Title: A Multiple-center Phase 2 Study of Acalabrutinib-Lenalidomide-Rituximab (ALR) with an Expansion Cohort of Acalabrutinib-Lenalidomide-Obinutuzumab (ALO) in Patients with Previous Untreated Mantle Cell Lymphoma

NCT03863184

Initial IRB Approval Date: 07 November 2018

Amendment History

- **Amendment #1 11 April 2019**
- **Amendment #2 10 April 2020**
- **Amendment #3 07 December 2021**
- **Amendment #4 31 July 2023**

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

AE	Adverse Event
AESI	Adverse events of special interest
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria For Adverse Events
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
WCM	Weill Cornell Medicine

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PROTOCOL SUMMARY

Full Title:
A Multiple-center Phase 2 Study of Acalabrutinib-Lenalidomide-Rituximab (ALR) with an Expansion Cohort of Acalabrutinib-Lenalidomide-Obinutuzumab (ALO) in Patients with Previous Untreated Mantle Cell Lymphoma

Short Title:
Acalabrutinib-Lenalidomide-Rituximab (ALR) for Untreated Mantle Cell Lymphoma

Clinical Phase:
Phase II

Principal Investigator:
Jia Ruan, M.D., Ph.D.

Sample Size:
N=34

Accrual Ceiling:
The study will enroll up to 38 patients to account for screening failure and early drop out.

Study Population:

Inclusion criteria:

- Histologically confirmed diagnosis of mantle cell lymphoma
- Age ≥ 18 years
- No prior systemic therapy for lymphoma
- Measurable disease defined by a tumor mass ≥ 1.5 cm in one dimension and measurable in two dimensions; patients with measurable spleen disease are allowed
- Treatment should be indicated according to the treating physician
- ECOG performance status ≤ 2
- Required initial laboratory parameters:

  Absolute neutrophil count (ANC) ≥ 1000 cells/mm^3

  Platelet count ≥ 75,000 cells/mm^3

  Calculated creatinine clearance ≥ 30 ml/min by Cockcroft-Gault formula

Total bilirubin ≤ 1.5 x ULN

AST/SGOT and ALT/SGPT ≤ 3.0 x ULN

- Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use low molecular weight heparin).
- All subjects must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.
- Patients of reproductive potential agree to use highly effective birth control throughout their participation in this study, for at least 28 days following study termination, and for 160 days for males and 12 months for females after the last dose of rituximab, 180 days for males and 18 months for females after the last dose of obinutuzumab.
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. 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). FCBP must either commit to continued abstinence from heterosexual intercourse or begin one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before and continue for at least 28 days after the last dose of lenalidomide (or 2 days after the last dose of acalabrutinib, whichever is longer). FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual activity with a FCBP through one week post last dose even if they have had a successful vasectomy. Men must also agree to refrain from sperm donation during the same timeframe. See Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Highly Effective Birth Control Methods.
- Understand and voluntarily sign an ICF prior to any study related assessments and procedures are conducted.
- Able to adhere to the study visit schedule and other protocol requirements.

Exclusion criteria:

- Patients with blastoid histology
- Patients with known or suspected CNS involvement
- Viral infection with HIV or hepatitis type B or C. Seropositive HBV patients are eligible if they are negative for HBV DNA by PCR and receive concomitant antiviral therapy during treatment and for additional six months after coming off study.
- Prior history of malignancies other than MCL unless the patient has been disease free for ≥ 5 years from the signing of the ICF. Exceptions include basal cell carcinoma or squamous cell carcinoma of the skin; carcinoma in situ of cervix; carcinoma in situ of breast, or localized prostate cancer

- Active uncontrolled systemic fungal, bacterial or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy and/or other treatment)
- Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
- Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
- Active bleeding or history of bleeding diathesis (e.g., hemophilia or von Willebrand disease).
- Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).
- Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer. Patients on moderate CYP3A inhibitors can be considered for study after a washout period of at least 7 days.
- Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
- Prothrombin time (PT)/INR or aPTT (in the absence of lupus anticoagulant) >2x ULN.
- Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
- History of significant cerebrovascular disease/event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.
- Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
- Patients with a history of toxic epidermal necrolysis or Stevens-Johnson syndrome
- Patients that are pregnant or breast feeding
- Known hypersensitivity to any study drug or excipients
- Patient on corticosteroids within two weeks prior to study entry, except for prednisone ≤ 20 mg/day or equivalent for purposes other than treating MCL
- Use of any other experimental drug or therapy within 28 days of baseline
- Patient at high risk for deep vein thrombosis not willing to take DVT prophylaxis
- Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study

- Known prior exposure to BTK inhibitor

Accrual Period:
07/2019 – 07/2022

Study Design:
This is a phase 2 study to evaluate the preliminary evidence of efficacy and safety of the combination of acalabrutinib, lenalidomide and rituximab (ALR), as well as acalabrutinib, lenalidomide and obinutuzumab (ALO), in previously untreated mantle cell lymphoma.

Study Duration:
Study includes an induction phase consisting of 12 cycles of ALR or ALO. Responding subjects will be eligible to enter a maintenance phase. Subjects will continue maintenance ALR or ALO. until disease progression, development of unacceptable toxicity, or voluntary withdrawal. Acalabrutinib and lenalidomide can be discontinued after 24 cycles of treatment (12 cycles of induction and 12 cycles of maintenance) for subjects achieving MRD-negative CR during maintenance phase. Subjects can be retreated with acalabrutinib and lenalidomide at time of disease progression.

Study Agent/ Intervention Description:

Cohort A: ALR in MCL, phase 2 study

- **Induction** (cycles 1 - 12)
  - 12 cycles, 1 cycle = 28 days
  - Acalabrutinib 100 mg BID continuous
  - Lenalidomide on days 1-21 (15 mg for cycle 1, then escalate as tolerated to 20 mg)
  - Rituximab 375 mg/m^2 on days 1, 8, 15, 21 of cycle 1 then day 1 of cycle 4, 6, 8, 10, 12

- **Maintenance** (cycle 13 – progression of disease or unacceptable toxicity)
  - Ongoing, 1 cycle = 28 days
  - Acalabrutinib 100 mg BID continuous
  - Lenalidomide 15 mg on days 1-21
  - Rituximab 375 mg/m^2 on day 1 of all even numbered cycles; e.g., 14, 16, 18, etc.

Cohort B: ALO in MCL, feasibility cohort

- **Induction** (cycles 1 - 12)
  - 12 cycles, 1 cycle = 28 days
  - Acalabrutinib 100 mg BID continuous
  - Lenalidomide on days 1-21 (15 mg for cycle 1, then escalate as tolerated to 20 mg)
  - Obinutuzumab on days 1, 8, 15 of cycle 1, day 1 of cycles 2-6, then every 2 cycles

- **Maintenance** (cycle 13 – progression of disease or unacceptable toxicity)

- Ongoing, 1 cycle = 28 days
- Acalabrutinib 100 mg BID continuous
- Lenalidomide 15 mg on days 1-21
- Obinutuzumab on day 1 of all even numbered cycles; e.g., 14, 16, 18, etc.

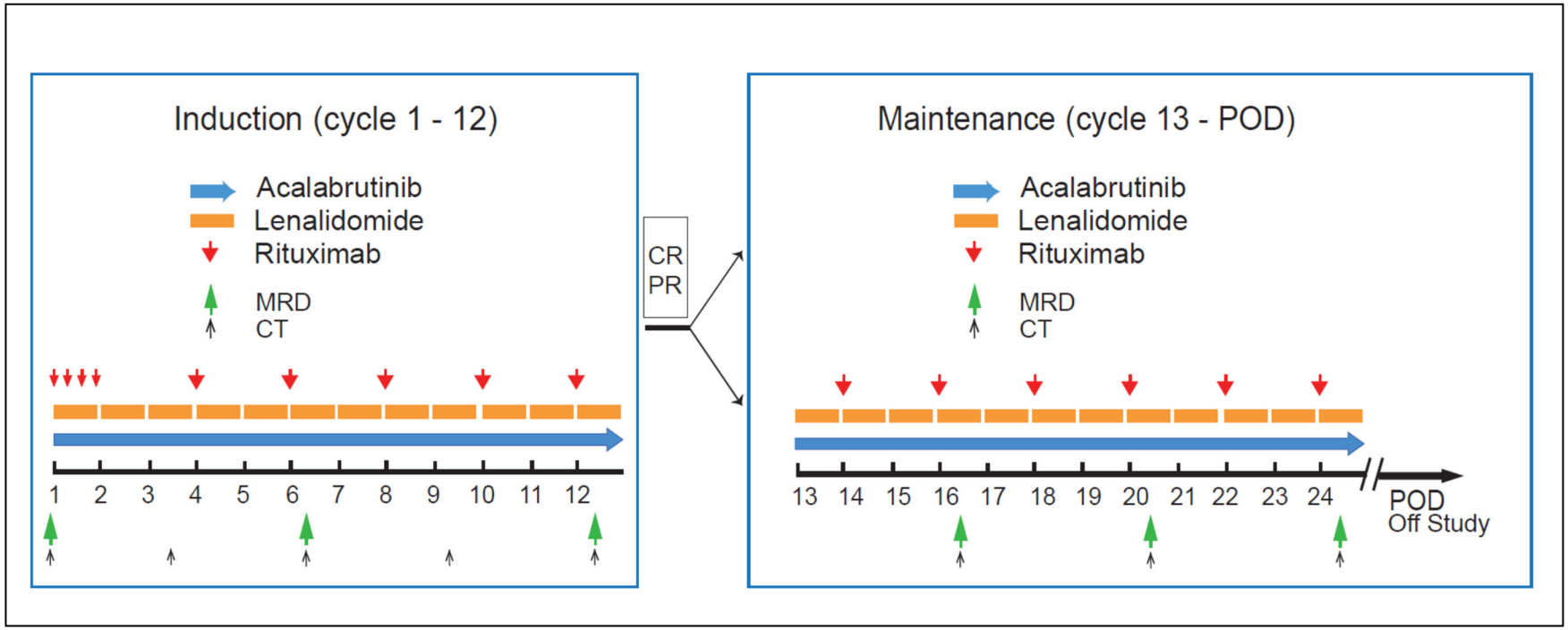
Primary Objective:
To determine the peripheral blood minimum residual disease (MRD)-negative complete response (CR) rate of the combination of ALR at the conclusion of 12 cycles of induction therapy.

Secondary Objectives:
- Safety and tolerability of the ALR combination
- Best overall response rate
- Complete response rate
- Progression free survival (time frame up to 2 years)
- Overall survival (time frame up to 2 years)
- Safety and feasibility of the ALO cohort

Exploratory Objectives:
- To evaluate peripheral blood MRD status during maintenance treatment.
- To estimate the response rate to the next subsequent therapy.
- To estimate the prevalence of adverse events over time.
- To estimate the quality of life of participants during the first 24 months of therapy.
- To correlate NGS mutational profile with response to treatment of the following genes: ATM, CCND1, TP53, KMT2D, NOTCH1, NOTCH2, WHSC1 and BIRC3.
- To evaluate the change in immune cells in peripheral blood, including T and NK cell subpopulations and the MDSC subset in response to treatment.
- To evaluate the cytokine profile (blood) in response to treatment.
- To analyze kinetics of changes of peripheral blood cell-free tumor DNA (cfDNA) in the plasma following study regimen and to evaluate cfDNA in the context of response status.
- To evaluate the immune metabolic profile (blood) pre-treatment, following ALR, and at time of progression.

Endpoints:
- The primary end point is to determine the peripheral blood MRD-negative CR rate (defined as MRD in peripheral blood $<10^{-6}$) of the ALR combination at the conclusion of 12 cycles of induction therapy.
- The secondary endpoints include progression-free survival (PFS), overall survival (OS), and time to next treatment of the ALR combination, as well as feasibility of ALO combination.

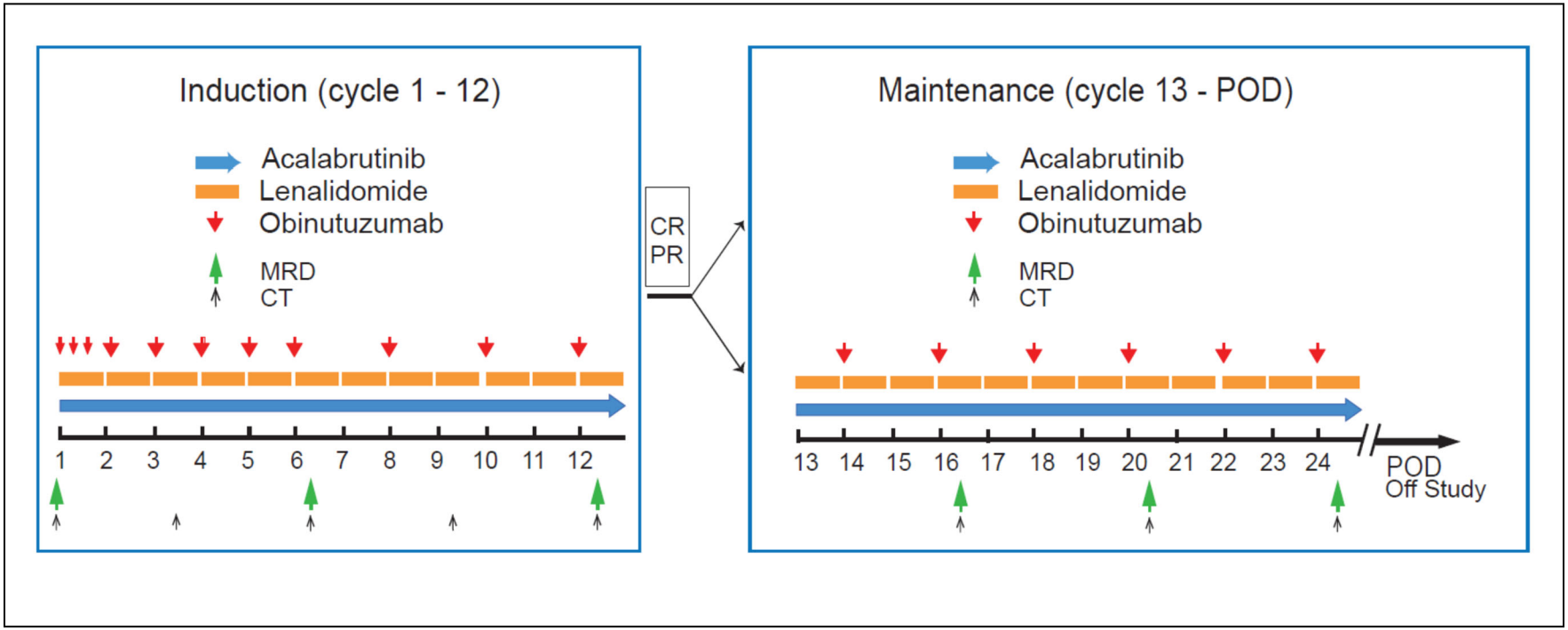
SCHEMA – ALR COHORT



Note

- Treatment includes 12 cycles of induction followed by maintenance. Patients will receive therapy until disease progression, development of unacceptable toxicity, or voluntary withdrawal. Acalabrutinib and lenalidomide can be discontinued after 24 cycles of treatment for subjects achieving MRD-negative CR during maintenance.
- MRD will be measured in peripheral blood at the conclusion of 6 and 12 cycles of induction treatment. Additional MRD measurements in peripheral blood will be collected every 4 cycles during maintenance.
- Imaging studies: PET/CT is required at baseline and time to confirm CR.

SCHEMA – ALO FEASIBILITY COHORT



Note

- Treatment includes 12 cycles of induction followed by maintenance. Patients will receive therapy until disease progression, development of unacceptable toxicity, or voluntary withdrawal. Acalabrutinib and lenalidomide can be discontinued after 24 cycles of treatment for subjects achieving MRD-negative CR during maintenance.
- MRD will be measured in peripheral blood at the conclusion of 6 and 12 cycles of induction treatment. Additional MRD measurements in peripheral blood will be collected every 4 cycles during maintenance.
- Imaging studies: PET/CT is required at baseline and time to confirm CR.

STUDY PROCEDURES – ALR

Table 1. Schedule of ALR Study Procedures[1]

Procedure	Screening	Treatment Phase								Therapy Discontinuation	Follow-up Phase
		Cycle 1				Subsequent cycles	Every 3 cycles Year 1	Every 4 cycles Year 2	Every 6 cycles Year 3-5		
		Day 1	Day 8±1	Day 15±1	Day 22±1	Day 1±3					Every 6 months
Staging											
Lymph node/tissue biopsy[2]	X										
Bone marrow aspirate & biopsy[3]	X						**Time to confirm CR**				
Staging CT scan (or MRI)[4]	X						X	X	X	X	
PET/CT[4]	X						**Time to confirm CR**				
MRD Assay[5]	X						Cycles 6 & 12	X	Every 6 cycles		
Laboratory Studies											
CBC with differential	X	X	X	X	X	X[12]				X	
CMP including LFT	X	X	X	X	X	X				X	
LDH, uric acid[14], phosphate[14], PT/INR[14], aPTT[14]	X	X	X	X	X	X				X	
Creatinine clearance[6]	X										
Thyroid function test TSH, T4, T3 uptake	X						X	X	X	X	
HBsAg, HBsAb, HBcAb, HCV, HIV[7]	X										
HBV DNA testing[7]	X						X	X	X	X	
Pregnancy testing[8]	X	X				X				X	
Buccal Swab / saliva sample[2]	X										
Other Evaluations											
Physical examination / vital signs[13]	X	X	X	X	X	X				X	
Height & weight	X	X				X				X	
ECOG performance status	X	X				X				X	
MIPI score	X										
12-lead ECG[9]	X										
FACT-Lym QOL questionnaires	X						X	X	X	X	
Concomitant medications	X	X	X	X	X	X				X	
Register Revlimid REMS® program	X										
Prescribe via Revlimid REMS®[10]		X				X					
Adverse events assessment		X	X	X	X	X	X	X	X	X	
Correlative studies[11]		X	X	X	X	X				X	
Obtain Follow-Up treatment											X

Obtain Follow-Up survival											X

[1] Unless otherwise specified, all screening requirements are within 28 days, all other assessments and procedures are +/- 3 days.
[2] LN/tissue biopsy has no time limit. Lymph node/tissue biopsy is required as necessary to confirm diagnosis. Additionally, one-time buccal swab or saliva sample collection for germline control should occur at screening, on treatment or off treatment.
[3] During the study bone marrow biopsy is required only if the patient has otherwise fulfilled the criteria for CR. Baseline BMBx has no time limit.
[4] Tumor assessment will be by means of PET/CT at Screening and at time to confirm CR. CT scan with contrast or MRI will be performed every 3 cycles year 1, every 4 cycles year 2, and every 6 cycles year 3 and beyond.
[5] MRD assays are collected at baseline, after cycles 6 and 12 of induction, and then every 4 cycles year 2 during maintenance and then every 6 cycles afterwards (years 3-5).
[6] Creatinine clearance (CrCl) is estimated using the Cockcroft-Gault formula where CrCl (mL/min) = (140 – age)(weight [kg]) / 72 (serum creatinine [mg/dL]; for females, the formula is multiplied by 0.85 (Cockcroft, 1976). Creatinine clearance should be calculated using actual body weight.
[7] All patients must be screened for hepatitis B and hepatitis C before starting treatment. Carriers of hepatitis B should be closely monitored, including HBV DNA testing at Screening, every 3 cycles year 1, every 4 cycles year 2, and every 6 cycles year 3 and beyond, and End of Treatment. For patients with evidence of prior HBV infection, HBV suppressive therapy is strongly recommended. HCV RNA viral load testing is suggested for patients with positive anti-HCV serology.
[8] 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 test (serum or urine) is required at Screening, Day 1 of each cycle, and end of treatment.
[9] 12-lead ECG is performed at screening/baseline, prior to maintenance, and as clinically indicated.
[10] Lenalidomide must be prescribed through and in compliance with the Revlimid REMS® program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the Revlimid REMS® program.
[11] Correlative study blood samples will be collected weekly for cycle 1, on C2D1, C4D1, and C6D1, then following the same frequency as the MRD collection and at time of progression.
[12]Consider weekly CBC for cycle 2 for subjects who have lenalidomide escalated from 15 mg to 20 mg.
[13] Allow telemedicine / virtual visits after cycle 3 of induction during cycles when there is no infusion treatment, where physical exam, vital signs, height and weight may not be collected.
[14] PT/INR/aPTT, as well as uric acid and phosphate assessments will be collected at baseline, and only if clinically indicated thereafter.

STUDY PROCEDURES – ALO

Table 2. Schedule of ALO Study Procedures[1]

Procedure	Screening	Treatment Phase							Therapy Discontinuation	Follow-up Phase
		Cycle 1			Subsequent cycles	Every 3 cycles Year 1	Every 4 cycles Year 2	Every 6 cycles Year 3-5		
		Day 1	Day 8±1	Day 15±1	Day 1±3					Every 6 months
Staging										
Lymph node/tissue biopsy[2]	X									
Bone marrow aspirate & biopsy[3]	X					**Time to confirm CR**				
Staging CT scan (or MRI)[4]	X					X	X	X	X	
PET/CT[4]	X					**Time to confirm CR**				
MRD Assay[5]	X					Cycles 6 & 12	X	Every 6cycles		
Laboratory Studies										
CBC with differential	X	X	X	X	X[12]				X	
CMP including LFT	X	X	X	X	X				X	
LDH, uric acid[14], phosphate[14], PT/INR[14], aPTT[14]	X	X	X	X	X				X	
Creatinine clearance[6]	X									
Thyroid function test TSH, T4, T3 uptake	X					X	X	X	X	
HBsAg, HBsAb, HBcAb, HCV, HIV[7]	X									
HBV DNA testing[7]	X					X	X	X	X	
Pregnancy testing[8]	X	X			X				X	
Buccal Swab[2]	X									
Other Evaluations										
Physical examination / vital signs[13]	X	X	X	X	X				X	
Height & weight	X	X			X				X	
ECOG performance status	X	X			X				X	
MIPI score	X									
12-lead ECG[9]	X									
FACT-Lym QOL questionnaires	X					X	X	X	X	
Concomitant medications	X	X	X	X	X				X	
Register Revlimid REMS® program	X									
Prescribe via Revlimid REMS®[10]		X			X					
Adverse events assessment		X	X	X	X	X	X	X	X	
Correlative studies[11]		X	X	X	X				X	
Obtain Follow-Up treatment										X

Obtain Follow-Up survival										X

[1] Unless otherwise specified, all screening requirements are within 28 days, all other assessments and procedures are +/- 3 days.
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[11] Correlative study blood samples will be collected weekly for cycle 1, on C2D1, C4D1, and C6D1, then following the same frequency as the MRD collection and at time of progression.
[12] Consider weekly CBC for cycle 2 for subjects who have lenalidomide escalated from 15 mg to 20 mg.
[13] Allow telemedicine / virtual visits after cycle 3 of induction during cycles when there is no infusion treatment, where physical exam, vital signs, height and weight may not be collected.
[14] PT/INR/aPTT, as well as uric acid and phosphate assessments will be collected at baseline, and only if clinically indicated thereafter.

1. STUDY OBJECTIVES

1.1 Primary Objective

To determine the peripheral blood minimum residual disease (MRD)-negative complete response (CR) rate of the combination of acalabrutinib + lenalidomide + rituximab (ALR) at the conclusion of 12 cycles of induction therapy.

1.2 Secondary Objectives

- Safety and tolerability of the ALR combination
- Best overall response rate
- Complete response rate
- Progression free survival (time frame up to 2 years)
- Overall survival (time frame up to 2 years)
- Safety and feasibility of the ALO cohort

1.3 Exploratory Objectives

- To evaluate peripheral blood MRD status during maintenance treatment.
- To estimate the response rate to the next subsequent therapy.
- To estimate the prevalence of adverse events over time.
- To estimate the quality of life of participants during the first 24 months of therapy.
- To correlate NGS mutational profile with response to treatment of the following genes: ATM, CCND1, TP53, KMT2D, NOTCH1, NOTCH2, WHSC1 and BIRC3.
- To evaluate the change in immune cells in peripheral blood, including T and NK cell subpopulations and the MDSC subset in response to treatment.
- To evaluate the cytokine profile (blood) in response to treatment.
- To analyze kinetics of changes of peripheral blood cell-free tumor DNA (cfDNA) in the plasma following study regimen and to evaluate cfDNA in the context of response status.
- To evaluate the immune metabolic profile (blood) pre-treatment, following ALR, and at time of progression.

2. BACKGROUND

2.1 Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is an incurable lymphoma with a median survival of 5-7 years. Standard front-line treatment usually includes chemoimmunotherapy and often involves aggressive approaches, yet most patients continue to relapse despite intensive therapy. The major therapeutic goals in patients with MCL are to prolong survival and improve quality of life. The unmet needs in MCL management in the frontline setting are to develop approaches that can be targeted to the appropriate patients based on disease biology, are well tolerated and accessible by

all patients, and can be administered in the outpatient community [1].

Over the past decade, four non-chemotherapy options, namely bortezomib, lenalidomide, ibrutinib, and most recently acalabrutinib, have been approved by the United States Food and Drug Administration for treatment of MCL [2-5]. Continuous therapy with BTK inhibitors in particular have shown impressive clinical activity with generally favorable toxicity profile in relapse/refractory setting. The introduction of novel agents corresponds with better outcomes in population studies, suggesting that the availability of new options that can be used sequentially may be extending survival. Furthermore, emerging data with novel agents and combinations is poised to challenge the conventional chemotherapy-based treatment paradigm in frontline setting, making effective and less toxic "chemo-free" treatment accessible to most MCL patients a tangible reality.

Recently published data from Weill Cornell Medicine (WCM) have shown that the combination of lenalidomide plus rituximab administered until progression is active and well tolerated as front-line therapy in patients with MCL with a complete response (CR) rate of 61%, a 2-year progression-free survival (PFS) of 85% and a 4-year PFS of 70%, demonstrating the feasibility of administering novel agents as effective induction and chronic maintenance therapy in the outpatient setting [6]. MRD status was sampled during long-term follow-up, and 6 of 7 patients with available samples achieved MRD negativity [7], providing the first proof-of-concept evidence that lenalidomide-based novel agent/combination have the potential to achieve MRD-negative remission. The apparent activity of the regimen warrants further evaluation, but attempts at improving the efficacy and tolerability as well as efforts to better define the patient subsets that might benefit most are also needed.

2.2 Application of Chemotherapy-free Novel Agents in MCL

Both lenalidomide-based and BTK inhibitor-based regimens have demonstrated significant clinical activities in MCL, with emerging evidence supporting moving rationally designed novel combinations into frontline setting. A brief summary of non-chemotherapy biologic agents/combination in MCL is provided as below.

2.2.1 Evidence with lenalidomide-based regimens

In MCL-001 and MCL-002 studies for relapsed / refractory disease, single agent lenalidomide given at 25 mg on days 1-21 every 28 days showed ORR of 28%-40%, CR 5-8% and DOR over 16 months [3,8]. The most common grade 3–4 adverse events associated with single agent lenalidomide included neutropenia (43-44%), thrombocytopenia (18-28%), and anaemia (8-11%). The addition of rituximab, given at 375 mg/m^2 weekly during cycle 1, to 20 mg lenalidomide, was safely tolerated and augmented activity in relapsed patients with ORR 53%, CR 31%, median PFS 14 months, and DOR 18 months [9]. When evaluated in 38 patients with previously untreated MCL, the combination of lenalidomide plus rituximab given as induction and maintenance therapy was highly effective and produced an ORR of 92% and 64% CR in evaluable patients. The median DOR and PFS was not reached after a median follow-up of 30 months. Treatment was well tolerated, with the most common grade 3-4 adverse events included neutropenia (50%), rash

(29%), thrombocytopenia (13%), tumor flare (11%), anemia (11%) and fatigue (8%). A response to treatment was associated with improvement in quality of life as measured by quality-of-life instrument [6]. Exploratory analyses were performed in some of these studies to evaluate predictive biomarkers for response and survival. The proliferation index Ki-67 was significantly associated with lower CR rate, DOR and survival in MCL-001 study [10]. The impact of SOX11 and TP53 expression and *IGHV gene* mutational status have not been reported in lenalidomide-based treatment.

2.2.2 Evidence with 1st generation BTK inhibitor ibrutinib-based regimens

Single agent Ibrutinib, given at a daily dose of 560 mg, demonstrated an ORR of 68% with 21% CR and a median DOR of 17.5 months in an international phase 2 study including 111 patients with relapsed or refractory MCL [4]. In a subsequent long-term follow-up study, the median treatment duration was reported at 8.3 months with 46% of patients treated for >12 months and 22% treated for ≥ 2 years. The 24-month PFS and OS rates were 31% and 47% [11]. When given in combination with rituximab which was administered weekly x 4 during cycle 1, then on day 1 of cycles 3-8, and thereafter once every other cycle up to 2 years to 50 relapsed MCL patients, the ORR was 88% with CR at 44% [12]. Treatment was well tolerated and only 10% discontinued treatment due to AEs. Ki-67 expression levels were assessed and divided into less than 50% (37 patients) and 50% or more (12 patients). Patients in the Ki-67 <50% group achieved 100% ORR with median DOR, PFS and OS not reached. Patients in the Ki-67 ≥50% group were significantly associated with worse treatment outcome, suggesting that Ki-67 might serve as a predictive biomarker of treatment responses to ibrutinib and rituximab combination in MCL. Based on data in R/R setting, an ongoing phase II single-center clinical trial at MDACC has evaluated a chemotherapy-free phase of ibrutinib-rituximab (IR) treatment (Part 1) until best response [13], followed by a shortened intense chemo-immunotherapy course of R-hyperCVAD alternating with high-dose methotrexate-araC (Part 2) among newly diagnosed MCL patients of ≤65 years. Ibrutinib was dosed at 560 mg orally, daily, continuously. Rituximab was dosed at 375 mg/m^2 IV weekly x 4 during cycle 1 (28 days cycle), then day 1 of cycles 3-12. In 50 evaluable patients, overall response rate (ORR) to chemotherapy-free therapy alone was 100%, with CR in 80% (40) and PR in 20% (10). The most common grade 1-2 non-heme AEs were fatigue (50), diarrhea (28), rash (29), myalgia (41), oral mucositis (52), peripheral neuropathy (19), nausea (25), blurred vision (19), edema (23), constipation (18), dry eyes (18), and dizziness (22). Grade 3 non-heme AEs included fatigue (4), nausea (2), infection (3) and dyspnea (2). Grade 3-4 heme AEs included lymphocytosis (22), thrombocytopenia (13) and leukopenia (15). MRD status was not reported in these studies.

2.2.3 Evidence with the next-generation BTK inhibitor Acalabrutinib

Acalabrutinib (also known as ACP-196 and/or Calquence®) is a selective, irreversible small molecule inhibitor of BTK currently under clinical investigation. Acalabrutinib is an investigational product. Calquence® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL). A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of acalabrutinib is provided in the Investigator Brochure. The Phase 2 ACE-LY-004 study assessed

acalabrutinib monotherapy in R/R MCL pts. 124 pts were treated with acalabrutinib at 100 mg BID until POD. Investigator-assessed ORR was 81% with 40% CR. The 12-mo PFS and OS rates were 67% (95% CI, 58%-75%) and 87%, respectively [14]. The most frequent AEs (≥20%) were Grade 1/2 and included headache (38%), diarrhea (31%), fatigue (27%) and myalgia (21%). Grade 3/4 AEs (≥5%) included neutropenia (10%), anemia (9%) and pneumonia (5%). There were no cases of atrial fibrillation. Treatment discontinuation rate due to AEs was only 6%. Importantly, acalabrutinib has not been associated with the cutaneous toxicity reported in trials with ibrutinib.

2.2.4 Data with Triple combination

The Nordic lymphoma group reported the triple combination therapy of ibrutinib-lenalidomide-rituximab (ILR) in 50 R/R MCL [15]. During induction, lenalidomide was given 15 mg po daily, days 1-21, ibrutinib 560 mg po days 1-28, rituximab 375 mg/m iv day 1 in cycle 1, then 1400 mg sc (or 375 mg/m iv) days 8, 15 and 22 in cycle 1, then day 1 in cycles 3, 5, 7, 9 and 11. During maintenance phase, responding patients continued with ibrutinib 560 mg po days 1-56 and rituximab sc 1400mg day 1 of each cycle until progression. The most common grade 3–4 adverse events were neutropenia (38%), infections (22%), and rash (14%). In evaluable patients, ORR was 83% with CR at 41% and PR at 41%. Median duration of response and PFS has not been reached. Of the 13 patients evaluable for MRD at 6 months, 7/12 patients have achieved molecular remission in blood and 7/13 in bone marrow. Interestingly, the outcomes of patients with mutant TP53 was comparable to patients with wildtype TP53, suggesting that the triple combination might overcome the poor prognosis associated with TP53 mutations.

The ILR triple combination has also been evaluated in frontline FL and R/R DLBCL studies. The Alliance A051103 trial evaluated the combination of lenalidomide, rituximab, and ibrutinib in patients with previously untreated follicular lymphoma [16]. Despite a high response rate, the activity of the regimen was challenged by poor tolerability related primarily to cutaneous toxicity (grade 3 rash at 36%). In R/R DLBCL, the ILR combination of ibrutinib 560 mg once daily, rituximab 375 mg/m^2 on day one for six cycles and escalating doses of lenalidomide was evaluated in a phase 1b study [17]. Preliminary data showed promising activity for patients with the non-GCB subtype. The most common grade 3-4 adverse events included neutropenia (33%), maculopapular rash (15%), and anemia (11%). Phase 2 portion of the global study is actively accruing at the dose level of lenalidomide 20 mg daily, days 1-21, ibrutinib 560 mg daily, and rituximab monthly x 6.

Taken together, these data suggest activity and feasibility of combining BTK inhibitor with immunomodulatory agent lenalidomide in MCL, but also suggest that a second-generation BTK inhibitor with less cutaneous toxicity, such as acalabrutinib, would be an optimal choice in the front-line setting.

2.3 ALR Study Rationale

There is no standard, one-size-fits-all induction treatment for patients with mantle cell lymphoma. Initial treatment for MCL varies but usually includes chemoimmunotherapy and often involves intensive approaches, such as high-dose chemotherapy and hematopoietic-cell transplantation. Treatment selection is influenced by age, coexisting conditions, and individual preferences.

Optimal treatment of patients with MCL, who are frequently older (median age, 65 years) and unsuitable candidates for intensive regimens, remains a clinical challenge.

Lenalidomide is a second-generation immunomodulatory compound that has pleiotropic antitumor effects, including stimulation of T-cell and natural killer (NK)–cell expansion, inhibition of tumor-associated angiogenesis and lymphangiogenesis and induction of lymphoma cell apoptosis through the down-regulation of cyclin D1 [18]. When combined with rituximab in vitro, lenalidomide augments antibody-dependent cell-mediated cytotoxicity by enhancing apoptosis and activation of NK-cell–mediated cytotoxicity and has been shown to overcome rituximab resistance in patients with lymphoma. In frontline setting, phase 2 data from Weill Cornell Medicine (WCM) have shown that the combination of lenalidomide plus rituximab is active and well tolerated with an ORR of 92% and a complete response (CR) rate of 61% in 36 evaluable patients [6]. The 4-year PFS of 70% is particularly notable relative to historical data reported on patients receiving outpatient-based chemotherapy regimens, where median progression-free survival ranged from 16.6 to 35.4 months. There remains room for improvement in efficacy, tolerability and better-defined treatment duration.

BCR signaling is necessary to sustain the viability of B cell malignancies via constitutive activation of NF-kB pathway. An antigen-driven origin of mantle cell lymphoma has been suggested whereby BCR activation contributes to proliferative signature of MCL lymphomagenesis [19]. BTK inhibitors provide therapeutic activity by blocking chronic BCR signaling leading to a decrease in NF-κB activity. Lenalidomide downmodulates IRF4, leading to an increase in IFNβ secretion and a decrease in NF-κB activity [20]. Combining BTK inhibitor and lenalidomide therefore appears to target key pathways in MCL which may increase therapeutic synergy and reduce overall resistance development. Additionally, combining acalabrutinib with lenalidomide + R may have theoretic advantage over ibruitnib with lenalidomide + R, given minimal impact of acalabrutinib on activation and expansion of NK/T cells compared to ibrutinib [21], which potentially preserves immunomodulatory amplification of lenalidomide on rituximab-induced ADCC.

The feasibility of the triple combination of BTK inhibitor + lenalidomide + rituximab in MCL has been demonstrated by the Nordic PHILEMON study which uses lenalidomide at 15 mg po daily, days 1-21, Ibrutinib 560 mg po days 1-28, and standard dose rituximab [15]. Furthermore, the triple combination was experimented in a phase 1 FL frontline study and a phase I/II R/R DLBCL study. Phase 2 recommended dose was lenalidomide at 20 mg daily, days 1-21, and ibrutinib at 560 mg daily in 28-day cycle for both studies [16]. Given the generally similar and well-tolerated profile of acalabrutinib and ibrutinib, we expect similar safety profile with the acalabrutinib, lenalidomide and rituximab combination in frontline MCL treatment. Because relapsed/refractory MCL has been associated with poor outcomes, every study to evaluate lenalidomide or BTK inhibitors to date, including the Nordic PHILEMON study, treatment has continued until disease progression.

Based on the relatively high clinical CR rate with frontline R2 regimen (CR 60%), and frontline IR regimen (CR 80%), we hypothesize that additional of BTK inhibitor acalabrutinib to R2 regimen would further synergize clinical activity of either agent and improve MRD negative CR rate from 60% to a target rate of 80%. The improvement in MRD CR rate would facilitate

response-adapted treatment algorithm during maintenance phase to allow for oral-drug free period to minimize AEs associated with chronic therapy. We therefore propose a single-arm phase 2 study to evaluate the preliminary evidence of efficacy and safety of the combination of acalabrutinib, lenalidomide and rituximab (ALR) in previously untreated mantle cell lymphoma. The study includes an induction phase consisting of 12 cycles of ALR. Subjects that respond to treatment will be eligible to enter a maintenance phase which will continue until disease progression, unacceptable toxicity, or voluntary withdrawal. A lead-in cohort of 6 subjects will serve as safety run-in.

2.4 Correlative Studies Background

The MRD evaluation has emerged as an attractive and highly sensitive tool for assessing the response to treatment in MCL [22]. Almost all patients with MCL present with PCR-detectable dissemination to PB or BM, and MRD assessment by RQ-PCR is feasible in about 85% of advanced-stage MCL. MRD response is a strong prognostic and predictive marker for subsequent clinical outcome, indicating that early MRD eradication should be a therapeutic goal in the treatment of MCL. It is therefore of major interest to elucidate the MRD response to novel treatment to select new strategies for further investigation. LymphoTrack–Miseq platform and customized algorithm will be applied to identify lymphoma-specific rearranged immunoglobulin gene region (VDJ) in pre-treatment tissue sample(s) and to detect MRD in posttreatment PB samples.

It is of clinical utility to pursue novel biomarkers and additional means of monitoring for MRD. It has been previously reported that cell-free circulating tumor DNA follows distinct kinetic patterns of clearance from plasma in response to treatment. Development of detectable circulating tumor DNA during surveillance identified a subset of patients at elevated risk of relapse months prior to clinically evident disease [23]. DNA will be quantified in our subjects during maintenance treatment. We will also explore associations of MRD status with genomic composition of MCL and immune microenvironment during treatment as predictive biomarkers for treatment sensitivity or resistance, with the following correlative study objectives.

- To analyze kinetics of changes of peripheral blood cell-free tumor DNA (cfDNA) in the plasma following study regimen and to evaluate cfDNA in the context of response status.
- To correlate NGS mutational profile with response to treatment of the following genes: ATM, CCND1, TP53, KMT2D, NOTCH1, NOTCH2, WHSC1 and BIRC3.
- To evaluate the change in immune cells in peripheral blood, including T and NK cell subpopulations and the MDSC subset in response to treatment.
- To evaluate the plasma cytokine profile in response to treatment.

2.5 ALO Study Expansion Rationale

Obinutuzumab is a type II, glyco-engineered, humanized anti-CD20 monoclonal antibody, which was superior to rituximab in MCL xenograft models. In the phase 2 GAUGUIN study, single agent obinutuzumab demonstrated clinical activity in patients with R/R MCL including those with

rituximab-refractory disease [1]. A number of frontline phase 2 trials which recruit older MCL patients are assessing the efficacy of bendamustine plus obinutuzumab (BO) combinations. They include the phase 2 single-arm multicenter study (NCT03311126) with BO chemoimmunotherapy induction followed by consolidation and maintenance with obinutuzumab, and the phase 2 trial with the triple combination induction therapy of bendamustine, obinutuzumab and venetoclax (NCT03872180). Obinutuzumab is also being evaluated with the chemo-free combination of ibrutinib plus venetoclax in a phase 1/2 study (OAsIs, NCT02558816). The study consists of a step-wise enrollment: step A with obinutuzumab plus ibrutinib combination in R/R MCL, step B with triple combination in R/R MCL, and step C with the triplet in treatment-naïve patients [2]. Patients in step C were treated with Obinutuzumab at 1000mg IV on C1D1, 8, 15, C2-6 D1 and every 2 months for up to 2 years. Preliminary data on 15 treatment-naïve patients showed ORR of 100% when assessed at end of cycle 2 treatment.

The combination of obinutuzumab with lenalidomide (LO) has demonstrated favorable safety and efficacy in patients with indolent B-cell NHL including follicular lymphoma. The phase 1b GALEN study established that patients with R/R FL could safely tolerate obinutuzumab 1000 mg IV administered on days 8, 15, and 22 of cycle 1 and on day 1 of cycles 2-6, in combination with 20 mg lenalidomide given on days 1 to 21 of a 28-day cycle. The LO combination was well tolerated and effective, providing ORR of 64% [3]. In the MD Anderson phase 1/2 study with LO for relapsed indolent B-cell NHL, 66 patients received Len at 20 mg given on days 1 to 21 of a 28-day cycle, plus obinutuzumab (1000mg) IV on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2-6, followed by maintenance every 2 months for a maximum of 30 months on study. The ORR for all pts was 98% with CR at 72% [4]. When given in the frontline setting for 90 patients with untreated high burden follicular lymphoma, the same MD Anderson LO treatment schedule achieved ORR of 98% with CR at 92%. The treatment was well tolerated with manageable toxicity profile, including grade 3/4 neutropenia at 16%, rash at 10% and lung infection at 4% and neutropenic fever at 1% [5].

Given the safety and efficacy data of obinutuzumab combinations in mantle cell lymphoma, and the impressive efficacy of obinutuzumab plus lenalidomide combination in indolent lymphoma, we hypothesize that the obinutuzumab-based triple combination of acalabrutinib-lenalidomide-obinutuzumab (ALO) has the potential to improve efficacy while maintaining safety and tolerability compared to the ALR combination in the frontline setting. We propose to add a feasibility cohort of 10 MCL patients to assess safety and preliminary efficacy with the ALO regimen. We recommend commencing the accrual of the ALO cohort following enrollment completion of the ALR cohort.

3. SUBJECT SELECTION

3.1 Study Population

Adults with previously untreated mantle cell lymphoma who meet the inclusion and exclusion criteria will be screened for eligibility. Screening procedures are outlined in Section 5, Schedule of Evaluations and unless otherwise specified, must take place within 28 days prior to initiation of

therapy. Approximately 28 subjects with previous untreated mantle cell lymphoma will be screened for enrollment and must meet the eligibility criteria below.

3.2 Inclusion Criteria

- Histologically confirmed diagnosis of mantle cell lymphoma
- Age ≥ 18 years
- No prior systemic therapy for lymphoma
- Measurable disease defined by a tumor mass ≥ 1.5 cm in one dimension and measurable in two dimensions; patients with measurable spleen disease are allowed
- Treatment should be indicated according to the treating physician
- ECOG performance status ≤ 2
- Required initial laboratory parameters:

  Absolute neutrophil count (ANC) ≥ 1000 cells/mm^3

  Platelet count ≥ 75,000 cells/mm^3

  Calculated creatinine clearance ≥ 30 ml/min by Cockcroft-Gault formula

  Total bilirubin ≤ 1.5 x ULN

  AST/SGOT and ALT/SGPT ≤ 3.0 x ULN
- Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use low molecular weight heparin).
- All subjects must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.
- Patients of reproductive potential agree to use highly effective birth control throughout their participation in this study, for at least 28 days following study termination, and for 160 days for males and 12 months for females after the last dose of rituximab, 180 days for males and 18 months for females after the last dose of obinutuzumab.
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. 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). FCBP must either commit to continued abstinence from heterosexual intercourse or begin one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before and continue for at least 28 days after the last dose of lenalidomide (or 2 days after the last dose of acalabrutinib, whichever is longer). FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual activity with a FCBP through one week post last dose even if they have had a successful vasectomy. Men must also agree to refrain from sperm donation during the same timeframe. See Appendix I: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Highly Effective Birth Control Methods.

- Understand and voluntarily sign an ICF prior to any study related assessments and procedures are conducted.
- Able to adhere to the study visit schedule and other protocol requirements.

3.3 Exclusion Criteria

- Patients with blastoid histology
- Patients with known or suspected CNS involvement
- Viral infection with HIV or hepatitis type B or C. Seropositive HBV patients are eligible if they are negative for HBV DNA by PCR and receive concomitant antiviral therapy during treatment and for additional six months after coming off study.
- Prior history of malignancies other than MCL unless the patient has been disease free for ≥ 5 years from the signing of the ICF. Exceptions include basal cell carcinoma or squamous cell carcinoma of the skin; carcinoma in situ of cervix; carcinoma in situ of breast, or localized prostate cancer
- Active uncontrolled systemic fungal, bacterial or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy and/or other treatment)
- Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
- Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
- Active bleeding or history of bleeding diathesis (e.g., hemophilia or von Willebrand disease).
- Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).
- Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer. Patients on moderate CYP3A inhibitors can be considered for study after a washout period of at least 7 days.
- Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
- Prothrombin time (PT)/INR or aPTT (in the absence of lupus anticoagulant) >2x ULN.
- Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.

- History of significant cerebrovascular disease/event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.
- Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
- Patients with a history of toxic epidermal necrolysis or Stevens-Johnson syndrome
- Patients that are pregnant or breast feeding
- Known hypersensitivity to any study drug or excipients
- Patient on corticosteroids within two weeks prior to study entry, except for prednisone ≤ 20 mg/day or equivalent for purposes other than treating MCL
- Use of any other experimental drug or therapy within 28 days of baseline
- Patient at high risk for deep vein thrombosis not willing to take DVT prophylaxis
- Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
- Known prior exposure to BTK inhibitor

4. REGISTRATION PROCEDURES

Patients will be centrally registered with the Weill Cornell Medicine (WCM), Division of Hematology and Medical Oncology, Joint Clinical Trials Office. To register a patient, email the following documents to your assigned registration contact:

- WCM Patient registration form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required.
- Fully executed HIPAA research authorization form (if separate from the consent document)
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers granted
- Redacted source documentation to verify eligibility

Central registration documents should be scanned/emailed Monday to Friday from 9:00 AM to 4:00 PM EST to study investigators and jctoiit@med.cornell.edu, along with all other assigned registration contacts for this study. Central registration information is reviewed and entered into the REDCap database by the Coordinating Center. Patients will be assigned a sequence number for the protocol. The registering institution will then be emailed a copy of the sequence number as confirmation of a completed registration. Subjects should NOT receive any study medication prior to receipt of registration confirmation. Note that attachments larger than 4.5 MB are not accepted, so larger attachments should be split into more than one email.

Registration of patients cannot occur until the Coordinating Center has received proper documentation from the registering institution of IRB approval, including a copy of the current approval letter, stamped consent and signed FDA Form 1572, along with other required regulatory documents. These documents will be requested at site activation and may be scanned/emailed to the Coordinating Center.

5. STUDY PROCEDURES

5.1 Study Design

This is a phase 2 study to evaluate the preliminary evidence of efficacy and safety of the combination of acalabrutinib, lenalidomide and rituximab (ALR), as well as the feasibility of acalabrutinib, lenalidomide and obinutuzumab (ALO), in previously untreated mantle cell lymphoma.

The study includes an induction phase consisting of 12 cycles of ALR or ALO. Responding subjects will be eligible to enter a maintenance phase. Subjects will continue maintenance ALR or ALO until disease progression, development of unacceptable toxicity, or voluntary withdrawal. Subjects in CR wishing to attempt stem cell collection following at least 6 months of induction treatment can hold lenalidomide for up to 30 days, and restart following stem cell collection.

Subjects will be monitored for MRD status in PB at baseline, and completion of 6 and 12 cycles of induction treatment using Adaptive Biotechnology Clonoseq assay, and then every 4 cycles. Acalabrutinib and lenalidomide can be discontinued after 24 cycles of treatment (12 cycles of induction and 12 cycles of maintenance) for subjects achieving MRD-negative CR for at least 4 months during maintenance phase, while rituximab or Obinutuzumab maintenance continues. Subjects can be retreated with adding back acalabrutinib and lenalidomide at time of disease progression.

5.1.1 Induction

Cohort A: ALR cohort

- Cycles 1-12, 1 cycle = 28 days
- Acalabrutinib 100 mg BID continuous
- Lenalidomide on days 1-21 (15 mg for cycle 1, then escalate as tolerated to 20 mg)
- Rituximab 375 mg/m^2 on days 1, 8, 15, 21 of cycle 1 then day 1 of cycle 4, 6, 8, 10, 12

Cohort B: ALO feasibility cohort

- Cycles 1-12, 1 cycle = 28 days
- Acalabrutinib 100 mg BID continuous
- Lenalidomide on days 1-21 (15 mg for cycle 1, then escalate as tolerated to 20 mg)
- Obinutuzumab on days 1, 8, 15 of cycle 1, day 1 of cycles 2-6, then every 2 cycles

5.1.2 Maintenance

Cohort A: ALR cohort

- Ongoing, 1 cycle = 28 days
- Acalabrutinib 100 mg BID continuous
- Lenalidomide 15 mg on days 1-21
- Rituximab on day 1 of all even numbered cycles; e.g., 14, 16, 18, etc.

Cohort B: ALO feasibility cohort

- Ongoing, 1 cycle = 28 days
- Acalabrutinib 100 mg BID continuous
- Lenalidomide 15 mg on days 1-21
- Obinutuzumab on day 1 of all even numbered cycles; e.g., 14, 16, 18, etc.

5.2 Schedule of Evaluations

Screening assessments and all scheduled study visits and assessments are outlined in **Table 1 (ALR) and Table 2 (ALO)**.

5.2.1 Screening Visit

Study screening begins when the subject signs the written informed consent document (ICD). All screening assessments must be completed within 28 days prior to Registration, with the exception of diagnostic biopsy which has no time limit. All baseline evaluations are to be done within 4 weeks prior to the start of Cycle 1 Day 1 treatment, unless otherwise specified.

- Diagnostic tissue biopsy slides available demonstrating mantle cell lymphoma (**No Time Limit**)
- Bone marrow aspirate and core biopsy (**No Time Limit**)
- Physical examination with history, vital signs including weight, and performance status
- Concomitant medications
- 12-lead Electrocardiogram
- PET scan
- CT scan (or MRI) of neck/chest/abdomen/pelvis (and other areas if indicated to evaluate sites of disease involvement)
- Complete blood count (CBC) with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- Coagulation profile with PT and aPTT
- Creatinine clearance
- Hepatitis B/C, HIV screening

- Thyroid function test (TSH, T4, T3 uptake)
- Pregnancy test (for female of childbearing potential)
- FACT-Lym quality-of-life questionnaires
-

5.2.2 Treatment Phase

5.2.2.1 Cycle 1 Day 1, then Day 1 of all subsequent cycles

- Physical examination with vital signs and performance status
- AE assessment
- Concomitant medications
- CBC with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- Pregnancy test (for females of childbearing potential) (see appendix I)
- Correlative blood samples (Cycles 1, 2, 4, 6, 7, 13,17, 21, 25, 29, 33 etc)
- Patients who discontinued oral medications and are on rituximab maintenance only, can have study visits on day 1 of cycles when treatment and laboratory studies are required.

5.2.2.2 Cycle 1, Days 8, 15, 22

- Physical examination with vital signs
- AE assessment
- Concomitant medications
- CBC with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- Correlative blood samples
- Subjects on ALO cohort can skip C1D22 visit

5.2.2.3 Cycles 4, 7, 10, 13, 17, 21, 25, then every 6 cycles onward

- Thyroid function test (TSH, T4, T3 uptake)
- HBV viral DNA in HBcAb positive, asymptomatic carrier
- CT scan (or MRI) of neck/chest/abdomen/pelvis (and other areas if indicated to evaluate sites of disease involvement); PET/CT to confirm CR

- Bone marrow aspirate and core biopsy (unilateral) only if otherwise in complete remission – not repeated once negative
- FACT-Lym quality-of-life questionnaires
- Correlative blood samples
- MRD assays at cycles 7 and 13, then every 4 cycles year 2 during maintenance, then every 6 cycles for years 3-5
- Telemedicine/virtual visits will be allowed after cycle 3 of induction during cycles when there is no infusion treatment, where physical exam and vital signs may not be collected.

5.2.3 Treatment Discontinuation

At treatment discontinuation, subjects will undergo off study evaluations within 28 days of last dose.

- Physical examination with vital signs and performance status
- AE assessment
- CBC with differential
- Serum chemistries to include TFT, CMP, LDH, phosphate and uric acid
- Concomitant medications
- HBV viral DNA in HBcAb positive, asymptomatic carrier
- Correlative blood samples
- Pregnancy test (for females of childbearing potential)
- CT scan (or MRI) of neck/chest/abdomen/pelvis (and other areas if indicated to evaluate sites of disease involvement); PET scan at discretion of investigator
- FACT-Lym quality-of-life questionnaires
- Telemedicine/virtual visits will be allowed where physical exam and vital signs may not be collected.
- Follow-up contact every 6 months until death

5.2.4 COVID-19 Pandemic-related Acceptable Protocol Modifications

- Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit

frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

- If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be reviewed by the investigator as soon as possible.

- Subject visits may be conducted via phone or video conference. If subjects are unable to be assessed by the study site, vital signs may be collected from another licensed practitioner, or collected by the subject or caregiver as needed. Physical exam (including body weight) may be collected from another licensed practitioner. Concomitant medication and AE assessments visits may be conducted via phone or video conference.

- If a subject is unable to come to the study site to pick up their oral study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations.

- Research sample collections may only be collected at the study site and are not to be collected if travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from visiting the study site at a sample collection time point.

5.3 Treatment Administration

5.3.1 Acalabrutinib Administration

Acalabrutinib may be administered in either the tablet or capsule formulation.

Acalabrutinib capsule is administered 100 mg BID and taken orally approximately every 12 hours. The capsules should be swallowed intact with water. Acalabrutinib can be taken with or without food. Subjects should not attempt to open capsules or dissolve them in water. If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the next dose. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Patients should avoid the concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix D) for both capsule and table form of acalabrutinib. Proton pump inhibitors or antacids should be avoided while taking acalabrutinib capsule.

The tablet form of Acalabrutinib is administered at the same dosage and frequency as the capsule. Administration of acalabrutinib maleate tablets with acid reducing agents such as proton

pump inhibitors does not impact the absorption; therefore no modification to dosing regimen is necessary.

5.3.2 Lenalidomide Administration

The lenalidomide starting dose will be based on baseline calculated creatinine clearance as follows:

Table 3. Lenalidomide Starting Dose Based on Renal Function at Study Entry

Baseline Calculated Creatinine Clearance (by Cockcroft-Gault)	Starting Lenalidomide Dose
≥ 60 ml/min	15 mg daily on Days 1 - 21 of each 28-day cycle
≥ 30 and < 60 ml/min	5 mg daily on Days 1 - 21 of each 28-day cycle

For patients with normal renal function (creatinine clearance ≥ 60 ml/min), the starting dose will be lenalidomide 15 mg daily with escalation to 20 mg if no excess toxicity. For patients with creatinine clearance ≥30 and <60 ml/min, the starting dose will be lenalidomide 5 mg daily with escalation to 10 mg if no excess toxicity. The lenalidomide dose may only be increased if the prior treatment cycle was completed without requiring dose modifications, interruptions or delays due to toxicity. Excess toxicity will be defined as grade 3 or 4 non-hematologic toxicity or grade 4 hematologic toxicity (see Section 6.1).

Prophylactic aspirin or low molecular weight heparin are to be given to patients with a high risk of developing DVT/PE or arterial thromboses unless contraindicated. High risk is defined as a history of DVT/PE, a known hypercoagulable state, and/or taking a concomitant medication associated with an increased risk for a thromboembolic event. Patients with diabetes mellitus or coronary artery disease are considered to be at high risk for arterial thromboembolic events.

Prescriptions for lenalidomide must be filled within 7 days. Dosing will be in the morning at approximately the same time each day. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed, or opened. 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. Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Accurate records will be kept of all oral drug administration (including prescribing and dosing). At study entry, patients will receive a Medication diary, and will be instructed on how to use the Medication diary. At monthly visits, the patient will bring the Medication diary along with all bottles of the study medication to the clinic. The Medication diary for the previous month will be reviewed and a new Medication diary will be given to the patient.

5.3.3 Rituximab Administration

Rituximab at standard dose of 375 mg/m^2 will be administered according to institutional standard. On each rituximab treatment day, patients are to be pre-medicated with diphenhydramine 50 mg IV or PO and acetaminophen 650 mg PO. Diphenhydramine (25 mg) and/or acetaminophen may be repeated if four hours elapse between the administration of the premedication and starting rituximab. Epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and any other medications and resuscitation equipment for the emergency management of severe allergic reactions must be available in the room where rituximab infusions are being performed. Where appropriate, rituximab biosimilars, such as Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), Riabni (rituximab-arrx), can be used instead of rituximab.

The initial rate during the first infusion should be 50 mg/hr. The rate may be increased, if tolerated, by 50-mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If administration is well tolerated during the first infusion, the initial rate during subsequent infusions of therapy may be increased to 100 mg/hr. If tolerated, the rate may be increased by 100-mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. For more information, see the package insert.

On days when acalabrutinib, lenalidomide and rituximab are given, rituximab should be administered after oral medications.

5.3.4 Obinutuzumab Administration

Each dose of obinutuzumab is 1000 mg, administered intravenously, with the exception of the first infusions in Cycle 1, which are administered on Day 1 (100 mg) and Day 2 (900 mg) (Table 4).

Table 4 Obinutuzumab Dosing Schedule

Cycle and Day of Administration		Dose of Obinutuzumab	Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hour if no infusion reaction occurred during the previous infusion. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.
	Day 8	1000 mg	If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.
	Day 15	1000 mg	
Cycles 2–6, Subsequent cycles	Day 1	1000 mg	
Additional cycles	Every 2 months, starting cycle 8	1000 mg	If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

If a planned dose of obinutuzumab is missed, administer the missed dose as soon as possible and adjust dosing schedule to maintain the time interval between doses. If appropriate, patients who do not complete the Day 1 Cycle 1 dose may proceed to the Day 2 Cycle 1 dose.

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps (e.g., Braun Infusomat® Space) should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥ 2 hours in order to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, access (either IV line or central venous catheter) should remain in place for at least 30 minutes from the end of infusion, and if no adverse events occur after 30 minutes, the IV access may be removed. During the maintenance phase, the IV access may be removed at the end of infusion if no adverse events occurred during the infusion.

All obinutuzumab infusions should be administered after premedication with oral acetaminophen (e.g., 650–1000 mg) and an antihistamine, such as diphenhydramine (50–100 mg), 30–60 minutes prior to starting each infusion (unless contraindicated). The use of prophylactic corticosteroids (e.g., prednisolone 100 mg IV or equivalent) is recommended prior to the first dose of obinutuzumab in Cycle 1. Corticosteroids may also be considered for subsequent infusions in

patients who are thought to be at high risk for IRRs, if deemed appropriate by the investigator. In patients who do not experience a Grade ≥ 2 IRR with their previous infusion (i.e., do not receive medication to treat IRR symptoms and do not experience infusion interruption), premedication for subsequent infusions may be omitted at the investigator's discretion.

Patients who are considered to have a high tumor burden and who are considered to be at risk for tumor lysis syndrome (TLS) by the investigator should also receive TLS prophylaxis prior to the initiation of treatment. These patients should be well hydrated. Starting 1–2 days before the first dose of obinutuzumab, it is desirable to maintain a fluid intake of approximately > 3 L/day. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator.

If a patient's previous infusion of obinutuzumab is well tolerated (defined by the absence of a ≥ Grade 2 IRR during a final infusion rate of ≥ 100 mg/hr), subsequent infusions will be administered at an initial rate of 100 mg/hr and increased by 100-mg/hr increments at 30-minute intervals, as tolerated, to a maximum rate of 400 mg/hr. If a hypersensitivity reaction or an IRR develops, the infusion should be temporarily interrupted or slowed down and concomitant medication may be administered if deemed appropriate by the investigator. Upon resolution of symptoms, the infusion will resume at one-half the previous rate (the rate being used at the time that the hypersensitivity or IRR developed) and infusion rate escalation may resume at the increments and intervals described. If the previous infusion rate was not well tolerated, as defined, instructions for the first infusion rate will be used. For more information, please see the package insert and the Obinutuzumab Investigator's Brochure.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Recommended Concomitant Medications/Procedures

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, analgesics, and antiemetics when appropriate.

5.4.1.1 Anticoagulation Consideration

Lenalidomide increases the risk of thrombotic events in patients 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), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased. Prophylactic aspirin or low molecular weight heparin are to be given to patients with a high risk of developing DVT/PE or arterial thromboses unless contraindicated. If prophylactic anti-coagulation is used, it should be held for platelet counts < 50,000/mm^3, and then restarted when platelet counts are above this level.

5.4.1.2 Prophylaxis for Tumor Lysis Syndrome and Tumor Flare

All patients should receive prophylaxis for TLS before the initiation of therapy. Prophylaxis will include appropriate hydration, administration of an agent to reduce uric acid, such as allopurinol

(or rasburicase IV for high risk patients with elevated uric acid levels before treatment). Laboratory results including electrolyte values will be assessed on a weekly basis during cycle 1 of treatment. If tumor flare occurs, symptomatic treatment will be up to the discretion of the investigator. For grade ≤ 2 symptoms, study drug can continue without dose modification along with symptomatic treatment with NSAIDS. For grade 3/4 symptoms, dose interruption and treatment with NDAIDS and steroid is recommended.

5.4.1.3 Prophylaxis for HBV Reactivation in Asymptomatic Carriers

All patients must be screened for hepatitis B before starting treatment. Carriers of hepatitis B should be closely monitored, including HBV DNA testing. For patients with evidence of prior HBV infection, HBV suppressive therapy with lamivudine, tenofovir, or entecavir is required during treatment and for additional six months after coming off study.

5.4.1.4 Use of Growth Factors and Anti-infection Prophylaxis

The use of colony stimulating factors (CSFs) (e.g., filgrastim, pegfilgrastim, and sargramostim) should be considered for patients who experience febrile neutropenia, prolonged grade 3 neutropenia (>7 days) and grade 4 neutropenia. Other anti-infection prophylaxis (e.g., acyclovir, levofloxacin, and other premedications) will be selected by the Investigator according to local practice and provided by the investigative site.

5.4.1.5 Anti-inflammatory Management

Short courses (≤14 days) of corticosteroid treatment for non-lymphoma-related medical reasons (e.g., rash, arthralgia, autoimmune cytopenias and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

5.4.2 Prohibited Concomitant Medications/Procedures

Any anti-cancer therapy is prohibited 28 days prior to Day 1 dosing and during the entire Treatment Period of the study. Warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) are prohibited.

5.4.2.1 Acalabrutinib Drug-drug Interactions

Acalabrutinib is not a strong direct inhibitor or inducer or CYP isoforms; thus, acalabrutinib, at the currently used clinical doses, is unlikely to be a perpetrator of a drugdrug interaction at the level of inhibition or induction of CYP isoforms. Acalabrutinib is partially metabolized by CYP3A; its exposure is affected when co-administered with strong CYP3A4 inducers or inhibitors. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix D) should be avoided when possible. If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong CYP3A4 inhibitor while on study, interrupt acalabrutinib. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of acalabrutinib. Should a moderate CYP3A inhibitor be required while on study, reduce acalabrutinib dose reduction to 100 mg once daily. If co-

administration of strong CYP3A inducer is unavoidable, increase acalabrutinib dosage to 200 mg every 12 hours.

The effect of agents that reduce gastric acidity (e.g., proton pump inhibitors or antacids) on acalabrutinib capsule absorption was evaluated in a healthy volunteer study. Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements and short-acting H2 receptor antagonists for a period of at least 2 hours when taking acalabrutinib. Specifically, take acalabrutinib 2 hours before taking an H2-receptor antagonist. For antacids, separate dosing by at least 2 hours (before or after taking acalabrutinib). Use of omeprazole, esomeprazole, lansoprazole or any other proton pump inhibitors (e.g., lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. Administration of acalabrutinib maleate tablets with acid reducing agents does not impact the absorption; therefore no modification to dosing regimen is necessary.

5.5 Duration of Therapy

The study includes an induction phase consisting of 12 cycles of ALR or ALO. Responding subjects will be eligible to enter a maintenance phase. Subjects will continue maintenance ALR or ALO until disease progression, development of unacceptable toxicity, or voluntary withdrawal. Acalabrutinib and lenalidomide can be discontinued after 24 cycles of treatment (12 cycles of induction and 12 cycles of maintenance) for subjects achieving MRD-negative CR during maintenance phase. Subjects have the option to complete study after a total of 3 years of study treatment at the discretion of the treating physician. Subjects can be retreated with acalabrutinib and lenalidomide at time of disease progression.

5.6 Duration of Follow Up

The Follow-up Period for each subject begins upon study treatment discontinuation. A treatment discontinuation safety visit occurs within 28 days of treatment discontinuation. Subjects will be followed for subsequent anti-lymphoma therapies and survival every 6 months according to the schedules described in Tables 1 and 2.

6. DOSING DELAYS/DOSE MODIFICATIONS

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 used as a guide for the grading of severity. Sections below describe safety run-in and stopping rules, dose reduction steps, instructions for initiation of a new cycle of therapy, and dose modifications during a cycle of therapy.

6.1 Safety Run-in and Stopping Rules

Cohort A: ALR cohort

This is an open-label phase 2 study with a safety run-in period. The study can be considered for full enrollment only after the first 6 evaluable subjects have completed the safety run-in period which is defined as 28 days of cycle 1 of treatment, with 2 or less of the 6 evaluable subjects

experiencing potentially drug-related excess toxicities during safety run-in observation. The decision to proceed to full enrollment vs study discontinuation will be made in a Weill Cornell Medicine Data and Safety Monitoring Board (DSMB) Meeting in conjunction with the Investigators after careful consideration of all available safety and laboratory information.

Definition of potentially drug-related excess toxicity during safety run-in phase include:

Hematologic:

- Grade 4 neutropenia (ANC <500/mm3) lasting for >7 days
- Life-threatening Grade ≥3 neutropenia (ANC <1,000/mm3) with fever ≥38.3ºC
- Grade 4 thrombocytopenia (<25,000/ mm3) that persists for ≥7 days
- Grade 3 thrombocytopenia associated with Grade ≥2 bleeding or requiring RBC or platelet transfusions

Non-Hematologic:

- Grade 3 tumor lysis syndrome if requiring dialysis
- Grade 3 rash that has not improved within 10 days to at least Grade 1 using a temporary drug hold of all study drugs and administration of up to 100 mg of prednisone PO or equivalent daily
- Grade ≥3 nausea, vomiting, or diarrhea uncontrolled by maximal supportive care and persisting greater than 7 days
- Treatment delay of any drug greater than 7 days for toxicity other than rash

In the safety run-in phase, if a subject ends treatment within the first cycle for reasons other than study drug(s) related toxicity (e.g. non-compliant, withdrawal of consent), they will be replaced. In addition, any subject that misses >7 days of acalabrutinib and/or lenalidomide for reasons other than rash will be replaced; subjects with AEs of rash that miss >10 days of acalabrutinib and/or lenalidomide will be replaced unless considered excessive toxicities. Any subject that requires rituximab discontinuation during the first cycle will be replaced.

Trial-wide stopping rule:
In the first 6 patients, if 2 or more experience potentially drug-related excess toxicities during the first cycle as defined in Section 6.1, the study team in conjunction with the DSMB will make a decision as to whether the treatment should be modified or the study halted.

After the first 16 patients, if the proportion of patients with drug-related grade 3 or higher non-hematologic AEs, as defined in Section 6.1, rise above 40% during the first cycle, the study team will temporarily suspend accrual to determine whether modification should be made to the protocol or the study should be halted due to unacceptable toxicity.

Cohort B: ALO feasibility cohort
We plan to expand the study to include a new cohort of 10 MCL patients who will receive treatment with the ALO regimen. The new cohort will contribute to the analysis of safety and feasibility secondary endpoints.

The ALO regimen will be considered feasible if all of the following conditions are met:

- No more than 2 of the 6 first evaluable subjects experiencing potentially drug-related excess toxicities during safety run-in observation, which is defined as 28 days of cycle 1 of treatment.
- No more than 2/10 patients per cohort stop treatment during the first year due to adverse events.

In the first 6 ALO cohort patients, if 2 or more experience potentially drug-related excess toxicities during the first cycle as defined below, the study team in conjunction with the DSMB will make a decision as to whether the treatment should be modified or the study cohort halted.

Definition of potentially drug-related excess toxicity during safety run-in phase include:
Hematologic:

- Grade 4 neutropenia (ANC <500/mm3) lasting for >7 days
- Grade ≥ 3 neutropenia (ANC <1,000/mm3) with fever ≥38.3ºC
- Grade 4 thrombocytopenia (<25,000/ mm3) that persists for ≥7 days
- Grade 3 thrombocytopenia associated with Grade ≥2 bleeding or requiring RBC or platelet transfusions

Non-Hematologic:

- Grade 3 tumor lysis syndrome if requiring dialysis
- Grade 3 rash that has not improved within 10 days to at least Grade 1 using a temporary drug hold of all study drugs and administration of up to 100 mg of prednisone PO or equivalent daily
- Grade ≥3 nausea, vomiting, or diarrhea uncontrolled by maximal supportive care and persisting greater than 7 days
- Grade ≥3 LFT elevations that has not improved with maximal supportive care and temporary hold of all study drugs, and persisting greater than 7 days
- Treatment delay of any drug greater than 7 days for toxicity other than rash

6.2 Acalabrutinib

Dose modifications for the following treatment-emergent toxicities are provided in Table 4:

- Grade 4 neutropenia (< 500/μL) for > 7 days
- Grade 3 thrombocytopenia in presence of significant bleeding
- Grade 4 thrombocytopenia
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy

- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity

Table 4. Drug Modification Actions for Acalabrutinib

Occurrence	Action
1st – 2nd	Hold acalabrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
3rd	Hold acalabrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (100 mg QD)
4th	Discontinue acalabrutinib

If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥ 4 weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. The maximum dose of acalabrutinib is 100 mg BID.

Treatment with acalabrutinib should be withheld for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Acalabrutinib should be discontinued in the event of an acalabrutinib toxicity lasting more than 28 day. Any other clinically important events where dose delays may be considered appropriate must be discussed with the Principal Investigator.

6.3 Lenalidomide

6.3.1 Lenalidomide Dose Modification Steps

Lenalidomide dose will be reduced if patients experience toxicity as defined below in Section 6.3.2. Once the lenalidomide dose has been reduced, no dose re-escalation is permitted. If a new cycle is delayed for more than 4 weeks, remove the patient from protocol therapy. . Patients who experience skin rash during cycle 1 which resolves to ≤ grade 1 prior to cycle 2 day 1, can restart lenalidomide at the same dose level of cycle 1 without dose escalation.

Table 5. Lenalidomide Dose Levels

	Current Lenalidomide Dose	**One Level Dose Reduction**
Dose Level +1	20 mg / day	15 mg / day
Dose Level 0	15 mg / day	10 mg / day
Dose Level -1	10 mg / day	5 mg / day
Dose Level -2	5 mg / day	5 mg every other day
Dose Level -3	5 mg every other day*	See below

* Lenalidomide 5 mg every other day on Days 1-21 every 28 days is the minimum lenalidomide dose. Lenalidomide will be discontinued in patients who cannot tolerate this dose.

6.3.2 Instructions for Lenalidomide Dose Modifications or Interruption

Dose delay and dose reduction rules are as follows and in the table below.

- Lenalidomide dose reduction steps are outlined in Section 6.3.1.
- For treatment interruptions during a cycle, the 28-day schedule of each cycle will continue to be followed. Missed doses of lenalidomide are not made up.
- For treatment interruptions that delay the scheduled start of a new cycle, when toxicity has resolved as required to allow the start of a new cycle (Section 6.5), the restart day of therapy becomes Day 1 of the next cycle when all study medications will restart.

Table 6. Lenalidomide Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
Grade 3 neutropenia associated with fever (temperature ≥ 38.5° C), Grade 4 neutropenia, or Grade 3 neutropenia > 7 days	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit 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 treatment is delayed for more than 4 weeks, discontinue all protocol therapy and notify the Principal Investigator.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit 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.
Platelet count < 50,000/mm³	• Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count is ≥ 50,000/mm³.
Non-blistering rash **Grade 3**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit 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.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.

Table 6. Lenalidomide Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
Neuropathy **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit 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 Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate. • Restart lenalidomide at investigator's discretion (maintain dose level). • See Anticoagulation Consideration (Section 8.1.1)
Tumor lysis syndrome ≥ Grade 3	• Interrupt therapy. • May resume study drug when the TLS resolves to ≤ Grade 1 (decrease one dose level)
Tumor Flare ≤ Grade 2	• at the investigators discretion, may initiate therapy with corticosteroid, NSAIDs and/or Narcotics • Continue Study drug
Tumor Flare Grade 3 or 4	• Hold (interrupt) dose and start corticosteroids, NSAIDs and/or Narcotics. • When toxicity resolves to ≤ grade 1 restart at next lower dose level
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

6.4 Dose Modification for Potential Overalapping Toxicities

Table 7: Dose Modification Schedule for Potential Overlapping Toxicities		
	Lenalidomide Dose	**Acalabrutinib Dose**
Dose Level +1	20 mg / day	100 mg BID
Dose Level 0	15 mg / day	100 mg BID
Dose Level -1	10 mg / day	100 mg BID
Dose Level -2	10 mg / day	100 mg QD
Dose Level -3	5 mg / day	100 mg QD

6.4.1 Neutropenia

For grade 3 or 4 neutrophil count decreased on day 1 of a cycle, delay lenalidomide and acalabrutinib until ANC improves to ≤ grade 2, then resume lenalidomide and acalabrutinib with one dose level reduction (Table 7) for all subsequent cycles.

For grade 3 or 4 neutrophil count decreased during a cycle, interrupt lenalidomide and acalabrutinib for the remainder of the cycle. Resume lenalidomide and acalabrutinib (if ANC ≤ grade 2) at the next cycle with one dose level reduction (Table 7) for all subsequent cycles.

For febrile neutropenia at any time during a cycle, interrupt or delay lenalidomide and acalabrutinib until toxicity improves to ≤ grade 2, then resume lenalidomide and acalabrutinib with one dose level reduction (Table 7) for all subsequent cycles.

6.4.2 Thrombocytopenia

For grade 3 or 4 platelet count decreased on day 1 of a cycle, delay lenalidomide and acalabrutinib until platelet count improves to ≤ grade 2, then resume lenalidomide and acalabrutinib with one dose level reduction (Table 7) for all subsequent cycles.

For grade 3 or 4 platelet count decreased during a cycle, interrupt lenalidomide and acalabrutinib for the remainder of the cycle. If platelets improve to ≤ grade 2, then resume lenalidomide and acalabrutinib the next cycle with one dose level reduction (Table 7) for all subsequent cycles.

6.4.3 Skin Rash

For grade 3 maculopapular rash, delay (day 1 of a cycle), or interrupt (days 2 through 28 of a cycle) lenalidomide and acalabrutinib until rash improves to ≤ grade 1, then resume with one dose level reduction of lenalidomide and acalabrutinib (Table 7) for the current and all subsequent cycles. Discontinue allopurinol if rash is thought to be at least possibly related to allopurinol.

For any rash with sloughing (Stevens-Johnson syndrome, toxic epidermal necrolysis) or Grade 3-4 bullous dermatitis, discontinue all treatment.

6.5 Rituximab

There will be no planned dose reduction for rituximab. Rituximab infusion should be interrupted for severe reactions, e.g., rapid tumor lysis. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Epinephrine, antihistamines, and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to rituximab (e.g., anaphylaxis). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms and laboratory abnormalities have completely resolved.

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.

In patients with an absolute lymphocyte count > 25,000/microliter, contact the principal investigator prior to first rituximab infusion. Patients should be monitored closely for tumor lysis syndrome and should receive appropriate supportive care (e.g., allopurinol, intravenous hydration, additional laboratory test monitoring, etc.).

6.6 Obinutuzumab

There will be no dose modifications of obinutuzumab. Treatment with obinutuzumab should be delayed for Grade 4 hematologic toxicity or clinically significant Grade ≥ 3 non-hematologic toxicity experienced at the time of scheduled dosing.

For hematologic toxicities, patients who experience Grade 4 toxicities should have their doses of obinutuzumab delayed for monitoring of resolution or improvement of toxicity. Dosing may resume upon the resolution of hematologic toxicity to Grade ≤ 3 or baseline status.

For non-hematologic toxicities, dosing may resume only upon resolution to Grade ≤ 2 or baseline. In addition, resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the benefits and risks to the patient and agreement between the investigator and the Sponsor-investigator.

For management of symptomatic AEs (including IRRs), see below.

- **Grade 4 (life threatening):** Stop infusion and permanently discontinue therapy.
- **Grade 3 (severe):** Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred). If patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy.
- **Grade 1&2 (mild and moderate):** Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion. If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose**.**

6.7 Instruction for Initiation of a New Cycle

A new course of treatment with all study medications may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1000/mm³;
- The platelet count is ≥ 50,000/mm³;
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity;
- Completion of 7-day rest period following the last dose of lenalidomide from previous cycle.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above.

6.8 Criteria for Removal from Study

Subjects who meet the following criteria should be discontinued from the study:

- Withdraw of consent
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- Disease progression
- Subject lost to follow-up or death
- Pregnancy or a positive pregnancy test
- Failure to achieve at least PR after 3 cycles (for patients requiring prompt cytoreduction, such as those with bulky or symptomatic disease) or 6 cycles (all others)
- Earlier evidence of nonresponse (including stable disease) that warrants change in therapy in the opinion of the treating physician

Subjects who complete less than 1 cycle of treatment and discontinue treatment for reasons other than toxicity will be replaced.

6.9 Treatment Adherence

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 drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary. Any unused Revlimid® (lenalidomide) should be returned in accordance with the Revlimid REMS® program.

7. PHARMACEUTICAL INFORMATION

7.1 Acalabrutinib (ACP-196)

7.1.1 Description

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. Acalabrutinib is orally bioavailable in humans and is suitable for formulating in capsules. Acalabrutinib is approved in the US for the treatment of adult patients with MCL who have received at least 1 prior therapy. It is also being evaluated for the treatment of patients with other B-cell malignancies.

7.1.2 Mechanism of Action

Acalabrutinib is a potent inhibitor of BTK in vitro and in vivo. Pharmacology models have been used to define kinase selectivity of acalabrutinib in comparison to other BTK inhibitors, and to investigate functional effects of on-target and off-target activities. Acalabrutinib shows improved selectivity for BTK compared with ibrutinib [24]. Functional inhibition of non-target cells (e.g., T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations.

7.1.4 Formulation, Packaging, and Storage

Acalabrutinib capsule is supplied as yellow and blue, opaque hard gelatin capsules, with 100 mg of acalabrutinib as the active ingredient for oral administration. Each capsule also contains compendial inactive ingredients: silicified microcrystalline cellulose, which is composed of microcrystalline cellulose and colloidal silicon dioxide, partially pregelatinized starch, sodium starch glycolate, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide and indigotine (FD&C Blue 2). Acalabrutinib will be provided in white, high-density polyethylene bottles. Procedures for proper handling and disposal should be applied according to standards established at each facility for cytotoxic drugs.

Acalabrutinib maleate tablets is supplied as 100mg, orange, oval, biconvex tablet, with debossment ‘ACA 100’ on one side and plain on the reverse. Acalabrutinib tablets contain 100 mg of acalabrutinib (equivalent to 129 mg of acalabrutinib maleate). Inactive ingredients in the tablet core are low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet coating consists of copovidone, ferric oxide yellow, ferric oxide red, hypromellose, medium-chain triglycerides, polyethylene glycol 3350, purified water and titanium dioxide. Acalabrutinib maleate tablets are packed in white, HDPE bottles containing a silica gel desiccant and should be stored according to the storage conditions as indicated on the label. Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F)

7.1.5 Warnings and Precautions

The following summarizes the experience with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Investigator’s Brochure.

Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in clinical trials with acalabrutinib.

The mechanism for hemorrhage is not well understood. Patients receiving antithrombotic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary.

Consider the benefit-risk of withholding acalabrutinib for at least 3 days pre- and post-surgery.

Subjects with hemorrhage should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

Infections

Serious infections (bacterial, viral, and fungal), including fatal events, have occurred in clinical studies with acalabrutinib. The most frequent reported Grade ≥3 infection was pneumonia (preferred term). Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus (HBV) reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred.

Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate.

Subjects with infection events should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anaemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate.

Subjects with cytopenias should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. Subjects should be closely monitored as appropriate.

Second Primary Malignancies

Events of second primary malignancies, including non-melanoma skin carcinomas, have been reported in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer (basal cell carcinoma).

Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor.

Atrial Fibrillation

Events of atrial fibrillation/flutter have occurred in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, or a previous history of atrial fibrillation.

Monitor for symptoms of atrial fibrillation and atrial flutter (e.g., palpitations, dizziness, syncope, chest pain, dyspnea) and obtain an ECG as clinically indicated. Subjects with atrial fibrillation should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

Important Potential Risks

There is one important potential risk for acalabrutinib monotherapy. Information related to this important potential risk is presented below. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Investigator's Brochure.

Hepatotoxicity

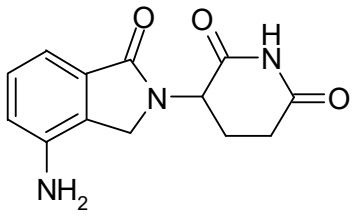
The mechanism underlying hepatotoxicity events of non-infectious etiology is currently unknown. Following a comprehensive review of hepatotoxicity events in the acalabrutinib clinical program, there was insufficient evidence to establish an association between hepatotoxicity events and acalabrutinib due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without treatment for patients with transaminase elevations. There is limited evidence regarding hepatotoxicity of non-infectious etiology from literature for other BTK inhibitors.

7.2 Lenalidomide

7.2.1 Description

Lenalidomide (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

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 has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

7.2.2 Mechanism of Action

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.

7.2.3 Pharmacokinetics and Drug Metabolism

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood

levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters:

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

7.2.4 Prescribing Information

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 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

7.2.5 Formulation, Packaging, and Storage

Lenalidomide will be supplied as capsules for oral administration. Lenalidomide will be shipped directly to patients. Bottle will contain a sufficient number of capsules for one cycle of dosing. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold. Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves. Procedures for proper handling and disposal should be applied according to standards established at each facility for cytotoxic drugs.

7.2.6 Warnings and Precautions

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, 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.

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

7.3 Rituximab

7.3.1 Description and Mode of Action

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. The antibody is an IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. 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. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.

7.3.2 Formulation, Packaging, and Storage

Rituximab is commercially available in 10 mL and 50 mL single-use vials with no preservative. The vials contain 100 or 500 mg of antibody in a sodium chloride solution (pH 6.5) containing polysorbate 80 and sodium citrate at a concentration of 10 mg/ ml.

The product exhibits long-term stability when refrigerated at 2 – 8° C for 24 hours and at room temperature for an additional 12 hours. Protect from direct sunlight. When diluted for infusion, stable for 24 hours when refrigerated at 2 – 8° C and for an additional 12 hours at room temperature. Because rituximab is a protein, it is essential to handle the product gently and to avoid foaming during product preparation and administration as this may lead to denaturing of the active antibody. Rituximab should be prepared as follows:

A. Refrigerate (2 – 8° C) all materials and solutions prior to use

B. Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks, and transfer tubing etc.

C. Transfer of the rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle

D. Transfer the appropriate amount of rituximab from the graduated syringe, into a partially filled IV pack containing sterile, pyrogen-free 0.9% sodium chloride solution, USP (saline solution); D5W may also be used as a diluent. The final concentration of rituximab in saline solution should be 1 to 4 mg/mL. Mix by inverting the bag gently. DO NOT USE A VACUUM APPARATUS to transfer the product from the syringe to the plastic bag.

7.3.3 Clinical Use

The antibody should be diluted into a final volume of 0.9% sodium chloride or 5% dextrose in water for a final concentration of 1-4 mg/ml. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody. Rituximab will be administered as an intravenous infusion at 375 mg/m2. Rituximab infusions will be administered to patients in an outpatient clinic setting. Oral pre-medication 650 mg of acetaminophen and 50-100 mg diphenhydramine hydrochloride will be administered 30 to 60 minutes prior to starting each infusion of rituximab. A peripheral or central intravenous line will be established. During the rituximab infusion, the patient's vital signs will be monitored every 15 minutes times 4 or until stable and then hourly until the infusion is discontinued. Available at the bedside prior to rituximab administration will be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for the emergency management of anaphylactoid reactions. The initial dose rate during a patient's first rituximab infusion should be 50 mg/hr. The dose rate may be increased, if tolerated, by 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If administration was well tolerated during a patient's first treatment with rituximab, the initial dose rate during subsequent treatment cycles may be increased to 100 mg/hr. If tolerated, the rate may be increased by 100-mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

7.3.4 Nursing Implications

- Observe carefully for infusion syndrome or hypersensitivity that may require temporary discontinuation of drug infusion and supportive care measures instituted as medically indicated (e.g. intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate when symptoms have completely resolved.
- Prophylaxis for infusion related events with acetaminophen and diphenhydramine
- Maintain good urine output to reduce risk of tumor lysis syndrome
- Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells ($\geq$ 25,000/mm3) with or without evidence of high tumor burden.

7.3.5 Warnings and Precautions

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, and mild hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate. Other adverse events included neutropenia, thrombocytopenia, asthenia, other hematologic events, cardiac and cardiopulmonary events, and tumor lysis syndrome.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%),

anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported.

In addition, there have been a limited number of postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).

Cardiac Events: Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

Cardiopulmonary Events: In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred (4-7/10,000 patients or 0.04-0.07%.) Nearly all fatal infusion-related events occurred in association with the first infusion.

Tumor Lysis Syndrome: Although rare, tumor lysis syndrome has been reported in postmarketing studies and is characterized in patients with a high number of circulating malignant cells (>25,000/μl) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

Hepatitis B Reactivation: Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose. A direct causal relationship between rituximab and HBV viral reactivation has not been established.

Renal Events: Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases, has led to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^2) or high tumor burden who experience tumor lysis syndrome.

Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis, have been reported rarely in patients treated with rituximab. Paraneoplastic pemphigus has been reported very rarely in NHL and CLL patients undergoing chemotherapy plus rituximab treatment. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

Additional Safety Signals: The following immune serious adverse events have been reported to

occur rarely (<0.1%) in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphgus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis

See the rituximab Investigator Brochure for additional details regarding safety experience with rituximab.

7.4 Obinutuzumab

7.4.1 Description and Mode of Action

Obinutuzumab is a humanized and glycoengineered type II anti-CD20 monoclonal antibody of the IgG1 subclass. It recognizes a specific epitope of the CD20 molecule found on B-cells. The molecular mass of the antibody is approximately 150 kDa. The enhanced affinity of obinutuzumab for the low and high affinity FcγRIIIa by glycoengineering translated into a significantly enhanced (5-100-fold) potency in ADCC assays in comparison to rituximab and ofatumumab

7.4.2 Formulation, Packaging, and Storage

Obinutuzumab is provided as a single 1000 mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50 mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188 and water for injection. Water meets the specified limits for “Water for Injections” according to Ph. Eur. monograph and “Water for Injection” according to USP monograph. The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For further instructions as well as information on in-use stability, see the packaging label.

7.4.3 Clinical Use

Cycle 1: The recommended dosage of obinutuzumab is 1000 mg administered over Day 1-and Day 2, and on Day 8 and Day 15 of the first 28-day treatment cycle. Two infusion bags should be prepared for the first dose: 100 mg for the first infusion and 900 mg for the second infusion.
Cycles 2-6: The recommended dosage of obinutuzumab is 1000 mg administered on Day 1 for each 28 day treatment cycle.

- Cycle 1 Day 1, 100 mg: Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
- Cycle 1 Day 2, 900 mg: If no IRR occurred during the previous infusion, administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. If the patient experienced an IRR during the previous infusion, start administration at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

- Cycle 1 Day 8 1000 mg, Day 15 1000 mg: If no IRR occurred during the previous infusion where the final infusion rate was ≥100 mg/hr, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If the patient experienced an IRR during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
- Cycles 2-6 Day 1 1000 mg: : If no IRR occurred during the previous infusion where the final infusion rate was ≥100 mg/hr, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If the patient experienced an IRR during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

7.4.4 Nursing Implications

Premedications are used to reduce the risk of IRRs. For the first infusion of obinutuzumab, corticosteroid premedication is mandatory. Premedication for subsequent infusions and other premedication should be administered as described below. Hypotension, as a symptom of IRR, may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration.

- Cycle 1: All patients
    - Intravenous corticosteroid (e.g. 100 mg prednisone, or 20 mg dexamethasone, or 80 mg methylprednisolone) at least 1 hour prior to obinutuzumab infusion.
    - Oral analgesic/anti-pyretic (e.g. 1000 mg acetaminophen/paracetamol) and anti-histaminic drug (e.g. 50 mg diphenhydramine) at least 30 minutes before Obinutuzumab infusion.
- All subsequent infusions:
    - Patients with no IRR during the previous infusion
        - Oral analgesic/anti-pyretic (e.g. 1000 mg acetaminophen/paracetamol) at least 30 minutes before Obinutuzumab infusion.
    - Patients with an IRR (Grade 1 or 2) with the previous infusion
        - Oral analgesic/anti-pyretic (e.g. 1000 mg acetaminophen/paracetamol) and anti-histaminic drug (e.g. 50 mg diphenhydramine) at least 30 minutes before Obinutuzumab infusion.
    - Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts $>25\times10^9$/L prior to next treatment
        - Intravenous corticosteroid (e.g. 100 mg prednisone, or 20 mg dexamethasone, or 80 mg methylprednisolone) at least 1 hour prior to obinutuzumab infusion.
        - Oral analgesic/anti-pyretic (e.g. 1000 mg acetaminophen/paracetamol) and anti-histaminic drug (e.g. 50 mg diphenhydramine) at least 30 minutes before obinutuzumab

7.4.5 Warnings and Precautions

Infusion Related Reactions (IRR)

The most frequently observed adverse drug reactions (ADRs) in patients receiving obinutuzumab were IRRs which occurred predominantly during infusion of the first 1000 mg. In patients with CLL who received the combined measures for prevention of IRRs (adequate corticosteroid, oral analgesic/anti-histamine, omission of antihypertensive medication), a decreased incidence of IRRs of all grades was observed. The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during subsequent administrations of obinutuzumab. In the majority of patients, irrespective of indication, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g., anaphylaxis). Patients with a high tumor burden and/or high circulating lymphocyte count in CLL [> 25×109/L] may be at increased risk of severe IRR. Patients should not receive further obinutuzumab infusions if they experience:

- acute life-threatening respiratory symptoms,
- a Grade 4 (i.e., life-threatening) IRR or,
- a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion).

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.

Hypersensitivity Reactions

Hypersensitivity reactions with immediate (e.g., anaphylaxis) and delayed onset (e.g. serum sickness), have been reported in patients treated with obinutuzumab. If a hypersensitivity reaction is suspected during or after an infusion (e.g., symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped and treatment permanently discontinued. Patients with known hypersensitivity to obinutuzumab must not be treated. Hypersensitivity may be clinically difficult to distinguish from infusion related reactions.

Tumor Lysis Syndrome

TLS, including fatal TLS, has been reported with obinutuzumab. Patients who are considered to be at risk of TLS [e.g., patients with a high tumor burden or a high circulating lymphocyte count (> 25 × 109/L)] and/or renal impairment (CrCl <70 mL/min)] should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g., allopurinol), or a suitable alternative such as a urate oxidate (e.g., rasburicase), prior to the infusion of obinutuzumab. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed. For treatment of TLS,

correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Neutropenia
Severe and life-threatening neutropenia including febrile neutropenia has been reported during treatment with obinutuzumab. Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. If treatment is necessary, it should be administered in accordance with local guidelines and administration of granulocyte colony-stimulating factors (G-CSF) should be considered. Any signs of concomitant infection should be treated as appropriate. Late onset neutropenia (occurring 28 days after the EoT) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/ stopped) may occur.

Thrombocytopenia
Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in Cycle 1 in patients with CLL treated with obinutuzumab. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of any concomitant therapies, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

Prolonged B-cell Depletion
B-cell depletion is defined as a CD19+ B-cell count of $< 0.07 \times 10^9$cells/L by flow cytometry (FACS) in whole blood and can only occur after at least one dose of study drug has been administered. B-cell recovery is defined as when B cells are no longer depleted (i.e., $\geq 0.07 \times 10^9$cells/L) and can only occur after the patient has completed study treatment. Prolonged B-cell depletion is defined as the absence of B-cell recovery 12 months after the end of treatment. In a large proportion of patients with relapsed NHL, CD19+ B-cell counts were markedly low at baseline, possibly as a result of previously administered therapy with an anti-CD20 antibody or other treatments. Treatment with obinutuzumab resulted in a further decrease in the number of CD19+ B cells. This is consistent with the anticipated pharmacodynamic effect of obinutuzumab, which is primarily aimed at the depletion of B cells. Follow-up data are sparse and determining the actual timepoint at which recovery occurs is difficult. Prolonged B-cell depletion may be related to the risk of progressive multifocal leukoencephalopathy (PML) and HBV, which are described and assessed separately.

Worsening of Pre-existing Cardiac Conditions
In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with obinutuzumab. These events may occur as part of an IRR

and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload.

Infections
Obinutuzumab should not be administered in the presence of an active infection and caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections. Serious, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported. In the FL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in maintenance. During the follow-up phase, grade 3–5 infections are observed more in patients who received obinutuzumab plus benda in the induction phase.

Hepatitis B Reactivation
HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including Obinutuzumab. HBV screening should be performed in all patients before initiation of treatment with obinutuzumab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active Hepatitis B disease should not be treated with obinutuzumab. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation. Please refer to respective protocols for detailed guidance on this subject.

Progressive Multifocal Leukoencephalopathy
PML has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to preexisting neurologic manifestations. The symptoms of PML are nonspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JCV DNA). Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Immunization
The safety of immunization with live or attenuated viral vaccines, following obinutuzumab therapy has not been studied and vaccination with live virus vaccines is notrecommended during treatment and until B-cell recovery.

8. CORRELATIVE BIOMARKER STUDIES

8.1 Biomarkers Program

The exploratory biomarkers program will include the following sample collection and tests as detailed in the Lab Manual. Frozen samples will be kept at the laboratories of Weill Cornell Medical College where they will be analyzed.

8.1.1 MRD analysis for molecular responses

Whole blood in 10mL purple-top tubes will be collected at baseline, after cycles 6 and 12 of induction, and every 4 cycles for year 2, and every 6 cycles for years 3-5 during maintenance.

8.1.2 Cell-free DNA and soluble plasma cytokine/biomarkers

Whole blood in 10mL purple-top tubes will be collected for cytokine studies at baseline, weekly for cycle 1, on C2D1, C4D1, and C6D1, then following the same frequency as the MRD collection and at time of progression. Cell-free DNA (cfDNA) will be collected in Streck tubes at baseline and MRD time points. Additionally, one-time buccal swab / saliva sample collection for germline control should occur at screening, on treatment or off treatment. Dr. Wayne Tam, Professor of hematopathology at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell will serve as an external investigator for cell-free DNA study analysis.

8.1.3 Circulating immune cells

Whole blood in 10mL purple-top tube will be collected at baseline, weekly for cycle 1, then on C2D1, C4D1, C6D1, and time of progression, and subject to real-time flow cytometric analysis of peripheral blood mononuclear cells (PBMCs) and TILs, including T-cell subsets, NK cells, and MDSC.

9. MEASUREMENT OF EFFECT

9.1 Radiographic Response

Response and progression will be evaluated in this study using the Lugano criteria for lymphoma response.[25] The response assessment time points are: every 3 cycles during year 1, every 4 cycles during year 2, and every 6 cycles until disease progression. Subjects should have PET/CT at baseline and at time to confirm CR. If an additional CT scan is performed earlier than the specified time points due to changes in the subject's clinical status, please also perform an additional response assessment at that time. Once a subject has progressed, no further response assessments are required.

PET-CT. PET-CT is the preferred imaging modality for baseline assessment, and for CR confirmation.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than

5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations.

9.1.1 Response Criteria

Response and Site	**PET-CT–Based Response**	**CT-Based Response**
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ	Not applicable	Spleen must have regressed by >

Response and Site	PET-CT–Based Response	CT-Based Response
enlargement		50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from

Response and Site	PET-CT–Based Response	CT-Based Response
		baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

- Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.
- * A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).
- † PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

9.1.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time

measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Duration of CR: The duration of CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9.1.3 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of documentation of progression or death from any cause.

9.1.4 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to death from any cause.

9.2 Molecular Response

All subjects will undergo evaluation for molecular evidence of disease in the peripheral blood at baseline, and after cycles 6 and 12 of induction. Subjects that are in at least PR will undergo evaluation of MRD during maintenance, including every 4 cycles during year 2, and every 6 cycles during years 3-5. MRD negative CR is defined as complete remission per Lugano criteria with undetectable MRD ($< 1x10^{-6}$) in peripheral blood using the AdaptiveBiotech Clonoseq assay.

Mantle cell lymphoma MRD
Adaptive Biotechnology ClonoSeq assay will be used to detect MRD in MCL during induction and maintenance. In addition, Clonoseq assay will be used to guide treatment intensity and duration during maintenance for patients achieving MRD negative CR as discussed in Section 5.1.

10. DATA REPORTING / REGULATORY CONSIDERATIONS

10.1 Data Collection

REDCap will be used to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients.

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting

tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

10.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. Acerta and Celgene will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design

This is an exploratory phase II study with a safety run-in period to evaluate the preliminary evidence of efficacy and safety of the combination of acalabrutinib, lenalidomide and rituximab (ALR) in previously untreated mantle cell lymphoma. If the data from this trial provide evidence of efficacy in this patient population, the treatment will be considered for further investigation. A total of 28 patients (24 eligible and evaluable patients, including the patients from the safety run-in period) will be enrolled in the ALR cohort.

We plan to expand the study to include a new cohort of 10 MCL patients who will receive treatment with the acalabrutinib, lenalidomide and Obinutuzumab (ALO) regimen. The new cohort will contribute to the analysis of safety and feasibility secondary endpoints.

The ALO regimen will be considered feasible if all of the following conditions are met:

- No more than 2 of the first 6 evaluable subjects experiencing potentially drug-related excess toxicities during safety run-in observation, which is defined as 28 days of cycle 1 of treatment.
- No more than 2/10 patients stop treatment during the first year due to adverse events.

11.2 Sample Size

The primary endpoint for this study is MRD-negative CR (defined as MRD in peripheral blood $<10^{-6}$) at the conclusion of 12 cycles of ALR induction therapy. We project to achieve at least 20% of absolute CR improvement with the ALR triplet from a historical CR of 60% with the lenalidomide plus rituximab doublet. The sample size required to estimate this improvement is 24, by an exact binomial test assuming an alpha level of 0.1 and power of 80%. Additional 4 patients will be enrolled to account for potential attrition so a total of 28 patients will be enrolled in the ALR cohort. We also plan to enroll 10 patients to the ALO feasibility cohort. Formal justification of the sample size for feasibility cohort is not required. In total, 38 patients will be enrolled in the study.

11.3 Analysis Plan for Endpoints

11.3.1 Primary Endpoints

The primary endpoint of CR will be calculated, and a 90% Clopper-Pearson confidence interval will be estimated via exact binomial proportions.

11.3.2 Secondary Endpoints

With adequate follow-up time, secondary endpoints of progression-free survival (PFS), overall survival (OS), and time to next treatment will be assessed by Kaplan-Meier survival analysis and 90% confidence intervals will be calculated using Greenwood's formula. PFS will be defined as the time from first treatment day until objective or symptomatic progression or death. OS will be defined as the time from first treatment day until death. TTNT will be defined as time from end of primary treatment to institution of next therapy.

11.3.3 Correlative Endpoints

The frequency of subjects experiencing adverse event will be tabulated. Paired t-test will be performed to assess the differences between baseline and the end of treatment for numerical variables, such as gene expression, immunophenotypic changes, cfDNA, etc. All p-values will be two-sided with statistical significance evaluated at the 0.1 alpha level. Ninety percent confidence intervals will be calculated to assess the precision of the obtained estimates. All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, NC).

12. ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Adverse Event Definition

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

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with NHL that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- 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

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory,

pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

Adverse Event Reporting Period

All AEs will be reported until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever comes first).. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours and AstraZeneca within 7 days of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

12.1.1 Adverse Event Characteristics and Related Attributions

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Sponsor-investigator/industry supporters in accordance with CFR 312.32 (IND Safety Reports).

Assessment of Severity of Adverse Events

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov)

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

- **Attribution** of the AE:
    - Definite – The AE *is clearly related* to the study treatment.
    - Probable – The AE *is likely related* to the study treatment.
    - Possible – The AE *may be related* to the study treatment.
    - Unlikely – The AE *is doubtfully related* to the study treatment.
    - Unrelated – The AE *is clearly NOT related* to the study treatment.

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current 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.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points 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?"

12.1.2 Recording of Adverse Events

All adverse events will be recorded on a patient specific adverse event log. The AE log will be maintained by the research staff and kept in the patient's research chart.

12.1.3 Reporting of AE to WCM IRB

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator and to the IRB according to the local IRB's policies and procedures in reporting adverse events. In the event of a multi-center study, the Principal Investigator will report adverse events and serious adverse events from all participating sites to the WCM IRB according to the IRB's policies and procedures in reporting adverse events.

12.2 Definition of SAE

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

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event

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

Adverse Events (AEs) for malignant tumours reported during a study should be assessed as Serious

AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy. SPM that occurred after 28 days from last dose, and was considered related to any of the study investigational products, will need to be reported and communicated to AZ/BMS/Genentech

Adverse Events of Special Interest (AESI) are events that may not typically be considered to meet the regulatory criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the timely review of safety data and narrative (may be requested by the FDA or the industry supporters). It can be e.g. a non-serious non-specific start of an event, which may be an early manifestation of a serious potential risk. The same SAE reporting form, assessment and reporting timelines apply to AESIs. For reporting purposes they need to be treated as if they were serious events even when these events are non-serious and do not meet seriousness criteria. The following events are adverse events of special interest (AESIs) for subjects exposed to acalabrutinib, and must be reported to the Sponsor-investigator and industry supporters expeditiously, irrespective of regulatory seriousness criteria or causality: Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)

Events not considered to be SAEs are hospitalizations for:

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

- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above. If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

The following event will NOT be considered SAE:

- Leukopenia and lymphopenia of any grade as these are expected pharmacodynamic outcomes of study treatment.
- Grade 3 or 4 neutropenia that is not accompanied by fever ≥ 100.4°F [38°C]) and improves to Grade ≤ 2 by Day 1 of the next cycle
- Grade 3 thrombocytopenia that does not result in bleeding and improves to Grade ≤ 2 by Day 1 of the next cycle
- Grade 3 or 4 anemia
- Grade 3 nausea or vomiting ≤ 7 days (in the absence of premedication or that can be managed with oral or IV anti-emetics)

12.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy. The IRB requires immediate reporting of all unexpected and study-related (definite or probable) adverse events. The following procedure will be followed for reporting SAE to the IRB:

- Complete the SAE Cover Sheet
- If the event is unexpected AND definitely or probably related to the study, complete the IRB Unexpected, Study-related Adverse Events, Incidents, and Information Reporting Form. This form should be submitted within 24 hours of investigator notification of the event.
- If the event is expected OR possibly or unrelated to the study, only the SAE Cover Sheet must be completed. These events will be reported to the IRB at the time of continuing renewal on the Adverse Event & IND Safety Reporting Cumulative Table.

Forms may also be downloaded from the IRB website at:
https://research.weill.cornell.edu/sites/default/files/immediate_reporting_policy.pdf

AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor-investigator is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by

the trial Sponsor-investigator to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

The Rituxan AESI are: none

The Gazyva AESI are:

- All TLS (irrespective of seriousness, causality or severity)
- Second Malignancies

Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- 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

Product complaints

A Product Complaint is defined as 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.

12.2.2 Reporting of SAE to FDA

Serious adverse events (SAEs) that are unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related. For multicenter trial, all participating study sites should NOT report SAEs to the FDA. Rather, participating sites should report SAEs to AZ/Acerta, Celgene and the primary study site, and the primary site will be responsible for reporting to FDA.

If an SAE occurs on this study, the event will be filed on a MedWatch 3500A form with the FDA. MedWatch 3500A (Mandatory Reporting) form is available at:
http://www.fda.gov/medwatch/getforms.html

***CDER INDs**:*
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
Office of Oncology Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32. For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure.
Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR§ 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed

to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630
Email: usds_aereporting-d@gene.com

Adverse event updates/IND safety reports
Acerta and Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE suspected of being related to the use of 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/EC promptly of these new serious and unexpected AE(s) or *significant risks to subjects*. The investigator must keep copies of all pertinent safety information on file, including correspondence with Celgene and the IRB/EC. All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

Pregnancies
Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of reproductive potential, regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, or within 160 days after the last dose of Rituxan or within 180 days after the last dose of Gazyva, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Acerta Pharma and Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to an obstetrician-gynecologist, (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy outcome and up to 1 year to monitor the baby, and must notify Acerta Pharma and Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form and Infant Follow-Up Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion, STILLBIRTH, NEONATAL DEATH, OR CONGENITAL ANOMALY), 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 Acerta Pharma and 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, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is

related to the in utero exposure to the IP should also be reported to Acerta Pharma and 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, or approved equivalent form.

Male Subjects
If a female partner of a male subject taking investigational product becomes pregnant while receiving the study drug or within 160 days after the last dose of Rituxan or within 180 days after the last dose of Gazyva, the male subject taking IP should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with IP are advised to continue complete abstinence or condom use during treatment and 28 days after stopping treatment.

Overdose
On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose assigned to a given patient, regardless of any associated adverse events or sequelae.

PO any amount over the protocol-specified dose
IV 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

12.2.3 Reporting of SAE to AstraZeneca

Time period for collection of adverse events
AEs will be collected from time of signature of informed consent form throughout the treatment period and including 30 days after the last dose of study treatment. After the signing of the ICF and prior to the first dose of study treatment all SAEs, regardless of causality, must be reported. All AEs will be reported until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever comes first). After this period, investigators should report SAEs or other AEs of concern that are believed to be related to prior treatment with study treatment. All SAEs that occur during the reporting period should be followed to resolution or until the investigator assesses the subject as stable, or until the subject is lost to follow up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

All SAEs/AESIs will be recorded and reported to the Sponsor-investigator or designee within 24 hours. The investigator will submit any updated SAE/AESI data to the Sponsor-investigator within 24 hours of it being available. Investigators are not obligated to actively seek AE or SAE data in former study subjects. However, if at any time after a subject's last visit the investigator learns of any SAE, including a death, that is considered to be reasonably related to the study treatment or study participation, the investigator may notify the Sponsor-investigator.

Reporting of serious adverse events to AstraZeneca

If the study is being conducted in multiple countries or multiple sites, Investigators or other site personnel inform Sponsor-investigator representatives of the SAE. The coordinating centre/Sponsor-investigator is responsible for informing AstraZeneca of the SAE. All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. SAEs related to the Investigational Product (IP) must be provided to AstraZeneca in an ongoing basis as individual case reports. SAEs unrelated to the IP must be provided to the AstraZeneca as individual case reports on an ongoing basis/ as a quarterly line listing. At the end of the Study a final unblinded summary line listing of all SAEs notified to the regulatory authority and/or AstraZeneca during the Study, must be provided to AstraZeneca to enable reconciliation of safety information held by AstraZeneca for its product(s). Send SAE reports (individual case reports and line listings) and accompanying cover page to AstraZeneca (TCS) via Email: AEmailboxclinicaltrialTCS@astrazeneca.com

SAEs that do not require expedited reporting to the Regulatory Authority/IRB/IEC still need to be reported to AstraZeneca as individual case reports on an ongoing basis/ provided as a quarterly listing.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to AstraZeneca at the same time these events are notified to the Regulatory Authority.

12.2.4 Reporting of SAE to BMS Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. 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-CL-MCL-PI-13239) 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.

All participating study sites must report SAEs to Celgene as described and within 24 hours of awareness. Participating sites should also report SAEs to the primary study site.

Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Ave,
Summit, NJ 07901
Telephone: (908) 673-9667
Toll Free: 1-800-640-7854
Fax: (908) 673-9115

E-mail: drugsafety@celgene.com

12.2.5 Exchange of Single Case Reports with Genentech

The investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MedWatch should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

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:

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Type of Report	**Timelines**
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

Case Transmission Verification of Single Case Reports

- The parties will verify that all single case reports have been adequately received by Genentech via the Investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by the Investigator to Genentech in the preceding time period.

- The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

- If discrepancies are identified, the Sponsor-investigator 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. The Sponsor-investigator shall receive reconciliation guidance documents within the 'Activation Package'.

- Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the Investigator to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at

https://www.fda.gov/media/69876/download

12.3 IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, 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 Acerta, BMS (Celgene) and Genentech as supporters of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
86 Morris Avenue
Building L
Summit, NJ 07901
Tel: (908) 673-9000

12.4 Reporting to Regulatory Authorities, Ethics Committees and Investigators

The investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

The Sponsor-investigator will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

The Sponsor-investigator will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

AGGREGATE REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

12.5 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This

requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

For studies involving collection of survival data the investigator after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject including pregnancy occurring in the partner of a male study subject] who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports.

Other Reports
The investigator will forward a copy of the Final Study Report to Genentech upon completion of the Study.

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

ga101-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by the Investigator. However, responses to all safety queries from regulatory authorities, Ethics Committees and Institutional Review Board or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. The Investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests from Regulatory Authorities and/or IRB/IEC for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SIGNAL MANAGEMENT AND RISK MANAGEMENT

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that the Investigator**,** as Sponsor of the Study, will be primarily

responsible for assessment of the benefit-risk balance of the Study.

If the Sponsor-Investigator issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist the Investigator with signal and risk management activities related to the Product within the Study.

Genentech will also provide the Sponsor-Investigator with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines. Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue. In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken. Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

13. DATA AND SAFETY MONITORING PLAN (DSMP)

This is a multi-institution study. The data and safety monitoring for this study will be overseen by the Weill Cornell IRB as well as the principal investigators from each site. The study will be reviewed by the Weill Cornell Medicine Data and Safety Monitoring Board (DSMB) as an independent means of data and safety monitoring. Enrollment information, adverse event and safety information, protocol changes, and other interim data will be evaluated by the DSMB on an annual basis. After each evaluation, the Board will provide the principal investigator with recommendations for protocol modification, continuation, or termination.

An interim safety analysis will be performed after the first 6 evaluable subjects have completed the safety run-in period which is defined as 28 days of cycle 1 of treatment, to ensure no more than 2 out of the 6 evaluable subjects experiencing potentially drug-related excess toxicities during safety run-in observation (Section 6.1). The decision to proceed to full enrollment vs protocol modification vs study discontinuation will be made in a Weill Cornell Medicine Data and Safety

Monitoring Board (DSMB) Meeting in conjunction with the Investigators after careful consideration of all available safety and laboratory information.

After the first 16 patients, if the proportion of patients with drug-related grade 3 or higher non-hematologic AEs, as defined in Section 6.1, rise above 40% during the first cycle, the study team will temporarily suspend accrual to determine whether modification should be made to the protocol or the study should be halted due to unacceptable toxicity.

Subjects will be followed continuously throughout the study. Subjects may be removed from study treatment as specified in Section 6.6. The cumulative AEs and SAEs will be reviewed by the Sponsor-investigator on an ongoing basis to identify safety concerns. Investigators will discuss with the IRB whether subjects currently receiving therapy may continue as planned, or whether the protocol should be amended to change the study therapy.

We plan to expand the study to include a new cohort of 10 MCL patients who will receive treatment with the ALO regimen. The new cohort will contribute to the analysis of safety and feasibility secondary endpoints.

The ALO regimen will be considered feasible if all of the following conditions are met:

- No more than 2 of the 6 first evaluable subjects experiencing potentially drug-related excess toxicities during safety run-in observation, which is defined as 28 days of cycle 1 of treatment.
- No more than 2/10 patients per cohort stop treatment during the first year due to adverse events.

In the first 6 ALO cohort patients, if 2 or more experience potentially drug-related excess toxicities during the first cycle as defined above the study team in conjunction with the DSMB will make a decision as to whether the treatment should be modified or the study cohort halted.

14. REFERENCES

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Appendix A: Cockcroft-Gault estimation of CrCl

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

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

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

Appendix B: International Prognostic Index (IPI) and MIPI Scores

International Prognostic Index (IPI)
One point is assigned for each of the following risk factors:

- Age greater than 60 years
- Stage III or IV disease
- Elevated serum LDH
- Eastern Cooperative Oncology Group performance status of 2, 3, or 4
- More than 1 extranodal site

IPI Score	Risk Group
0 - 1	Low risk
2	Low-intermediate risk
3	High-intermediate risk
4 - 5	High risk

Source: A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factor Project. NEJM 1993;329:987-94

Mantle Cell Lymphoma International Prognostic Index (MIPI) (Hoster, 2008)
MIPI score = [0.03535 x age (years)]
+ [0.6978 (if ECOG >1)]
+ [1.367 x $\log_{10}$(LDH/ULN)]
+ [0.9393 x $\log_{10}$(WBC count per 10^{-6} L)]

MIPI Score	Risk Group
< 5.7	Low risk
≥ 5.7 and < 6.2	Intermediate risk
≥ 6.2	High risk

Source: A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008 Jan 15;111(2):558-65.

Appendix C: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix D: Known Strong in Vivo Inhibitors or Inducers of CYP3A

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	carbamazepine[f]
clarithromycin[b]	phenytoin[f]
conivaptin[b]	rifampin[f]
grapefruit juice[c]	St John's wort[f]
indinavir	
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[d]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the Medical Monitor of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 11 June 2015:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Appendix E: Deauville Criteria for PET Scan Interpretation

Interpretation

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

Scoring per the five point scale

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

Appendix F: New York Heart Association (NYHA) Classification for Congestive Heart Failure

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix G: FACT-Lym (Version 4)

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

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

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

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

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

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

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

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
P2	I have certain part of my body where I experience pain ……..0		1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin) ……..0		1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature) …….0		1	2	3	4
ES3	I have night sweats ……0		1	2	3	4
LYM1	I am bothered by itching ……...0		1	2	3	4
LYM2	I have trouble sleeping at night …….0		1	2	3	4
BMT6	I get tired easily …….0		1	2	3	4
C2	I am losing weight …….0		1	2	3	4
Ga1	I have a loss of appetite …….0		1	2	3	4
H18	I have trouble concentrating ……..0		1	2	3	4
N3	I worry about getting infections ……0		1	2	3	4
LEU6	I worry that I might get new symptoms of my illness ……...0		1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment ……0		1	2	3	4
BRM9	I have emotional ups and downs ……...0		1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future ……...0		1	2	3	4

Appendix H: Correlative Studies Laboratory Instructions

1. Draw research blood tubes at each designated sample timepoint as defined and outlined in the laboratory manual using standard venipuncture techniques.

2. Label the vacutainer tubes with the patient's identification (patient number and patient initials), date and time of blood draw (dd-MMM-yyyy format for the date, i.e. 01-JAN-2003, and 24:00 hour clock format for the time).

3. Bring Cornell samples to the Clinical Translational Core Lab (CTCL) within 1 hour of lab draw for immediate processing according to lab manual.

4. For subjects treated at consortium subsites, please following the following instructions.
   a. Process blood samples for plasma at local core facility within 1 hour of lab draw, store samples at -80ºC freezer, and ship in batch to WCMC according to lab manual.
   b. Ship samples to NYPH-WMC via overnight FEDEX at the address provided below. Avoid deliveries on Friday, weekends and on holidays.

Weill Cornell Medical College Clinical Translational Core Lab
1300 York Ave
Suite A635
New York, NY 10065

5. For detailed sample preparation protocol, please contact the WCM Lymphoma IIT listserv.
Email: lymIITlabs@med.cornell.edu

Appendix I: 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 Revlimid REMS®.

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, 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.

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

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.

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or 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.