Bendamustine and Rituximab Induction Therapy and Maintenance Rituximab and Lenalidomide in Previously Untreated CLL/SLL

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PI: Julie Chang, MD
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Phase II Study of Bendamustine and Rituximab Induction Chemoimmunotherapy Followed by Maintenance Rituximab (Rituxan®) and Lenalidomide (Revlimid®) in Previously Untreated Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

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INVESTIGATOR SIGNATURE PAGE

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The signature below confirms that I have read this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Name: _____

Investigator Signature: _____ Date: _____

STUDY PERSONNEL

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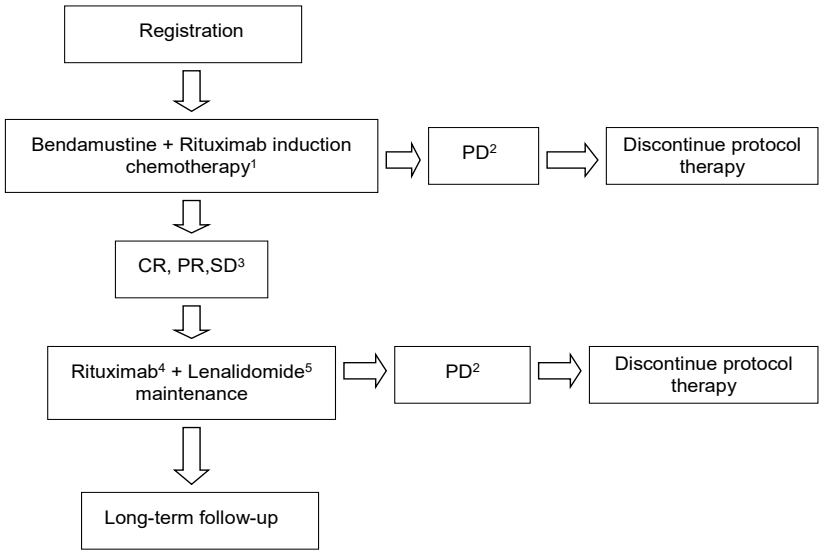
1 Schema



[1]Induction chemoimmunotherapy with bendamustine 90 mg/m^2/day IV days 1 & 2 every 28 days; rituximab 500 mg/m^2 day 1 (375 mg/m^2 cycle 1) every 28 days (1 cycle = 28 days). Rituximab may be given cycle 1, day 2-5 in subjects at high risk for the cytokine release syndrome. A total of 6 cycles will be administered, with disease assessment after cycles 3 and 6 of induction therapy. Subjects with objective response after 4 cycles of bendamustine + rituximab (BR) are eligible to proceed to maintenance therapy if toxicities are limiting further BR induction therapy, or if the treating physician determines that further BR induction therapy would be associated with excessive risk for additional toxicities.

[2]Subjects with progressive disease (PD) at any time during induction or maintenance therapy will discontinue protocol therapy. Formal disease assessments are performed after cycles 3 and 6 of induction therapy and every 4 cycles during maintenance lenalidomide.

[3]Subjects with stable disease (SD) and evidence of objective response may continue to maintenance at investigator discretion.

[4]Rituximab maintenance administered as 375 mg/m^2 IV on day 1 of odd-numbered cycles (cycles 1,3,5,7,9,11,13,15,17,19,21,23) of each 28-day cycle for a total of 12 doses.

[5]Lenalidomide maintenance administered as 5 mg/day on days 1-21 of cycles 1-24 (28-day cycles), with dose escalation up to 10 mg/day on days 1-21 allowed (see Sections 9.2.1.5 and 9.2.1.6 for criteria required to escalate the dose of lenalidomide).

2 Protocol Synopsis

PROTOCOL TITLE: Phase II study of bendamustine and rituximab induction chemoimmunotherapy followed by maintenance rituximab (Rituxan®) and lenalidomide (Revlimid®) in previously untreated chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

UWCCC PROTOCOL NUMBER:	HO11414
DATE PROTOCOL FINAL:	10/17/13
INDICATION:	Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), previously untreated with cytotoxic chemotherapy.
STUDY PHASE:	Phase II

BACKGROUND AND RATIONALE:

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) represent different clinical manifestations of a shared hematologic disorder with a typically indolent but incurable course.[1] Multiple treatments have proven beneficial in CLL/SLL, including alkylating agents, nucleoside analogues, anthracyclines, and various combinations of these agents. Multiple combination chemotherapy regimens in CLL/SLL employing the monoclonal anti-C20 antibody rituximab have demonstrated a probable synergistic benefit related to potential chemo-sensitization properties of rituximab.[2-4] Recent data in indolent non-Hodgkin lymphoma (NHL) have also shown a role for rituximab in treating minimum residual disease in the setting of maintenance therapy following induction chemotherapy.[5-10]

Standard therapy options for patients requiring treatment who are healthy enough to tolerate chemotherapy are typically fludarabine-based regimens. However, regimens such as FCR chemotherapy (fludarabine, cyclophosphamide, rituximab) are often too toxic for older adults to tolerate, and have significant short-term as well as long-term toxicities (i.e., myelodysplasia, prolonged cytopenias). Bendamustine is an agent receiving FDA approval in 2008 for treatment of chronic lymphocytic leukemia and more recently receiving FDA approval in indolent NHL that has progressed within 6 months of rituximab or a rituximab-containing regimen. Multiple reports suggest that bendamustine may have a toxicity profile that is more tolerable than other standard chemotherapy regimens including CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) or fludarabine-based regimens.[11-13] Previous experience with bendamustine with or without rituximab in indolent NHL histologies and CLL has demonstrated response rates from 40-90%.[11,13-16] However, progression-free survival (PFS) with this combination has been variable, although outcomes are improved in the setting of rituximab-sensitive disease.[13,15,17-19]

The response rates and acceptable toxicity profile of bendamustine have generated interest in its use for front-line therapy of CLL and SLL. A prospective, multicenter randomized phase III trial compared bendamustine with chlorambucil for treatment of symptomatic CLL that had not previously received therapy.[20] Patients were treated with bendamustine 100 mg/m^2 IV days 1 & 2 of 28 day cycles for up to 6 treatment cycles. Among the 319 enrolled patients, PFS favored bendamustine (21.6 months versus 8.3 months). Objective response rates were also higher for bendamustine compared with chlorambucil (68% versus 31%).[20] A report from the German CLL

study group (protocol CLL2M) addressed the activity of bendamustine + rituximab (BR) in previously untreated CLL. A total of 117 patients received bendamustine 90 mg/m^2 + rituximab 375 mg/m^2 every 28 days X 6 cycles. An overall RR of 90.9% was observed, with 32.7% achieving complete responses (CRs), 2.7% with nodular partial responses and 55.5% with partial responses (PRs). At 18 months, 75.8% remained with durable remissions.[21] Toxicity of BR was reasonable, with <10% of treatment courses complicated by grade ≥3 anemia or thrombocytopenia, and grade ≥3 infections observed in only 5.1% of courses. Recent data have also shown response rates, PFS, and toxicity with BR are superior to the standard regimen of rituximab + CHOP chemotherapy in indolent NHL.[12] An ongoing German CLL Study Group trial is comparing FCR versus BR in newly diagnosed CLL (clinicaltrials.gov, NCT00769522).

The German CLL Study Group CLL10 trial compared the efficacy of BR versus FCR for newly diagnosed CLL.[22] The results from the CLL10 trial have been recently published, and demonstrated more severe neutropenia and infections with FCR chemotherapy. Although median PFS was improved in the overall population with FCR (55.2 months versus 41.7 months), ***there was no difference in median progression-free survival with FCR versus BR chemotherapy in patients older than age 65.*** One strategy of interest in improving PFS after induction therapy is the incorporation of maintenance therapy. The benefit of maintenance rituximab has already been established in other NHL histologies.[5-8,10,23] In addition, several reports have shown benefit of lenalidomide in multiple NHL histologies, with a trend for improved benefit in the setting of lower tumor burden.[24,25] Two additional studies (CALGB 10404 and the German CLLM1 trial) have reported improvement in PFS when lenalidomide maintenance is administered to patients with higher-risk, previously untreated CLL.[26,27] There are additional data showing good efficacy and acceptable toxicity profile with the combination of rituximab and lenalidomide in relapsed/refractory CLL.[28]

Given the minimal toxicities and proven activity of rituximab in the maintenance setting for treatment of indolent NHL,[5-10] rituximab appears to be an ideal agent for use in combination therapy following induction chemotherapy in CLL/SLL. In addition, safety data exist to support maintenance therapy with rituximab for at least 2 years following induction chemotherapy.[5-10] Lenalidomide is also an appealing option for maintenance therapy in this setting based on recent data showing its activity in CLL and the convenience of its oral dosing. Lenalidomide is an immunomodulatory drug that has already received FDA approval for treatment of multiple myeloma and myelodysplastic syndrome with presence of the 5q deletion. In general, lenalidomide has been observed to be well tolerated, with common toxicities including neutropenia, thrombocytopenia, rash, constipation, diarrhea, and fatigue. Preliminary data show significant activity of lenalidomide in CLL, with response rates in relapsed/refractory CLL and NHL ranging from 25% to 70%, including responses in patients who have fludarabine-refractory disease.[29,30] There are additional data demonstrating an association between increased likelihood of objective response in NHL and low tumor burden.[24,25]

More recent data have suggested improved efficacy and an acceptable toxicity profile with the combination of rituximab and lenalidomide. A report of the activity of lenalidomide (dosed at 10 mg daily on days 9-28 of each 28-day treatment cycle) combined with rituximab for up to 12 therapy cycles found promising response rates in patients with relapsed and refractory CLL. All patients had received prior fludarabine-based chemotherapy, and 59 patients were evaluable for response. An ORR of 64% was observed, including 8% CRs and 5% CRs with incomplete hematologic recovery.[31] In a single institution phase II study of rituximab 375 mg/m^2 on day 1 and lenalidomide 20 mg/day orally days 1-21 every 28 days for up to 6 treatment cycles, outcomes on 30 patients with previously untreated CLL were reported. Of 28 patients evaluable for response, an overall response rate of 85% was observed with an impressive 79% achieving CRs.[32,33] These data suggest that lenalidomide + rituximab have promising response rates and appear to ₊have

improved efficacy compared with single-agent lenalidomide.[29,30]We propose a treatment strategy where patients are treated with induction chemoimmunotherapy consisting of rituximab + bendamustine for 6 cycles, followed by initiation of maintenance rituximab and lenalidomide among patients achieving an objective response (i.e., at least stable disease with some tumor shrinkage) to induction therapy. The goal of maintenance therapy will be to capitalize on the cytoreduction following induction chemotherapy with a maintenance regimen that has also shown promising activity in CLL, in order to allow for improved PFS in this population.

A completed clinical protocol through the Wisconsin Oncology Network (WON) investigated the activity of lenalidomide as a single-agent in maintenance therapy administered after induction chemoimmunotherapy with bendamustine/rituximab in relapsed and refractory CLL/SLL (HO08405, RV-CLL/SLL-PI-397), and is now a published manuscript.[34]This study ultimately showed no improvement in median PFS at 18.3 months compared with previously reported activity of bendamustine + rituximab chemotherapy without maintenance therapy in the relapsed/refractory CLL/SLL setting (median PFS 15.2 reported by the German CLL Study Group).[35] Progressive disease and toxicities were the primary reasons for discontinuation of protocol therapy, and only 6 subjects were able to complete the entire 12 months of maintenance therapy per protocol. The small number of patients able to receive the full maintenance therapy likely limited the ability to assess the activity of maintenance lenalidomide after BR induction.

Three recent large, multicenter, randomized, placebo controlled trials of maintenance lenalidomide have been reported in previously untreated high-risk CLL and relapsed/refractory CLL. These studies demonstrated improvement in PFS with maintenance lenalidomide compared with placebo.[36,37] This previous experience with maintenance lenalidomide lends further support for investigating lenalidomide-based maintenance therapy in the previously untreated setting of CLL/SLL. Given the improved activity in relapsed CLL with the combination of rituximab + lenalidomide compared with single-agent lenalidomide, the combination of rituximab + lenalidomide in the maintenance setting is of particular interest as a novel means of improving upon remissions after first-line chemotherapy.

STUDY DESIGN:

This is a phase II single arm, open-label study evaluating the efficacy and safety of the combination of induction chemoimmunotherapy with bendamustine and rituximab followed by maintenance therapy with rituximab and lenalidomide in subjects with CLL or SLL who have not received any prior cytotoxic chemotherapy for their disease (i.e., prior single-agent rituximab is permitted). The study will be carried out at the University of Wisconsin Carbone Cancer Center (UWCCC)..

The subject participation will include a screening period, treatment period, and a follow-up period. The treatment period will extend from the first dose of study drug treatment (day 1, cycle 1 of induction chemoimmunotherapy) until any of the following: completion of the entire course of induction and maintenance therapy; progressive disease (PD); an unacceptable adverse event (AE); the initiation of alternate anti-neoplastic therapy; or a decision by the subject or by the investigator to discontinue treatment; or death. The induction chemoimmunotherapy regimen consists of bendamustine and rituximab for 6 cycles, followed by initiation of maintenance therapy with rituximab and lenalidomide among subjects achieving an objective response to induction therapy (i.e., complete or partial response; stable disease with objective evidence of tumor shrinkage). Subjects with objective response after 4 cycles of bendamustine + rituximab (BR) are eligible to proceed to maintenance therapy if toxicities are limiting further BR induction therapy, or if the treating physician determines that further BR induction therapy would be associated with excessive risk for additional toxicities.

To minimize toxicity with induction chemotherapy, we have chosen a dose of bendamustine at 90 mg/m^2/day on days 1 & 2 every 28 days for a total of 6 cycles. Rituximab will be administered at a dose of 500 mg/m^2 IV on day 1 of each cycle of induction chemoimmunotherapy (375 mg/m^2 cycle 1 only); however, patients at high-risk for cytokine release syndrome may receive rituximab on day 2 of induction therapy. In select circumstances in subjects at high risk for cytokine release syndrome and/or tumor lysis syndrome, rituximab may be administered as late as day 5 of cycle 1 (this alternative dosing of rituximab applies to cycle 1 of induction therapy only). Lenalidomide and rituximab maintenance will be initiated 6-12 weeks after the 6th cycle of chemotherapy, and continued for a total of 24 cycles. Maintenance therapy will continue for a maximum of 24 cycles or until unacceptable toxicity or progression of disease.

Maintenance therapy will begin once there has been adequate hematologic recovery (ANC ≥1000/μL and platelets ≥50,000/μL) and other criteria as outlined in Section 7.5 have been met. Rituximab will be administered at a dose of 375 mg/m^2 IV on day 1 of every odd-numbered 28 day cycle (cycles 1,3,5,7,9,11,13,15,17,19,21,23) for a maximum of 12 doses during the maintenance phase. Subjects will receive concurrent lenalidomide 5 mg orally daily on days 1-21 of cycles 1-24 (28 day cycles). If subjects do not experience adverse effects from lenalidomide, dose escalation up to 10 mg orally daily on days 1-21 of each 28 day cycle will be allowed at the start of cycle 2 or at the start of any subsequent cycle (see Section 9.2.1.5 and 9.2.1.6 for criteria required to escalate the dose of lenalidomide to 10 mg/day on days 1-21). Lenalidomide dose escalation is only allowed at the start of a new cycle to a maximum dose of 10 mg/day on days 1-21. Subjects entering maintenance with reduced renal function (i.e., creatinine clearance ≥40 but <60 mL/min) will start lenalidomide at a dose of 5 mg every other day on days 1-21. There is no dose modification of rituximab based on reduced renal function. Among subjects without excessive toxicity or evidence of progression, treatment with lenalidomide will continue for up to 24 cycles (cycle 1-24) and treatment with rituximab will continue for up to 12 doses (administered every odd-numbered cycle during cycles 1,3,5,7,9,11,13,15,17,19,21,23). If subjects have excessive toxicity from lenalidomide, ongoing maintenance therapy with rituximab alone is permitted after lenalidomide is discontinued. After completing 24 cycles of maintenance therapy, subjects will then be observed for evidence of PD with clinical assessments every 3 months for at least 2 years.

STUDY ENDPOINTS

Primary:

- The primary objective is progression-free survival (PFS). Tumor measurements and disease assessments will be performed at the time of screening, following cycles 3 and 6 of induction chemotherapy, every 4 cycles during the maintenance portion of treatment, and at the end of treatment (EOT). Subjects with clinical evidence of progression prior to a planned disease assessment will be evaluated at the time of clinically suspected progression. Follow-up visits for disease assessment will occur every 3 months after the EOT visit until PD, initiation of alternate anti-neoplastic therapy, decision by the subject to withdraw from the study, or death. The follow-up period will begin after the EOT visit, and all subjects will be followed for at least 2 years after completion of therapy or until death or progression and until the last patient has been followed for at least 1 year following completion of therapy.

Secondary:

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- To determine objective response rates (CR + PR). As described in the primary objective, formal disease assessments including imaging will be performed after cycles 3 and 6 of induction chemotherapy and every 4 cycles during the maintenance portion of treatment. Response and progression in cases of SLL will be evaluated using the International Working Group Criteria[38] for response in lymphoma. Response and progression in cases of CLL will be evaluated in this study using the Revised IWCLL Criteria[39] for response in CLL. Radiological methodologies, techniques and/or physical examination, established at baseline for the assessment and measurement of each identified lesion will be used for all subsequent assessments.
- To determine toxicities observed with induction chemotherapy and maintenance therapy. Safety evaluations will be based on the incidence, intensity, and type of adverse events (AEs) and clinical laboratory results. Drug doses will be modified as required based on toxicity as assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
- To determine overall survival. Overall survival will be determined from the date of enrollment until death from any cause.

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- **STUDY DURATION:** Anticipated accrual period of 30 months, with a follow-up period of at least 2 years after completion of therapy or until death or progression and until the last subject has been followed for at least 1 year following completion of therapy.

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TOTAL SAMPLE SIZE: Approximately 36 subjects are planned for enrollment.

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DOSING REGIMEN(S):

Induction chemoimmunotherapy:

- Bendamustine 90 mg/m^2 IV days 1 & 2 every 28 days X 6 cycles
- Rituximab 500 mg/m^2 IV day 1 every 28 days X 6 cycles (375 mg/m^2 IV cycle 1 only, day 1-5)

Maintenance phase:

- Rituximab 375 mg/m^2 IV on day 1 of every odd-numbered 28-day cycle (cycles 1,3,5,7,9,11,13,15,17,19,21,23) for a maximum of 12 doses during the maintenance phase.

Lenalidomide 5 mg orally daily on days 1-21 of each 28-day cycle for 24 cycles (maintenance cycles 1-24); dose escalation to 10 mg orally daily on days 1-21 will be allowed at the start of cycle 2 or at the start of any subsequent cycle in subjects with acceptable toxicities (see Section 9.2.1.5 and 9.2.1.6 for criteria needed to escalate the dose of lenalidomide to 10 mg/day on days 1-21). Lenalidomide dose escalation is only

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STUDY DRUG SUPPLIES:

Bendamustine is commercially available.

For study participants, rituximab will be provided by Genentech, Inc. at no charge.

For study participants, Celgene Corporation will provide lenalidomide at no charge through the Revlimid REMS® program.

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allowed at the start of a new cycle up to a maximum dose of 10 mg/day on days 1-21. Subjects entering maintenance with a CrCl ≥40 and <60 mL/min will begin dosing at 5 mg every other day on days 1-21.	

3 Schedule of Study Assessments

Baseline assessments will be within 28 days of C1D1.

	Baseline[1]	C1-6 Induction chemotherapy D1 (±4 days)	Maintenance cycles 1-6 rituximab + lenalidomide (28-day cycles, +/- 10 days)	Maintenance cycles 7-24 rituximab + lenalidomide (28-day cycles, +/- 10 days)	End of treatment[20]	Follow-up phase[2] Every 3 months for 2 years (± 3 weeks)
Informed consent	X					
Medical history & medications[3]	X[1]					
Physical exam, vital signs, weight, height,[4] ECOG performance status	X[1]	X	X[5] (D1 each cycle)	X[5] (D1 each odd-numbered cycle)	X	X
Bone marrow aspirate & biopsy	X[6]		X[6]			
CLL cytogenetic analysis	X[7]					
Hematology profile[8]	X[1]	X[8]	X[8]	X[8]	X	X
Chemistry profile[9]	X[1,9]	X[9]	X[9]	X[9]	X	X
Beta-2 microglobulin level	X					
Tumor lysis syndrome (TLS) assessment[10]		X[10]	X[10]	X[10]		
Immunoglobulin levels[11]	X	X[11]	X[11]	X[11]	X	X[11]
Hepatitis screening[19]	X					
Thyroid Function[12]	X		X[12]	X[12]	X	X[12]
Pregnancy testing[13]	X		X[13]	X[13]		
CT of the chest & abdomen / pelvis[14]	X[14]	X[14]	X[14]	X[14]	X[14,20]	X[14]
PET imaging[15]	X[15]	X[15]	X[15]	X[15]	X[15,20]	X[15]
Formal Disease assessment (CT scans, palpated disease, and other assessable disease)[14]	X[1]	X[14]	X[14] Every 4 cycles	X[14] Every 4 cycles		X[14]
Record adverse events	X	X	X	X	X	X[16]
Allopurinol prophylaxis		X[17]	X[17]	X[17]		
Bendamustine infusion		X				
Rituximab infusion		X	X	X		

			(cycles 1,3, 5)	(cycles 7,9,11 13,15, 17,19,21,23)		
Register subject into Revlimid REMS ® program		X[18]				
Lenalidomide administration			X (cycles 1-6)	X (cycles 7-24)		

[1] If screening assessments (i.e., baseline history, physical exam, laboratory evaluations) were done within 7 days of C1D1, they do not need to be repeated at study day 1. The exception to this is baseline disease assessments; baseline CT scans and bone marrow biopsy/aspirate may be performed within 6 weeks of C1D1.

[2]The follow-up phase of therapy will begin 30 days after the last dose of lenalidomide is administered and will continue for up to 2 years or until death, progression of disease, or start of a new anti-cancer therapy. After 2 years of follow-up, subjects will be followed annually for 5 years for survival and disease progression.

[3]Include all prior anti-cancer therapies and pre-existing medical conditions.

[4]Start of protocol only.

[5]**Clinical assessments** to be performed on day 1 of each 28-day cycle during cycles 1-6 of maintenance rituximab + lenalidomide, then day 1 of each odd-numbered cycle during maintenance rituximab + lenalidomide cycles 7-24. In subjects who discontinue lenalidomide but continue receiving maintenance rituximab per protocol, clinical assessments may be performed on day 1 of odd-numbered cycles even prior to cycle 7.

[6]**BM aspirate and biopsy** to be done within 6 weeks prior to C1D1. A repeat BM biopsy is required after cycle 6 of chemotherapy in subjects with BM involvement at enrollment who have achieved a possible CR to induction chemotherapy based on imaging studies and improvement in hematologic parameters. In subjects being evaluated with CLL response criteria, investigators should note that 2 bone marrow biopsies performed ≥ 2 months apart are required to confirm a complete response. In subjects who appear to have improved their objective response (i.e., partial to complete response) with maintenance lenalidomide, a BM biopsy may be indicated to confirm the CR.

[7]**CLL cytogenetic analysis** should include analysis for presence of $11q^-$, ATM/Cen11; $17p^-$, p53/Cen17; 13q-, D13S319/LAMP1; and trisomy 12, D1273/MDM2 by fluorescence in situ hybridization (FISH). Baseline assessment of IgV_H gene mutation status by ZAP70 and/or CD38 positivity is preferred, but not mandatory. If CLL mutation analysis has been performed within 12 months prior to enrollment, repeat analysis is not required. Cytogenetic analyses may be performed on bone marrow aspirate or on peripheral blood.

[8]**Hematology profile** (CBC, differential, platelets) is required within 48 hours of cycles 2-6 of induction chemotherapy (hematology profile prior cycle 1, day 1 may be performed within 7 days. Hematology profiles are required within 48 hours prior to day 1 of each maintenance cycle during cycles 1-24. Hematology profiles are required weekly (±48 hours) during cycle 1 of maintenance lenalidomide. In addition, in any maintenance cycle where the lenalidomide dose is escalated or re-escalated or treatment is interrupted for more than 4 weeks, subjects will have weekly (±48 hours) hematology profiles performed for at least 4 consecutive weeks. Subjects who are on a stable lenalidomide dose (without escalation or interruption) for ≥1 cycle of maintenance will require hematology profiles every 4 weeks. In study subjects who discontinue lenalidomide but continue receiving rituximab per protocol, labs are not required on even cycles, including those prior to cycle 7.

[9]**Chemistry profile includes** sodium, potassium, chloride, CO_2 (bicarbonate) calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, lactate dehydrogenase (LDH), and uric acid. Chemistry profile is to be obtained at screening, within 7 days of cycle 1, day 1 of induction, and within 48 hours prior to day 1 of induction cycles 2-6 and maintenance cycles 1-24. In study subjects who discontinue lenalidomide but continue receiving rituximab per protocol, labs are not required on even cycles, including those prior to cycle 7.

[10]**Tumor lysis syndrome (TLS) assessment** will consist of sodium, potassium, chloride, CO_2 (bicarbonate), calcium, magnesium, phosphorus, BUN, creatinine, LDH, and uric acid. In subjects at high-risk for TLS (see Section 9.3.1 for definition of subjects at high-risk), TLS assessments must be repeated on cycle 1, day 2 of induction therapy. Subsequent TLS laboratory monitoring during the first week of induction therapy beyond cycle 1, day 2 will be at investigator discretion depending on clinical status and change in laboratory values (see Appendix I: Cairo-Bishop definition of tumor lysis syndrome). TLS assessments are required on day 1 of maintenance cycle 1, in any cycles where lenalidomide dosing is escalated/re-escalated, or if lenalidomide dosing is held for >4 weeks. Refer to Section 9.3.1 for guidelines on use of allopurinol and/or rasburicase for TLS prophyalxis during induction and maintenance therapy.

[11]**Immunoglobulin levels** (quantitative serum levels of IgA, IgG, IgM) should be evaluated at baseline, at the end of induction chemotherapy (at least 4 weeks after C6D1 of induction chemotherapy but prior to C1D1 of maintenance therapy), and before maintenance cycles 5, 9, 13, 17, 21, and the EOT. Please note that the schedule for immunoglobulin level evaluation corresponds to the schedule for disease assessments (i.e., CT imaging and/or PET imaging) after every 4 cycles of maintenance therapy. During the follow-up phase after completion of maintenance therapy, immunoglobulin levels should be monitored approximatelyevery 6 months.

[12]**Thyroid Stimulating Hormone (TSH)** level is required at screening, within 48 hours prior to cycle 1, day 1 of maintenance therapy, and within 48 hours prior to maintenance cycles 5, 9, 13, 17, 21, and the EOT. T3 and T4 levels may be assessed as clinically indicated. Please note that the schedule for thyroid function evaluation corresponds to the schedule for disease assessments after every 4 cycles of maintenance therapy. During the follow-up phase after completion of maintenance therapy, TSH levels should be monitored approximately every 6 months.

[13]**Pregnancy tests for females of childbearing potential**. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24

consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy testing must be performed with a method of serum or urine testing with a sensitivity of at least 50 mIU/mL. Pregnancy testing in FCBP will occur at baseline and prior to maintenance as follows: Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide cycle 1 (prescriptions must be filled within 7 days). The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at day 14 and day 28 post the last dose of lenalidomide (see Appendix B: Risks of fetal exposure, pregnancy testing guidelines and acceptable birth control methods).

[14]Formal disease assessment to be repeated after cycles 3 and 6 of induction therapy, then after every 4 cycles during the maintenance phase of treatment (i.e., after maintenance cycles 4, 8, 12, 16, 20, and 24). **CT imaging of the abdomen and pelvis is must include oral and IV contrast; CT imaging of the chest does not require IV contrast.** During the follow-up phase of treatment, use of CT imaging is at the treating physician's discretion, and may or may not be used as part of the disease assessment. **CT imaging** (and PET imaging, if clinically indicated) must be performed within 6 weeks of enrollment. Subjects with CLL and without clinically significant lymphadenopathy (defined as lymph nodes measuring ≤ 1.5 cm in greatest dimension) at baseline will not require repeat CT imaging as part of ongoing disease assessments. All PRs and CRs in cases of CLL evaluated by the Revised IWCLL 2008 (Appendix H) must be confirmed by repeat scans at least 2 months after the criteria for response are first met. Timing of alternate cycle efficacy assessments will be reset following a confirmation or response assessment. Confirmatory scans can be done 4 months after initial response is noted, investigators do not have to schedule a separate scan at the 2 month interval for confirmation of response. If investigators perform 2 month confirmatory scan for response, then timing of alternate cycle efficacy assessments will be reset following a confirmation of response assessment (see section 7.1.1). In cases of CLL, bone marrow biopsy and flow cytometry of both bone marrow and blood are required to confirm a CR

[15]**PET imaging** is required at the end of treatment only for subjects being evaluated with small lymphocytic lymphoma response criteria who have residual masses on CT imaging or in subjects with areas of increased uptake on baseline PET imaging who require re-assessment to determine CR status; subsequent PET scans are only required if clinically indicated as part of disease assessment.

[16]An additional safety assessment will be done 30 days (+/- 2 days) following the last dose of study drug.

[17]Subjects **who are determined to be at high-risk for TLS** (see Section 9.3.1 for definition of TLS risk) are required to receive allopurinol 300 mg orally daily or twice daily for 14 days at the start of induction chemotherapy. Subjects must receive their first day of allopurinol prophylaxis on C1D1 of induction chemotherapy, but preferably 1-2 days prior to C1D1. Alternatively, subjects at high-risk for TLS with intolerance to allopurinol or judged to be at increased risk for TLS even with allopurinol prophylaxis, should be considered for treatment with rasburicase. For all other subjects (i.e., not meeting high-risk criteria for TLS), use of allopurinol during induction therapy is at the discretion of the investigator**.** Subjects not meeting criteria for a partial or complete response after induction therapy should receive allopurinol prophylaxis 300 mg orally daily for 10 days beginning 2 days prior to the start of cycle 1 of maintenance therapy.

[18]Subjects must be registered into Revlimid REMS® program prior to prescribing lenalidomide. Ideally, this should occur prior to cycle 6 of induction therapy. All physicians who prescribe lenalidomide for research subjects enrolled in to this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program. Drug will be shipped on a per patient basis by contract pharmacy to the clinic site. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

[19]Hepatitis screening to include hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody screening.

[20]For subjects who discontinue lenalidomide early and continue with rituximab, the EOT visit may occur 30 days (+/- 2 days) after cycle 23, day 1 dosing of rituximab, and also be inclusive of the 30-day safety visit. For these subjects completing 23 cycles of rituximab (stopping lenalidomide early), restaging will occur after cycle 23 of rituximab. For subjects stopping all maintenance or induction cycles prematurely, the EOT visit may occur 30 days (+/-2 days) after the last dose of study drug, to also be inclusive of the 30-day safety visit**.** Subjects are allowed to have restaging imaging up to 8 weeks after the final dose of study drug.

4.0 Glossary of Abbreviations

Abbreviation	***Term***
5-HT_3	5-hydroxytryptamine (serotonin)
AE	Adverse event
ANC	Absolute neutrophil count
B-ALL	B-cell acute lymphoblastic leukemia
BM	Bone marrow
BSA	Body surface area
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRC	Clinical Research Committee
CRF	Case report form
CRCO	Central Research Coordinating Office
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DLBCL	Diffuse large B cell lymphoma
DOT	Disease Oriented Team
DSMB	Data Safety Monitoring Board
EC	Ethics committee
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Agency
EOT	End of treatment
FCBP	Females of childbearing potential
FCR	Fludarabine, cyclophosphamide, rituximab
FDA	United States Food and Drug Administration
FISH	Fluorescence in situ hybridization
G-CSF	Granulocyte colony stimulating factor
GCLLSG	German CLL study group

GCP	Good clinical practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous/intravenously
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
MRN	Medical record number
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PFS	Progression-free survival
PD	Progressive disease
PET	Positron-emission tomography
PR	Partial response
SAE	Serious adverse events
SD	Stable disease
SLL	Small lymphocytic lymphoma
SOP	Standard operating procedure
SPM	Second primary malignancy
TLS	Tumor lysis syndrome
TPD	Therapeutic Products Directorate (Canada)
ULN	Upper limit of laboratory normal
UWCCC	University of Wisconsin Carbone Cancer Center
WON	Wisconsin Oncology Network
WWDSS	Celgene Corporation Worldwide Drug Safety Surveillance

5 Background and Rationale

5.1 Introduction

5.1.1 Diagnosis and natural history of CLL/SLL

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) represent different clinical manifestations of a shared hematologic disorder with a typically indolent but incurable course. Generally, a peripheral blood lymphocyte count >5000 monoclonal B-cell lymphocytes/microliter is defined as the threshold to separate CLL from SLL.[1] Despite the relatively arbitrary division between CLL and SLL, clinical trials often strictly separate these diagnoses. Only diseases meeting criteria for CLL are included in studies that are typically limited to CLL as a single entity. In contrast, SLL is often excluded from trials focusing on CLL, and equally as frequently is excluded from trials of indolent non-Hodgkin lymphoma (NHL) because of its traditionally lower rates of response compared with other indolent NHL subtypes. Unfortunately, this has led to limited progress in developing new treatment modalities for SLL and has limited options for clinical trial participation in patients with SLL. A recent report from M.D. Anderson Cancer Center focused on comparing outcomes in patients with CLL and SLL, with data from 2126 patients retrospectively identified from 1985 until 2005. Rates of response, survival, and failure-free survival were ultimately found to be no different between patients classified as CLL or SLL.[1] Based on these factors collectively, the clinical trial design we propose will focus on the populations of CLL and SLL together, recognizing the commonalities between these diagnoses.

5.1.2 Current treatment for CLL/SLL

Although CLL/SLL is typically an indolent disease with a multiply relapsing course after response to various treatments, CLL/SLL remains incurable in the majority of cases. Although some patients achieve long-term remissions with potentially curative options such as allogeneic stem cell transplantation, the older age of most patients at diagnosis and availability of a suitable donor makes this approach impractical for most patients.[2] Therefore, for the overwhelming majority of patients with CLL/SLL, the goal of disease management is palliation of symptoms and optimization of disease control with intermittent therapeutic intervention.

Multiple treatments have proven beneficial in CLL/SLL, including alkylating agents, nucleoside analogues, anthracyclines, and various combinations of these agents.[2] Rituximab, a monoclonal antibody directed against CD20, has shown limited activity as a single-agent in CLL/SLL presumably due to the generally weak expression of CD20 in CLL/SLL. However, multiple combination chemotherapy regimens in CLL/SLL employing rituximab have demonstrated a probable synergistic benefit related to potential chemo-sensitization properties of rituximab.[2-4] Standard therapy options for patients requiring treatment who are healthy enough to tolerate chemotherapy are typically fludarabine-based regimens. However, regimens such as FCR chemotherapy (fludarabine, cyclophosphamide, rituximab) are often too toxic for older adults to tolerate, and have significant short-term as well as long-term toxicities (i.e., myelodysplasia, prolonged

cytopenias). Bendamustine is an agent receiving FDA approval in 2008 for treatment of chronic lymphocytic leukemia and more recently receiving FDA approval in indolent NHL that has progressed within 6 months of rituximab or a rituximab-containing regimen. Multiple reports suggest that bendamustine may have a toxicity profile that is more tolerable than other standard chemotherapy regimens including CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) or fludarabine-based regimens.[11-13]

5.2 Experience with Bendamustine

5.2.1 Bendamustine biochemistry: *in vitro* and *in vivo* studies

Bendamustine is a promising chemotherapy agent for treatment of CLL/SLL with a substantial record of activity in indolent NHL and CLL. Bendamustine has been available for several decades in Europe, with evidence of activity in several hematologic and solid tumors.[40] Following its development in 1963 in the German Democratic Republic, bendamustine was initially available in Europe from 1971 until 1992 under the name Cytostasan®. Then in 1993, bendamustine was marketed by Ribosepharm GmbH as Ribomustin® and more recently has been made available for investigation in the United States through Cephalon, Inc. as Treanda™. The anti-neoplastic effects of bendamustine are related to its dual functional properties of both an alkylating agent and a nitrogen mustard.[40] Through these unique cytostatic properties, bendamustine is able to inhibit DNA transcription, replication, and repair. In addition, some data have suggested that bendamustine's improved chemical stability compared with other nitrogen mustards may enable the compound to have more efficient DNA alkylating properties. These unique properties of bendamustine also enable it to exhibit only partial cross-resistance with other alkylating agents.[40,41]

Bendamustine has demonstrated *in vitro* activity in multiple tumor cell lines, including drug-resistant human breast cancer,[41,42] CLL,[42,43] indolent NHL,[44,45] and myeloid leukemia.[46] More recently, *in vitro* studies have investigated the effect of the monoclonal antibody rituximab on the activity of bendamustine. For example, studies using the cell lines DOHH-2 and WSU-NHL (cell lines derived from CD20+ lymphomas) and cells freshly isolated from humans with B-CLL demonstrated a significant reduction in the dose of bendamustine required to induce apoptosis with the addition of rituximab, supporting a syngergistic effect between bendamustine and rituximab.[4,47]

5.2.2 Clinical activity of bendamustine in relapsed and refractory CLL/SLL

The clinical activity of bendamustine has been reported in Hodgkin lymphoma,[48] NHL,[11,15,17,18] CLL,[20,21,49,50] myeloma,[51] breast cancer,[52] and lung cancer.[53] Several of the earlier reports showing significant activity in NHL were predominantly European studies in relapsed indolent NHL, with bendamustine given as monotherapy or in combination with other agents. In this setting, objective response rates between 50-90% were observed in these studieswhich often included patients with heavily pretreated disease.[45,54,55] More recently reported experience in indolent NHL and CLL with single-agent bendamustine

doses ranging from 50-120 mg/m^2 given for 2 consecutive days every 3-4 weeks yielded response rates ranging from 40-75%.[19,50,56,57] Notably, single agent bendamustine for treatment of relapsed CLL was associated with the lower rates of response compared with other indolent NHL subtypes, which is consistent with experience in other chemotherapeutic trials. Bendamustine at a dose of 90 mg/m^2/day IV on days 1 and 2 in combination with rituximab has shown response rates exceeding 70-90%, but with CLL/SLL comprising the minority of patients and many patients either not refractory to rituximab or rituximab-naïve.[11,14,58-60] In comparison, other regimens combining rituximab with nucleoside analogues in relapsed and refractory CLL and indolent NHL have shown similar response rates of 70-75%.[61,62]

Despite the high objective response rates with bendamustine when combined with rituximab in relapsed and refractory indolent NHL, the observed durations of remission have been quite variable (Table 1). Although several reports of bendamustine monotherapy or bendamustine + rituximab have reported PFS exceeding 1 to 2 years, many of these studies include less heavily pretreated patients and patients who are not refractory to rituximab or are rituximab-naïve.[11,55,58-60] In a report by Rummel *et al* among 63 patients with relapsed/refractory non-Hodgkin lymphoma, a PFS of 30 months was reported with the combination of rituximab and bendamustine, but with none of the patients having received prior rituximab.[11,60] Another study by Robinson *et al* in 66 patients with relapsed, refractory NHL found high overall response rates of 92% with bendamustine + rituximab, with a median PFS of 23 months. However, this study excluded patients who were rituximab-refractory.[15] A recently reported multicenter study treating 78 patients with relapsed and refractory CLL (28% refractory to fludarabine) reported an overall response rate of 59%, and median PFS of 14.7 months.[13] In a multi-center study of 76 patients reported by Friedberg *et al*, response rates and PFS were reported among a less favorable subgroup of NHL patients with relapsed and rituximab-refractory disease treated with bendamustine monotherapy. Among these patients, the objective response rate was quite high at 77%, but the median duration of response was only 6.7 months.[19] Similarly, Kahl *et al* reported a high objective response rate of 75% among 100 patients with relapsed, rituximab-refractory indolent NHL (21% with SLL). However, the observed median PFS was 9.3 months.[18] These results provide conflicting information about the use of bendamustine in relapsed/refractory NHL; primarily, that response rates are high with bendamustine but with a disappointing duration of remission when patients are refractory to rituximab.

Table 1. Bendamustine + rituximab in relapsed, refractory indolent NHL and CLL

	N	Regimen	Response rate			PFS
			Overall	CR/ CRu	PR	
Rummel *et al*[11,60] Relapsed; no prior R	63 FL 38% MCL 25%	B 90 mg/m^2 D1,2 R 375 mg/m^2 D1 Cycles q4 weeks (max 4 cycles)	90%	60%	30%	24, 30 mos
van der Jagt *et al*[59] Relapsed; not R-refractory (37% with prior R) MPT= 1	66 FL 61% SLL 15% MCL 18%	B 90 mg/m^2 D2,3 R 375 mg/m^2 D1 Cycles q4 weeks (max 6 cycles)	94%	41%	53%	Not yet reached
Weide R *et al*[14] Relapsed, refractory disease MPT= 2	54 CLL 39% FL 26% Transformed 11%	B 90 mg/m^2 D1,2 M10 mg/m^2 D1 R 375 mg/m^2 weekly (cycle 1) Cycles q4 weeks (max 6 cycles)	96%	41%	55%	CLL: 17 months Indolent NHL: NR
Robinson *et al*[15] Relapsed; not R-refractory MPT= 1 (56% with prior R)	67 FL 61% SLL 15% MCL 18%	B 90 mg/m^2 D2,3 R 375 mg/m^2 D1 Cycles q4 weeks (max 4-6 cycles)	92%	41%/ 14%	38%	23 mos
Friedberg *et al*[19] (bendamustine monotherapy) Relapsed, R-refractory, MPT= 2	76 61% follicular 16% SLL 20% Transformed disease	B 120 mg/m^2 D1,2 Cycles q3 weeks (median 5 cycles)	77%	15%/ 19%	43%	6.7 mos
Kahl *et al*[18] (bendamustine monotherapy) Relapsed, R-refractory MPT = 2	100 62% FL 21% SLL 16% MZL	B 120 mg/m^2 D1,2 Cycles q3 weeks (max 6-8 cycles)	75%	14%/3%	58%	9.3 mos
Fischer *et al*[13] Relapsed, refractory CLL	78 All with CLL 28% fludarabine-refractory	B 70 mg/m^2 D1,2 R 500 mg/m^2 D1 (max 6 cycles)	59%	9%	47.4% (+ 2.6% with nodular PR)	Median EFS 14.7 mos

Abbreviations: B=bendamustine, CR=complete response, CRu=unconfirmed complete response, FL=follicular lymphoma, M=mitoxantrone, MCL=mantle cell lymphoma, MPT=median prior therapies, MZL=marginal zone lymphoma, NR=not reported, PR=partial response, R=rituximab.

5.2.3 Bendamustine in previously untreated CLL/SLL

The response rates and acceptable toxicity profile of bendamustine have generated interest in its use for front-line therapy of CLL and SLL (Table 2). A prospective, multicenter randomized phase III trial compared bendamustine with chlorambucil for treatment of symptomatic CLL that had not previously received therapy.[20] Patients were treated with bendamustine 100 mg/m^2 IV days 1 & 2 of 28-day cycles for up to 6 treatment cycles. Among the 319 enrolled patients, PFS favored bendamustine (21.6 months versus 8.3 months). Objective response rates were also higher for bendamustine compared with chlorambucil (68% versus 31%).[20] A report from the German CLL study group (protocol CLL2M) addressed the activity of bendamustine + rituximab (BR) in previously untreated CLL. A total of 117 patients received bendamustine 90 mg/m^2 IV on days 1 & 2 and rituximab 500 mg/m^2 IV on day 1 every 28 days X 6 cycles. An ORR of 90.9% was observed, with 32.7% CRs, 2.7% with nodular PRs, and 55.5% with PRs. At 18 months, 75.8% remained in ongoing remission.[21] Toxicity of BR was reasonable, with <10% of treatment courses complicated by grade ≥3 anemia or thrombocytopenia, and grade ≥3 infections were observed in only 5.1% of courses.[21] Recent data have also shown response rates, PFS, and toxicity with BR is superior to the standard regimen rituximab + CHOP chemotherapy in indolent NHL.[12] The German SLL Study Group CLL10 trial compared FCR versus BR in newly diagnosed CLL.[22] The median PFS for patient treated with BR chemotherapy was 41.7 months, and there was no difference in PFS between patients treated with FCR versus BR chemotherapy among the subgroup of adults aged >65 years. In addition, there were significantly more infectious complications among adults aged >65 years treated with FCR.

Table 2. Bendamustine ± rituximab in previously untreated CLL

	N	Regimen	Response rate	PFS

			Overall	CR/CRu	PR	
Fischer *et al* [21] GCLLSG CLL2M Median age 64	117	B 90 mg/m^2 D1,2 R 375 mg/m^2 C1D1 R 500 mg/m^2 C2-6 Cycles q4 weeks (max 6 cycles)	90.9%	32.7%	55.5%	75.8% in remission at >18 months Median PFS NR
Knauf *et al*[20]	319	B 100 mg/m^2 D1,2 versus Chlorambucil (Chl) Cycles q4 weeks (max 6 cycles B)	B 68% Chl 31%	B 31% Chl 2%		B = 21.6 months Chl = 8.3 months
GCLLSG CLL10 trial		FCR vs BR	FCR 95% BR 96%	FCR 40% BR 31%		BR = 41.7 months FCR = 55.2 months

Abbreviations: B=bendamustine; BR=bendamustine + rituximab; Chl=chlorambucil; CR=complete response; CRu=unconfirmed complete response; FCR=fludarabine, cyclophosphamide, rituximab; GCLLSG=German CLL study group; NR=not reached; PR=partial response; R=rituximab.

5.2.4 FDA approval of bendamustine for CLL/SLL

Bendamustine received FDA approval for treatment of CLL in March of 2008 based on the promising results of 2 clinical studies.[20,63] A large international phase III randomized clinical trial of bendamustine versus chlorambucil in previously untreated CLL patients (n=319) demonstrated a significant improvement in objective response rates and median PFS favoring bendamustine (Table 2).[20] In this study, bendamustine was given as a dose of 100 mg/m^2/day IV days 1 and 2 every 28 days for a total of up to 6 cycles. Within the bendamustine-treated group, the overall response rate was 68% (31% of all responses were CRs) compared with 31% in the chlorambucil treated group (2% of all responses were CRs). Median PFS of 21.6 months was observed with bendamustine versus 8.3 months with chlorambucil (p<.0001).[20] In another multicenter phase II study of bendamustine in patients with relapsed CLL, bendamustine again demonstrated good efficacy but with more toxicity in this relatively heavily pretreated population. Patients received bendamustine 70 mg/m^2/day IV days 1 and 2 every 28 days in combination with rituximab for up to 6 cycles. The efficacy data in 23 patients treated with bendamustine and rituximab demonstrated an overall response rate of 65.2% and a CR rate of 13%. Toxicity primarily consisted of myelosuppression and infections, with grade 3 or 4 hematologic toxicities occurring in 10-15% of all treatment cycles. In addition, 6 events of grade 3 or 4 infections occurred, as well as 3 deaths from pneumonia and urosepsis.[63]

5.3 Experience with Lenalidomide

5.3.1 Lenalidomide pharmacology and *in vitro* experience

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer anti-tumor and anti-metastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.[1] In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T-cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production.[2] Upregulation of T-cell derived IL-2 production is achieved at least in part through increased AP-1 activity.[64]

Increased production of IL-2 and IFN-gamma also leads to augmentation of natural killer cell number and function.[65] Previous experience in multiple myeloma cell lines has demonstrated the direct ability of lenalidomide to induce apoptosis and G1 growth arrest.[3]

5.3.2 Clinical experience in multiple myeloma

Revlimid® (lenalidomide) is FDA approved in combination with dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. Based on phase I studies with lenalidomide and the observed myelosuppression beyond day 28 at the 25 mg and 50 mg daily dose levels, the dose schedule most widely used in recent phase II and III studies has been lenalidomide doses up to 25 mg daily on days 1-21, repeated every 28 days.[66,67]

A multicenter, randomized phase II trial compared 2 syncopated dose schedules of lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma, with all patients receiving treatment on days 1-21 of a 28-day cycle. Patients treated with 15 mg twice daily experienced more myelosuppression and dose reductions compared with patients treated with 30 mg once daily. Anti-myeloma activity was observed with each dose and schedule of single-agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone.[68] A phase II trial utilizing lenalidomide plus dexamethasone for newly diagnosed multiple myeloma patients was reported by the Mayo Clinic, with lenalidomide given orally 25 mg daily on days 1-21 and dexamethasone given orally 40 mg daily on days 1-4, 9-12, and 17-20 of each 28 day cycle. Thirty-one of 34 patients achieved an objective response, including 2 (6%) achieving a CR, and 11 (32%) meeting criteria for both very good partial response and near CR, resulting in an overall objective response rate of 91%. Forty-seven percent of patients experienced grade 3 or higher non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%).[69]

Celgene Corporation sponsored 2 multicenter, randomized, double-blinded, placebo-controlled phase III trials [1 U.S. (MM-009) and 1 international (MM-010)] trial in patients with relapsed or refractory multiple myeloma], enrolling more than 350 patients.[70] Patients could not be refractory to dexamethasone, and were randomized to receive dexamethasone with lenalidomide or dexamethasone + placebo. Patients received

dexamethasone 40 mg orally daily on days 1-4, 9-12 and 17-20, and lenalidomide or placebo at a dose of 25 mg daily on days 1-21 of each 28 days cycle. After 4 cycles, there was a pre-determined reduction of the dexamethasone dose to 40 mg daily on days 1-4 repeated every 28 days. In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that patients receiving the combination of lenalidomide and dexamethasone had significantly longer times to progression and higher response rates than those treated with single-agent dexamethasone.[70] These studies led to the FDA approval of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma in patients that have received at least one prior therapy.

5.3.3 Clinical experience in myelodysplastic syndromes (MDS)

Revlimid® (lenalidomide) is also approved 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. An exploratory trial in 43 MDS patients with transfusion-dependent or symptomatic anemia was conducted at the University of Arizona.[71] Patients received lenalidomide at doses of 10 mg or 25 mg per day on days 1-21, repeated every 28 days. All enrolled patients had achieved no response to erythropoietin or had a high endogenous erythropoietin level. Response rates were similar across the different dose schedules used. Responses were observed in 24 patients overall (56%) including 21 patients with a major response and 20 patients with sustained transfusion independence. After a median follow-up of 81 weeks, the median duration of major response had not been reached after more than 48 weeks. Neutropenia and thrombocytopenia were the most common adverse events, and resulted in dose delays or reductions in 25 patients (58%).

Celgene Corporation sponsored a multicenter trial (MDS-003) of 148 MDS patients with a clonal interstitial deletion involving chromosome 5q31.1. Lenalidomide was given at a dose of 10 mg on days 1-21 (repeated every 28 days) to 44 patients, and at a dose of 10 mg daily to the other 104 patients. Transfusion-independence was achieved in 93 patients (64%), with a median hemoglobin increase of 3.9 g/dL. Cytogenetic response was achieved in 76% of transfusion-independent patients with 55% achieving a cytogenetic complete response. With a median follow-up of 9.3 months, the median response duration had not been reached. Neutropenia (39%) and thrombocytopenia (35%) were the most common adverse events requiring dose delays or reductions.[72] Another Celgene sponsored trial (MDS-002) included patients with low- to intermediate-1 risk MDS (n=215). Among the 166 patients with documented low- to intermediate-1 risk MDS, 84 patients (51%) responded to treatment. Transfusion-independence was achieved in 54 patients (33%) and 30 patients (18%) achieved a minor response (defined as a ≥50% decrease in blood transfusion requirements). The median duration of transfusion-independence was 41 weeks.[72] These data collectively led to the FDA approval of lenalidomide for MDS with the 5q chromosomal deletion.

5.3.4 Clinical experience in leukemia and lymphoma with lenalidomide

Preliminary data show significant activity of lenalidomide in CLL, with response rates in relapsed/refractory CLL and indolent and aggressive NHL ranging from 25% to 70%

(Table 3).[24,25,29,73-75] These results with single-agent lenalidomide were particularly impressive given that 36% and 51% of patients in 2 of the larger CLL studies had disease which was fludarabine-refractory.[29,30] Additional data have demonstrated an association between increased likelihood of objective response in NHL and low tumor burden (<50 cm^2 of measurable disease).[24,25]

A recent report of lenalidomide in previously untreated CLL demonstrated clinically significant single-agent activity.[76] In the original study design, patients were treated with lenalidomide 10 mg daily on days 1-21 of each 28 day cycle, with 5 mg weekly dose escalations to the target dose of 25 mg/day. However, severe toxicities (tumor lysis syndrome and fatal sepsis) in the first 2 patients enrolled led to amendment of the treatment protocol to a lenalidomide starting dose of 2.5 mg/day on the same dosing schedule followed by monthly dose escalations to target dose of 10 mg/day. A total of 25 patients were treated on the amended dosing schedule, with 56% of patients achieving a partial response. Of the 14 responders, the duration of response was 16.6 months (range 5-28.7 months). Toxicities observed most commonly were tumor flare (88% of patients with some degree of tumor flare) but all were grade 1-2. Grade 3 and 4 neutropenia occurred in 72% of patients, but with only 5 episodes of febrile neutropenia.[76] Interestingly, rebound lymphocytosis was noted during the 1 week break from drug therapy, further supporting the potential benefit of a continuous dosing scheduling as proposed in the study protocol.

Table 3. Outcomes of lenalidomide in relapsed/refractory lymphoma subtypes†

	N	ORR	PFS
Ferrajoli *et al*[30] Phase II, R/R CLL (27% FB-refractory)	44 MPT 5	32% 3 CR, 11 PR	NR 73% alive with median follow-up time of 14 months
Chanan-Khan *et al*[29] Phase II, R/R CLL (51% FB-refractory)	45 MPT 3	47% 4 CR, 17 PR	NR
Witzig *et al*[74] Phase II, indolent NHL	43 SLL 18 FL 22 MPT 3	23% 2 CR, 1 CRu, 7 PR	4.4 mos (>16.5 mos in responders)
Tuscano *et al*[24] Phase II, MCL	15 MPT 4	53% All responses in patients with tumor burden <50 cm^2 and time since last RB of ≥230 days	5.7+ mos
Wiernik *et al*[77] Phase II, aggressive NHL	49 MPT 4	35% 2 CR, 4 CRu, 11 PR	7.5 mos versus 1.9 mos (longer PFS in patients with low tumor burden and ≥230 days since last RB)
Lossos *et al*[25] Phase II, DLBCL	26 MPT 3	19% 1 CR, 2 CRu, 2 PR 50% in subset with lower disease burden, longer time since prior RB	7.4 mos versus 1.9 mos (longer PFS in patients with low tumor burden and ≥230 days since last RB)
Wang *et al*[75] Phase I/II study of RB + LD in MCL (all with prior RB)	10‡ MPT 1-4	70%‡ 3 CR, 4 PR	NR

Abbreviations: CR=complete response, CRu=unconfirmed complete response, DLBCL=diffuse large B-cell lymphoma, FB=fludarabine, FL=follicular lymphoma, LD=lenalidomide, MCL=mantle cell lymphoma, MPT=median prior therapies, NR=not reported/not yet reached, PR=partial response, RB=rituximab, R/R=relapsed/refractory.
†All patients treated with lenalidomide 20-25 mg/day days 1-21 every 28 days.
‡Includes 7 patients treated at maximum tolerated LD dose of 20 mg/day as determined in phase I portion of study and 3 patients treated at 20 mg/day dose level in phase II portion of study; no responses observed at the 10 mg and 15 mg dose levels.

5.3.5 Lenalidomide Adverse Events

Most frequently reported adverse events observed during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting, diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, urinary tract infection, upper respiratory infection, cellulitis, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, fractures, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, stroke, convulsions, dizziness, spinal cord compression, syncope, disease progression, and death not otherwise specified.[72]

5.4 Maintenance Therapy with Rituximab + Lenalidomide

5.4.1 Experience with rituximab maintenance therapy in indolent NHL

One strategy to improve the durations of remission in CLL and SLL is the use of maintenance therapy for treatment of minimal residual disease following cytoreductive induction chemotherapy. This method has already demonstrated benefit in improving PFS in indolent lymphomas, although with the majority of data limited to follicular lymphoma (Table 4).[5-7,9,10] ECOG 1496 did include approximately 15% of enrolled patients as SLL, although limited conclusions about the specific added benefit of rituximab maintenance are difficult to extrapolate from this subgroup.[5] These data with maintenance rituximab collectively led to FDA approval in January 2011 of rituximab maintenance therapy for patients with previously untreated CD-20 positive follicular B-cell non-Hodgkin lymphoma who achieve a response to rituximab in combination with induction chemotherapy.

Given the minimal toxicities and proven activity of rituximab in the maintenance setting, rituximab appears to be an ideal agent for use in combination therapy following induction chemotherapy in CLL/SLL. In addition, safety data exist to support maintenance therapy with rituximab for at least 2 years following induction chemotherapy.

Table 4. Maintenance rituximab in indolent NHL subtypes

	N	MR dosing	PFS
PRIMA[6] Induction chemo (R-CHOP, R-CVP, R-FCM) followed by MR versus OBS	N=1217 All with FL Previously untreated FL	375 mg/m^2 IV every 8 weeks for 2 years (total 12 doses)	3 year PFS MR 74.9% OBS 57.6% (p<.0001)
EORTC 20981[9] R-CHOP or CHOP induction followed by MR versus OBS	N=465 All with FL Relapsed/refractory FL	375 mg/m^2 IV every 3 months for 2 years (total 8 doses)	Median PFS MR 3.7 years OBS 1.3 years (p<.001)
ECOG 1496[5] CVP → OBS CVP → MR	N= 387 FL 282 SLL 57 (15%) Previously untreated NHL	375 mg/m^2 IV weekly X 4 every 6 mos for 2 years (total 16 doses)	3 year PFS: MR 68% OBS 33% (p<.0001)

Abbreviations: CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone chemotherapy; CVP=cyclophosphamide, vincristine, prednisone chemotherapy; FCM=fludarabine, cyclophosphamide, mitoxantrone chemotherapy; FL=follicular lymphoma; MR=maintenance rituximab; NHL=non-Hodgkin lymphoma; OBS=observation; PFS=progression-free survival; SLL=small lymphocytic lymphoma.

5.4.2 Rationale for lenalidomide maintenance

As described in Section 5.3.4, existing data show significant activity of lenalidomide in CLL, with response rates in relapsed/refractory CLL and indolent and aggressive NHL ranging from 25% to 70% (Table 2).[24,25,29,73-75] More recent data have also demonstrated the activity of lenalidomide in previously untreated CLL.[76] Previous reports have demonstrated an association between increased likelihood of objective response in NHL and low tumor burden (<50 cm^2 of measurable disease).[24,25] Given the anticipated minimal residual disease expected after induction chemotherapy with bendamustine and rituximab, lenalidomide further emerges as an appealing maintenance therapy option.

5.4.3 Secondary malignancy risk with lenalidomide maintenance

A possible small increased risk of second primary malignancy (SPM) has been described with lenalidomide therapy in clinical trials involving treatment of a broad range of hematologic malignances. A summary of the available data to date for SPM with lenalidomide was recently distributed to investigators in a confidential notice from Celgene Corporation dated March 15, 2011. An updated confidential safety notice from Celgene Corporation dated January 5, 2018 provides additional data supporting that overall rates of invasive SPMs have been similar for patients receiving versus not receiving

lenalidomide in randomized CLL/lymphoma trials. However, this updated safety notice from January 2018 described what may be a signal of an increased risk of B-cell neoplasms (particularly B-cell acute lymphoblastic leukemia, B-ALL) in CLL patients exposed to lenalidomide.

Data are available on rates of SPM in subjects with CLL and other non-Hodgkin lymphoma histologies treated with lenalidomide. Nine Celgene-sponsored studies in non-Hodgkin lymphoma (including indolent B-cell histologies, aggressive B-cell histologies, mantle cell lymphoma, and mature T-cell lymphomas), noted 9 of 527 subjects have experienced a reported SPM (1.7%), including 8 solid tumors and 1 new primary hematologic malignancy. Among 4 Celgene-sponsored clinical studies in subjects with CLL, 2 of 184 (1.1%) of lenalidomide-treated subjects experienced a SPM (Celgene safety notice, 3.15.2011).

As mentioned previously, there may be an increased trend for a potential causal relationship between lenalidomide exposure and risk for B-cell neoplasms. A detailed review of safety data from 3 Celgene sponsored studies (CLL-002, CLL-008 and CLL-009) identified 4 cases of B-ALL among 484 lenalidomide-exposed subjects (0.8% risk). In the CLL-002 (CONTINUUM) study,[37] randomizing subjects to lenalidomide versus placebo maintenance following induction therapy for relapsed/refractory CLL, there were 3 cases of B-cell neoplasms among 157 lenalidomide-treated patients. These 3 cases included 1 event of B-ALL (0.6%), 1 event of Hodgkin lymphoma, and 1 event of diffuse large B-cell lymphoma. No events of B-ALL of other B-cell neoplasms were reported in the placebo group (n=154). In the CLL-008 (ORIGIN) study,[78] elderly patients with previously untreated CLL were randomized to lenalidomide versus chlorambucil. Three cases of B-cell neoplasms (1.3%) were reported among 224 subjects treated with lenalidomide; these events included B-ALL (n=2) and Hodgkin lymphoma (n=1).

A recent report of the CLLM1 trial randomized 89 high-risk patients with measurable minimal residual disease in a 2:1 fashion to lenalidomide (n=60) versus placebo (n=29), with lenalidomide administration until disease progression.[27] After a median observation time of 17.9 months, the hazard ration for progression-free survival was 0.168 (95% CI 0.074-0.379). Recently 2 events of B-ALL in the lenalidomide arm led to discontinuation of the lenalidomide treatment arm of the study. There were no events of B-ALL in the smaller placebo arm of the trial.

Results from CALGB 10404 administered lenalidomide on days 1-21 of each 28-day cycle following fludarabine-based induction therapy. In this large trial of 342 patients, no increased rate of secondary primary malignancies or second primary hematologic malignancies were observed.[26] This study limited duration of maintenance to 6 months.

In conclusion, the risk for development of SPM and especially hematologic SPM remains an area of uncertainty and for which careful monitoring is required. Dose modification of lenalidomide to allow periods of marrow recovery may provide benefit in decreasing risk of second malignancies (i.e., comparing dosing strategy of CLL M1 with CALGB 10404). To maximum benefit of maintenance and improve safety of the described risks, lenalidomide dosing will be modified to days 1-21 of each 28 day cycle.

5.4.4 Lenalidomide + rituximab combination therapy

Promising efficacy and an acceptable toxicity profile have been reported with the combination of rituximab and lenalidomide. A report of the activity of lenalidomide (dosed at 10 mg daily on days 9-28 of each 28-day treatment cycle) combined with rituximab for up to 12 therapy cycles found promising response rates in patients with relapsed and refractory CLL. All patients had received prior fludarabine-based chemotherapy, and 59 patients were evaluable for response. An ORR of 64% was observed, including 8% CRs and 5% CRs with incomplete hematologic recovery.[31] In a single institution phase II study of rituximab 375 mg/m^2 on day 1 and lenalidomide 20 mg/day orally days 1-21 every 28 days for up to 6 treatment cycles, outcomes in 30 patients with previously untreated CLL were reported. Of 28 patients evaluable for response, an overall response rate of 85% was observed with an impressive 79% achieving CRs.[32,33] These data suggest that the combination of lenalidomide + rituximab has promising response rates and appears to have improved efficacy compared with single-agent lenalidomide.[29,30]

5.4.5 Rationale for maintenance rituximab + lenalidomide in previously untreated CLL/SLL

Patients with CLL/SLL harboring mutations that result in dysfunction of the p53 tumor suppressor gene are associated with higher rates of chemotherapy-resistance and poorer survivals.[79-84] Although de novo p53 mutations have been reported in CLL/SLL, the majority of functional losses of p53 in CLL/SLL occur in the setting of 17p or 11q deletions. The tumor suppressor gene p53 maps to 17p13.1, and up to two-thirds of CLL/SLL patients with 17p deletions are found to harbor p53 mutations.[84-90] The ataxia telangiectasia gene (ATM) is the principal activator upstream of the p53 protein in response to DNA double-strand breaks. Mutations of ATM occurring in a subset of CLL/SLL patients with 11q deletions may lead to functional loss of p53, resulting in higher rates of chemotherapy-resistance in patients with 11q- CLL/SLL.[91-94]

At least 3 separate large multicenter randomized trials (i.e., German CLL Study Group CLL4,[95] United Kingdom Leukemia Research Foundation CLL4,[96] US intergroup E2997[97]) have demonstrated poorer outcomes for patients harboring the 17p deletion, with shorter durations of remission and in some cases, significantly inferior overall survival. Based on the innate chemotherapy-resistance of CLL/SLL with 11q and 17p deletions, considering a novel immunomodulatory therapy approach with maintenance rituximab + lenalidomide following induction chemotherapy is a rationale first-line approach, even in younger patients who may be fit enough to tolerate up-front FCR chemotherapy. In older patients or patients with co-morbidities in the setting of newly diagnosed CLL/SLL requiring therapy, the high rates of toxicity with FCR chemotherapy makes a rituximab + bendamustine induction regimen an appealing option regardless of cytogenetic risk profile.

FCR chemotherapy has been associated with the longest progression-free survival to date, although the toxicity of this regimen often precludes its use in older patient populations or patients with medical comorbidities. A prospective phase II trial of 300 previously untreated CLL patients reported from MD Anderson Cancer Center found a 6 year failure-free survival of 51% and 6 year overall survival of 77% with FCR

chemotherapy. The median time to progression was 80 months.[98] Cytogenetic studies were available in 222 of the enrolled patients, but with only 8 patients demonstrating a 17p deletion. Of these patients with 17p deletions, only 2 achieved a completed response. The toxicity of this regimen is highlighted by the risks of acute and delayed myelosuppression and infections with this regimen, with 10% rate and 4% rate of serious grade ≥3 opportunistic post-treatment infections in the first 1 and 2 years post-chemotherapy, respectively.[98] Relevant pretreatment characteristics independently associated with inferior response and outcomes were age ≥70 years and presence of 17p deletion. Although these data reported by MD Anderson demonstrate impressive durations of remission, the number of older adults were small (only 14% of patients age 70 or older) with a relatively small fraction of patients with the adverse 17p deletion. [98] Despite the small number of enrolled patients with the 17p deletion, it was highlighted that this subgroup fared poorly in terms of chemotherapy response and duration of response with FCR chemotherapy.

For younger, fit patients, FCR remains a recommended first-line chemotherapy in many cases. However, the above data from MD Anderson reports a single-institution experience, and superiority of FCR over FR (fludarabine + rituximab) or BR (bendamustine + rituximab) chemotherapy has not been proven. A randomized trial comparing FCR and FR is underway in the US intergroup (CALGB 10404). In phase II trials, overall survival rates appear to be similar with these regimens, but toxicity is lower with FR.[99] A recent report by the German CLL Study Group of BR in previously untreated CLL reported an overall response rate of 88% and CR rate of 23.1%. This study included 25.6% of patients age 70 or older, and also included 26% of patients with the adverse cytogenetics 17p or 11q deletions. Although the median observation is relatively brief at 27.0 months, 90.5% of patients are alive with median EFS of 33.9 months.[35] The German CLL Study Group CLL10 trial compared the efficacy of BR versus FCR for newly diagnosed CLL.[22] The results from the CLL10 trial have been recently published, and demonstrated more severe neutropenia and infections with FCR chemotherapy. Although median PFS was improved in the overall population with FCR (55.2 months versus 41.7 months), ***there was no difference in median progression-free survival with FCR versus BR chemotherapy in patients older than age 65.***

However, there is sufficient data regarding the efficacy and favorable toxicity of bendamustine + rituximab to consider this regimen as a standard upfront therapy for CLL/SLL in all patient groups, regardless of age, fitness, or ability to tolerate even more toxic regimens (i.e., FCR or other fludarabine-containing regimens). Bendamustine has received an FDA approved indication for treatment of CLL, both in upfront treatment of disease and in the relapsed/refractory setting based on the compelling data supporting its efficacy in this disease. As cited above, the German CLL Study Group report reported a median PFS of 33.9 months in a population treated with BR that included >25% of patients older than age 70.[35] In addition, this was a multicenter trial including over 40 sites, further lending to the strength of the data.[35] In contrast, the data reported from MD Anderson with an impressive median time to progression of 80 months with FCR chemotherapy was a single-institution trial (e.g., inherent selection bias) with only 13% of enrolled patients older than age 70.[98,100] As described above, the long-term report of outcomes from this study independently identified older age as an adverse prognostic indicator in this study population.[98] The German CLL Study Group CLL10 trial (FCR versus BR chemotherapy

as front-line therapy in CLL) reported a favorable median PFS of 41.7 months in patients treated with front-line BR, although notably this study excluded patients with the high-risk 17p deletion.[22]

The conclusions from these data are: 1.) BR is a highly active induction regimen in CLL in the first-line setting, 2.) Randomized data show no benefit with FCR versus BR in adults older than age 65 in the CLL10 trial,[22], 3.) Both short-term and long-term toxicities were more favorable with BR chemotherapy compared with reported toxicities with FCR; this was further verified by the CLL10 trial.[22] Therefore, standard clinical practice at the University of Wisconsin is to offer both BR or fludarabine-based regimens to all patients as reasonable first-line strategies, with physicians collaborating with patients to guide the final decision based on the probable risk-to-benefit ratio of treatment depending on their individual health issues, clinical behavior and biological features of their CLL/SLL, and concerns regarding toxicities.

In all populations with adverse cytogenetic risk disease, consideration of a novel therapy approach with the combination of the biologic agents rituximab + lenalidomide is a reasonable consideration. A recent report by Ferrajoi and colleagues reported their experience with rituximab + lenalidomide in 59 patients with relapsed/refractory CLL (all had received prior fludarabine, 88% had received prior FCR), including 25% of enrolled patients having 17p deletions. An impressive 64% response rate was observed, with a treatment failure rate of 42% after a median follow-up of 14 months. Most interestingly, there was no difference in objective response rate and time to treatment failure for patients with the 17p deletion versus those with other baseline cytogenetic risk disease. Given the poor outcomes associated with FCR chemotherapy in 17p deletion CLL, consideration of a less toxic induction chemotherapy regimen following by therapy with the novel biologic combination of rituximab + lenalidomide is particularly promising for younger and fitter patients with poor cytogenetic risk factors at baseline. ***This role maintenance therapy containing lenalidomide is further strengthened by 2 recent randomized, placebo-controlled trials of single-agent lenalidomide maintenance after induction chemotherapy in both previously untreated and relapsed/refractory CLL. Both studies showed significant improvement in PFS with lenalidomide with acceptable toxicity and tolerability.***[36,37]

5.5 Investigational Rationale

Bendamustine is a recently FDA-approved agent with activity in CLL/SLL, including significant activity in the setting of fludarabine-refractory disease. The efficacy of bendamustine with a favorable toxicity profile has been demonstrated in previously untreated CLL/SLL, and ongoing studies are comparing up-front use of bendamustine versus fludarabine-based chemotherapy regimens. As the majority of patients with newly-diagnosed CLL/SLL are over the age of 60 and more at risk from significant toxicity from fludarabine-based regimens, evaluation of a bendamustine-based regimen in this population may offer the possibility of improved PFS with lesser toxicity. It is notable to emphasize that there was no difference in PFS between patients >65 years of age treated with FCR versus BR in the CLL10 trial of first-line CLL therapy; however, there was significantly more neutropenia and infections with FCR.[22] In younger patients, the presence of 11q and 17p deletions that confer increased risk of chemotherapy resistance

further supports the potential advantageous role for a novel immunomodulatory maintenance therapy after initial cytoreduction.

The incorporation of a maintenance therapy to overcome the shorter remission durations that are typical for this patient population is a reasonable and feasible option. In considering potential options for treatment of CLL/SLL as a maintenance strategy following induction chemotherapy, lenalidomide and rituximab are appealing options based on their convenient dosing schedules and recent evidence of acceptable toxicity and promising efficacy in combination therapy.

6. Study Objectives and Endpoints

6.1 Primary Objective

- The primary objective is progression-free survival for patients entering the maintenance therapy phase with rituximab and lenalidomide after induction therapy with bendamustine and rituximab (beginning cycle 1, day 1 of maintenance chemotherapy):
    - Progression is defined as radiographic or clinical progression as defined by the specified standard response criteria for CLL/SLL or initiation of a new anti-neoplastic therapy in the absence of progression.
    - Tumor measurements and disease assessments will be performed at the time of screening, following cycles 3 and 6 of induction chemotherapy, every 4 cycles during the maintenance portion of treatment, and at the end of treatment (EOT).
    - Subjects with clinical evidence of progression prior to a planned disease assessment will be evaluated at the time of clinically suspected progression.
    - Follow-up visits for disease assessment will occur every 3 months after the EOT visit until PD, initiation of alternate anti-neoplastic therapy, decision by the subject to withdraw from the study, or death.

6.2 Secondary Objectives

- To determine objective response rates (CR + PR):
    - Disease assessments including imaging will be performed after cycles 3 and 6 of induction chemotherapy and every 4 cycles during the maintenance portion of treatment.
    - Response and progression in cases of SLL will be evaluated using the International Working Group Criteria for response in lymphoma.[38] Response and progression in cases of CLL will be evaluated in this study using the Revised IWCLL 2008 Criteria for Response in CLL (see Appendix H: Assessment of response).[39]
    - Radiological methodologies, techniques and/or physical examination, established at baseline for the assessment and measurement of each identified lesion will be used for all subsequent assessments.

- To determine toxicities observed with induction chemotherapy and maintenance therapy:
    - Safety evaluations will be based on the incidence, intensity, and type of adverse events (AEs) and clinical laboratory results.
    - Drug doses will be modified as required based on toxicity as assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
- To determine overall survival:
    - Overall survival will be determined from the date of enrollment until death from any cause.

7 Investigational Plan

7.1 Overall Design

Subjects meeting eligibility criteria will begin treatment as described below. All subjects will undergo bone marrow biopsy, CT imaging, and/or PET imaging within 6 weeks prior to enrollment. CLL FISH panel (as described in Section 3.0, Schedule of study assessments) must be completed within at least 12 months prior to enrollment.

7.1.1 Induction chemoimmunotherapy

- Bendamustine 90 mg/m^2/day IV days 1 and 2, administered every 28 days for a total of 6 cycles.
- Rituximab 500 mg/m^2 IV day 1 administered every 28 days (cycle 1 only, rituximab administered at a dose of 375 mg/m^2 IV, which may be given on day 2 of cycle 1 for subjects with significant lymphocytosis at risk for the cytokine release syndrome). In select circumstances, in subjects at high risk for cytokine release syndrome and/or tumor lysis syndrome, rituximab may be administered as late as day 5 of cycle 1 (this alternative dosing of rituximab applies to cycle 1 of induction therapy only).
- Cycles of induction chemoimmunotherapy are repeated every 28 days for a maximum of 6 cycles.

All subjects will undergo CT imaging and bone marrow biopsy within 6 weeks prior to enrollment. CLL FISH panel (as described in Section 3.0, Schedule of study assessments) must be completed within at least 12 months prior to enrollment. During induction chemotherapy, repeat disease assessments will be performed following cycles 3 and 6 of therapy. Treatment will be discontinued for progressive disease, excessive toxicity, or the subject's decision to discontinue therapy. At completion of induction therapy, subjects with CT imaging consistent with possible complete response (CR) will undergo bone marrow evaluation to verify a CR. Subjects with possible CR with residual masses of undetermined significance at the end of induction therapy will undergo PET imaging to evaluate their remission status. Responses to therapy in subjects with leukemic manifestations of disease as CLL will be assessed by the Revised IWCLL 2008 criteria for CLL.[39] Subjects

with primarily lymphomatous manifestation of disease as SLL will be assessed according to the revised Cheson criteria for NHL.[38] All PRs and CRs in cases of CLL will be confirmed by repeat scans at the next scheduled assessment, as outlined in the study calendar. A bone marrow biopsy is required in cases of CLL to confirm CR at least 2 months after the other clinical and laboratory criteria for response are met. Confirmation of complete or partial responses is not required in SLL. Timing of alternate cycle efficacy assessments will be reset following a confirmation of response assessment. In subjects who discontinue induction treatment after 4 cycles, a formal disease assessment does not need to be repeated prior to beginning maintenance therapy.

Subjects achieving an objective response (i.e., PR, CR, or stable disease with tumor shrinkage not meeting criteria for PR) to bendamustine and rituximab induction chemotherapy will begin maintenance therapy with rituximab and lenalidomide 6-12 weeks following the last cycle of induction chemotherapy (i.e., 6-12 weeks from cycle 6, day 1, of induction therapy). Subjects achieving stable disease following induction therapy with an objective response may proceed to maintenance therapy at the discretion of the treating physician. Subjects with objective response after 4 cycles of bendamustine + rituximab (BR) induction therapy are eligible to proceed to maintenance therapy if toxicities are limiting further BR induction therapy, or if the treating physician determines that further BR induction therapy would be associated with excessive risk for additional toxicities.

7.1.2 Maintenance therapy

- Rituximab 375 mg/m^2 IV on day 1 of every odd-numbered cycle X 24 cycles (cycles 1,3,5,7,9,11,13,15,17,19,21,23) for total of 12 doses.
- Lenalidomide 5 mg orally daily on days 1-21 of each 28-day cycle X 24 cycles (cycles 1-24 of maintenance therapy):
    - Subjects entering maintenance with CrCl ≥40 and <60 mL/min will begin dosing at 5 mg every other day on days 1-21. If subjects tolerate treatment without requiring dose modifications, interruptions, or delays due to toxicity, they may, at investigator discretion, escalate in a step-wise manner during subsequent cycles to: 5 mg daily on days 1-21, and then to 10 mg daily on days 1-21.
- At the start of cycle 2 of maintenance (or at the start of a subsequent cycle), lenalidomide may be escalated to 10 mg/day on days 1-21 if toxicity allows (see Sections 9.2.1.5 and 9.2.1.6 for criteria needed to escalate the dose of lenalidomide to 10 mg/day on days 1-21).

Maintenance therapy will begin within 6-12 weeks after the last dose of induction chemotherapy (i.e., 6-12 weeks from cycle 6, day 1 of induction chemotherapy) once there has been recovery of the neutrophils to ≥1000/μL and recovery of platelets to ≥50,000/μL, and the other criteria in Section 7.5 have been met. Subjects are allowed to dose de-escalate and re-escalate lenalidomide during the course of maintenance therapy based on the criteria described in Sections 9.2.1.2, 9.2.1.5, and 9.2.1.6. ***If lenalidomide must be held for >12 weeks due to toxicity, subjects must discontinue lenalidomide but are eligible to continue maintenance rituximab as defined by the treatment protocol.***

If rituximab therapy must be held for >12 weeks due to toxicities, subjects will discontinue rituximab but may continue lenalidomide maintenance therapy as defined by the treatment protocol. If subjects are not able to resume either rituximab or lenalidomide maintenance for >12 weeks due to toxicities or issues unrelated to protocol therapy (e.g., other medical complications, surgery, ect), the subject must withdraw from protocol therapy.

Subjects will undergo reassessment of disease after every 4 cycles of maintenance therapy, and at the end of treatment (EOT). However, subjects who have findings on clinical or laboratory exam suggesting progression of disease must undergo CT imaging at the time of suspected progression to reassess their disease status.

7.1.3 Follow-up phase

At the time of treatment discontinuation for any reason, subjects will undergo end of treatment (EOT) evaluations. Whenever possible, restaging CT scans (with or without repeat PET imaging) and a clinical assessment of any other sites of evaluable disease should be performed within 30 days of treatment discontinuation. In addition, a safety assessment will be done approximately 30 days following the last dose of study drug.

Subjects who complete the full course of maintenance therapy will immediately begin the follow-up phase of the protocol. During this period of long-term follow-up, subjects will be evaluated at 3 month intervals for 2 years with a physical examination and repeat imaging as indicated to evaluate for evidence of disease progression. After 2 years of long-term follow-up in the absence of progression, the frequency of ongoing care and assessment will be at the discretion of the subject's treating physician. However, it is recommended that reassessment of the subject's disease status be performed by repeat imaging at least every 6 months. Information on the subject's survival and progression status will be updated annually for up to 5 years following completion of therapy.

For subjects who discontinue therapy due to progression, information on the subject's survival will be updated annually for up to 5 years following the time of progression.

Subjects who discontinue treatment early due to toxicity or the subject's decision to discontinue treatment (but not to withdraw consent from the protocol), follow-up with clinical and/or radiographic reassessment approximately every 3 months will be continued until evidence of progression or up to 2 years. After 2 years of follow-up, the frequency of ongoing care and assessment will be at the discretion of the subject's treating physician, although it is recommended that reassessment of the subject's disease status be performed by repeat imaging at least every 6 months. Information on the subject's survival and progression status will be updated annually for up to 5 years after discontinuation of therapy.

7.1.4 Discontinuation of Study Treatment

Treatment will continue until completion of the protocol therapy (6 months of induction therapy and 24 cycles of maintenance therapy) or the occurrence of any of the following events:

- Disease progression, defined as clinical, laboratory, or radiographic criteria for progression as defined in the response criteria (Appendix H).
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Discontinuation of protocol treatment for any reason.
- Initiation of alternative anti-cancer therapy, even in the absence of progression.
- Major violation of the study protocol.
- Withdrawal of consent.
- Lost to follow up.
- Death.
- Suspected pregnancy

7.2 Screening and Eligibility

The investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 3.0, Schedule of study assessments, and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

Approximately 36 subjects with CLL/SLL will be screened for enrollment and must meet the eligibility criteria below.

7.2.1 Induction Inclusion criteria

1. Histologically confirmed CLL/SLL.
2. No prior cytotoxic chemotherapy for their disease; prior therapy with single-agent rituximab is permitted.
3. Understand and voluntarily sign an informed consent document.
4. Age ≥18 years at the time of signing the informed consent document.
5. In cases of SLL, subjects must have at least one bidimensionally measurable lesion; one of the measurements must be ≥1.5 cm in one dimension.
6. ECOG performance status of ≤2 at study entry (see Appendix A).
7. Laboratory test results within these ranges:
    - Absolute neutrophil count ≥1500/μL

- Platelet count ≥100,000/μL
- Subjects with neutrophils <1500/μL or platelets <100,000/μL with splenomegaly or extensive bone marrow involvement as the etiology for their cytopenias are eligible
- Subjects must have adequate renal function with a creatinine clearance of ≥40 mL/min as determined by the Cockcroft-Gault calculation
- Total bilirubin ≤2X upper limit laboratory normal (ULN); subjects with non-clinically significant elevations of bilirubin due to Gilbert's disease are not required to meet these criteria
- Serum transaminases AST (SGOT) and ALT (SGPT) ≤5X ULN
- Serum alkaline phosphatase ≤5X ULN

8. Disease-free of prior malignancies for ≥2 years with the exception of basal or squamous cell skin carcinoma, carcinoma "in situ" of the breast or cervix, or localized prostate cancer (treated definitively with hormone therapy, radiotherapy, or surgery).
9. Life expectancy of at least 3 months.
10. All study participants must be willing to be registered into the mandatory Revlimid REMS® program after completion of induction chemoimmunotherapy and prior to maintenance therapy, and be willing and able to comply with the requirements of the Revlimid REMS® program.
11. Subjects must not have a known history of hypersensitivity to mannitol.
12. Prior therapy with rituximab is permitted, even in the setting of rituximab-refractory disease.
13. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
14. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (subjects intolerant to aspirin may use warfarin or low molecular weight heparin*) if clinically indicated*.
15. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by the Revlimid REMS® program) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they

have had a successful vasectomy. See Appendix B: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

7.2.2 Induction Exclusion criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent document or complying with the protocol treatment.

2. Pregnant or breast-feeding females. Lactating females must agree not to breast-feed while taking lenalidomide.

3. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
4. Subjects are not eligible if there is a prior history or current evidence of central nervous system or leptomeningeal involvement.
5. Known hypersensitivity to thalidomide.
6. Concurrent use of other anti-cancer agents or treatments.
7. Known to be positive for HIV or infectious hepatitis (type B or C).
8. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical or breast cancer, or other cancer from which the subject has been disease free for at least 2 years.
9. Severe or life-threatening anaphylaxis or hypersensitivity reaction when previously exposed to rituximab or other monoclonal antibody therapy.
10. Chronic hepatitis B or hepatitis C infection.
11. New York Heart Association class 3-4 heart failure.
12. More than one grade 2 or higher transaminase elevation.

7.3 Registration

Each subject enrolled in the study is to be registered with the UWCCC OnCore database at study entry.
At the time of registration, the following will be verified in OnCore:

- IRB approval at the registering institution
- Subject eligibility
- Existence of a signed informed consent form
- Existence of a signed authorization for use and disclosure of protected health information
- Accrual assessed for subject to enter study

Treatment cannot begin prior to registration and must begin within ≤7 days following registration. Baseline tests must be completed within the guidelines as outlined in Section 3.0, Schedule of study assessments. All required baseline symptoms must be documented and graded.

7.4 Visit Schedule and Assessment

Screening assessments and study visits and assessments are outlined in Section 3.0, Schedule of study assessments.

A description and schedule of planned disease assessments during protocol therapy are outlined in Section 7.1.1, Induction chemoimmunotherapy and Section 7.1.2, Maintenance therapy above. At treatment discontinuation, subjects will undergo EOT evaluations as described in Section 7.1.3, Follow-up phase. A safety assessment will be done approximately 30 days following the last dose of study drug.

7.5 Criteria for Initiation of Rituximab and Lenalidomide Maintenance Therapy

After receiving 6 cycles of induction therapy with bendamustine and rituximab, subjects may proceed to maintenance therapy with rituximab and lenalidomide. Subjects with objective response after 4 cycles of bendamustine + rituximab (BR) are eligible to proceed to maintenance therapy if toxicities are limiting further BR induction therapy, or if the treating physician determines that further BR induction therapy would be associated with excessive risk for additional toxicities. Maintenance therapy with lenalidomide must begin 6-12 weeks following the last dose of induction chemotherapy (i.e., 6-12 weeks following cycle 6, day 1 of bendamustine + rituximab). The following inclusion and exclusion criteria must be met prior to initiating maintenance therapy with lenalidomide.

7.5.1 Inclusion criteria for initiation of rituximab and lenalidomide maintenance therapy

- Response evaluation at the completion of 6 cycles of induction therapy with bendamustine and rituximab must demonstrate a PR or CR. Subjects with SD but with evidence of an objective response to induction chemotherapy may proceed to maintenance therapy at investigator discretion. Subjects with objective response after 4 cycles of bendamustine + rituximab (BR) are eligible to proceed to maintenance therapy if toxicities are limiting further BR induction therapy, or if the treating physician determines that further BR induction therapy would be associated with excessive risk for additional toxicities.
- ANC ≥ 1000/μL
- Platelet count ≥ 50,000/μL
- Calculated (method of Cockroft-Gault) creatinine clearance of ≥40 mL/min; 24 hour urine collection may also be performed to assess creatinine clearance. If creatinine

clearance is ≥40 mL/min and <60mL/min prior to cycle 1 of maintenance therapy, the starting dose of lenalidomide is dose level -1 (5 mg every other day on days 1-21).

- Any drug-related rash or neuropathy that may have occurred has resolved to ≤grade 1 severity.
- Tumor lysis syndrome (TLS) has not exceeded grade 1 severity during previous cycle (see Appendix I: Cairo-Bishop definition of tumor lysis syndrome).
- If TLS ≥grade 2 during any previous cycle, electrolyte abnormalities have resolved to ≤grade 0 severity (see Appendix I: Cairo-Bishop Definition of Tumor Lysis Syndrome).
- Any other drug-related non-hematologic toxicities that may have occurred have resolved to ≤grade 2 severity.
- Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix B: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
- All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the Revlimid REMS® program.

7.5.2 Exclusion criteria for initiation of lenalidomide maintenance therapy

- Progressive disease following induction therapy with bendamustine and rituximab.
- Uncontrolled hyperthyroidism or hypothyroidism.
- Uncontrolled autoimmune hemolytic anemia or thrombocytopenia.
- Disease transformation (active), i.e., Richter's syndrome, prolymphocytic leukemia.

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

8 Drug Administration, Formulation, and Procurement

8.1 Drug Administration

8.1.1 Rituximab

Rituximab will be provided by Genentech for participants in this study. Rituximab will be administered at 500 mg/m^2 IV on day 1 of each induction chemotherapy cycle (cycle 1 only, rituximab administered at a dose of 375 mg/m^2 IV), for a total of 6 induction chemotherapy cycles. Subjects with high circulating lymphocyte counts at high risk for the cytokine release syndrome may be given rituximab on day 2 of cycle 1. In select circumstances, in subjects at high risk for cytokine release syndrome and/or tumor lysis syndrome, rituximab may be administered as late as day 5 of cycle 1 (this alternative dosing of rituximab applies to cycle 1 of induction therapy only). Subjects demonstrating tumor lysis syndrome and receiving aggressive hydration for prophylaxis may have reduced physiologic reserve to tolerate any degree of cytokine release syndrome without risk for additional complications. In these circumstances, delaying rituximab as late as day 5 of cycle 1 is acceptable to reduce additional complications. Given the long half-life of rituximab (median half-life of 32 days), this flexibility in dosing of rituximab during cycle 1 only will not have a clinically significant impact on the response to induction chemoimmunotherapy.

Rituximab should be administered by IV infusion, per the package insert instructions.

The amount of drug to be administered will be based on body surface area (BSA). The preferred method for calculating body surface area is the Mosteller formula[101] (see Appendix C) on cycle 1, day 1. At some participating community sites, the Dubois formula[102] is the primary BSA calculation used as part of an electronic medical record and drug ordering template. In such cases, calculations using the Dubois formula are permitted as long as there is no more than a 10% difference in dosing between the Mosteller and Dubois calculations. If a >10% difference in drug dosing is observed, then the Mosteller calculation must be used. The drug doses calculated on cycle 1, day 1 of chemotherapy administration will be used at subsequent visits. However, if the subject experiences a >10% change in body weight from the weight used for the most recent BSA calculation, then drug doses must be recalculated with the more recent body weight. **Rituximab dosing is permitted to be rounded according to institutional standard to ±5% of the calculated dose.**

At treating institutions with a ***rapid rituximab infusion protocol*** in place for eligible subjects, rituximab dosing may be administered per the treating institution's rapid infusion protocol. Recommendations for eligibility to receive rituximab by a rapid infusion protocol are:

- At least the 2nd or greater rituximab infusion of either the induction or maintenance phase of treatment.
- Previous rituximab infusion not turned off due to symptoms of possible or probable rituximab-induced infusion reaction and/or cytokine release syndrome.

- Most recent circulating lymphocyte count <5000 lymphocytes/μL within 4-6 weeks of rituximab infusion.
- Less than 6 months from last rituximab infusion.

Subjects experiencing adverse events may need study treatment modifications (See Section 9).

Complete information on drug formulation, preparation, and adverse effects of rituximab is outlined in Appendix D.

8.1.2 Bendamustine

Bendamustine will be obtained commercially, and will not be supplied by the study supporters. Available bendamustine products for use include Treanda®, generic bendamustine, and Bendeka™. Per institutional standards, bendamustine doses may be rounded within 10% of the calculated dose based on the subject's BSA to accommodate at least half vial size increments (50 mg for bendamustine).

The initial dose of bendamustine will be 90 mg/m^2/day administered IV on days 1 and 2 of each induction chemotherapy cycle (total of 6 induction chemotherapy cycles). Bendamustine will be infused over ≈30-60 minutes for Treanda® and generic bendamustine, and will be infused over ≈10 minutes for the Bendeka™ product. The amount of drug to be administered will be based on BSA calculated using the Mosteller formula preferentially, although the Dubois calculation may be used as an alternative (see Appendix C; also refer to Section 8.1.1 above for complete details as to when the Dubois calculation may be an acceptable alternative). The same BSA will be used for each dose calculation unless the subject experiences a >10% change in body weight from the weight used for the most recent BSA calculation. **Bendamustine dosing is permitted to be rounded according to institutional standard to ±5% of the calculated dose.**

Subjects experiencing adverse events may need study treatment modifications (See Section 9).

Complete information on drug formulation, preparation, and adverse effects of bendamustine is outlined in Appendix E.

8.1.3 Lenalidomide

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 7 days for females of childbearing potential and 14 days for all other risk categories. Drug will be

shipped on a per patient basis by the contract pharmacy to the clinic site. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle**.

After receiving 6 cycles of induction therapy with bendamustine and rituximab, subjects with objective response (i.e., CR, PR, or SD with objective improvement) may proceed to rituximab and lenalidomide maintenance therapy. Maintenance therapy with lenalidomide must begin 6-12 weeks following the last dose of induction chemotherapy (i.e., 6-12 weeks following cycle 6, day 1 of bendamustine + rituximab). The inclusion and exclusion criteria as outlined in Section 7.5 must be met prior to initiating maintenance therapy with rituximab and lenalidomide.

The starting dose of lenalidomide maintenance for investigation is 5 mg/day, orally on days 1-21 of each 28-day cycle for up to 24 cycles. Subjects with CrCl ≥40 and <60 mL/min will initiate therapy at 5 mg every other day on days 1-21. Dosing will be at approximately the same time each day. Prescriptions must be filled within 7 days. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Subjects who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Subjects experiencing adverse events may need study treatment modifications (See Section 9).

Complete information on drug formulation and adverse effects of lenalidomide is outlined in Appendix F.

8.2 Record of Administration and Treatment Compliance

Accurate records will be kept of all study drug administration (including prescribing and dosing) and maintained in the source documents. Clear documentation will be recorded of dose modifications made based on observed toxicities.

Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused study drug and empty study drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit and reconcile with the subject diary. Any unused Revlimid® (lenalidomide) should be returned to the study site for disposition in accordance with the Revlimid REMS® program.

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

9 Dose Modifications and Interruptions

9.1 Induction Dose Modification Guidelines

9.1.1 Rituximab Dose Modifications During Induction

The dose of rituximab will not change based upon hematologic toxicity. Rituximab administration and dose modification must follow labeling instructions and guidelines. Please refer to the approved product label for instructions. Subjects who develop severe infusion reactions should have the rituximab infusion discontinued and have supportive care measures instituted as medically indicated (e.g., IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduced rate, after symptoms have completely resolved. Subjects requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary events, and those with high numbers of circulating malignant cells (>25,000/mm^3) with or without evidence of high tumor burden. In subjects who develop viral hepatitis, rituximab should be discontinued and appropriate treatment, including antiviral therapy, initiated***. If a subject is unable to receive the entire dose of rituximab on day 1 due to a hypersensitivity reaction, the dose may be finished on day 2.***

In select circumstances, in subjects at high risk for cytokine release syndrome and/or tumor lysis syndrome, rituximab may be administered as late as day 5 of cycle 1 (this alternative dosing of rituximab applies to cycle 1 of induction therapy only). Subjects demonstrating tumor lysis syndrome and receiving aggressive hydration for prophylaxis may have reduced physiologic reserve to tolerate any degree of cytokine release syndrome without risk for additional complications. In these circumstances, delaying rituximab as late as day 5 of cycle 1 is acceptable to reduce additional complications. Given the long half-life of rituximab (median half-life of 32 days), this flexibility in dosing of rituximab during cycle 1 only will not have a clinically significant impact on the response to induction chemoimmunotherapy

9.1.2 Bendamustine Dose Modifications During Induction

On the first day of each new treatment cycle and before each bendamustine dose, the subject will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the CTCAE version 4.0.

The following dose-reduction rules for bendamustine should be followed (Tables 5-6):

If toxicities occurred at 90 mg/m^2, reduce to 70 mg/m^2; if toxicity occurred at 70 mg/m^2, reduce to 50 mg/m^2; if toxicity occurred at 50 mg/m^2, reduce to 40 mg/m^2, if toxicity occurred at 40 mg/m^2, discontinue bendamustine and withdraw the subject from the study protocol. If the dose of bendamustine is reduced due to toxicity, it will not be re-escalated later in the study.

Note: If one drug is held during induction therapy, both drugs should be held.

Table 5. Bendamustine Dose Reduction Steps†

Bendamustine dose level	Bendamustine dose reduction
Starting dose	90 mg/m^2
-1	70 mg/m^2
-2	50 mg/m^2
-3	40 mg/m^2
-4	Discontinue bendamustine and withdraw from study protocol.

†If subjects have disease-related splenomegaly or significant BM involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

Table 6. Bendamustine Dose Modification guidelines

NCI-CTCAE category	Severity	Dose modification
Hematologic†	Neutrophil <1000/μL on day 1 of cycles 2-6	Initiation (day 1) of cycles 2-6 should be delayed until the neutrophil count is ≥1000/μL and the platelet count is ≥75,000/μL.† If day 1 is delayed by more than 2 weeks, then bendamustine should be resumed at the next lower dose level.
	Platelets <75,000/μL on day 1 of cycles 2-6	
	Grade 4 neutropenia with fever/infection	Initiation (day 1) of cycles 2-6 should be delayed until the neutrophil count is ≥1000/μL without evidence of fever or infection and the platelet count is ≥75,000/μL.† Bendamustine should then be resumed at the next lower dose level.
	Grade 4 neutropenia lasting ≥7 days	
	Grade 4 platelets for ≥7 days or a platelet count <10,000/μL at any time	
Nausea, emesis, or diarrhea in the absence of maximal prophylaxis	≥Grade 3	Continue treatment, but with institution of maximum prophylactic therapy, including a 5-HT$_3$ antagonist for nausea and emesis, and loperamide, or a comparable antidiarrheal agent, for diarrhea. Events of grade 4 toxicity require holding treatment until resolution of toxicity to ≤grade 2 with use of maximum prophylaxis.
Nausea, emesis, or diarrhea with maximal prophylaxis	≥Grade 3	Hold bendamustine for up to 2 weeks or until the toxicity returns to ≤grade 2, and restart at the next lower dose. If treatment is delayed by more than 2 weeks, treatment with bendamustine must be discontinued.
All other non-hematologic toxicities	≥Grade 3	

†If subjects have disease-related splenomegaly or significant BM involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

9.2 Maintenance Dose Modification Guidelines

Maintenance therapy with lenalidomide and rituximab will begin concurrently (i.e., cycle 1, day 1 of maintenance therapy will include initiation of the first maintenance rituximab infusion and the first dose of lenalidomide).

9.2.1 Lenalidomide

9.2.1.1 General Lenalidomide Dose Modification Guidelines

On the first day of each new maintenance cycle, the subject will be evaluated for possible toxicities that may have occurred after the previous doses. Toxicities are to be assessed according to the CTCAE, version 4.0.

The starting dose of lenalidomide for investigation is 5 mg orally daily on days 1-21 of each 28-day cycle (5 mg every other day on days 1-21for subjects with CrCl ≥40 and <60 mL/min). At the start of cycle 2 of maintenance (or at the start of a subsequent cycle), lenalidomide may be escalated to 10 mg/day on days 1-21 (or 5 mg daily on days 1-21, for subjects starting with every other day dosing) of each 28-day cycle if toxicity allows (see Sections 9.2.1.5 and 9.2.1.6). Dose escalations may only occur at the start of a new cycle of therapy. The following Sections outline additional specifics related to dose modifications during lenalidomide maintenance.

The following dose-reduction rules should be followed (Tables 7-10) during lenalidomide maintenance therapy:

Table 7. Lenalidomide Dose Reduction Steps.*

Dose level	Lenalidomide daily on days1-21 (28-day cycles)
+1	10 mg daily on days 1-21
Starting dose (level 0)	5 mg daily on days 1-21
-1 (starting dose for subjects with CrCl ≥40 and <60 mL/min)	5 mg every other day during days 1-21*
-2	Discontinue lenalidomide and withdraw subject from study protocol*

* Lenalidomide 5 mg every other day on days 1-21 is the minimum lenalidomide dose. Lenalidomide will be discontinued in subjects who cannot tolerate this dose. However, subjects who experience toxicity requiring dose reduction while receiving lenalidomide 5 mg every other day on days 1-21 may, at the discretion of their physician, have their dose held until toxicity resolves as described in Tables8-10, and then restart lenalidomide 5 mg every other day on days 1-21. If the same toxicity recurs at lenalidomide 5 mg every other day on days 1-21, strong consideration should be given to discontinuing lenalidomide.

9.2.1.2 Instructions for Dose Modifications or Interruption During Lenalidomide Maintenance

As the primary dose-limiting toxicity of lenalidomide is myelosuppression, a hematologic profile will be evaluated weekly during the first cycle of lenalidomide maintenance.

Hematologic toxicities will be evaluated at the time of every blood draw during lenalidomide maintenance according to the CTCAE version 4.0, and dose adjustments or interruptions will be made based on these hematologic profiles. Subjects who are on a stable lenalidomide dose (without escalation or interruption) for ≥ 1 cycle of maintenance will require hematologic surveys every 4 weeks. Subjects will be monitored for tumor lysis syndrome risk with laboratory parameters on day 1 of each maintenance cycle as outlined in Section 3, Schedule of study assessments.

At any time that dosing is escalated or re-escalated or lenalidomide dosing is interrupted for more than 4 weeks, at the time that lenalidomide is resumed subjects will undergo weekly hematologic surveys for 4 consecutive weeks. Subjects will be informed of potential adverse events associated with lenalidomide and will be instructed to report any adverse effects that occur during treatment. Subjects will be assessed with a clinical exam on day 1 of each cycle during cycles 1-6 of the maintenance phases of therapy. During cycles 7-23 of maintenance therapy, clinical exam is required on day 1 of odd-number cycles only (i.e., cycles 7,9,11,13,15,17,19,21,23) to coincide with dosing of rituximab. Dose adjustments will be made based on hematology and chemistry profiles, subject self-reporting of symptoms and Tables 8, 9, and 10 below.

If toxicities requiring dose reduction per Tables 8, 9, or 10 occur during lenalidomide maintenance therapy, subjects will be required to reduce dosing to the next lower dosing level (Table 7). For example, subjects experiencing toxicity at the starting dose of 5 mg/day on days 1-21 will not escalate up to 10 mg/day on days 1-21, but will reduce the dose to 5 mg every other day on days 1-21. ***Re-escalation of lenalidomide dosing is allowed at the investigator's discretion with the requirement that the criteria in Section 9.2.1.5 and 9.2.1.6 are met at the time of an attempted dose re-escalation.***

There are some circumstances when toxicities not specifically addressed in Tables 8-10 may require, in the opinion of the treating physician, temporary dose holding or dose reduction of lenalidomide to preserve patient safety (example: grade 2 rash that does not meet criteria for a dose hold per Table 10, but is progressive with possible attribution to lenalidomide). In such cases, dose interruption or dose reduction (by one dose level) of lenalidomide is permitted, provided it is clearly documented in the subject's record the reason for the dose interruption or dose reduction. If subjects required dose interruption of lenalidomide for a toxicity at physician discretion (not specifically listed as requiring dose modification per Tables 8-10), the treating physician may resume lenalidomide dosing at the same dose level or lower dose level once the toxicity has improved to an acceptable level. However, subjects cannot resume dosing of lenalidomide following a dose interruption instituted per physician discretion until the patient is evaluated on day 1 of the subsequent treatment cycle.

Dose delay and dose reduction rules for lenalidomide maintenance are detailed in Tables 8, 9, and 10 below, and also include:

- Lenalidomide dose modification steps are outlined in Table 7 above.
- For treatment interruptions during a cycle, the 28-day schedule of each cycle should continue to be followed. Missed doses of lenalidomide are not made up.

- For treatment interruptions that delay the scheduled start of a new cycle of lenalidomide maintenance, when toxicity has resolved as required to allow the start of a new cycle (Section 9.2.1.4), the restart day of therapy becomes day 1 of the next cycle and treatment begins as planned for that new cycle.
- A subject who cannot receive the next cycle of lenalidomide maintenance within 12 weeks of the planned start of the next cycle due to persistence of lenalidomide-related toxicity or non-drug related events (e.g., non-elective surgery) must discontinue lenalidomide. However, they are eligible to continue receiving maintenance rituximab as outlined per the study protocol.

Table 8. Dose modification of lenalidomide for hematologic toxicities

NCI-CTC Toxicity	Dose modification
Grade 3 neutropenia associated with fever (temperature ≥38.5º C) or Grade 4 neutropenia	Hold (interrupt) lenalidomide dosing, and follow CBC weekly. • If the neutrophil count recovers to ≥750/μL without fever prior to day 21 of the cycle, restart lenalidomide at the next lower dose level and continue through day 21. Otherwise, omit lenalidomide for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • G-CSF may be used at the investigator's discretion. • If the neutrophil count has not recovered to ≥750/μL within 12 weeks of holding lenalidomide (whether G-CSF is given or not), then lenalidomide must be discontinued. ***Note that grade 4 neutropenia during maintenance therapy with lenalidomide requires expedited reporting as a serious adverse event (Table 13, section 11.4).***
Thrombocytopenia, grade 3 (platelet count ≥25,000/μL to < 50,000/μL)	Hold prophylactic anti-coagulation, and follow CBC weekly. If the platelet count recovers to ≥ 50,000/μL, restart prophylactic anti-coagulation
Thrombocytopenia, ≥grade 4 (platelet count <25,000/μL)	Hold (interrupt) lenalidomide dosing, and follow CBC weekly. • If the platelet count recovers to ≥25,000/μL (≤grade 3) prior to day 21 of the cycle, restart lenalidomide and continue through day 21. Otherwise, omit lenalidomide for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If the platelet count has not recovered to ≥25,000/μL within 12 weeks of holding lenalidomide, then lenalidomide must be discontinued. ***Note that grade 4 thrombocytopenia during maintenance therapy with lenalidomide requires expedited reporting as a serious adverse event (Table 13, section 11.4).***
If lenalidomide dosing is held for >12 continuous weeks due to hematologic toxicities, then lenalidomide must be discontinued. Subjects are eligible to continue receiving maintenance rituximab per the study protocol.	

Table 9. Dose modifications of lenalidomide for tumor lysis syndrome and tumor flare reaction

NCI-CTC Toxicity	Dose modification
Tumor lysis syndrome (TLS), ≥grade 2 (see Section 9.3.1 for guidelines on prophylaxis and Appendix I for Cairo-Bishop TLS grading scale)	• Hold (interrupt) lenalidomide (missed doses are not made up). • First episode: restart lenalidomide at the current dose with appropriate TLS prophylaxis (Section 9.3.1) after resolution of electrolyte abnormalities to grade 0. • Subsequent episodes: restart lenalidomide with TLS prophylaxis (Section 9.3.1) after resolution of electrolyte abnormalities to grade 0. At physician discretion, lenalidomide may be restarted at the current dose or be reduced by 1 dose level. • First or subsequent episodes: chemistry tests should be performed at a minimum on day 1, 3 and 8 (±1 day for the day 3 and 8 laboratory assessments) following initiation of lenalidomide to monitor for TLS. Subjects should be closely monitored for signs of TLS for at least 1 week after resuming treatment.
TLS, grade 1 (see Appendix I for Cairo-Bishop TLS grading scale) or other laboratory abnormalities concerning for TLS	• The following should be provided: vigorous intravenous hydration and increased dosing of allopurinol or initiation of rasburicase therapy as needed to reduce hyperuricemia and until correction of electrolyte abnormalities. • Lenalidomide maintenance will be continued at the same dose without interruption or dose reduction.
Tumor flare reaction (TFR) (no recommended prophylaxis)	TFR ≥grade 1: • May be treated with NSAIDs (i.e., ibuprofen 400-600 mg orally every 4-6 hours as needed). TFR ≥grade 2: • May be treated with corticosteroids, if desired. If corticosteroids are used, the following dosage schedule is recommended: prednisone 20 mg PO daily x 7 days followed by 10 mg PO daily x 7 days. • Narcotic analgesics may be added as needed for pain control.
If lenalidomide dosing is held for >12 continuous weeks due to non-hematologic toxicities, then lenalidomide must be discontinued. Subjects are eligible to continue receiving maintenance rituximab per the study protocol.	

Table 10. Dose modification of lenalidomide for non-hematologic toxicities

NCI-CTC Toxicity	Dose modification
Non-blistering rash ≥grade 3, possibly or likely attributable to lenalidomide	If grade 3 non-blistering rash occurs: • Hold (interrupt) lenalidomide, follow with weekly clinical assessments. • When the toxicity resolves to ≤grade 1, restart lenalidomide at the next lower dose level. • If the rash has not recovered to ≤grade 1 within 12 weeks of holding lenalidomide, then lenalidomide must be discontinued and the subject must be removed from the study. If grade 4 non-blistering rash occurs: • Discontinue lenalidomide. • Remove subject from study.
Desquamating (blistering) rash of any grade possibly attributable to lenalidomide	Discontinue lenalidomide. Remove subject from study.
Neuropathy ≥grade 3	If grade 3 neuropathy occurs: • Hold (interrupt) lenalidomide dose and follow at least weekly with clinical assessments. • If the toxicity resolves to ≤grade 1, restart lenalidomide at the next lower dose level. • If recovery of neuropathy to ≤grade 1 has not occurred within 12 weeks of holding lenalidomide, the lenalidomide must be discontinued and the subject removed from the study. If grade 4 neuropathy occurs: • Discontinue lenalidomide. • Remove subject from study.
Venous thrombosis, embolism (≥grade 3)	Hold (interrupt) lenalidomide and start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level).
Other non-hematologic toxicity (≥grade 3)	Hold (interrupt) lenalidomide dose. Follow weekly with clinical assessment. At the discretion of the investigator, an assessment may be made over the phone and documented, rather than assessing the subject in clinic. If the toxicity resolves to ≤grade 2: • Restart lenalidomide at the next lowest dose level. • If the toxicity has not recovered to ≤grade 2 within 12 weeks of holding lenalidomide, then lenalidomide must be discontinued and the subject must be removed from the study.
Any other clinically significant toxicity regardless of attribution to lenalidomide	Dose interruption and/or reduction is permitted per MD discretion and must be clearly documented in the medical record. See section 9.2.1.2 for details.

9.2.1.3 Summary Criteria for Initiation of Maintenance Cycles and Dose Escalation

Different hematologic and renal parameters are required for initiating the first cycle of maintenance, each subsequent cycle of lenalidomide maintenance, and for dose-escalation of maintenance, Table 11 summarizes and compares these criteria for each phase of maintenance therapy. This table is only a summary, see sections 9.2.1.4; 9.2.1.5; 9.2.1.6 for additional cycle initiation and dose escalation criteria.

Table 11.Summary Criteria for Lenalidomide Maintenance

	Criteria to Start Cycle 1 of Maintenance	Criteria to Start Subsequent Cycles of Maintenance	Criteria to Dose Escalate
ANC/uL	≥1000	≥ 750	≥ 1000
Patelets/uL	≥ 50,000	≥ 25,000	≥ 50,000
CrCl (mL/min)	≥ 40*	≥ 40	≥ 60*

*If creatinine clearance is ≥40 mL/min and <60 mL/min the starting dose of lenalidomide is at a dose level -1 (5 mg every other day on days 1-21).Dose escalation is permitted for CrCl ≥ 40 and <60 mL/min if the prior treatment cycle was well tolerated without any dose modifications, interruptions, or delays due to toxicity. Escalation will be done in a step-wise manner (one dose level per cycle).

9.2.1.4 Criteria Required for Initiation of Subsequent Cycles of Lenalidomide Maintenance.

Criteria required to begin day 1 of each new cycle of lenalidomide maintenance therapy (Table 11):

- ANC ≥750/μL
- Platelets ≥ 25,000/μL
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity.
- Absence of laboratory TLS by Cairo-Bishop criteria (Appendix I). Subjects may receive their first cycle or subsequent cycles of lenalidomide upon correction of electrolyte abnormalities.
- If TLS ≥grade 2 during previous cycle (see Appendix I for Cairo-Bishop TLS grading scale), electrolyte abnormalities have resolved to ≤grade 0 severity.
- Any other non-hematologic drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.
- Calculated (method of Cockroft-Gault) creatinine clearance must be ≥40 mL/min (creatinine clearance may also be assessed by 24 hour urine collection).

- Any other clinically significant toxicity with a possible, probable, or definite attribution to lenalidomide requiring a physician discretion dose hold or reduction has been resolved.
- Completed previous cycle without a dose hold >4 weeks for lenalidomide.

If the above criteria are not met on day 1 of a maintenance cycle, lenalidomide should just be held and rituximab may be administered per the protocol schedule. It is recommended that patients be followed weekly with initiation of lenalidomide once above criteria are met. If hematologic criteria were not met on day 1 of a maintenance cycle, then only a CBC with differential needs to be repeated to verify eligibility to start a subsequent treatment cycle. If >3 weeks have passed with monitoring CBCs for maintenance cycle eligibility, then the entire panel of maintenance day 1 labs will need to be repeated. If a lenalidomide dose reduction was taken during the previous cycle, and the cycle was completed without requiring further dose modification, then the next cycle will start at the same reduced dose of lenalidomide. **If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled day 1**, then the new cycle will be started with a one-level dose reduction of lenalidomide.

9.2.1.5 Criteria Required for Lenalidomide Dose Escalation or to begin a new cycle after a dose hold of greater than 4 weeks

Criteria required for initial dose escalation to lenalidomide 10 mg/day on days 1-21 from the starting dose of lenalidomide 5 mg/day on days 1-21, or to escalate from every other day dosing to daily dosing at 5 mg/day on days 1-21, or to begin a new cycle after a dose hold of ≥4 weeks must be met on day 1 of the cycle during which escalation is planned (Table 11):

- ANC ≥1000/μL
- Platelets ≥50,000/μL
- Calculated (method of Cockroft-Gault) creatinine clearance must be ≥60 mL/min (creatinine clearance may also be assessed with 24 hour urine collection). In subjects with CrCl ≥40 and <60 mL/min, dose escalation of lenalidomide in a stepwise manner (e.g. 5 mg every other day to 5 mg daily on days 1-21; 5 mg daily to 10 mg daily on days 1-21) is permitted if the prior treatment cycle was well-tolerated without requiring any dose modifications, interruptions, or delays due to toxicity.
- The subject has completed at least one full cycle of lenalidomide maintenance without experiencing any toxicity that requires dose interruption or reduction if dose escalating.
- The subject has not experienced ≥grade 1 TLS (see Appendix I for Cairo-Bishop TLS grading scale) during the previous cycle of lenalidomide maintenance.
- The subject has not experienced ≥grade 1 tumor flare during the previous cycle of lenalidomide maintenance.
- Dose escalations may only occur at the start of a new cycle of therapy.

- Subjects should be monitored for TLS, with the tumor lysis laboratory panel (Section 3, Schedule of study assessments) performed on day 1.
- TLS prophylaxis with allopurinol and hydration as described in Section 9.3.1 must also be employed with lenalidomide dose escalation.
- Any other clinically significant toxicity with a possible, probable, or definite attribution to lenalidomide requiring a physician discretion dose hold or reduction as described in section 9.2.1.2 has been resolved.

When lenalidomide dosing is escalated to 10 mg/day on days 1-21, subjects must be dispensed 5 mg tablets during the first cycle to allow for dose modification mid-cycle if required. Thereafter, it is *recommended* but not required that subsequent cycles of lenalidomide at a dose of 10 mg/day on days 1-21 be dispensed as 5 mg tablets.

In cycles where there is a proposed dose escalation or dose re-escalation, subjects must be seen for a clinical evaluation and physical exam on day 1 of the cycle, regardless of whether a study visit is pre-designated per the study calendar.

9.2.1.6 Criteria Required for Dose Re-Escalation Following Dose Reductions due to Neutropenia, Thrombocytopenia, Tumor Lysis Syndrome, or Tumor Flare:

- If a subject has had a lenalidomide dose reduction for neutropenia or thrombocytopenia, and has since completed one full cycle of lenalidomide maintenance without experiencing any toxicity that requires dose interruption or reduction, then lenalidomide dose re-escalation is permitted. The lenalidomide dose may be increased by one dose level (Table 7) at the initiation of a new cycle of therapy.
- If a subject has had a lenalidomide dose reduction for tumor lysis syndrome or tumor flare, and has since completed one full cycle of lenalidomide maintenance without experiencing a laboratory TLS or ≥grade 1 TLS or without experiencing ≥grade 1 tumor flare, and without experiencing any toxicity that requires dose interruption or reduction, then lenalidomide dose re-escalation is permitted. The lenalidomide dose may be increased by one dose level (Table 7) at the initiation of a new cycle of therapy.
- Lenalidomide doses may be re-escalated in a step-wise fashion up to a maximum dose of 10 mg daily on days 1-21 of each 28-day cycle.
- TLS prophylaxis with allopurinol and hydration as described in Section 9.3.1 should be considered if clinically indicated based on the discretion of the treating physician.

In cycles where there is a proposed dose escalation or dose re-escalation, patients must be seen for a clinical evaluation and physical exam on day 1 of the cycle, regardless of whether a study visit is pre-designated per the study calendar.

9.2.2 Rituximab

9.2.2.1 Dose modification guidelines for rituximab maintenance therapy

There are no hematologic criteria for initiation of maintenance rituximab. However, subjects must meet the hematologic and non-hematologic parameters as defined for dosing guidelines of lenalidomide above (Section 9.2.1) in order to receive rituximab concurrent with lenalidomide on day 1 of each odd-numbered cycle.

The following guidelines (Table 12) will require consideration of delayed dosing or omission of rituximab during any cycle of maintenance therapy. If subjects have possible or probable rituximab-mediated recurrent toxicities with maintenance therapy, they are eligible to complete lenalidomide maintenance as defined by the study protocol.

Table 12. Dose modification of rituximab for toxicities

NCI-CTC Toxicity	Dose modification
≥Grade 3 infusion reaction and/or cytokine release syndrome possibly or likely attributable to rituximab	• If grade 3 infusion reaction and/or cytokine release syndrome occurs, consider increasing steroid and anti-histamine prophylaxis with subsequent infusions. If grade 3 infusion reaction and/or cytokine release syndrome recurs, may consider discontinuation of rituximab. • If grade 4 infusion reaction and/or cytokine release syndrome occurs (e.g., anaphylactic shock, severe hypotension), rituximab must be discontinued.
≥Grade 3 toxicity likely attributable to rituximab	• If recurrent ≥grade 3 toxicity is observed that, in the opinion of the investigator, is likely attributable to rituximab, consideration should be made for discontinuation of rituximab. Patients who discontinue rituximab are eligible to complete lenalidomide per the protocol schedule.
Neutropenia, particularly in setting of severe and unexplained nadir in neutrophil count with relative stability in hemoglobin and platelet counts	• Consider possibility of delayed immune-mediated rituximab-induced neutropenia, which may be observed at any time during an extended treatment course with rituximab. • Immuned-mediated rituximab-induced neutropenia is not a contra-indication to ongoing rituximab therapy. However, administration of growth factor is recommended to increase ANC > 1000/μL prior to next rituximab dose if this etiology for neutropenia is suspected.
Hypogammaglobulinemia	• Levels of serum immune globulins below the lower limits of normal in the setting of clinically significant and recurrent infections (i.e., sinusitis, upper respiratory infections, pneumonia, cellulitis, colitis, etc.) may warrant discontinuation of rituximab. Patients who discontinue rituximab are eligible to complete lenalidomide per the protocol schedule.
Subjects who discontinue rituximab are permitted to complete maintenance cycles with lenalidomide per the protocol schedule.	

9.3 Concomitant Therapy

Subjects should receive full supportive care, including transfusions of blood products, antibiotics, and anti-emetics when appropriate.

9.3.1 Tumor lysis syndrome (TLS) prophylaxis

Tumor lysis syndrome (TLS) may be a risk in subjects with high-tumor burden CLL/SLL initiating induction chemotherapy with bendamustine and rituximab. Tumor lysis syndrome has been reported in patients with CLL treated with bendamustine.[103]

Allopurinol prophylaxis is to beconsidered for subjects during induction chemotherapy based on the risk for tumor lysis syndrome. In high-risk subjects allopurinol is mandatory during induction phase of therapy. In non high-risk subjects, allopurinol is at the discretion of treating physicians.

Subjects who are determined to be at high-risk for TLS are required to receive allopurinol 300 mg orally daily or twice daily for 14 days at the start of induction chemotherapy. Subjects must receive their first day of allopurinol prophylaxis on the day of induction chemotherapy, but preferably 1-2 days prior to initiation of chemotherapy. Alternatively, subjects at high-risk for TLS with intolerance to allopurinol or judged to be at increased risk for TLS even with allopurinol prophylaxis, should be considered for treatment with rasburicase for TLS prophylaxis.

Subjects will be defined as high-risk for TLS if they meet any of the following:

- Baseline uric acid ≥7.5 mg/dL
- Bulky disease (one or more masses >10 cm), measuring >10 cm in at least one direction of a bimensionally measurable lesion)
- Elevated LDH (> 2X/ULN)
- Elevated WBC (>100,000/μL)
- Serum creatinine >1.5X/ULN

For all other subjects (i.e., not meeting high-risk criteria for TLS), use of allopurinol during induction therapy is at the discretion of the investigator.

Fatal TLS and life-threatening TLS have been associated with the use of lenalidomide in CLL.[104] Although the majority of TLS cases have occurred during the first or second cycle of lenalidomide, subjects may be at higher risk for TLS when lenalidomide is re-started after treatment interruptions or when the lenalidomide dose is escalated or re-escalated.

Allopurinol prophylaxis (300 mg/day for 10 days; starting 2 days prior to day 1 of maintenance) should be considered in subjects not meeting criteria for a partial or complete response prior to the start of cycle 1 of maintenance therapy.

Subjects should be instructed to maintain adequate hydration and maintain urinary output during lenalidomide maintenance. To maintain fluid intake, subjects should be instructed to drink 8-10 eight ounce glasses of water each day for the first 14 days of cycle 1. Hydration levels should be adjusted according to age and clinical status, and lowered if

the subject's cardiovascular status indicates the possibility of volume overload. Additional oral hydration should be considered after treatment interruptions or when the lenalidomide dose is escalated or re-escalated.

9.3.2 Tumor flare reaction (TFR) prophylaxis

There is no recommended prophylactic therapy for tumor flare reaction during lenalidomide maintenance.

9.3.3 Hematopoietic Growth Factors

Subjects are allowed to receive G-CSF to maintain the neutrophil count during both the induction and maintenance portion of therapy. Prophylactic G-CSF is permitted during cycle 1 of induction and maintenance therapy in subjects with prior history of treatment-related neutropenia or possible increased risk of treatment-related neutropenia.

9.3.4 Prophylactic anti-coagulation

Lenalidomide increases the risk of thrombotic events in subjects who are at high risk or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone) and erythropoietin, the risk of thrombosis is increased. Based on previous experience in multiple myeloma, this thrombotic risk appears to be highest in the setting of high-volume disease that has not achieved a remission. In this population those that will have achieved an objective response prior to receiving lenalidomide, the thrombotic risk is hypothesized to be low enough not to warrant required empiric thromboembolic prophylaxis. However, in individual subjects who are felt to be at higher risk for thromboembolic events, empiric anticoagulation is allowed with warfarin, low-molecular weight heparin, or anti-factor Xa inhibitors. If prophylactic anti-coagulation is used, it should be held for platelets counts <50,000/μL and resumed once platelet counts are ≥50,000/μL.

9.3.5 Prohibited concomitant therapy

Concomitant use of other anti-cancer therapies, including radiation or other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

10 Data Safety Monitoring Plan

10.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports).
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification is of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

10.1.1 Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for trials without an acceptable external DSMB are as follows:

a.) Intermediate monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC. Subjects being treated in this study protocol will be monitored according to this intermediate monitoring category.

10.1.2 Protocol Summary Reports

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (semi-annually). The PSR provides a cumulative report of SAEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

10.2 Safety Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Sponsor to Genentech within five (5) calendar days from request by Genentech.

11 Adverse Event Reporting Requirements

11.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after the initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination (prior to completing all protocol-directed therapy), whichever is earlier. After this period, investigators should only report SAEs that are possibly, probably, or definitely attributed to prior study treatment.

11.2 Assessment of Adverse Events

An **adverse event** is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL/SLL that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention or if the investigator considers them to be adverse events.
- Clinically Significant Laboratory Abnormalities: The investigator must appraise and document all abnormal laboratory results for their clinical significance. If an abnormal laboratory result is considered clinically significant, the value must be recorded in the research chart on the Adverse Events Log.

Attribution

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

RELATIONSHIP	DESCRIPTION
Unrelated	The AE is clearly NOT related to treatment. A clinical event in which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, past medical history of a similar event, the patient's disease state, intercurrent illness, or environmental factors.
Unlikely	The AE is doubtfully related to treatment. A clinical event with a temporal relationship to study drug administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the adverse event to a concomitant drug, past medical history of a similar event, the patient's disease state, intercurrent illness, or environmental factors.
Possible	The AE may be related to treatment. A clinical event with a reasonable temporal association with administration of the study drug, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Probable	The AE is likely related to treatment. A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Definite	The AE is clearly related to treatment. A clinical event in which a relationship to the use of the study drug seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).

Expectedness of Adverse Events

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

Celgene, Genentech and the UWCCC all have specific language regarding Adverse Event assessment and reporting. This protocol requires additional reporting to the FDA based on the Investigational New Drug (IND) designation of the study (please refer to section 11.4.1). Participating investigators should review the following information carefully, and if an event meets criteria for reporting for any one of these entities, the event should be reported following the guidelines in Section 11.4.1 and 11.4.

11.2.1 Procedures for Eliciting, Recording, and Reporting Adverse Events

11.2.1.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

11.2.1.2 Protocol Specific Instructions for Recording Adverse Events

Toxicities and adverse events will be scored using CTCAE, version 4.0. A copy of the CTCAE, version 4.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the subject's outcome. The investigator must evaluate each adverse experience for its relationship to the study drug(s) and for its seriousness.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

   If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single

diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 11.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if possibly, probably, or definitely attributed to prior study drug exposure per section 11.3. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE per section 11.3.2 and 11.3.

11.2.1.3 Protocol Specific Instructions for Reporting Adverse Events

a) General Adverse Event Reporting

All AEs and SAEs will be recorded in the research chart on the Adverse Event Log, regardless of whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means. Each reported AE or SAE will be described by its duration (i.e., start and end dates), seriousness criteria if applicable, suspected relationship (attribution) to the study drugs (see following guidance), and actions taken. A trained investigator should review each event.

Only the worst grade toxicity for a specific AE should be reported on the electronic case report form (eCRF) within each reporting period. A reporting period is defined as each treatment cycle, or the interval between each follow-up visit.

Anticipated grade 1 toxicities that are excluded from reporting on the electronic case report form (must be recorded on AE log if deemed clinically significant):

- Leukopenia (WBC decreased)
- Lymphopenia (Absolute lymphocyte count decreased)
- Neutropenia (Absolute neutrophil count decreased)
- Anemia (decreased hemoglobin)

b) Expedited Adverse Event Reporting

Serious Adverse Events: See section 11.3 for details.

Non-Serious Expedited Reporting Requirements: See section 11.3.3.1 for details.

Pregnancy: See section 11.3.3.1 for details.

Second Primary Malignancies: See section 11.3.3.1 for details.

11.3 Expedited Adverse Event Reporting

11.3.1 SAE Reporting

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table 13 below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

11.3.2 Determine the reporting time line for the SAE in question by using the following table 13. Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death.
- Is life-threatening, meaning that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
- Requires subject hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity, which is defined as a substantial disruption of a subject's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important (significant) medical event, with medical and scientific judgment exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above has occurred.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious.
- Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.
- Suspected pregnancy.
- A secondary primary malignancy in a patient who has received lenalidomide.

Table 13. Reporting Requirements for Serious Adverse Events (UW Carbone Cancer Center requirements)

NOTE: Investigators MUST immediately report to the *UWCCC* and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).
An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: See section 11.3.3 for additional protocol-specific exceptions to and requirements of expedited reporting

Expedited AE reporting timelines are defined as:

- 24-Hour; 5 Calendar Days – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- 10 Calendar Days – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 events

11.3.3 Additional Protocol-Specific Instructions, Requirements, and Exceptions to Expedited Reporting

11.3.3.1 Protocol-Specific Expedited Reporting Requirements

A. Non-Serious Expedited Reporting Requirements

The following toxicities must be reported expeditiously, irrespective of regulatory seriousness criteria:

Maintenance
- Grade 4 Neutrophil count decreased
- Grade 4 Platelet count decreased

Report to the UWCCC (saenotify@uwcarbone.wisc.edu):
Follow the SAE 24 hour reporting directions in section 11.3.4

B. Pregnancy

If a female subject becomes pregnant or is suspected to be pregnant while receiving investigational therapy, within 28 days of last dose of lenalidomide, or within 90 days after the last dose of RITUXAN, a report should be completed and expeditiously submitted as an SAE. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to RITUXAN and/or lenalidomide should be reported as an SAE. See appendix B for information on risks, pregnancy, testing, and acceptable birth control methods with the use of lenalidomide. See appendix G for guidelines on reporting pregnancies to Celgene.

Report to the UWCCC (saenotify@uwcarbone.wisc.edu):
Follow the SAE 24 hour reporting directions in section 11.3.4

C. Second Primary Malignancies

A possible small increased risk of second primary malignancy (SPM) has been described with lenalidomide therapy in clinical trials involving treatment of a broad range of hematologic malignances. A summary of the available data to date for SPM with lenalidomide was recently distributed to investigators in a confidential notice from Celgene Coporation dated March 15, 2011.[105] Based on these data provided, Celgene requires that events of second primary malignancies documented during the course of protocol treatment and during the study follow-up period be reported as SAEs.

Report to the UWCCC (saenotify@uwcarbone.wisc.edu):
Follow the SAE 24 hour reporting directions in section 11.3.4

11.3.3.2 Protocol-Specific Exceptions to Expedited Reporting

The following toxicities are anticipated and will **NOT** require expedited reporting:

Any Time Point
- Grade 1 – 4 Myelosuppression

- Grade 3 – 4 Lymphocyte count decreased
- Grade 3 – 4 While blood cell count decreased

Induction

- Grade 3 – 4 Neutrophil count decreased
- Grade 3 – 4 Platelet count decreased

Maintenance

- Grade 3 Neutrophil count decreased
- Grade 3 Platelet count decreased

11.3.4 General procedures for SAE reporting

Serious adverse event – reported within 24 hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 5 calendar days a final initial report is required to be submitted, all available subsequent SAE documentation must be submitted electronically along with a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. Follow up reports should be submitted, as needed, when additional information becomes available. All information is entered and tracked in the UWCCC database.

As applicable, the Sponsor-Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the sponsor-investigator reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators (see section 11.4.1).

For a multiple-institutional clinical trial the sponsor-investigator is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

See Section 11.3.5 for detailed instructions on SAE reporting.

Serious adverse event – reported within 10 days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if further action is required. Follow up reports should be submitted, as needed, when additional information becomes available. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the industry collaborators, and the FDA (if applicable)and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the sponsor-investigator reviews the event to determine whether the SAE requires reporting to the FDA (see section 11.4.1) and other participating investigators.

For a multiple-institutional clinical trial the sponsor-investigator is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

See Section 11.3.5 for detailed instructions on SAE reporting.

11.3.5 Expedited Reporting of Serious Adverse Events

- Complete the following for all reports, regardless of reporting period:
- FDA MedWatch Form 3500A
- OnCore SAE Details Report
- Serious Adverse Event Routing Form

Complete the following for all SAE reports::

- Sponsor-Investigator Determination Form for FDA Reporting of Safety Events Form (Sponsor-Investigator Review)
- Genentech Safety Reporting Fax Cover Sheet

A. <u>SAE Requiring *24* Hour Reporting Occurs at UWCCC:</u>

1. Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website, Data and Safety Monitoring page (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for 24 hour initial and follow-up reports. **A final initial report is required to be submitted within 5 calendar days of the initial 24 hour report.**

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Julie Chang, MD (Study Chair) jc2@medicine.wisc.edu
c) Any other appropriate parties listed on the SAE Routing Form

2. Report to Industry Collaborators:

Submit the following items to Celgene:

- FDA MedWatch Form 3500A
- Source documentation as applicable

Celgene Corporation
Global Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922

Fax:(908) 673-9115
e-mail: drugsafety@celgene.com
Please reference Protocol RV-CLL/-PI-0689.

Submit the following items to Genentech:

- Genentech Safety Reporting Fax Cover Sheet
- FDA MedWatch Form 3500A
- Source documentation as applicable

Genentech Safety
Fax: 650-225-4682
Alternate Fax: 650-225-5288
Phase: 888-835-2555

3. Report to the IRB:

Consult the UW-IRB website (kb.wisc.edu/hsirbs) for reporting guidelines.

B. <u>SAE Requiring 10 Day Reporting Occurs at UWCCC:</u>

1. Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for DOTs** on the UWCCC website, Data and Safety Monitoring page (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for 10 day reports.

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Julie Chang, MD (Study Chair) jc2@medicine.wisc.edu
c) Any other appropriate parties listed on the SAE Routing Form

2. Report to Industry Collaborators:

Submit the following items to Celgene:

- FDA MedWatch Form 3500A
- Source documentation as applicable

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Global Drug Safety and Risk Management
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Berkeley Heights, NJ 07922

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- FDA MedWatch Form 3500A
- Source documentation as applicable

Genentech Safety
Fax: 650-225-4682
Alternate Fax: 650-225-5288
Phase: 888-835-2555

3. Report to the IRB:

Consult the UW-IRB website (kb.wisc.edu/hsirbs) for reporting guidelines.

C. Other Reporting Requirements:

Reporting to the FDA
Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

See section 11.4 for details on how to report.

The Sponsor-investigator reviews the SAE for possible requirement for reporting to the FDA, as described in detail in section 11.4.1. The Sponsor-investigator is responsible for the final determination of adverse event attribution to study drug. The Sponsor-investigator will assess the adverse event for appropriate need for reporting to the FDA (see section 11.4.1).

11.4 Sponsor-Investigator Adverse Event Reporting Responsibilities

All serious adverse event reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatments provided. The sponsor-investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present. The sponsor-investigator is responsible for reporting adverse events to the UWCCC, industry collaborators Celgene and Genentech (sections 11.4.2 and 11.4.3), and the FDA (section 11.4.1) as described below.

As the UWCCC Principal Investigator is acting as the Sponsor-Investigator (i.e., the PI holds the IND), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. Serious Adverse Events occurring on studies on which a UW PI is

acting as sponsor-investigator must be reported to the FDA within the appropriate time frame (see section 11.4.1). Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

11.4.1 Sponsor-Investigator AE reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. These requirements will include:

- Directly reporting to the FDA as soon as possible but no later than 15 calendar days any adverse events determined to be serious, unexpected, and reasonably related to the study drugs.
- Directly reporting to the FDA as soon as possible but no later than 7 calendar days any unexpected fatal or life-threating suspected adverse reaction.
- Preparation and submission of IND Annual Reports.

Sponsor-Investigator (i.e, HO11414 Protocol PI) Reporting requirements to FDA:

The Sponsor-Investigator (i.e., HO11414 Protocol PI) is required to notify the FDA of any adverse events associated with the use of study drug that meets 3 criteria:

1.) The event was serious. An event is considered serious if resulted in:
    - Death
    - A life-threatening adverse drug event
    - Inpatient hospitalization of prolongation of existing hospitalization
    - Persistent or significant incapacity of substantial disruption of the ability to conduct normal life functions
    - A congenital anomaly/birth defect
    - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).
2.) The event was unexpected (i.e., not included as an anticipated or known toxicity in the drug prescribing information or investigational drug brochure). This includes any incident, experience, or outcome that:
    - Is unexpected in terms of the nature, severity, or frequency in relation to the research risks that are described in the research protocol and informed consent document, Investigator's Brochure, and prescribing information or other study documents AND
    - The characteristics of the subject population being studied AND

- Suggests that the research places subjects of others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

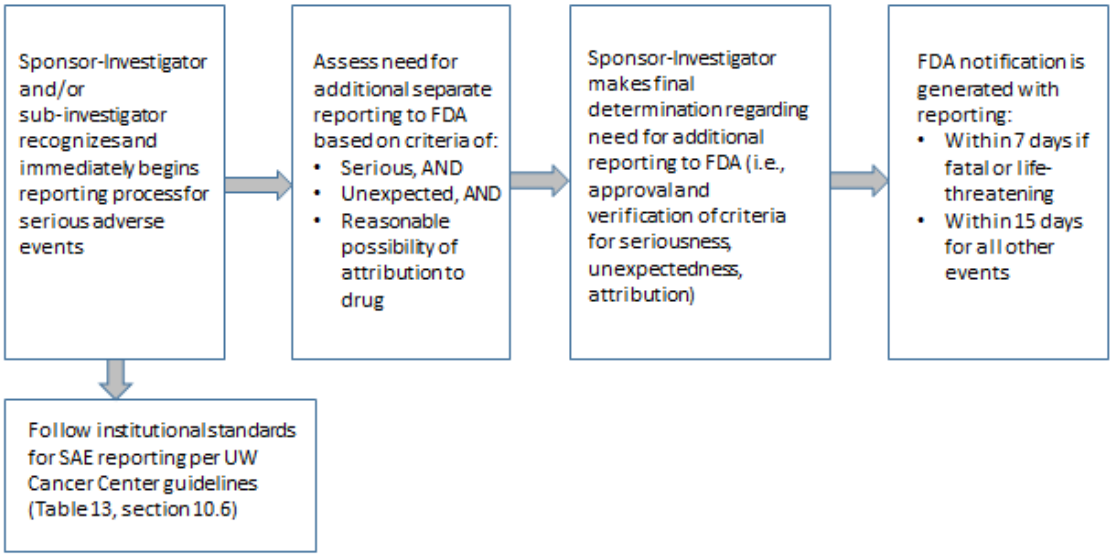
3.) There is a reasonable possibility that the adverse event was associated with the use of the drug.

Examples of "reasonable possibility":

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (i.e., Stevens-Johnson syndrome, angioedema)
- One of more occurrences of an event that is not commonly associated with a drug exposure, but is otherwise uncommon in the population exposed to the drug
- An aggregate analysis of specific events observed in the clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group. Aggregate analysis of adverse events will be analyzed with results reported quarterly in the regulatory binders, and also reported in research meeting minutes. The results of these aggregate analyses will also be reported in the IND annual report to the FDA.

The duration of required safety reporting to the FDA will continue throughout all protocol therapy. **Serious adverse events that occur more than 30 days after the last administration of investigational agent will also require reporting if there is reasonable likelihood of attribution of the adverse event to the investigational agen**t.

Figure 1: Reporting responsibilities of Sponsor-Investigators to the FDA under 21 CFR 312.64(b) for serious and unexpected suspected adverse events.



Print the FDA Medwatch form and applicable source documentation, and fax to:

FDA Safety Reporting
FAX: 301-796-9845

Send Paper copies (1 original and 2 copies) of the FDA MedWatch Form 3500A and applicable source documentation to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

11.4.2 Sponsor-Investigator AE Reporting to Celgene

See Section 11.3 for summary instructions for SAE reporting for this study. Serious adverse events (SAE) are defined above (Section 11.3.2). The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within the reporting timeframes in Table 13. The written report must be completed and supplied to Celgene by facsimile or email within the reporting timeframes in Table 13. The

initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (**RV-CLL/-PI-0689**) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporation Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922

Fax:(908) 673-9115
e-mail: drugsafety@celgene.com
Please reference Protocol RV-CLL/-PI-0689.

11.4.3 Sponsor-Investigator AE Reporting to Genentech

See Section 11.3 for summary instructions for SAE reporting for this study.
Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports, regardless of relatedness to RITUXAN will be transmitted to Genentech within the reporting timeframes in Table 13.
  - Additional Reporting Requirements to Genentech include the following:
- Any reports of pregnancy following the start of administration with RITUXAN will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- A final cumulative Case Transmission Verification of Adverse events reported previously from study start date to study end date will be provided to Genentech by the Sponsor-Investigator.
- All Non-serious Adverse Events will be compiled into a report and provided to Genentech by the Sponsor-Investigator once all study subjects are off treatment. In addition to all SAE's, pregnancy reports and AESI's the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
  - Data related to the Product usage during pregnancy or breastfeeding

- Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
- Lack of therapeutic efficacy
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

11.4.4 Product complaints to Genentech

Recently the FDA announced an update to the Post Marketing Safety Reporting regulation which requires the Marketing Authorization Holder (i.e., Genentech/Roche) to report product complaints to the FDA. A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Product complaints **with** an AE should be reported via e-mail to: usds_aereporting-d@gene.com OR 650-238-6067

Product complaints **without** an AE should be reported via e-mail to Kaiseraust.global_impcomplaint_management@roche.com

All complaints must be filed within 15 calendar days. Complaints can be reported using a Medwatch, CIOMS, or any Genentech-approved response reporting form.

11.4.5 Sponsor-Investigator AE Reporting to the Institutional Review Board (IRB) and Institutional Data Safety Monitoring Board (DSMB)

The principal investigator is required to notify his/her IRB of a serious adverse event according to institutional policy.

11.4.6 Adverse event updates/IND safety reports

Celgene and Genentech shall notify the investigator via an IND Safety Report 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.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The investigator shall notify his/her IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects, according to institutional policy.

The investigator must keep copies of all AE information, including correspondence with Celgene, Genentech and the IRB on file (see Section 16.2 for records retention information).

12 Sponsor-Investigator Responsibilities and Oversight

12.1 Reporting Responsibilities to FDA

A full description of FDA adverse event reporting requirements by the Sponsor Investigator are detailed in Section 11.4.1. The conduct of the study will comply with all FDA safety reporting requirements. These requirements will include:

- Directly reporting to the FDA adverse events determined to be serious, unexpected, and reasonably related to the study drugs.
- Regular review of aggregate adverse events at least every 3 months to determine if an increase in frequency of adverse events requires reporting to the FDA.
- Preparation and submission of IND Annual Reports (due annually each January).

IND Annual Reports
If the FDA has granted an IND number, it is a requirement of 21 CFR 212.33, that an annual report is provided to the FDA within 60 days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive, Suite 700
Berkeley Heights, NJ 07922

In IND Annual Reports are generated a copy of this report should be forwarded to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

12.2 Protocol Deviations

The Sponsor-investigator will review the protocol deviation log within 14 business days of the discovery of each deviation occurrence.

13 Response Criteria

Baseline lesion assessments must occur within 6 weeks of study drug administration as indicated in Section 3, Schedule of study assessments. Efficacy assessments are scheduled to occur at the end of cycles 3 and 6 of induction therapy. During the maintenance phases of treatment, efficacy assessments will be performed every 4 months.

Response and progression in cases of CLL will be evaluated using the revised Cheson Criteria.[38] Response and progression in cases of SLL will be evaluated using the International Working Group guidelines for CLL.[39] These criteria are outlined in detail in Appendix H. Radiological methodologies, techniques and/or physical examination, established at baseline for the assessment and measurement of each identified lesion will be used for all subsequent assessments.

14 Protocol Amendments/Deviations

14.1 Protocol Amendments

Any amendment to this protocol must be agreed to by the principal investigator and reviewed by study supporters (i.e., Celgene and Genentech). Amendments should only be submitted to the local IRB after consideration of study supporters' reviews. Written verification of IRB approval will be obtained before any amendment is implemented.

14.2 Protocol Deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the investigator will notify the IRB in writing of such deviation from protocol according to local policy. In addition, the investigator will inform the DSMC of the event around the protocol deviation, to determine if the subject should be removed from protocol therapy.

Non-emergency minor deviations from the protocol will be permitted with approval of the principal investigator.

15 Statistical Considerations

15.1 Overview

This single arm, open-label phase II study will be carried out an academic medical center as well as community practice sites. Participating centers will include the University of Wisconsin Carbone Comprehensive Cancer Center. The primary efficacy endpoint of this study is progression free survival (PFS).

15.2 Sample Size Calculation

The primary efficacy endpoint of this study is progression-free survival (PFS) from the initiation of the maintenance therapy (PFS calculated beginning cycle 1, day 1 of maintenancy therapy). A standard induction regimen in newly diagnosed CLL and SLL with the highest reported overall response rates and PFS is the fludarabine, cyclophosphamide, and rituximab (FCR) chemotherapy regimen. Based on a recent randomized trial of the fludarabine and cyclophosphamide (FC) chemotherapy versus FCR chemotherapy, the observed 3-year PFS rate was 65% in patients receiving FCR chemotherapy versus 45% in the FC chemotherapy.[106] The Kaplan-Meier estimates for the 2-year PFS probability were approximately 0.8 for the FCR chemotherapy and 0.6 for the FC chemotherapy arm. These values on PFS with FCR serve as a reasonable benchmark by which the proposed induction and maintenance regimen can be compared. For this study, we consider a 2-year PFS probability of 0.6 or less as clinically irrelevant.

This study will test the null hypothesis that the 2-year PFS probability for subjects entering the maintenance therapy is at most 0.6 *(*equivalent to a median PFS of 32.6 months assuming an exponential distribution for PFS) versus the alternative that it is greater than 0.6. In the table below are given the required effective sample size for the maintenance phase of the study under various settings, assuming completion of accrual in 24-36 months, a follow-up of 24 months (after the last patient has entered the maintenance phase), an exponential distribution for PFS, a one-sided significance level of α=0.10, using the Brookmeyer-Crowley method.

	2-year PFS probability for subjects entering maintenance		
Power	0.75 (Median PFS=57.8 months)	0.8 (Median PFS=74.6 months)	0.85 (Median PFS=102.4 months)
0.8	41	22	13
0.85	51	**27**	16
0.9	65	35	21

In order to detect the 2-year PFS probability with power 0.85, the required effective sample size is **27** subjects. Assuming that up to 25% of the subjects in the induction therapy will not do well enough (CR, PR or SD) to enter the maintenance therapy or drop out after induction for reasons unrelated to objective response, a total of 36 subjects will be enrolled into the induction phase over 2.5-3.5 years.

15.3 Statistical Analysis Plan

15.3.1 Primary endpoint

The analysis will be undertaken when each subject has been potentially followed for a minimum of 24 months. For each subject, time to progression will be defined as the number of days from the day of first lenalidomide and rituximab maintenance therapy (cycle 1, day 1 of maintenance therapy) to the day subject experiences an event of disease progression, initiation of alternate anti-neoplastic chemotherapy even in the absence of progression, or death, whichever comes first. If a subject has not experienced an event at the time of analysis, the subject's data will be censored at the date of the last available evaluation. The 2-year PFS probability will be estimated using the Kaplan-Meier method. The null hypothesis that the 2-year PFS probability is at most 0.6 will be tested versus that alternative hypothesis that it is greater than 0.6. A statistically significant result will support the development of a phase III trial. PFS will be summarized using point estimate of the median PFS, and associated 90% confidence intervals. The confidence interval will be computed using the Brookmeyer-Crowley method. The data will be presented graphically using Kaplan-Meier plots.

15.3.2 Secondary endpoints

Objective response will be analyzed descriptively and summarized with the sample proportion and 90% confidence interval for the proportion of subjects with objective response. Toxicities will be summarized in a similar way. Data from all subjects who receive any study drug will be included in the safety analyses. The severity of the toxicities will be graded according to the NCI CTCAE, version 4.0 whenever possible. Frequency tables (type of toxicity and grade) for all toxicities with an attribution of possible or definite treatment related will be provided.

For a given subject, overall survival (OS) will be defined as the number of days from the date of enrollment to the day the subject dies. Survival times of subjects who are still alive at the end of the follow-up period will be censored. OS will be summarized using point estimates of the median overall survival, along with the 95% confidence interval. Survival data will be presented graphically using Kaplan-Meier plots.

15.4 Accrual Rate

Based on our experience with studies involving CLL/SLL subjects at UWCCC and affiliated sites, we anticipate an accrual rate of approximately 10-12 subjects per year. Therefore, it is expected that accrual will be completed within 3 years.

16 Regulatory Considerations

16.1 Investigator Responsibilities with Study Monitoring and Auditing

Investigator responsibilities are set out in the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The investigator will permit study-related audits by Celgene, Genentech or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPD), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.
The investigator, or a designated member of the investigator's staff, must be available at some time during audit visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Celgene and/or Genentech representative so that the accuracy and completeness may be checked.

16.2 Study Records Requirements

All study records will be retained for at least 2 years after the investigation is completed. The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). These records and documents include copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, 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; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]). The investigator agrees to adhere to the document/records retention procedures by signing the protocol.

16.3 Institutional Review Board/Ethics Committee Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC 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 Subjects and Part 56 Institutional Review Boards.

The investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the investigator to the IRB/EC for approval. The investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

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

16.4 Informed Consent

The investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the investigator's study files.

16.5 Subject Confidentiality

Identifiable patient information will be maintained at the enrolling site. All source documentation will be maintained within the subject's research chart which will be accessible only to authorized personnel. Study data will be collected in the UWCCC Oncore database. Subject data will be coded, with the link to demographic information maintained within the Oncore database. The study PI, statistician, and research team at UWCCC will have access to this information and will manage the study data. Data will be maintained per federal guidelines.

Celgene and Genentech affirm the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, the study supporters (i.e., Celgene and Genentech) require the investigator to permit representatives of Celgene Corporation and Genentech, 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 subject's statement of informed consent, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

16.6 Premature Discontinuation of Study

The responsible local clinical investigator as well as Celgene and Genentech have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center or all participating centers. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.

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

17 References

1. Tsimberidou AM, Wen S, O'Brien S, et al. Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2007;25:4648-56.
2. Abbott BL. Chronic lymphocytic leukemia: recent advances in diagnosis and treatment. Oncologist 2006;11:21-30.
3. Huhn D, von Schilling C, Wilhelm M, et al. Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. Blood 2001;98:1326-31.
4. Chow KU, Sommerlad WD, Boehrer S, et al. Anti-CD20 antibody (IDEC-C2B8, rituximab) enhances efficacy of cytotoxic drugs on neoplastic lymphocytes in vitro: role of cytokines, complement, and caspases. Haematologica 2002;87:33-43.
5. Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 Study. J Clin Oncol 2009;27:1607-14.
6. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377:42-51.
7. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-8.
8. van Oers MH, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood 2006;108:3295-301.
9. van Oers MH, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 2010;28:2853-8.
10. Taverna CJ, Bassi S, Hitz F, et al. First results of long-term rituximab maintenance treatment in follicular lymphoma: Safety analysis of the randomized phase III trial SAKK 35/03. J Clin Oncol 2009;27(15s):abstract 8534.
11. Rummel MJ, Al-Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 2005;23:3383-9.
12. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany) Blood 2009;114(22):abstract 405.
13. Fischer K, Cramer P, Busch R, et al. Bendamustine Combined With Rituximab in Patients With Relapsed and/or Refractory Chronic Lymphocytic Leukemia: A Multicenter Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011;29:3559-66.
14. Weide R, Pandorf A, Heymanns J, Koppler H. Bendamustine/Mitoxantrone/Rituximab (BMR): a very effective, well tolerated outpatient chemoimmunotherapy for relapsed and refractory CD20-positive indolent malignancies. Final results of a pilot study. Leuk Lymphoma 2004;45:2445-9.

15. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4473-9.
16. Rummel MJ, Atta J, Welslau M, et al. Bendamustine and rituximab (BR) are effective in the treatment of relapsed or refractory indolent and mantle-cell lymphomas: Long-term follow-up of a phase II study. J Clin Oncol 2007;25(18s):abstract 8034.
17. Cheson BD, Friedberg JW, Kahl BS, Van der Jagt RH, Tremmel L. Bendamustine produces durable responses with an acceptable safety profile in patients with rituximab-refractory indolent non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2010;10:452-7.
18. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. Cancer 2010;116:106-14.
19. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008;26:204-10.
20. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27:4378-84.
21. Fischer K, Cramer P, Stilgenbauer S, et al. Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: A multicenter phase II trial of the German CLL Study Group (GCLLSG). Blood 2009;114(22):abstract 205.
22. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2016;17:928-42.
23. Hainsworth JD, Litchy S, Shaffer DW, Lackey VL, Grimaldi M, Greco FA. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005;23:1088-95.
24. 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 2007;110(11):abstract 2563.
25. Lossos IS, Wiernik PH, Justice G, et al. Lenalidomide response in relapsed/refractory diffuse large B-cell non-Hodgkin's lymphoma. Blood 2007;110(11):abstract 2564.
26. Ruppert AS, Byrd JC, Heerema NA, et al. A genetic risk-stratified, randomized phase 2 intergroup study of fludarabine/antibody combinations in symptomatic, untreated chronic lymphocytic leukemia (CLL): Results from Cancer and Leukemia Group B (CALGB) 10404 (Alliance). Journal of Clinical Oncology 2017;35:7503-.
27. Fink AM, Bahlo J, Robrecht S, et al. Lenalidomide maintenance after first-line therapy for high-risk chronic lymphocytic leukaemia (CLLM1): final results from a randomised, double-blind, phase 3 study. Lancet Haematol 2017;4:e475-e86.
28. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2013;31:584-91.
29. 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;24:5343-9.
30. Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;111:5291-7.
31. Ferrajoli A, Badoux X, O'Brien S, et al. The combination of lenalidomide and rituximab induces complete and partial responses in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2010;116(21):abstract 1395.

32. Fowler NH, McLaughlin P, Kwak L, et al. Lenalidomide and rituximab for untreated indolent non-Hodgkin's lymphoma. J Clin Oncol 2009;27(15s):abstract 8548.
33. Fowler NH, McLaughlin P, Hagemeister FB, et al. Complete response rates with lenalidomide plus rituximab for untreated indolent B-cell non-Hodgkin's lymphoma. J Clin Oncol 2010;28(15s):abstract 8036.
34. Chang JE, Havighurst T, Kim K, et al. Bendamustine + rituximab chemoimmunotherapy and maintenance lenalidomide in relapsed, refractory chronic lymphocytic leukaemia and small lymphocytic lymphoma: A Wisconsin Oncology Network Study. British journal of haematology 2016.
35. Fischer K, Cramer P, Busch R, et al. Bendamustine in Combination With Rituximab for Previously Untreated Patients With Chronic Lymphocytic Leukemia: A Multicenter Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012;30:3209-16.
36. Fink AM, Bahlo J, Sandra R, et al. Lenalidomide Maintenance after Front Line Therapy Substantially Prolongs Progression Free Survival in High Risk CLL: Interim Results of a Phase 3 Study (CLL M1 study of the German CLL Study Group). Blood 2016;128:229-.
37. Foà R, Schuh A, Zaritskey A, et al. Results of the Phase 3 Study of Lenalidomide Versus Placebo As Maintenance Therapy Following Second-Line Treatment for Patients with Chronic Lymphocytic Leukemia (the CONTINUUM Trial). Blood 2016;128:230-.
38. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.
39. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56.
40. Gandhi V. Metabolism and mechanisms of action of bendamustine: rationales for combination therapies. Semin Oncol 2002;29:4-11.
41. Strumberg D, Harstrick A, Doll K, Hoffmann B, Seeber S. Bendamustine hydrochloride activity against doxorubicin-resistant human breast carcinoma cell lines. Anticancer Drugs 1996;7:415-21.
42. Konstantinov SM, Kostovski A, Topashka-Ancheva M, Genova M, Berger MR. Cytotoxic efficacy of bendamustine in human leukemia and breast cancer cell lines. J Cancer Res Clin Oncol 2002;128:271-8.
43. Schwanen C, Hecker T, Hubinger G, et al. In vitro evaluation of bendamustine induced apoptosis in B-chronic lymphocytic leukemia. Leukemia 2002;16:2096-105.
44. Chow KU, Boehrer S, Geduldig K, et al. In vitro induction of apoptosis of neoplastic cells in low-grade non-Hodgkin's lymphomas using combinations of established cytotoxic drugs with bendamustine. Haematologica 2001;86:485-93.
45. Rummel MJ, Mitrou PS, Hoelzer D. Bendamustine in the treatment of non-Hodgkin's lymphoma: results and future perspectives. Semin Oncol 2002;29:27-32.
46. Staib P, Schinkothe T, Kimski T, Other A. In vitro modulation of Ara-CTP accumulation in fresh AML cells by bendamustine in comparison with fludarabine, 2CdA, and gemcitabine [abstract]. Blood 1999;94:63a.
47. Rummel MJ, Chow KU, Hoelzer D, Mitrou PS, Weidmann E. In vitro studies with bendamustine: enhanced activity in combination with rituximab. Semin Oncol 2002;29:12-4.
48. Herold M, Keinert K, Ang G. Risk adapted combined radio- and chemotherapy in Hodgkin’s disease – 10 year follow up. Onkologie 1999;22:310-13
49. Rummel MJ. Bendamustine in chronic lymphocytic leukemia and refractory lymphoma. Semin Hematol 2008;45:S7-10.
50. Bergmann MA, Goebeler ME, Herold M, et al. Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. Haematologica 2005;90:1357-64.
51. Ponisch W, Mitrou PS, Merkle K, et al. Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with

melphalan and prednisone--a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). J Cancer Res Clin Oncol 2006;132:205-12.
52. Hoffken K, Merkle K, Schonfelder M, et al. Bendamustine as salvage treatment in patients with advanced progressive breast cancer: a phase II study. J Cancer Res Clin Oncol 1998;124:627-32.
53. Koster W, Heider A, Niederle N, et al. Phase II trial with carboplatin and bendamustine in patients with extensive stage small-cell lung cancer. J Thorac Oncol 2007;2:312-6.
54. Herold M, Schulze A, Niederwieser D, et al. Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma: results of a randomised phase III trial (OSHO# 19). J Cancer Res Clin Oncol 2006;132:105-12.
55. Heider A, Niederle N. Efficacy and toxicity of bendamustine in patients with relapsed low-grade non-Hodgkin's lymphomas. Anticancer Drugs 2001;12:725-9.
56. Lissitchkov T, Arnaudov G, Peytchev D, Merkle K. Phase-I/II study to evaluate dose limiting toxicity, maximum tolerated dose, and tolerability of bendamustine HCl in pre-treated patients with B-chronic lymphocytic leukaemia (Binet stages B and C) requiring therapy. J Cancer Res Clin Oncol 2006;132:99-104.
57. Kath R, Blumenstengel K, Fricke HJ, Hoffken K. Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia. J Cancer Res Clin Oncol 2001;127:48-54.
58. Williams ME CP, Tulpule A, et al. A phase II multicenter study of bendamustine HCl plus rituximab in relapsed indolent B-cell and mantle-cell non-Hodgkin's lymphoma (NHL) J Clin Oncol 2006;24(18s) abstract 7528.
59. van der Jagt RH, Cohen P, Cheson B, et al. Phase II results of bendamustine in combination with rituximab in relapsed indolent and mantle-cell non-Hodgkin's lymphoma. Blood 2006;108(11):abstract 2710.
60. Rummel MJ, Atta J, Welslau M, et al. Bendamustine and rituximab (BR) are effective in the treatment of relapsed or refractory indolent and mantle-cell lymphomas: long-term follow-up of a phase II study. J Clin Oncol 2007;25:Abstr 8034.
61. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 2005;23:4070-8.
62. Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 2006;24:1575-81.
63. Fischer K, Stilgenbauer S, Schweighofer CD, et al. Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): a multicentre phase II trial of the German CLL Study Group (GCLLSG). Blood 2007;110(11):abstract 3106.
64. 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;305:1222-32.
65. Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood 2001;98:210-6.
66. Zangari M, Tricot G, Zeldis J, Eddlemon P, Saghafifar F, Barlogie B. Results of phase I study of lenalidomide for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT). Blood 2001;98:abstract 3226.
67. Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002;100:3063-7.
68. Richardson PG, Jagannath S, Schlossman R., Zeldenrust S, Rajkumar SV, al. e. A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of two CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM). Blood 2003;100:abstract 825.

69. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005;106:4050-3.
70. Dimopoulos MA, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23:2147-52.
71. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Engl J Med 2005;352:549-57.
72. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1782-91.
73. Ferrajoli A, O'Brien SM, Faderl SH, et al. Lenalidomide induces complete and partial responses in patients with relapsed and treatment-refractory chronic lymphocytic leukemia (CLL). Blood 2007;108(11):abstract 305.
74. Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27:5404-9.
75. Wang M, Fayad L, Hagemeister F, Neelapu S, Bell N, Byrne C. A phase I/II study of lenalidomide (Len) in combination with rituximab (R) in relapsed/refractory mantle cell lymphoma (MCL) with early evidence of efficacy J Clin Oncol 2007;25(18s):abstract 8030.
76. Chen CI, Bergsagel PL, Paul H, et al. Single-agent lenalidomide in the treatment of previously untreated chronic lymphocytic leukemia. J Clin Oncol 2011;29:1175-81.
77. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-7.
78. Chanan-Khan A, Egyed M, Robak T, et al. Randomized phase 3 study of lenalidomide versus chlorambucil as first-line therapy for older patients with chronic lymphocytic leukemia (the ORIGIN trial). Leukemia 2017;31:1240-3.
79. Dohner H, Fischer K, Bentz M, et al. p53 gene deletion predicts for poor survival and non-response to therapy with purine analogs in chronic B-cell leukemias. Blood 1995;85:1580-9.
80. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910-6.
81. Krober A, Seiler T, Benner A, et al. V(H) mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood 2002;100:1410-6.
82. Oscier DG, Gardiner AC, Mould SJ, et al. Multivariate analysis of prognostic factors in CLL: clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors. Blood 2002;100:1177-84.
83. Krober A, Bloehdorn J, Hafner S, et al. Additional genetic high-risk features such as 11q deletion, 17p deletion, and V3-21 usage characterize discordance of ZAP-70 and VH mutation status in chronic lymphocytic leukemia. J Clin Oncol 2006;24:969-75.
84. Rossi D, Cerri M, Deambrogi C, et al. The prognostic value of TP53 mutations in chronic lymphocytic leukemia is independent of Del17p13: implications for overall survival and chemorefractoriness. Clin Cancer Res 2009;15:995-1004.
85. Gaidano G, Newcomb EW, Gong JZ, et al. Analysis of alterations of oncogenes and tumor suppressor genes in chronic lymphocytic leukemia. Am J Pathol 1994;144:1312-9.
86. el Rouby S, Thomas A, Costin D, et al. p53 gene mutation in B-cell chronic lymphocytic leukemia is associated with drug resistance and is independent of MDR1/MDR3 gene expression. Blood 1993;82:3452-9.
87. Wattel E, Preudhomme C, Hecquet B, et al. p53 mutations are associated with resistance to chemotherapy and short survival in hematologic malignancies. Blood 1994;84:3148-57.
88. Lens D, Dyer MJ, Garcia-Marco JM, et al. p53 abnormalities in CLL are associated with excess of prolymphocytes and poor prognosis. British journal of haematology 1997;99:848-57.
89. Barnabas N, Shurafa M, Van Dyke DL, Wolman SR, Clark D, Worsham MJ. Significance of p53 mutations in patients with chronic lymphocytic leukemia: a sequential study of 30 patients. Cancer 2001;91:285-93.

90. Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood 2004;103:3278-81.
91. Austen B, Powell JE, Alvi A, et al. Mutations in the ATM gene lead to impaired overall and treatment-free survival that is independent of IGVH mutation status in patients with B-CLL. Blood 2005;106:3175-82.
92. Stankovic T, Weber P, Stewart G, et al. Inactivation of ataxia telangiectasia mutated gene in B-cell chronic lymphocytic leukaemia. Lancet 1999;353:26-9.
93. Stankovic T, Hubank M, Cronin D, et al. Microarray analysis reveals that TP53- and ATM-mutant B-CLLs share a defect in activating proapoptotic responses after DNA damage but are distinguished by major differences in activating prosurvival responses. Blood 2004;103:291-300.
94. Schaffner C, Stilgenbauer S, Rappold GA, Dohner H, Lichter P. Somatic ATM mutations indicate a pathogenic role of ATM in B-cell chronic lymphocytic leukemia. Blood 1999;94:748-53.
95. Stilgenbauer S KA, Busch R, et al. 17p Deletion predicts for inferior overall survival after fludarabine-based first line therapy in chronic lymphocytic leukemia: first analysis of genetics in the CLL4 Trial of the GCLLSG. Blood 2005;106:abstract 715.
96. Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet 2007;370:230-9.
97. Grever MR, Lucas DM, Dewald GW, et al. Comprehensive assessment of genetic and molecular features predicting outcome in patients with chronic lymphocytic leukemia: results from the US Intergroup Phase III Trial E2997. J Clin Oncol 2007;25:799-804.
98. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112:975-80.
99. Byrd JC, Rai K, Peterson BL, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. Blood 2005;105:49-53.
100. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 2005;23:4079-88.
101. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
102. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine 1916;17:863-71.
103. Elefante A, Czuczman MS. Bendamustine for the treatment of indolent non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Am J Health Syst Pharm 2010;67:713-23.
104. 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;25:5047.
105. Kaplan MM, Hingeley H. A study of the Out-Patient Clinic services for the mentally retarded at the Muscatatuck State School. Am J Ment Defic 1958;63:517-23.
106. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164-74.
107. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;87:4990-7.
108. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. British journal of haematology 2004;127:3-11.

Appendix A – 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 house work, 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.

Appendix B: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. 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. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the Revlimid REMS® program.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential or pregnant female, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential or pregnant female.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the

entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

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 patients with neutropenia.

Pregnancy testing

Must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.

- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.
- Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused lenalidomide must be returned as instructed through Revlimid REMS® program.

Appendix C: Body Surface Area Calculations

The preferred method for calculating body surface area is with the **Mosteller formula**:[101]

BSA (m^2)= [Height(cm) X Body weight (kg)/3600]$^{1/2}$

At some participating community sites, the Dubois formula[102] is the primary BSA calculation used as part of an electronic medical record and drug ordering template. In such cases, calculations using the Dubois formula are permitted as long as there is no more than a 10% difference in dosing between the Mosteller and Dubois calculations. If a >10% difference in drug dosing is observed, then the Mosteller calculation must be used.

Dubois formula:[102]

BSA (m^2)= 0.007184 X [Body weight (kg)]$^{0.425}$ X [Height (cm)]$^{0.725}$

The same BSA will be used for each dose calculation of bendamustine and rituximab unless the subjects experiences a >10% change in body weight from the weight used for the most recent BSA calculation.

Appendix D: Rituximab Formulation, Preparation, and Adverse Effects

1.A. Other names

Rituxan™, IDEC-C2B8, chimeric anti-CD20 monoclonal antibody, NSC#687451

1.B. Classification and mode of action:

Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. It binds with high affinity to CD20-positive cells, performs human effector functions *in vitro*, and depletes B cells *in vivo*. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

1.C. Storage and stability

Rituximab vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight.

Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 24 hours. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2° to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

1.D. Preparation

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% sodium chloride or 5% dextrose in water. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

1.E. Administration

Rituximab is administered intravenously. An in-line filter is not required. The initial rate is 50 mg/hr for the first 30-60 minutes. If no toxicity is seen, the rate may be escalated gradually in 50 mg/hour increments at 30-minute intervals to a maximum of 400 mg/hr. If the first dose is well-tolerated, the initial rate for subsequent doses is 100 mg/hr, increasing gradually by 50 mg/hr increments to maximum rate of 400 mg/hr. If the patient experiences fever and rigors, the antibody infusion is discontinued. The severity of the side effects should be evaluated. If the symptoms improve, the infusion is continued initially at one-half the previous rate. Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after one hour of observation, the intravenous line may be discontinued. Institutions may follow standard practice for infusion of Rituximab if different from the above guidelines.

Oral pre-medication (two 325 mg tablets of acetaminophen and 50 to 100 mg of oral diphenhydramine) may be administered 30 to 60 minutes prior to starting each infusion of rituximab. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion. The subject should be treated according to the best available local practices and procedures.

1.F. Availability

Rituximab will be provided for subjects in this study: Preservation-free injection 10 mg/ml, in 10 and 50 mL single-unit vials

1.G. Side effects – Please refer to package insert

General: Rituximab is associated with hypersensitivity reactions which may respond to adjustments in the infusion rate. Hypotension, bronchospasm, and angioedema have occurred in association with rituximab infusion as part of an infusion-related symptoms complex. Rituximab infusion should be interrupted for severe reactions and can be resumed at a 50% reduction in rate when symptoms have completely resolved. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, and corticosteroids should be available for immediate use in the events of a reaction during administration.

Cardiovascular: Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Subjects who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Subjects with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

Tumor lysis syndrome: Rituximab rapidly decreases both benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in subjects with high numbers of circulating malignant lymphocytes. Subjects with high tumor burden (bulky lesions) may also be at risk. Subjects at risk of developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for subjects who develop tumor lysis syndrome. Following treatment for and resolution of tumor lysis syndrome, subsequent rituximab therapy was administered in conjunction with prophylactic therapy for this syndrome in a limited number of cases.

Hepatitis B virus: Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some subjects with hematologic malignancies treated with rituximab. The majority of subjects received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

1.H. Incidence of adverse effects

Incidence more frequent (>5%):

Fever, chills, rigors, asthenia, headache, angioedema, hypotension, myalgia, dizziness, fatigue, throat irritation, abdominal pain, nausea, vomiting, leukopenia, thrombocytopenia, neutropenia, rhinitis, bronchospasm, pruritis, rash, urticaria

Incidence less frequent (1-5%):

Flushing, arthralgia, diarrhea, anemia, cough, hypertension, lacrimation disorder, pain, hyperglycemia, back pain, peripheral edema, paresthesia, dyspepsia, chest pain, anorexia, anxiety, malaise, tachycardia, agitation, insomnia, sinusitis, conjunctivitis, abdominal enlargement, postural hypotension, LDH increase, hypocalcemia, hyperesthesia, respiratory disorder, shortness of breath, tumor pain, pain at injection site, bradycardia, hypertonia, tachycardia, nervousness, bronchitis, and altered sense of taste.

Incidence rare (<1%):

Anaphylaxis, severe infusion-related adverse events which may result in death. Tumor lysis syndrome: subject with a high tumor burden or with a high number (50,000/mm^3) of circulating malignant cells may be at higher risk of severe infusion-related events. When treated with rituximab, some subjects with a history of hepatitis B may experience reactivation of their hepatitis that may be life-threatening.

1.I. Nursing/subject implications

Monitor blood pressure, pulse, respiration, and temperature every 15 minutes X 4 or until stable and then hourly until the infusion is completed.

Have epinephrine for subcutaneous injections, diphenhydramine for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions available.

Monitor and alter infusion rates in the presence of toxicities.

Rituximab shows no significant effect on bone marrow reserve and no apparent increased rate of infections in heavily pretreated, relapsed lymphoma subjects.

Prophylaxis for tumor lysis syndrome should be used in subjects with high tumor burden, particularly with markedly elevated numbers of circulating malignant cells.

Appendix E: Bendamustine Formulation, Preparation, and Adverse Effects

I. Drug formulation and preparation

I.A. Other names

Treanda™, SDX-105, Bendeka™

Bendamustine is available in several formulations, including Treanda™ (available in liquid and powder formulations infused over 30-60 minutes), and Bendeka™ (a ready-to-dilute formulation available to infuse over 10 minutes). Bendeka™ was introduced in the market in December 2015 by Teva Pharmaceuticals, with the simultaneous decision by Teva to stop manufacturing Treanda™ during roll-out of Bendeka™. Generic marketing and availability of bendamustine is anticipated to be unpredictable in the months following introduction of the Bendeka™ product. Bendeka™ and Treanda™ are nearly identical in action and toxicities, and can be used interchangeably for administration of induction chemotherapy per the study protocol depending on availability of the bendamustine product and institutional preference.

1.B. Classification and mode of action:

Bendamustine is a DNA alkylating agent with amphoteric properties due to the nitrogen mustard group and butyric acid side chain. Bendamustine has multiple mechanisms of action related to the alkylating activity of the 1-methyl-benzimidazole moiety and the nitrogen mustard group.

Bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases, thus directly inhibiting DNA replication, transcription, and repair. At equitoxic concentrations, bendamustine induces more DNA double-strand breaks than other alkylating agents (i.e., melphalan, cyclophosphamide, and carmustine). In addition, these breaks also appear to be more durable and less easily repaired than those induced by other agents. Bendamustine has also demonstrated pro-apoptotic activity in combination with other anti-cancer agents in several in vitro tumor models, including in primary tumor cells from CLL and non-Hodgkin lymphoma subjects. Treatment with bendamustine HCl has also demonstrated down-regulation of several cell cycle mitotic checkpoint regulators, including polo-like kinase 1 (PLK-1), aurora kinase A and cyclin B1. Bendamustine shows only partial cross-resistance with other alkylating agents when investigated in a variety of cell lines, which may be related to the relatively slow repair rate associated with this agent. No evidence of *in vitro* drug resistance to bendamustine was observed when the drug was tested in paried tumor cells expressing various drug resistance mechanisms including the

overexpression of P-glycoprotein, of multi-drug resistant-associated protein (MRP), or dihydrofolate reductase (DHFR).

I.C Storage and stability

Bendamustine vials should be stored at refrigerated temperatures of 2° to 8°C (36° to 46°F) and protected from light. Bendamustine is stable for 5 hours when stored at normal room temperature conditions, 15°C to 30°C (59°F to 86°F). Bendamustine is a cytotoxic anticancer agent and should be handled according to the recommended procedures described in the current edition of the American Society of Health-System Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling cytotoxic drugs.

The Bendeka product is supplied in multi-dose vials. Although it does not contain any anti-microbial preservative, Bendeka is bacteriostatic. The partially used vials are stable for up to 28 days when stored in its original carton under refrigeration 2-8°C or 36-46°F). Each vial is not recommended for more than a total of 6 dose withdrawals.

1.D. Preparation

The single-use vials should be opened and reconstituted as close to the time of subject administration as possible. Each vial of bendamustine should be reconstituted with 20 mg of sterile water for injection, shaken gently for about 2 minutes, and then inspected for clarity of solution. If the solution is not clear after 2 minutes, the vials should be shaken for an additional 3 minutes and inspected again. If the solution is not clear after 15 minutes, vials should be set aside and a replacement vial should be used. The final concentration within the vial is 5.0 mg/mL.

Immediately dilute the reconstituted solution in a 500 mL IV bag of normal saline, using appropriate venting procedures. The amount of reconstituted solution to be withdrawn from the vials should be calculated using the following formula:

[Dose of study drug (mg) ÷ Vial concentration (mg/mL)] = Volume of drug solution (mL)

The time from the start of product reconstitution to the completion of the transfer to the IV bag should not exceed 30 minutes.

1.E. Administration

The bendamustine solution should be used promptly after reconstitution and dilution. The route of administration is by IV infusion over 30-60 minutes for Treanda™ and over 10 minutes for Bendeka™. The infusion line would be primed with drug solution. If medical conditions necessitate, e.g., fluid management issues of infusion reactions, the infusion may be given over a longer period of time, though the infusion should be ≤120 minutes. In-line filters are not required for administration. Refer to the Pharmacy Manual for more detailed instructions.

1.F. Availability

Commerical: Bendamustine is a white to off-white, crystalline powder. Mannitol is contained in the finished product as an excipient to enhance solubility during reconstitution of the powder. Bendamustine is lyophilized due to long-term instability in aqueous medium. Bendamustine is available in 100 mg single use vials.

Bendeka is a clear colorless-yellow 25 mg/mL solution supplied in multi-dose vials (100 mg/4 mL vials).

1.G. Drug interactions

No formal pharmacokinetic drug-drug interactions have been determined for bendamustine. However, bendamustine's active metabolites are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have the potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of P450 CYP1A2 (e.g., omeprazole, smoking) have the potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites.

1.H. Side effects – Please refer to package insert

Hematologic: neutropenia (grade 3 or 4 neutropenia in up to 25% of treated subjects), thrombocytopenia infrequently requiring transfusions, and anemia.

Infections: increased risk of infections (e.g., pneumonia) and sepsis have been reported following treatment with bendamustine.

Infusion reactions and anaphylaxis: have been reported commonly in clinical trials with symptoms including fever, chills, pruritis, and rash. Rare reports of anaphylactic or anaphylactoid reactions have occurred.

Tumor lysis syndrome: reported in several subjects treated with bendamustine, primarily during the first cycle of therapy.

Skin reactions: reported reactions include rash, toxic skin reactions, and bullous exanthema

Elevated LFT's: reported increase in total bilirubin and transaminases in up to 30% of subjects in some clinical trials.

Gastrointestinal: frequent reporting of nausea, vomiting, and stomatitis.

1.I. Fequency of adverse effects:

Frequent adverse events: asthenia, fatigue, malaise, and weakness; dry mought; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis; nausea, vomiting, and diarreha. Hematologic toxicity is very frequent including grade 3 and 4 neutropenia and thrombocytopenia. Mild elevation of liver function tests (total bilirubin and transaminases).

Less common adverse events: hypersensitivity reactions, skin eruptions, fevers, chills, hypertension, pyrexia, and neutropenic infection.

1.J. Nursing/subject implications

Subjects require close monitoring during the first infusion for evidence of hypersensitivity reaction, which is an uncommon but serious side effect with bendamustine.

Hematologic toxicity is the primary dose-limiting toxicity, and hematologic nadirs should be expected in the third week of therapy.

Infection, including pneumonia and sepsis, have been reported following treatment with bendamustine, usually in combination with myelosuppression. Subjects with myelosuppression need education regarding monitoring for signs of fever or infection.

Prophylaxis for tumor lysis syndrome should be considered in subjects with high tumor burden, or elevated uric acid and/or LDH.

Subjects should be educated on supportive measures for management of nausea, vomiting, diarrhea, constipation, and stomatitis.

1.K. References

Investigator's Brochure,Bendamustine HCl for injection, version 04 (Dec. 2014).

Appendix F: Lenalidomide Formulation, Preparation, and Adverse Effects

1.A. Other names:

CC-5013, Revlimid®

1.B Indications and usage

Revlimid® (lenalidomide) is indicated for the treatment of subjects 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. Revlimid® is also approved in combination with dexamethasone for the treatment of subjects with multiple myeloma that have received at least one prior therapy.

1.C. Classification and mode of action

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

1.D. Storage and stability

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

1.E. Preparation

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml.

Lenalidomide is available in capsule formulation at doses of 5 mg, 10 mg, 15 mg, and 25 mg capsules.

1.F. Administration and availability

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements all physicians who prescribe lenalidomide for research

subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 7 days for females of childbearing potential and 14 days for all other risk categories.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies.

Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Lenalidomide is supplied as capsules for oral administration.

1.G. Special Handling Instruction

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

1.H. Drug interactions

Results from in vitro metabolism studies and non-clinical studies have shown that lenalidomide is not metabolized by nor inhibits of induces the cytochrome P450 pathway and unlikely to be subject to P450-based metabolic drug interactions. Co-administration of lenalidomide with warfarin does not have an effect on the pharmacokinetics of warfarin.

1.I. Adverse effects

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulites, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

General: Fatigue is common with lenalidomide, reported in up to 50% of subjects. Subjective fever and generalized edema has occurred in up to 20% of treated subjects.

Hematologic: Neutropenia is a common complication of treatment with lenalidomide, although the incidence of neutropenic fever is relatively uncommon (<10%). Thrombocytopenia is common, but severe thrombocytopenia requiring platelet transfusions is uncommon.

Skin: Rash and pruritis have been reported frequently (>30%) with lenalidomide.

Gastrointestinal: Some previous experience with lenalidomide have reported diarrhea in almost half of subjects, although most cases tend to be low-grade diarrhea. Constipation and nausea have been reported in up to 25% of subjects.

Respiratory: Symptoms of nasopharyngitis, dyspnea, and cough have been reported in up to 20-25% of subjects.

Musculoskeletal: Arthralgias and cramping have been reported relatively frequently during treatment with lenalidomide.

Neurologic: Dizziness and headache have occurred with up to 20% of subjects treated with lenalidomide. Peripheral neuropathy is relatively uncommon (<10%).

1.J. Investigator's Brochure, Revlimid® (lenalidomide, CC-5013), March 2006.

Appendix G: Guidelines on Reporting Suspected or Confirmed Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

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

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

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporation Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922

Fax: **(908) 673-9115**
E-mail: **drugsafety@celgene.com**

Appendix H: Assessment of Response

Criteria for response will utilize the Revised IWCLL 2008[39] for response which includes clinical, hematologic, and bone marrow features as derived from the initial NCI-WG 1996.[107]

	Assessment	Complete response (All criteria below)	Partial response	Progressive disease ≥1 criteria below	Stable disease
1	Lymph nodes (by physical examination and CT scans†)	Absence of lymphadenopathy > 1.5 cm on physical exam and CT scan	≥50% reduction of as many as 6 measurable lymph nodes	≥ 50% increase in products of ≥2 nodes on two consecutive determinations 2 weeks apart (at least 1 node must be ≥ 2 cm); new palpable lymph nodes.	Subject has not achieved either a CR or PR and does not meet criteria for PD
2	Liver and/or spleen size (by physical examination), if abnormal at baseline	No hepatomegaly or splenomegaly	≥50% reduction	≥50% increase	
3	Lymphocytes (per µL)	<5000/µL, no clonal B-cells by flow cytometry;	≥50% decrease from baseline values	≥50% increase in lymphocytes (to ≥5000/ µL)	
4	Polymorphonuclear cells (cells/µL)	≥1500	≥1500 or ≥50% increase from baseline		
5	Platelets (per µL)	>100,000	>100,00 or ≥50% increase from baseline (untransfused)		
6	Hemoglobin (g/dL)	>11 (untransfused)	>11 or ≥50% increase from baseline (untransfused)		
7	Bone marrow lymphocytes (%)‡	<30, no nodules	Nodular lymphocytes in marrow		
8	Duration of response	≥ 2 months	≥ 2 months		
9	Other			Transformation (Richter's, PLL)	

†CT scans (chest, abdomen, pelvis) are required to confirm response at least 2 months after initial determination of complete or partial response.

‡Bone marrow examination is required only to confirm complete response at least 2 months after initial determination of complete response.

Response and Progression Criteria for CLL

Complete Response (CR)

Complete remission (CR) requires all of the following for a period of at least two months from completion of therapy:

- Absence of lymphadenopathy > 1.5 cm on physical exam and CT scan.
- No hepatomegaly or splenomegaly on physical exam (a CT scan also may be used to assess).
- No clonal B-cells in the blood by flow cytometry.
- Normal CBC as exhibited by polymorphonuclear leukocytes ≥ 1,500/μL platelets > 100,000/μL, hemoglobin > 11.0 g/dL (untransfused); lymphocyte count < 5,000/μL.
- Bone marrow aspirate and biopsy must be normocellular for age with < 30% of nucleated cells being lymphocytes. Lymphoid nodules may be present but must be T-cell in origin. If these are demonstrated to be clonal B-cells, subjects should be considered to be a partial response. Additionally, if bone marrow is positive by two color flow cytometry for CLL cells, it should be considered a partial response. If the marrow is hypocellular, a bone marrow should be performed in 2-3 months. If blood counts fail to recover (polymorphonuclear leukocytes < 1,500/μL, platelets < 100,000/μL) at the time of the response evaluation but there is otherwise no evidence of CLL otherwise, a repeat determination should be performed at the time of count recovery.

Complete Response with incomplete recovery (CRi)

Subjects who fulfill the criteria for CR after induction with the exception of a persistent cytopenia (CR with incomplete recovery, CRi) that is believed to be treatment-related will be considered a CRi. As stated above, subjects falling into this category should ideally undergo a repeat bone marrow when counts recover fully. If the bone marrow at this time reveals no CLL, these subjects will be considered to be in complete remission at that time

Partial Response (PR)

Partial response (PR) requires a ≥ 50% decrease in peripheral lymphocyte count from pre-treatment value, ≥ 50% reduction in lymphadenopathy of as many as 6

measurable lymph nodes, and/or ≥ 50% reduction in splenomegaly and/or hepatomegaly for a period of at least two months from completion of therapy. Additionally, these subjects must have one of the following:

- Polymorphonuclear leukocytes ≥ 1,500/μL or 50% improvement from pretreatment value
- Platelets > 100,000/μL or 50% improvement from pre-treatment value
- Hemoglobin > 11.0 g/dL (untransfused) or 50% improvement from pretreatment value

Stable disease (SD)

Stable disease is defined as less than a PR (see above) but is not PD (see below).

Progressive disease (PD)

Progressive disease (PD, non-responders) requires the following:

- ≥ 50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥ 2 cm); appearance of new palpable lymph nodes.
- ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5,000/μL.
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes).
- The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels >2 g/dL or to < 10 g/dL, or by a decrease of platelet counts > 50% or to < 100,000/μL, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenias cannot be used to define disease progression.

International Working Group Criteria for response in NHL (Cheson, JCO 2007)

Response	Definition	Nodal masses	Spleen, Liver	Bone marrow
CR	Disappearance of all evidence of disease	FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemitstry should be negative.[2]
		Variably FDG-avid or PET negative; regression to normal size on CT[1]		
PR	Regression of measurable disease and no new sites	50% decrease in SPD of up to 6 largest dominant nodes or masses;[3] no increase in size of the other nodes	>50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to biopsy; cell type should be specified
		FDG-avid or PET positive prior to therapy; one of more PET positive at previously involved site		Subjects who achieve CR by the above criteria, but have persistent morphologic bone marrow involvement will be considered PR[4]
		Variable FDG-avid or PET negative; regression on CT		
SD	Failure to attain CR/PR or PD	FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET		
		Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD[5]	Any new lesion or increase by >50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis;[6] >50% increase in SPD of more than one node;[7] or >50% increase in longest diameter of a previously identified node >1 cm in short axis	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
		Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		

Abbreviations: CR=complete remission; FDG[^{18}F]=fluorodeoxyglucose; PET=positron emission tomography; CT=computed tomography; PR=partial remission; SPD=sum of the product of the diameters; SD=stable disease; PD=progressive disease.

[1]Lymph nodes/nodal masses ≤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 long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.

[2]A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data becomes available demonstrating a clear difference in subject outcome.

[3]These nodes or masses should be selected according to all of the following; they should be clearly measurable in at least 2 perpendicular dimentions; if possible they should be from disparate regionsof the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

[4]When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, subjects should be considered partial responders.

[5]Lymph nodes should be considered abnormal if the long axis is >1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1-1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes ≤1.0 X ≤1.0 cm will not be considered as abnormal for relapse or PD.

[6]Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In subjects with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

[7]To be considered progressive disease, a lymph node with a diameter of the short axis of <1.0 cm must increase by ≥50% and to a size of 1.5 X 1.5 cm or more than 1.5 cm in the long axis.

Time to Progression

Time to progression will be measured as the time from when the subject started treatment to the time the subject is first recorded as having disease progression, or the date of death if the subject dies due to causes other than disease progression.

Time to Treatment Failure

Time to treatment failure will be measured as the time from when the subject started treatment to the time the subject is withdrawn due to: adverse events, progressive disease/insufficient therapeutic response, death, failure to return, and refused treatment/did not cooperate/withdrew consent. The date of last dose of treatment will be used as the date of event in the case that PD was not recorded earlier.

Survival

Survival will be measured as the time from start of treatment to the date of death or the last date the subject was known to be alive.

Time to Response

For subjects who achieve a major objective response (CR or PR of measurable disease), the time to response will be assessed as the time from start of treatment to the date of response.

Appendix I: Cairo-Bishop Definition of Tumor Lysis Syndrome[108]

Table 14: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Uric Acid	≥ 476 µmol/l (≥ 8.0 mg/dl) or 25% increase from baseline
Potassium	≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous	≥1.45 mmol/l (≥ 4.5 mg/dl) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline
Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a subject has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).	

Table 15: Cairo-Bishop Definition of Clinical TLS

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

ULN, Upper limit of normal

*Not directly attributable to a therapeutic agent

Table 16: Cairo-Bishop Grading System for TLS

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

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

Appendix J: Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl):
(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \quad (\textbf{Males})$$

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85 \quad (\textbf{Females})$$