on C1D1**…

Reason for change:

To define permitted concomitant corticotherapy for patients receiving Rituximab.

28. The amendment updated section 12.2 of the protocol

Current language:

Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and unilateral biopsy during treatment is required only if patients has otherwise fulfilled the criteria for CR. The bone marrow procedure should be performed 28 days after the criteria for CR have otherwise been met.

Amended language:

Bone Marrow Biopsy

Unilateral bone marrow biopsy during treatment is required only if patients has otherwise fulfilled the criteria for CR. The bone marrow procedure should be performed 28 days after the criteria for CR have otherwise been met.

Reason for change:

Bone marrow aspirate has been deleted to assess CR only on tumor biopsy, because the aspirate will be of little added value.

34. The amendment updated section 15.2.2 of the protocol – Quality of Life time points / Data collection and timing

Current language:

Quality of life will be assessed at 3 time points (refer to Table 2:):

- at screening/baseline (within 7 days prior to randomization),
- after cycle 2 (C3D1)
- after cycle 4 (C5D1),
- and at time of discontinuation from treatment

A ± 7 days time window will be allowed.

Amended language:

Questionnaires must be filled out by the patient at 7 pre-specified time points (see below and Table) when the patient comes for a scheduled visit. They will be handed out by a nurse or the treating physician/investigator, and ideally are collected again soon after the patient has filled it out.

Patients will be asked to complete the questionnaire as completely and accurate as possible. The average time to complete the questionnaire is around 10-15 minutes. The reasons for not completing the questionnaire will be recorded

Quality of life will be assessed at 7 time points (refer to Table 2:)

- at screening/baseline (within 7 days prior to randomization),
- after cycle 2 (C3D1)
- after cycle 4 (C5D1),
- after cycle 6 (C7D1),
- after cycle 8 (C9D1),
- and at time of discontinuation from treatment

A ± 7 days time window will be allowed.

Reason for change:

To allow further assessment of Quality of Life.

35. The amendment updated section 20 of the protocol

Current language

Habermann TM, Izidore S, et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma..*J Clin Oncol* 23, 5347-5356, Jan 21. 2009.

Amended language

Habermann TM, Lossos IS, Justice G, Vose JM, Wiernik PH, McBride K, Wride K, Ervin-Haynes A, Takeshita K, Pietronigro D, Zeldis JB, Tuscano JM. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma.Br J Haematol. Feb 2009, (Epub ahead of print).

Deleted language

Tuscano JM, Lossos IS, Justice G, et al. Lenalidomide Oral Monotherapy Produces a 53% Response Rate in Patients with Relapsed/Refractory Mantle-Cell Non-Hodgkin's Lymphoma. *Blood* (ASH Annual Meeting Abstracts), Nov 2007; 110: 2563

Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide Response in Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma is related to Tumor Burden and Time from Rituximab Treatment.*Blood (Ash Annual Meeting Abstracts)*. Nov 2007; 110:2565

Added language

Zinzani PL, Witzig TE, Vose JM, et al. Efficay and Safety of Lenalidomide Oral Montherapy in patients with Relapsed or Refractory mantle-Cell Lymphoma: Results of an international Study . *Blood* (ASH Annual Meeting Abstract); Nov. 2008; 112: 262.

Reason for change

Literature update

36. The amendment update appendix 21.5 for assessment of progressive disease

Current language

Progressive disease (PD) in PR patients or nonresponders

• Appearance of any new lesion, with GD > 10mm if nodes, during or at the end of therapy

Amended language

• Appearance of any new lesion, with **GD > 15mm** if nodes, during or at the end of therapy

Reason for change

The large diameter of new lesion has been increase for a better discrimination of the new lesion.