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STUDY TITLE: **A Phase IB/II Trial of Lenalidomide (Revlimid®), Ixazomib and Rituximab (RIXAR) as Front-line Therapy for High Risk Indolent B cell Lymphoma**

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SUPPORT:

Millennium, Takeda Oncology
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SUPPLIED AGENTS:

Lenalidomide
Ixazomib

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OTHER AGENT:

Rituximab

Summary of Changes

Protocol Date	Section	Change
8.3.2016		Initial IRB approval
2.2.2017		Removing Mitchell Smith and adding Brian Hill as PI/Sponsor
3.24.2017	4 / Appendix V	Updating FLIPI requirement to ≥ 5 nodal sites
3.24.2014	6	Antiviral prophylaxis therapy is now required
3.24.2017	11	Adding +/- 3 day window for day 1 visits
3.24.2017	13.1	Adding Overture database
10.11.2017	Schedule of Events	Correcting footnotes to be consistent with calendar and adding footnote 17
10.11.2017	1.6.3	Removing section, MRD testing is not available
10.11.2017	4.1.7	Clarifying heme parameters for patients with heavy disease burden
10.23.2018	3.1	Clarifying Phase 2 dose level.
10.23.2018	Page 1-2	Updating Co-Investigators and study personnel, adding Florida
10.23.2018	Schedule of Events Footnote 14	Adding a window of +/- 7 days for follow-up visits
10.23.2018	Schedule of Events	Adding a window of +/- 2 days for C 1-3 days 8 and 15
10.23.2018	Schedule of Events	Adding HIV testing for screening
10.23.2018	Table 7-3	Removal of Action of ANC dose modification
10.23.2018	6.2	Removing Dose Escalation section
10.23.2018	Appendix VI	Clarifying Blood Specimen Handling Instructions
04.23.2019	Page 1-2	Updating Co-Investigators, adding regional sites
04.23.2019	Tables 7-2 and 7-3	Dose Adjustment Criteria Update
04.23.2019		Phase 2 Cohort Changes
09.05.2019	Page 2	Updating Co-Investigators
09.05.2019	Tables 7-2 and 7-3	Clarifying Dose Adjustment Criteria
12.02.2019	Page 2	Removing Regional Co-Investigators
12.02.2019	Section 7.1.2	Clarifying Dose Adjustment Criteria
01.18.2022	Page 1-2	Updating Co-Investigators and research coordinator on cover page.

Protocol Date	Section	Change
01.18.2022	Section 10.1.2	Removing Dr. Eric Hsi and adding Dr. Sarah Ondrejka as laboratory contact. Updating medical secretary and contact information.
04.11.2022	Page 5	Updated duration of study
04.11.2022	Section 6.6	Updated duration of follow up
04.11.2022	Schedule of Events Footnote 14	Updated follow up duration for 2 years and CT Chest. Abdomen and Pelvis, Neck frequency.
04.11.2022	Schema	Updated duration of follow up
04.11.2022	Study Parameters and Schedule of Events Footnote 14	Updated follow up duration for 2 years and CT Chest. Abdomen and Pelvis, Neck frequency.

<p>PROTOCOL SUMMARY</p> <p>A Phase II Trial of Lenalidomide (Revlimid®), Ixazomib and Rituximab (RIXAR) as Front-line Therapy for High Risk Indolent B cell Lymphoma (CASE1414)</p>
<p>Phase: II</p>
<p>Number of Patients: 33-42</p>
<p>Study Objectives:</p> <p>Primary(Phase I): To determine the maximum tolerated dose and toxicity of the combination of oral ixazomib and lenalidomide plus rituximab in patients with previously untreated low-grade B cell lymphoma having high tumor burden by GELF criteria or FLIPI 3-5</p> <p>Secondary (Phase II):</p> <ul style="list-style-type: none"> • To determine overall response rate in an expanded cohort at the MTD for follicular lymphoma (FL) • Duration of response, time to progression, progression free survival, time to treatment failure and overall survival • Create tissue microarray from paraffin embedded tissue for future studies. • Assessment of baseline lymphocyte subsets as prognostic markers. • Assessment of blood flow cytometric evaluation of minimal residual disease post-treatment correlation with PFS
<p>Overview of Study Design:</p>

This study combines three classes of agents that have non-overlapping mechanisms of action and toxicity profiles, with each pair having demonstrated clinical evidence of benefit without unexpected toxicity. We use the lenalidomide-rituximab backbone, feasible and active in lymphoma, and add a novel oral proteasome inhibitor to potentially enhance efficacy, minimize toxicity and limit patient visits for treatment.

Patients with previously untreated low-grade B cell lymphoma having high tumor burden by GELF criteria or FLIPI 3-5 (for FL only) will be treated with the combination of oral ixazomib + lenalidomide + rituximab.

The primary objective was to determine the maximum tolerated dose and toxicity of this regimen. The study used a standard 3 + 3 design to determine the MTD during cycle 1. There were three dose levels for escalation, 12 patients total. The MTD was determined to be DL3. There will be one expansion cohort of 18 patients with follicular lymphoma

Study Population:

- Adult patients with previously untreated low-grade B cell lymphoma with high tumor burden by GELF criteria and/or FLIPI 3-5 (for FL only).
- ECOG PS 0-2.
- Adequate organ function.
- No grade 3 (or grade 2 with pain) neuropathy.
- Able to swallow pills.
- Not requiring ongoing treatment with drugs that strongly induce CYP3A.
- Agree to contraceptive measures if fertile.

Duration of Study:

Patients will receive treatment for 1 year and are assessed for response 1-3 months later (up to 15 months total).

Following treatment for 1 year, patients will be assessed per clinical standards, generally every 3 months (+/- 7 days) for 2 years.

Study accrual will be over 2 years, with 15 month additional as above, for total of 39 months.

Schedule of Events

Parameter	Pre-study ¹	Day 1 of Every Cycle ^{2 (+/-3)}	Cycle 1 Day 8 ^(+/-2)	Cycle 1 Day 15 ^(+/-2)	Cycle 1 Day 22	Restaging ¹² and Follow-up ¹⁴
Assignment of FLIPI scores ²	X					
Notation of GELF criteria ²	X					
History and Physical examination	X	X				X
Performance Status	X	X				X
Tumor Measurements by Physical Exam (if applicable)	X	X				X
CBC and Differential	X ³	X	X ⁴	X ⁴	X ⁴	X
Serum Chemistries (electrolytes, AST, ALT, total bilirubin, direct bilirubin ⁵ , creatinine, glucose, alkaline phos, and calcium)	X ⁷	X	X	X		X
LDH	X	X	X	X		X
Beta-2-microglobulin	X					
HIV testing	X					
Uric acid	X	X Cycles 3-6 only if > ULN prior cycle	X	X		
Monoclonal protein determination ¹³	X	X ¹³				X ¹³
Bone marrow aspirate biopsy If not known to be involved	X (up to 90 days)					After cycle 12 if in CR ⁶
Pregnancy test (for women of child-bearing potential) ⁷	X ⁷					
Hepatitis B surface antigen and core antibody testing ⁸	X ⁸					
T4, TSH	X	Day 1 Cycle 7 only				X ¹⁵
Immunodeficiency Panel ¹⁶	X	Day 1 cycle 7 only				After cycle 12
Creatinine clearance	X	calculated				
CT Chest, Abdomen, and Pelvis; Neck	X ⁹					After cycles 3 and 6 ¹⁰

(if involved)						
PET/CT Scan	X ⁹					After cycle 12 ¹¹
Baseline Symptoms/AE Evaluation ¹⁷	X	X	X	X		X

Schedule of Events

On rituximab treatment days 8 and 15 of cycle 1, patients will be assessed by a nurse for toxicity, and CBC, serum chemistries, LDH and uric acid will be performed. Pre-study parameters can be up to 30 days prior to start of treatment, except bone marrow aspirate and biopsy can be up to 90 days, if not known to be positive for lymphoma

1. Cycles are every 28 days. Patients may be evaluated in the office more frequently at the physician's discretion.
2. Yes/No should be entered for each criterion of GELF and FLIPI, as well as absolute calculation of FLIPI-1 and FLIPI-2. **(See Appendix V).**
3. At baseline: please record the absolute lymphocyte count.
4. Cycles 2 and 3 for dose escalation cohorts *only* : CBC and differential is required on Days 8, 15 and 22. Other labs (chem, LDH, UA) should be done days 8, 15 of cycle 1 only, not in cycles 2-3
5. Direct bilirubin is required only if total bilirubin is elevated.
6. Repeat bone marrow biopsy core and aspirate only if positive at baseline and otherwise meets criteria for CR.
7. Within 2 weeks of start of induction treatment. For definition of woman of childbearing potential (WOCBP) see lenalidomide (Revlimid®) REMS program. Before starting lenalidomide (Revlimid®): WOCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative. Female subjects will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. **During study participation and for 28 days following discontinuation from the study:** WOCBP with regular cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study. In addition to the required pregnancy testing, the Investigator must confirm with WOCBP that she is continuing to use two reliable

methods of birth control at each visit. Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood. Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation. If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, study drug must be immediately discontinued.

8. Patients must be tested for hepatitis B surface antigen within 6 weeks of randomization. Liver function tests and quantitative PCR assay for HBV levels in serum to be performed monthly until 6 months following last rituximab dose for HBcAb positive patients. Further, consideration should be given to treat such patients with anti-viral prophylaxis (e.g., lamivudine 100mg po QD) prior to, during, and for 6 months after completion of the last dose of rituximab. Patients who are positive for HBsAg (surface antigen) are not allowed to enroll on study.
9. If PET/CT scan has been done, do not need separate diagnostic quality CT unless the only measurable disease is in the mesentery and not measurable without oral contrast, in which case CT abdomen/pelvis with oral/IV contrast should be done prior to treatment.
10. CT scans (chest/abdomen/pelvis; neck if involved) should be done to evaluate response every 3 months (12 weeks). If a PET/CT is done, then CT does not need to be done, unless the only initially measurable disease was in the mesentery and not measurable without oral contrast, in which case CT abdomen/pelvis with oral/IV contrast should be done.
11. Once patient enters PET negative complete remission, then only CT's (chest/abdomen/pelvis, include neck if previously involved) need to be done in follow-up
12. Restaging will be 8 - 12 weeks after day 1 cycle 12 (or after day 1 of last cycle of treatment if stopped early). Repeat bone marrow only if it was involved prior to treatment and patient otherwise meets criteria for CR.
13. Monoclonal protein (M-protein) blood determination includes: serum immunofixation, quantitative IgG, IgA, IgM,. If M-protein is detected, the abnormal value will be checked every other cycle beginning with cycle 2, and during follow-up at months 6, 12, 24, 36, 48 and 60 (each \pm 30 days) or until the patient comes off the study
14. FOLLOW-UP: per clinical standards, generally every 3 months (+/- 7 days) for 2 years, then every 6 months (+/- 7 days) years 2, or as clinically indicated, with: History and Physical examination, Performance Status, Tumor Measurements by Physical Exam (if applicable), CBC and Differential, Serum Chemistries and LDH. CT [Chest, Abdomen, and Pelvis, Neck if previously involved] at months 6, 12, and 24 (each \pm 30 days). Follow-up visit and CT schedule should count from end of treatment restaging scan. Once the patient has disease progression or otherwise meets criteria for treatment failure, patient can be followed for survival by telephone or other contact without in-person visit or protocol-mandated CT scans.

15. Thyroid functions at baseline, pre- cycle 7, at re-staging and once 6 months later
16. Immunodeficiency Panel: One anti-coagulated (prefer purple-top) tube sent to Tomsich Flow laboratory. See Appendix VI for details. Draw at baseline, before cycle 7 and again at restaging after cycle 12.
17. Baseline Symptoms and AE assessments should be done on days 8 and 15 for Cycle 1 only. For Cycles 2 and 3, assessments will be performed on Day 1

SCHEMA
Population (N = 33-42)

Previously untreated indolent B-cell lymphoma

High risk =

- (1) high tumor burden (by GELF criteria; see Appendix 1) AND/OR
- (2) FLIPI 3-5 for FL patients (see Appendix 1)

ECOG PS 0-2

Adequate organ function



Induction Treatment (28 days (4 weeks) per cycle, for 12 cycles):

Ixazomib oral at 4.0 mg on days 1, 8, 15 +
Lenalidomide oral 20 mg/day days 1-21 +
Rituximab IV 375 mg/m²
days 1, 8, 15 of cycle 1,
day 1 only of cycles 2-6,
day 1 only of cycles 8, 10 and 12



Disease Assessment

Evaluation every 3 cycles (12 weeks)
while on treatment.

Scans after cycles 3, 6, and 12.

Continue treatment unless:

Disease progression
Unacceptable toxicity
Patient withdraws consent



Follow up

Assess for response and study related toxicities 2-3 months after last dose
of study drug.

Follow per standard clinical measures for disease progression and survival
for 24 months after the last dose of study drug.

ABBREVIATIONS

ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
AE	Adverse Event
Akt	Protein Kinase B
AL	Amyloid Light-Chain
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AP-1	Activator Protein 1
AST	Aspartate Aminotransferase
AUC	Area Under Curve
Bcl-2	B-Cell Lymphoma 2
bFGF	Basic Fibroblast Growth Factor
BSA	Body Surface Area
BCRP	Breast Cancer Resistance Protein
CAEPR	Comprehensive Adverse Events and Potential Risks List
CBC	Complete Blood Count
CCCC	Case Comprehensive Cancer Center
CCF	Cleveland Clinic Foundation
CD4	Cluster of Differentiation 4
CHO	Chinese Hamster Ovary
CHOP	Cyclophosphamide, Hydroxydoxorubicin, Oncovin, Prednisone
CL	Clearance
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
CMV	Cytomegalovirus
CR	Complete Response
CrCl	Creatinine Clearance
CRu	Complete Response, Unconfirmed
CRF	Case Report Form
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CVA	Cerebrovascular Accident
CVP	Cyclophosphamide, Vincristine, Prednisone
CYP1A2	Cytochrome P450 1A2
CYP3A	Cytochrome P450 3A
DDI	Drug-Drug Interaction
Dex	Dexamethasone
DFS	Disease-Free Survival
dL	Deciliter
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response

DSTC	Data Safety and Toxicity Committee
DVT	Deep Vein Thrombosis
ECOG	Eastern Cooperative Oncology Group
Fab	Fragment Antigen-Binding
Fc	Fragment Crystallizable
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed, Paraffin Embedded
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GELF	Groupe d'Etude des Lymphomes Folliculaires
GI	Gastrointestinal
GM	Gram
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HTB	High Tumor Burden
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDB	Investigational Drug Branch
IND	Investigational New Drug
INF	Interferon
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
iNHL	Indolent Non-Hodgkin Lymphoma
INR	International Normalized Ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IV	Intravenous
IWG	International Working Group
L	Liter
LDH	Lactate Dehydrogenase
LenDex	Lenalidomide plus Dexamethasone
M	Meter
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

Min	Minute
mL	Milliliter
mm	Millimeter
MM	Multiple Myeloma
M-Protein	Monoclonal Protein
MRI	Magnetic Resonance Imaging
MRD	Minimal Residual Disease
MRP2	Multidrug Resistance Associated Protein
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NDMM	Newly Diagnosed Multiple Myeloma
NEC	Not Elsewhere Classified
NHL	Non-Hodgkin Lymphoma
NK	Natural Killer
NOS	Not Otherwise Specified
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PE	Pulmonary Embolism
PET	Positron Emission Tomography
PFS	Progression-Free Survival
Pgp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PO	Orally
PRMC	Protocol Review and Monitoring Committee
QD	One a Day
R	Rituximab
R2	Rituximab-Lenalidomide
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine, Prednisone
RevDex	Revlimid and Dexamethasone
R-HyperCVAD	Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, Methotrexate, Cytarabine
RIXAR	Lenalidomide (Revlimid®), Ixazomib, and Rituximab
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	Relapsed and/or Refractory
RRAL	Relapsed/Refractory Primary Systemic Light Chain (AL) Amyloidosis
RRMM	Relapsed/Refractory Multiple Myeloma
SAE	Serious Adverse Event
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma

SMA	Safety Management Attachment
SOC	Standard of Care
SPD	Sum of Products of the Diameters
TBD	To Be Determined
TEAE	Treatment-Emergent Adverse Event
TLS	Tumor Lysis Syndrome
TMA	Tissue Microarray
TNF	Tumor Necrosis Factor
TTF	Time to Treatment Failure
TTP	Thrombotic Thrombocytopenic Purpura
TTP	Time to Progression
TW	Twice Weekly
UH	University Hospitals
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
VEGF	Vascular Endothelial Growth Factor
VR-CAP	Rituximab, Cyclophosphamide, Doxorubicin, Prednisone, Bortezomib
W	Weekly
WCOBP	Woman of Child-Bearing Potential
WM	Waldenstrom's Macroglobulinemia

TABLE OF CONTENTS

SCHEMA

1.0 INTRODUCTION

- 1.1 Indolent Non-Hodgkin Lymphoma (iNHL)
- 1.2 Ixazomib
- 1.3 Lenalidomide (Revlimid®)
- 1.4 Rituximab
- 1.5 Rationale
- 1.6 Lab Correlative Studies

2.0 OBJECTIVES

- 2.1 Primary Objective
- 2.2 Secondary Objectives
- 2.3 Study Endpoints

3.0 STUDY DESIGN

- 3.1 Overview
- 3.2 Number of Patients
- 3.3 Duration of Study

4.0 PATIENT SELECTION

- 4.1 Inclusion Criteria
- 4.2 Exclusion Criteria
- 4.3 Inclusion of Women and Minorities

5.0 REGISTRATION

6.0 TREATMENT PLAN

- 6.1 Agent Administration
 - 6.1.1 Ixazomib
 - 6.1.2 Lenalidomide
 - 6.1.3 Rituximab
- 6.2 Dose Escalation
- 6.3 Definition of Dose Limiting Toxicity
- 6.4 General Concomitant Medications and Supportive Care Guidelines
- 6.5 Duration of Therapy
- 6.6 Duration of Follow Up

7.0 DOSE DELAYS / DOSE MODIFICATIONS

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

- 8.1 Adverse Events and Potential Risk List
 - 8.1.1 Ixazomib
 - 8.1.2 Lenalidomide
 - 8.1.1 Rituximab
- 8.2 Definitions
 - 8.2.1 Adverse Events
 - 8.2.2 Significance of an Adverse Event

- 8.2.3 Serious Adverse Events
- 8.2.4 Expectedness
- 8.2.5 Attribution
- 8.3 Reporting Procedures for All Adverse Events
- 8.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events
- 8.5 Data Safety Toxicity Committee

9.0 PHARMACEUTICAL INFORMATION

- 9.1 Ixazomib
- 9.2 Lenalidomide
- 9.3 Rituximab

10.0 CORRELATIVE / SPECIAL STUDIES

- 10.1 Tissue Microarray
- 10.2 Flow Cytometry on Peripheral Blood

11.0 STUDY PARAMETERS AND CALENDAR

- 11.1 Study Parameters
- 11.2 Calendar

12.0 MEASUREMENT OF EFFECT

13.0 RECORDS TO BE KEPT/REGULATORY CONSIDERATIONS

- 13.1 Data Reporting
- 13.2 Regulatory Considerations

14.0 STATISTICAL CONSIDERATIONS

REFERENCES

APPENDICES

APPENDIX I

ECOG Performance Status

APPENDIX II

Cockcroft-Gault formula for Creatinine Clearance

APPENDIX III

Potential CYP1A2 and CYP3A4 Interactions

APPENDIX IV

Patient Pill Diary

APPENDIX V

Risk Factors: GELF Tumor Burden Criteria and FLIPI Score

APPENDIX VI

Blood Specimen Handling

1.0 INTRODUCTION

1.1 Indolent B Cell Non-Hodgkin Lymphoma (iNHL)

Indolent B cell non-Hodgkin lymphoma (iNHL) consists of several categories of lymphoid malignancies arising from B cells. The most common type of iNHL in the U.S. is follicular lymphoma. Other less common types include small lymphocytic lymphoma, marginal zone lymphoma (nodal, extranodal and splenic) and lymphoplasmacytic lymphoma. While they differ as to molecular drivers and in some clinical behavior, these iNHL are often grouped together as treatable, but not curable, B cell lymphoproliferative disorders. As such, they are often approached similarly in the clinic with observation if there are no signs or symptoms related to the disease, and treatment indicated when signs or symptoms of disease occur. As patient selection can significantly affect outcomes, patient populations in most current studies of untreated iNHL have been divided into low and high tumor burden (HTB) populations according to GELF criteria, with HTB iNHL representing higher risk disease and worse outcomes. Low tumor burden patients who require therapy may receive as a single agent the anti-CD20 monoclonal antibody rituximab. The most common therapy for untreated HTB indolent NHL remains rituximab (R) combined with standard cytotoxic chemotherapy, usually CHOP, CVP or bendamustine. Another way to stratify iNHL in terms of survival prognosis is the follicular lymphoma (FL) international prognostic index (IPI) FLIPI, although these data antedated use of rituximab. FLIPI-2 was updated in the rituximab era. FLIPI scores of 3-5 are associated with shorter TTP after therapy and OS. While the GELF criteria and FLIPI were developed for FL, they have been applied to all subtypes of iNHL. Of note, is that there are no data that early treatment even in these groups alters outcome.

Few series of patients with HTB iNHL treated with rituximab-chemotherapy have reported long-term follow-up (i.e., median follow-up >4 years), and in these latter reports the 4-year time to progression (TTP) and overall survival (OS) rates were 44-56% and 83-90%, respectively. In addition, more tolerable therapeutic regimens for patients with HTB iNHL who are older or have comorbidities and other contraindications to chemotherapy are an unmet medical need. Encouraging data from phase 1 and 2 trials examining non-cytotoxic therapy for untreated patients with iNHL have been reported. Several trials have administered rituximab-lenalidomide (R2), leading to the ongoing randomized phase 2 trial (RELEVANCE) of R2 compared with R-chemotherapy.

Bortezomib is a proteasome inhibitor with encouraging activity in relapsed or refractory iNHL and mantle cell lymphoma. It has been combined with R-chemo in lymphoma trials, as well being effective and well-tolerated in combination with lenalidomide in myeloma. We carried out a phase 1B/2 trial of R-bortezomib as initial therapy for HTB iNHL.

Based on the above findings that R2 as well as R + proteasome inhibitor are promising regimens for therapy of iNHL, and that lenalidomide + various proteasome inhibitor combinations are highly active against another B cell disorder myeloma, combining R2 + a proteasome inhibitor is a rational concept to study as initial therapy in HTB iNHL. For this study we have chosen to use the novel oral proteasome inhibitor ixazomib to decrease expected neurotoxicity and to reduce patient visits and injections.

1.2 Ixazomib (MLN9708)

1.2.1 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB)

1.2.2 Clinical Experience

As ixazomib has been recently approved in the setting of myeloma, but remains investigational for lymphoma, data continue to accumulate and the most current IB should be consulted for detailed information. Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapse/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, 2 phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with lenalidomide (Revlimid) and Dexamethasone (RevDex) versus placebo/RevDex. Both trials are combining ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, clinical pharmacology studies have evaluated drug-drug interactions with ketoconazole, clarithromycin, and rifampin, as well as the effect of food, renal impairment, and hepatic impairment on the PK of ixazomib. Studies evaluating the safety and pharmacokinetics (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of RRMM are ongoing.

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.2.4) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia

(28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

1.2.3 Pharmacokinetics and Drug Metabolism

After oral dosing, absorption of ixazomib is rapid with a median first time to maximum observed plasma concentration (T_{max}) of approximately 1 hour postdose. The plasma exposure (AUC) of ixazomib increases in a dose-proportional manner over a dose range of 0.2 to 10.6 mg based on population PK analysis. The absolute oral bioavailability (F) of ixazomib is estimated to be 58% based on population PK analysis. A high-fat meal reduced ixazomib C_{max} by 69% and AUC_{0-216} by 28%. This indicates that a high-fat meal decreases both the rate and extent of absorption of ixazomib. Therefore, ixazomib should be dosed at least 2 hours after food or 1 hour before food.

The steady-state volume of distribution of ixazomib is large and is estimated to be 543 L based on a population PK model. Based on in vitro plasma protein binding measurements on samples from clinical studies (Studies C16015 and C16018), ixazomib is highly bound to plasma proteins (99%). Ixazomib concentrations are higher in whole blood than in plasma, indicating extensive partitioning of ixazomib into red blood cells, which are known to contain high concentrations of the 20S proteasome.

Metabolism appears to be the major route of elimination for ixazomib. In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450 (CYP) and non-CYP proteins. At concentrations exceeding those observed clinically (10 μ M), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (\square 1%). At 0.1 and 0.5 μ M substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, non-CYP proteins contribute to the clearance of ixazomib and no specific CYP isozyme predominantly contributes to the clearance of ixazomib. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor would be expected.

Ixazomib is neither a time-dependent inhibitor nor a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYPs 1A2, 2B6, and 3A4/5 activity or corresponding immunoreactive protein levels. Thus, the potential for ixazomib to produce DDIs via CYP isozyme induction or inhibition is low.

Ixazomib is not a substrate of BCRP, MRP2 and OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Ixazomib is unlikely to cause or be susceptible to clinical DDIs with substrates or inhibitors of clinically relevant drug transporters.

The geometric mean terminal half-life ($t_{1/2}$) of ixazomib is 9.5 days based on population PK analysis. For both IV and oral dosing, there is an approximately average 3-fold accumulation

(based on AUC) following the Day 11 dose for the twice-weekly schedule and a 2-fold accumulation (based on AUC) following the Day 15 dose for the once-weekly schedule.

Mean plasma clearance (CL) of ixazomib is 1.86 L/hr based on the results of a population PK analysis. Taken together with the blood-to-plasma AUC ratio of approximately 10, it can be inferred that ixazomib is a low clearance drug. Using the absolute oral bioavailability (F) estimate of 58% (also from a population PK model), this translates to an apparent oral plasma clearance (CL/F) of 3.21 L/hr. The geometric mean renal clearance for ixazomib is 0.119 L/hr, which is 3.7% of CL/F and 6.4% of CL estimated in a population PK analysis. Therefore, renal clearance does not meaningfully contribute to ixazomib clearance in humans. Approximately 62% of the administered radioactivity in the ADME study (Study C16016) was recovered in the urine and 22% of the total radioactivity was recovered in the feces after oral administration. Only 3.2% of the administered ixazomib dose was recovered in the urine as unchanged ixazomib up to 168 hours after oral dosing, suggesting that most of the total radioactivity in urine was attributable to metabolites.

The PK of ixazomib was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor, and hence no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. Consistently, in a population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. Based on information from the clinical rifampin DDI study, ixazomib C_{max} and AUC_{0-last} were reduced in the presence of rifampin by approximately 54% and 74%, respectively. Therefore, the co-administration of strong CYP3A inducers with ixazomib is not recommended.

Mild or moderate renal impairment ($CrCL \geq 30$ mL/min) did not alter the PK of ixazomib based on the results from a population PK analysis. As a result, no dose adjustment is required for patients with mild or moderate renal impairment. In a dedicated renal impairment study (C16015), unbound AUC_{0-last} was 38% higher in patients with severe renal impairment or ESRD patients requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is appropriate in patients with severe renal impairment or ESRD requiring dialysis. Pre- and post-dialyzer concentrations of ixazomib measured during the hemodialysis session were similar, suggesting that ixazomib is not readily dialyzable, consistent with its high plasma protein binding (99%).

The PK of ixazomib is similar in patients with normal hepatic function and in patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (total bilirubin <1.5 times the upper limit of normal [ULN]), based on the results from a population PK analysis. Consequently, no dose adjustment is required for patients with mild hepatic impairment. In a dedicated PK study in patients with moderate (total bilirubin >1.5 to 3 times the ULN) or severe (total bilirubin >3 times the ULN) hepatic impairment (Study C16018), unbound dose-normalized AUC_{0-last} was 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. Therefore, a reduced starting dose of ixazomib is appropriate in patients with moderate or severe hepatic impairment.

There was no statistically significant effect of age (23-91 years), sex, body surface area (1.2 - 2.7 m²), or race on the clearance of ixazomib based on the results from a population PK analysis.

1.2.4 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, non-hematologic cancers, and lymphoma) have been treated in studies evaluating the oral ixazomib formulation. These patients have been treated with different doses of ixazomib either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m ² TW MTD: 2.0 mg/m ² DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m ² W MTD: 2.97 mg/m ² DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m ² W MTD: 2.97 mg/m ² DLT: nausea, vomiting, diarrhea, syncope RP2D ^a : 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m ²) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A ^a : 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B ^a : 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose ^a W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose ^a W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose ^a W
C16010 RRMM N = 200	PO, W, with LenDex versus placebo- LenDex	4.0 mg W
C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16013 RRMM N = 9	PO, W, with LenDex	4.0 mg W
C16014 Symptomatic MM N=701	PO, combination with LenDex	ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=28	PO, combination with Dex	Part A: ixazomib 3.0 mg on Day 1 Part B: ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle
C16017 RR follicular lymphoma N=58	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45	Part A: PO, Day 1 of 15-day cycle Part B: PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
TB- MC010034 RRMM N = 10	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

Abbreviations: RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area; Dex=dexamethasone; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RR= relapsed and/or refractory; RRAL= relapsed and/or refractory systemic light chain amyloidosis RRMM = relapsed and/or refractory multiple myeloma; TBD = to be determined; TW = twice weekly; W = weekly; RP2D= recommended phase 2 dose.

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

a Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m² BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m² BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m² BSA dosing.

1.2.5 Overview of the Oral Formulation of Ixazomib

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib Studies (C16003, C16004, C16007, and C16009) are shown in Table 1-2.

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	1.1.1.1.2 Oral Single Agent Total n = 201 n (%)
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhoea	88 (44)
Vomiting	77 (38)
Constipation	46 (23)
Abdominal pain	33 (16)
General disorders and administration site conditions	151 (75)
Fatigue	103 (51)
Pyrexia	51 (25)
Oedema peripheral	27 (13)
Asthenia	31 (15)
Nervous system disorders	92 (46)
Headache	29 (14)
Dizziness	26 (13)
Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)
Decreased appetite	64 (32)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	1.1.1.1.2 Oral Single Agent Total n = 201 n (%)
Anaemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash macular ^a	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnoea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

Source: Ixazomib Investigator’s Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens.

The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	1.1.1.1.3 Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Subjects with at Least One Adverse Event	163 (94)
Gastrointestinal disorders	139 (80)
Nausea	65 (38)
Diarrhoea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Oedema peripheral	61 (35)
Asthenia	20 (12)
Nervous system disorders	115 (66)
Headache	28 (16)
Dizziness	34 (20)
Neuropathy peripheral	45 (26)
Metabolism and nutrition disorders	91 (53)
Decreased appetite	25 (14)
Hypokalaemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anaemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular ^a	29 (17)
Rash macular ^a	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	1.1.1.1.3 Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Dyspnoea	26 (15)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

Source: Ixazomib Investigator’s Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

Data from ongoing blinded pivotal trials (C16010) are not included.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash..

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors [3], non-Hodgkin’s disease, Hodgkin’s disease [4], relapsed and/or refractory multiple myeloma (RRMM) [5; 6], relapsed or refractory systemic light chain amyloidosis (RRAL) [7], and newly diagnosed multiple myeloma (NDMM) [8; 9; 10]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of ixazomib.

1.2.6 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involves 2 studies (C16003 and C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE.

Study C16003 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.(11, 12) Study C16004 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM.(13, 14, 15) Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

In the dose escalation component of both studies, patients had multiple myeloma that had relapsed following at least 2 lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were to be enrolled into 1 of 4 expansion cohorts, including a relapsed and refractory cohort, a

carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a VELCADE-relapsed cohort.

Final study results are currently being analyzed, but preliminary data suggest that ixazomib has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated. Please refer to the ixazomib IB and SMA for further information.

1.2.7 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating ixazomib in combination with agents commonly used across treatment settings. The development of ixazomib in combination with lenalidomide with dexamethasone (LenDex) in patients with NDMM who are transplant eligible or ineligible involves 2 studies (C16005 and C16008) with similar study designs except for a few key differences, namely the schedules of ixazomib and dexamethasone. Ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

All 3 studies are phase 1/2, with phase 1 focusing on safety and phase 2 on efficacy (and further characterization of safety). Please refer to the ixazomib IB and SMA for further information.

1.2.8 Clinical Trial Experience Using Intravenous Formulation of Ixazomib

See the IB for descriptions of the 2 studies that investigated IV ixazomib in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.2.9 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA.

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of ixazomib for the treatment of patients with advanced malignancy.

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

1.3 Lenalidomide (Revlimid®)

1.3.1 Background

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF. (1) In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production. (2) Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity. (3)

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis (4). In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone.

1.3.2 Indications and Usage

Lenalidomide (Revlimid®) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Lenalidomide (Revlimid®) is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy. In 2013 it was approved for treatment of patients with mantle cell lymphoma who were previously treated and whose treatment had included bortezomib.

1.3.3 Adverse Events

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.

Patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with lenalidomide as induction therapy (treatment for several cycles to reduce number of cancer cells) and/or bone marrow transplant followed by lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

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

1.4 Rituximab

1.4.1 Background

Rituximab is a chimeric mouse/human anti-CD20 monoclonal antibody that is approved by the FDA for several indications, including treatment of indolent, B-cell non-Hodgkin lymphoma. Anti-tumor activity is achieved through antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. Additional evidence demonstrates that rituximab has anti-proliferative effects and can induce apoptosis in malignant B-lymphocytes by directly disrupting intracellular signaling pathways.

The CD20 antigen is an attractive target for immunotherapeutic agents as it does not internalize on antibody binding. In phase 1 studies serum antibody levels were detected in all patients immediately after the intravenous infusion. At the usually used dose serum antibody levels can be detected 1 month after antibody therapy. In patients with high tumor burden with splenomegaly the antibody half-life can be as short as 1.6 days.

1.4.2 Clinical experience

Among patients with relapsed or refractory low-grade NHL, a standard 4-week course of weekly rituximab at 375 mg/m² induces response rates of 50% with a median progression-free survival of 12 months. (54) When used in the first-line setting, approximately 70-75% of patients respond to single-agent rituximab with durable responses of 18 months. Rituximab is well tolerated in single-agent studies and myelosuppressive effects are mild. The most frequent toxicities are transient, Grade 1 and 2 fever, chills, and myalgias that occur with the first infusion of rituximab and abate with subsequent treatments. More grade 3 and 4 pulmonary symptoms, hypotension, and chills were observed when rituximab was used to treat bulky disease.

With demonstrated high efficacy and low toxicity in single-agent studies, rituximab has been combined with traditional cytotoxic chemotherapy in multiple studies. Several recent trials have reported impressive response rates and durable remissions for patients with indolent NHL treated with rituximab combinations. Rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP) was compared to the same regimen without rituximab (CVP) in a randomized trial of 321 previously untreated patients with stage III-IV follicular NHL. The ORR and CR rates were 81% and 41% for patients treated with R-CVP versus 57% and 10% for patients who received CVP alone. Patients in the R-CVP arm also had a significant improvement in time to progression (TTP) with a median of 30 months of follow-up (median TTP 32 months for R-CVP versus 15 months for CVP, $p < .0001$).

The use of rituximab as maintenance therapy to maintain partial or complete remissions after initial therapy has also been evaluated. This strategy attempts to take advantage of the agent's ease of administration and favorable efficacy and toxicity profile.

In the PRIMA study, 1217 patients received cytotoxic chemotherapy plus rituximab as per standard practice. Of patients who achieved a complete or partial response (1019/1217, 84%), 505 patients were randomized to receive rituximab maintenance versus 513 randomized to observation. The PFS in the group that got rituximab maintenance was 74.9% versus 57.6% in the group that did not. Rituximab essentially cut the risk of progression in half. The CR/CRu rate was 71.5% with

rituximab and 52.2% without. Infectious grades 2-4 were the most common adverse event occurring in 39% of those who got maintenance rituximab and 24% of those who did not.

Rituximab with lenalidomide (R2) is effective and may be synergistic. Lenalidomide may increase CD20 expression and enhance ADCC to augment rituximab activity. Rituximab appears to enhance the ADCC-promoting activity of lenalidomide.

1.5 Study Rationale

Indolent B cell lymphomas are considered incurable with current standard therapy, even with multi-agent chemotherapeutic regimens such as R-CHOP or high dose chemotherapy with autologous stem cell support. Since the advent of antibody-based therapy (rituximab, radioimmunotherapy) however, survival has improved. As more intense standard chemotherapy does not lead to cure, novel agents with alternative mechanisms of action are being investigated. These are generally used in the relapsed/refractory setting to demonstrate activity, then moved earlier in the treatment plan.

Lenalidomide (Revlimid®) has significant single agent activity in relapsed aggressive non-Hodgkin lymphoma, with response rates of 35% including a CR rate of 12%. (14) In-vitro studies have shown synergy when Lenalidomide and rituximab are combined. Lenalidomide is able to enhance the natural killer cell and monocyte mediated antibody dependent cellular cytotoxicity of this monoclonal antibody. Recent studies combining lenalidomide and rituximab have shown promising activity (overall response rate 90%, complete response rate 66%) with no unexpected toxicities. (63, 64) A CALBG trial using this lenalidomide and rituximab biological doublet demonstrated benefit with addition of rituximab to lenalidomide [Leonard, ASH 2011].

We completed a phase II trial of combination Velcade® and rituximab for untreated high tumor burden indolent non-Hodgkin lymphoma, The treatment regimen consists of Velcade® 1.6mg/m² days 1, 8, 15 and 22 and rituximab 375mg/m² every week x 4 doses for cycle 1 and then day 1 of cycles 2 and 3. Each cycle lasted 5 weeks. After cycle 1 the response rate was 29%, all partial responses, but after the three planned induction cycles the overall response rate (ORR) doubled to 59% and the complete response rate (CR) was 24%. This biological doublet combination is active and well tolerated. No grade 4 toxicities occurred. Grade 3 toxicities consisted of lymphopenia, partial small bowel obstruction and fatigue (all in 1 patient). No cytopenias or neurotoxicity was seen. Velcade® and rituximab provide an attractive treatment combination for indolent NHL because each agent has demonstrated efficacy as monotherapy and they are generally well tolerated with non-overlapping toxicities. Each agent has a unique mechanism of action that when coupled together should minimize malignant cell cross-resistance. Each agent also appears to promote apoptotic activity though negative effects on bcl-2. Two Velcade® /rituximab treatment regimens were evaluated in a randomized phase II study for patients with relapsed, refractory low grade NHL. Treatment Arm A treated patients with Velcade® 1.3 mg/m² twice weekly on days 1, 4, 8, and 11 of a 21-day cycle in combination with 4 doses of rituximab 375mg/m² given on days 1, 8, and 15 of cycle 1 and day 1 of cycle 2. Patients on Treatment Arm B receive Velcade® 1.6mg/m² weekly on days 1, 8, 15, and 22 of a 35-day cycle with 4 doses of rituximab 375mg/m² weekly on days 1, 8, 15, and 22 of cycle 1. Study end points include ORR, time to progression, and safety and tolerability data. At the time of this report 81 patients were enrolled on the study, and preliminary safety data are available for 60 patients. Grade 3 or 4 adverse events have occurred in 54% of patients on Arm A (twice weekly Velcade®), and 18% of patients on Arm B (weekly Velcade®), with no grade 4 events on Arm B. The most common grade 3 or 4 adverse events included nausea and/or vomiting (15% Arm A, 3% Arm B), diarrhea (4% Arm A, 9% Arm B), peripheral neuropathy (8% Arm A, 3% Arm B) and fatigue (4% Arm A, 6% Arm B). Based on

preliminary data the response rate is 51% in Arm A and 54% in Arm B.

Combinations of proteasome inhibitors with standard chemotherapy also appears safe effective, exemplified by combination of Velcade in mantle cell lymphoma with either R-HyperCVAD part A (E1405) or with R-CHOP without vincristine (VR-CAP). In multiple myeloma, another indolent B cell malignancy, combination of proteasome inhibitors and Imids are effective and well-tolerated therapy, having become a standard approach both as initial therapy and at relapse. Drawing on these investigations in myeloma, combining Velcade® and lenalidomide is feasible and has resulted in promising clinical activity. In both trials the maximum tolerated dose of lenalidomide was 25mg daily day 1 – 14 and Velcade® 1.3mg/m² twice a week for 2 weeks.

Lenalidomide, Velcade® and rituximab are all active as single agents in patients with NHL, with response rates of about 29- 35%, 13.3%-33% and 34%-72% respectively when used in the relapse setting in patients with B-cell lymphoma. (14, 48, 49, 74, 75, 76) Response rates can be improved when lenalidomide is combined with rituximab with an overall response rate of 86% and complete response rate of 79%. (63) Similarly we also get improved response rates when Velcade® is combined with rituximab, with overall response rates of 59% and complete responses of 25%. However, all 3 drugs have not been used together. Here we propose to use an oral proteasome inhibitor with improved toxicity profile and ease of administration.

We will develop this novel biological triplet (RIXAR) by adding ixazomib to the R2 platform as initial therapy of high risk/HTB indolent lymphoma.

We hypothesize that this novel biological triplet combination will: (1) have enhanced efficacy, assessed by an increase in overall and complete response rates, as well as more durable responses; (2) be a safe and well tolerated alternative to traditional cytotoxic chemotherapy in this patient population.

This combination will target not just the neoplastic B-cell but will also be an attempt at reprogramming the microenvironment and infiltrating immune cells in an attempt to increase, deepen and lengthen responses. This approach may very well be the paradigm shift needed to impact the course of indolent B-cell lymphoma.

To test our hypothesis, we will conduct a single-arm, phase IB/II clinical trial in which patients with untreated, low-grade B-cell NHL will receive an induction course of lenalidomide, ixazomib and rituximab limited to 1 year of therapy.

1.6 Correlative Testing

1.6.1 Tissue Microarray

One of the limitations of laboratory tissue sample analysis has been the cumbersome process of processing individual tissues. Tissue microarray is a technique where by multiple tissues can be processed simultaneously using high through-put technologies. A full set of tissue samples from this study can be stored on a single glass slide and processed simultaneously for DNA, RNA or protein targets. This provides the ideal method of storing tissues samples so that they can be processed at a future time when more information on prognostic and predictive factors become available.

1.6.2 Baseline T-Lymphocyte Subsets

Nodal tissue from B-cell lymphomas also harbor T-cells. Jaffe and colleagues speculated that the

T-cells, which are normal, were interacting with the malignant clone in a functional way. They speculated that this may represent part of the host immune response against the neoplasm. Other groups continued to work on this and concluded that the infiltrating T-cells could either be helping or hindering the neoplasm.

More recently Dave et al were able to show that the molecular signature of tumor infiltrating cells in lymph node biopsies of patients with follicular lymphoma provides prognostic information. Of note, the molecular signature was of the non-malignant tumor infiltrating cells, including T-cells, monocytes and dendritic cells. Also, T-lymphocyte subsets predict prognosis independently of the Follicular Lymphoma International Prognostic Index (FLIPI). CD4+ T-cells, interfollicular CD68+ cells (macrophages) are associated with a poor outcome and Follicular FOXP3+ cells, CD8+ cells, and programmed death 1 + cells (PD-1) are associated with a good prognosis. We have shown that absolute NK cells at baseline are a prognostic factor in follicular lymphoma. We plan to perform flow cytometry on peripheral blood obtained at diagnosis to evaluate baseline NK and T-lymphocyte subsets and correlate this to response to therapy and outcomes (DFS, PFS and OS).

2.0 STUDY OBJECTIVES

2.1 Primary Objective (Phase I)

To determine the maximum tolerated dose (MTD) and toxicity of the combination of oral ixazomib and lenalidomide plus rituximab in patients with previously untreated low-grade B cell lymphoma having high tumor burden by GELF criteria or FLIPI 3-5 (for FL only).

2.2 Secondary Objectives (Phase II)

- To determine overall response rate in an expanded cohort at the MTD for follicular lymphoma
- Duration of response, time to progression, progression free survival, time to treatment failure and overall survival.
- Create tissue microarray from paraffin embedded tissue for future studies.
- Assessment of baseline lymphocyte subsets as prognostic markers.

2.3 Study Endpoints

Primary Endpoints (Phase I)

- Maximum tolerated dose (MTD) and toxicity of the combination of oral ixazomib and lenalidomide plus rituximab in this patient population. The MTD was determined to be 4 mg of Ixazomib.

Secondary Endpoints (Phase II)

In an expanded cohort at the MTD for follicular lymphoma:

- Overall response rate (by IWG criteria) (ORR)
- Duration of response (DOR)
- Time to progression (TTP)
- Progression free survival (PFS)
- Time to treatment failure (TTF)
- Overall survival (OS)

3.0 STUDY DESIGN

3.1 Overview of Study Design

Phase I

- Patients with previously untreated low-grade B cell lymphoma having high tumor burden by GELF criteria and/or FLIPI 3-5 will be treated with the combination of oral ixazomib + lenalidomide + rituximab.
- The primary objective was to determine the maximum tolerated dose and toxicity of this regimen. The study proceeded using a standard 3 + 3 design for determination of MTD during cycle 1. There were three dose levels for escalation. The MTD was determined to be DL3.

Phase II

For the phase II portion of the study, one expansion cohort of 18 patients with follicular lymphomawill be treated at the at the MTD (DL3) ,
Patients will be treated for 12 cycles of 4 week duration, unless disease progresses, unacceptable toxicity occurs or patient withdraws consent.

3.2 Number of Patients

The phase 1 portion enrolled 12 patients. There will be one expansion cohort of 18 patients each.

Patients will be considered enrolled on the study when they sign informed consent.

3.3 Duration of Study

Patients will receive treatment for 1 year and assessed for response 1-3 months later (up to 15 months total). They will then be followed per usual clinical standard of care.

Study accrual will be over 2 years, with 15 month additional as above, for total of 39 months

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

4.0 PATIENT SELECTION

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility.

4.1 Inclusion Criteria

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

_____ 4.1.1 Patients must have histologically confirmed, low-grade B-lymphocyte NHL by the World Health Organization Classification:

- Follicular lymphoma grades 1, 2, and 3a
- Marginal zone B-cell lymphoma, including extranodal (MALT), nodal and splenic

CASE1414 RIXAR

Protocol Version 8, 4/11/2022

- Excluding:
- Small lymphocytic lymphoma
- Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (WM)

_____ 4.1.2 Must have stage 2, 3 or 4 disease, with either high tumor burden by GELF criteria and/or FLIPI 3-5 (for FL) (see Appendix V for definition of nodal groups for FLIPI).

_____ 4.1.2.1 To meet GELF criteria, patient must have at least one criterion (answer yes or no for each criterion):

_____ Nodal or extranodal mass > 7 cm (document here the largest/longest single nodal or extranodal mass diameter)

- Largest size: _____

_____ At least 3 nodal masses: each > 3.0 cm in longest dimension

_____ Systemic symptoms due to lymphoma or B symptoms

_____ Splenomegaly with spleen > 16 cm by CT scan

_____ Evidence of compression syndrome (e.g., ureteral, orbital, gastrointestinal) or pleural or peritoneal serous effusion due to lymphoma (irrespective of cell content)

_____ Leukemic presentation ($> 5.0 \times 10^9/L$ malignant circulating follicular cells)

_____ Cytopenias (absolute neutrophil count $< 1.0 \times 10^9/L$, hemoglobin < 10 gm/dL, and/or platelets $< 100 \times 10^9/L$).

AND/OR

_____ 4.1.2.2 To meet FLIPI criteria for FL (see Appendix V for lymph node diagram), patient must have a score of 3, 4, or 5 (one point each for below criterion; answer yes or no for each criterion):

_____ Age > 60 years

_____ Ann Arbor stage III-IV

_____ Hemoglobin level < 12 mg/dL

_____ ≥ 5 nodal areas (see Appendix V for nodal diagram)

_____ Serum LDH level above normal

_____ 4.1.2.3 FLIPI2 (see Appendix V)

FLIPI 2 is not a criterion for this study, but we would like to capture the elements and calculate FLIPI 2 for the protocol population

Each patient should be assessed for the presence or absence of the following 5 adverse prognostic factors (adverse factor in italics):

- 1) Age (*> 60 years* vs. 60 years or less)
- 2) Hemoglobin level (*< 120 g/L* vs. 120 g/L or higher)
- 3) $\beta 2$ -microglobulin (*above normal* vs. normal or below)
- 4) Largest involved lymph node (*> 6 cm* vs. 6cm or lower)
- 5) Bone marrow (*involved by histology* vs. not involved)

_____ 4.1.3 Must have previously untreated lymphoma. A short (< 2 week) course of steroids for symptom palliation is permitted. Prior involved field radiotherapy for symptom palliation is permitted as long as there is measurable disease outside the radiation port. If radiotherapy has been given, there should be at least 7 days between last treatment and beginning of protocol therapy.

_____ 4.1.4 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (see section 11.0)

_____ 4.1.5 Age \geq 18 years. Because no dosing or adverse event data are currently available on the use of ixazomib in combination with lenalidomide in patients <18 years of age, children are excluded from this study.

_____ 4.1.6 Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
ECOG PS = _____
Date: _____

_____ 4.1.7 Patients must have adequate hematologic, hepatic, and renal function as defined below. Patients who do not meet hematologic parameters (ANC, Platelets, Hemoglobin) for inclusion/exclusion due to marrow infiltration by disease are still eligible for the study):

_____ 4.1.7.1 Absolute neutrophil count (ANC) \geq 1,000/mcL
Absolute neutrophil count: _____
Date of Test: _____

_____ 4.1.7.2 Platelet count \geq 75,000/mcL
Platelet count: _____
Date of Test: _____

Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.

_____ 4.1.7.3 Total bilirubin \leq 1.5 x the upper limit of the normal range (ULN)
Total bilirubin: _____
Date of Test: _____

_____ 4.1.7.4 AST (SGOT) \leq 3 x institutional upper limit of normal
AST (SGOT): _____
Date of Test: _____

_____ 4.1.7.5 ALT (SGPT) \leq 3 x institutional upper limit of normal
ALT (SGPT): _____
Date of Test: _____

_____ 4.1.7.6 Calculated creatinine clearance \geq 30 mL/min/1.73 m² (see Appendix II)
Creatinine clearance: _____
Date of Test: _____

See section below, "Dosing Regimen", regarding lenalidomide dose adjustment for calculated creatinine clearance \geq 30ml/min and < 60ml/min.

_____ 4.1.8 Participants must agree to ongoing anticoagulation as prophylaxis against deep vein thrombosis (DVT) using aspirin (81 or 325 mg) daily, warfarin or low molecular weight heparin, or a patient already taking another oral anticoagulant (e.g. direct thrombin inhibitors for atrial fibrillation) may continue that agent.

_____ 4.1.9 All study participants must be willing to register with the mandatory RevAssist program and be willing to comply with its requirements..

_____ 4.1.10 All study participants must be registered into the mandatory lenalidomide (Revlimid) REMS® program, and be willing and able to comply with the requirements of the REMS® program.

A woman of childbearing potential (WOCBP) 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 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

Female patients who are WOCBP must agree to practice:

- 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
- True abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
- A WOCBP must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10-14 days prior to and again within 24 hours of starting therapy with lenalidomide Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the lenalidomide (Revlimid) REMS® program.

Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

_____ 4.1.11 Subjects must have the ability to understand and the willingness to sign a written informed consent document and HIPAA consent document. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

4.2 Exclusion Criteria

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

_____ 4.2.1 Patients who are receiving any other investigational agents.

_____ 4.2.2 Female patients who are lactating or have a positive serum pregnancy test during the screening period.

_____ 4.2.3 Major surgery within 14 days before enrollment.

_____ 4.2.4 Radiotherapy within 14 days before enrollment. If the involved field is small (single nodal area), 7 days will be considered a sufficient interval between treatment and beginning of protocol therapy.

_____ 4.2.5 Known central nervous system involvement with the disease under study.

_____ 4.2.6 Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

_____ 4.2.7 Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

_____ 4.2.8 Systemic treatment, within 14 days before the beginning of protocol therapy, with CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort.

Lists including medications or substances known or with the potential to interact with specific CYP450 enzymes are provided in Appendix III.

_____ 4.2.9 Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. Specifically, prior desquamating rash or erythema nodosum during prior thalidomide or other similar agents.

_____ 4.2.10 Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib or lenalidomide including difficulty swallowing.

_____ 4.2.11 Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

_____ 4.2.12 Patient has \geq Grade 2 peripheral neuropathy on clinical examination during the screening period.

_____ 4.2.13 Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

_____ 4.2.14 Any prior use of lenalidomide (Revlimid®) or Velcade®.

_____ 4.2.15 Known seropositivity for, or active viral infection with, HIV, HBV (unless due to vaccination), or HCV. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with lenalidomide and ixazomib. In addition, these patients are at increased risk of lethal infections when treated with marrow suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

_____ 4.2.16 Pregnant or breastfeeding women are excluded from this study because lenalidomide has known teratogenic effects. Because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with lenalidomide, breastfeeding should be discontinued if the mother is treated with lenalidomide. These potential risks may also apply to other agents used in this study.

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic and will be provided a study number by calling the research coordinator listed on the cover page.

6.0 TREATMENT PLAN

6.1 Agent Administration

Appropriate dose modifications for lenalidomide, ixazomib and rituximab are described in Section 7.0

Reported adverse events and potential risks of lenalidomide, ixazomib and rituximab are described in Section 8.0.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.1.1 Ixazomib Administration

The ixazomib drug product is provided in strengths of 4.0-, 3.0-, 2.3-, 2.0-, 0.5-, and 0.2 mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.0 mg	Size 2	Swedish orange
0.5 mg	Size 3	Dark green

For additional details, please see the ixazomib IB.

Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and

CASE1414 RIXAR

Protocol Version 8, 4/11/2022

adjustments of ixazomib dose (see Section 7.0).

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 0.5, 2.0, 3.0 and 4.0 mg ixazomib.

The prescribed administration of ixazomib doses in this study is 2.0, 3.0 or 4.0 mg ixazomib on days 1, 8 and 15 of each 28 day cycle.

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Ixazomib should be taken on an empty stomach (no food or drink) at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Ixazomib Destruction

Investigational ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

Pregnancy

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus; however, lenalidomide has known severe adverse effects. Therefore, female patients participating in this study must avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients must use effective methods of contraception through defined periods during and after study treatment as specified in the inclusion/exclusion criteria (Section 4.1.10).

6.1.2 Lenalidomide Administration

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 lenalidomide (Revlimid) REMS® program. Per standard lenalidomide (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 lenalidomide (Revlimid) REMS® program.

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

Dosing Information

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

Lenalidomide Starting Dose Based on Renal Function at Study Entry

Baseline Calculated Creatinine Clearance (by Cockcroft-Gault)	Starting Lenalidomide Dose (20 mg)
≥ 60 ml/min	20 mg daily on Days 1 - 21 of each 28-day cycle
≥ 30 and < 60 ml/min	10 mg daily on Days 1 - 21 of each 28-day cycle

Patients started with a reduced lenalidomide dose due to baseline calculated creatinine clearance ≥ 30 ml/min but < 60 ml/min, may have their lenalidomide dose gradually increased in a step-wise manner at the start of Cycle 2 or at the start of subsequent treatment cycles, if they tolerated the prior treatment cycle without requiring dose modifications, interruptions or delays due to toxicity. Lenalidomide dose titrations are permitted in 5 mg increments on the same dosing schedule up to the maximum allowable target dose. The lenalidomide dose may only be increased once every 28 days (or less frequently), and may only be increased if the prior treatment cycle was completed without requiring dose modifications, interruptions or delays due to toxicity.

Dosing will be in the morning at approximately the same time each day. Prescriptions must be filled within 7 days for females of child bearing potential and 14 days for all other risk categories.

Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules.

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.

Pregnancy Testing

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

Unused Study Drug Supplies

Celgene will instruct the Investigator on return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

Special Handling Instructions

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

6.1.3 Rituximab (Rituxan ®)

Mode of Action

Rituximab is a chimeric murine/human IgG1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas, binds with high affinity to CD20+ cells, performs human effector functions in vitro, and depletes B cells in vivo. The Fab domain of rituximab binds to CD20 on B-

lymphocytes and the Fc domain recruits immune effector functions to mediate B cell lysis in vitro. The biological effect is manifested by B-cell depletion.

Storage and Stability

Intact vials of rituximab are stored at refrigerated temperatures of 2 - 8°C Celsius (36 - 46° Fahrenheit). Protect vials from direct sunlight. Once diluted to a concentration of 1 - 4 mg/mL in polyvinylchloride or polyolefin IV bags containing normal saline or 5% dextrose, product is stable for up to 24 hours at 2 - 8° C, and at room temperature for an additional 12 hours after refrigeration (for a maximum period of 36 hours) if protected from light.

Preparation

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 - 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

Administration

Rituximab is administered intravenously. An in-line filter is not required. Rituximab infusion rates and monitoring should be per institutional guidelines.

Available at the bedside prior to rituximab administration will be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and resuscitation equipment for the emergency management of anaphylactoid reactions. Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Availability

Commercially available: Please see Package Insert for further information.

6.1.4 Preparation, Reconstitution, and Dispensing

Ixazomib and lenalidomide are anticancer drugs and as with other potentially toxic compounds caution should be exercised when handling ixazomib capsules.

For rituximab see Section 6.1.3.

6.1.4.1 Packaging and Labeling

Ixazomib: The study drug ixazomib capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

The capsules are individually packaged using cold-form foil-foil blisters that are in a child-resistant carton. There are 3 capsules in each wallet/carton.

Lenalidomide: Celgene Corporation will supply lenalidomide (Revlimid®) to study participants at no charge through Celgene's Revlimid Risk Evaluation and Mitigation Strategy™ (REMS) (formerly known as RevAssist® Program). Lenalidomide will be shipped directly to patients. Lenalidomide will be supplied as capsules for oral administration. Bottles will contain a sufficient number of capsules for one cycle of dosing.

Lenalidomide supplies are dispensed in individual bottles of capsules. Each bottle will identify the

contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: "Caution: New drug - Limited by Federal Law to Investigational Use." The study drug label must be clearly visible. Additional labels must not cover the Celgene label.

Lenalidomide Special Handling Instructions: Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

6.1.4.2 Storage, Handling, and Accountability

Ixazomib: Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because ixazomib is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact. The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (e.g., from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules.

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

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

6.1.4.3 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

6.2 Dose Escalation

Not applicable to Phase II.

Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Lost to follow-up
- Progressive disease
- Study terminated
- Other

Patients who are withdrawn from the Phase 1B portion of the study prior to completion of cycle 1, except if removed for DLT, will be replaced. Other patients taken off study prior to the first evaluation, unless for progressive disease, will be replaced.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

6.3 Definition of Dose-Limiting Toxicity

Dose limiting toxicity will be defined as any of the following AEs that occur any time from the initial dose of study treatment, with severity graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0:

A DLT is defined as any of the following treatment-related AE that occurs during the first cycle graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0:

- Grade 4 neutropenia lasting ≥ 7 days;
- Grade 3 or 4 neutropenia complicated by fever (a single temperature of $>38.3^{\circ}\text{C}$ (101°F) or a sustained temperature of $\geq 38^{\circ}\text{C}$ (100.4°F) for more than one hour) or infection;
- Grade 4 thrombocytopenia;
- Grade 3 thrombocytopenia complicated by hemorrhage;
- Grade 3 or 4 anemia.
- Grade ≥ 3 non-hematologic toxicity except for alopecia, fatigue or anorexia lasting < 7 days, or Grade 3 nausea and/or vomiting that persists for < 2 days with appropriate supportive care. Treatment delay of more than 2 weeks in the initiation of the subsequent cycle of treatment because of a lack of adequate recovery of treatment related hematological or non-hematologic toxicities.

CASE1414 RIXAR

Protocol Version 8, 4/11/2022

Treatment Assignment

Patients will be assigned to the next available dose level during the phase 1B portion of the study. Subsequent expansion cohorts will be enrolled at the MTD level.

6.4 General Concomitant Medications and Supportive Care Guidelines

6.4.1 Excluded Concomitant Medications and Procedures

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: if there were to be a drug-drug interaction with an inducer, ixazomib exposure would be decreased):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

The following medicinal products and procedures are prohibited during the study.

- Any antineoplastic treatment other than study drugs
- Radiation therapy
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day
- Excluded foods and dietary supplements include St. John's wort

6.4.2 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT₃ serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Millennium Clinical or Medical Representative. Their use should follow published guidelines and/or institutional practice. Erythropoietin will not be allowed in this study.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- All patients should receive antiviral therapy with acyclovir or valacyclovir (400 mg BID) while on treatment and for six months after the last dose of study drug..
- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.4.3 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal

function given reported NSAID-induced renal failure in patients with decreased renal function.

- **Pregnancy:** It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus; however, lenalidomide has known severe adverse effects. Therefore, female patients participating in this study must avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients must use effective methods of contraception through defined periods during and after study treatment as specified in the inclusion/exclusion criteria (Section 4.1.10).

6.4.4 Management of Clinical Events Associated with Ixazomib

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB.

Prophylaxis against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir or valacyclovir are to be used prophylactically while on treatment and for six months after the last dose of study drug..

Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Fluid deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

Prophylactic anti-diarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of anti-diarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. Rash due to lenalidomide and rituximab have also been reported. Rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash with ixazomib is most commonly reported within the first 3 cycles of therapy. The rash with either agent alone is often transient, self-limiting, and is typically Grade 1 to 2 in severity. As there are no data about rash with this combination, caution should be exercised; however, bortezomib + lenalidomide in combination for myeloma have not led to significant increase in rash.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (e.g., prednisone \leq 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib and lenalidomide should be modified per protocol and re-initiated at a

reduced level, per protocol.

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (e.g., using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). The rare risks of Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS Syndrome) and pemphigus vulgaris have been reported in ixazomib-containing oncology studies (or blinded studies containing ixazomib/placebo) when given in a multi-therapy regimen in combination with agents associated with skin reactions. These reactions should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Tables 7-1 A and 7-2). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. All efforts should be made to administer Growth Factor to avoid dose delays or reductions. Ixazomib and lenalidomide administration should be modified as per dose modification recommendations in the protocol when neutropenia occurs (see Tables 7-1 A, 7-1 B, and 7-2). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

Fluid Deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib, as well as with rituximab. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib; other cases have been reported with rituximab. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors. Treatment would be discontinued.

Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

6.5 Duration of Therapy

Therapy will be continued for 12 cycles or until unacceptable toxicity.

6.6 Duration of Follow Up

Patients will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first

Following treatment for 1 year, patients will be assessed per clinical standards, generally every 3 months (+/- 7 days) for 2 years.

The clinical course of each adverse event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause, up to 3 months.

Serious adverse events (SAE) that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.0 DOSING DELAYS / DOSE MODIFICATIONS

7.1 Dose-Modification Guidelines

All toxicity grading is NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Note: Patients at risk of developing tumor lysis syndrome (TLS) should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop tumor lysis syndrome.

7.1.1 Rituximab

If rituximab infusion reactions occur that are not manageable by standard institutional procedures, rituximab dose should be divided over 2 days, with 10-25% of the dose on day 1 and the rest on day 2. Also, prednisone at up to 60 mg (or equivalent other glucocorticoid) may be given at about 13, 7 and 1 hour before rituximab is started on day 1. If rituximab cannot be safely administered despite these maneuvers due to toxicity, rituximab will be discontinued, but the patient will remain on study treatment with the other two agents.

7.1.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

Treatment will use a cycle length of 28 days. For a new cycle of treatment to begin:

- ANC must be $\geq 1,000/\text{mm}^3$.
- Platelet count must be $\geq 75,000/\text{mm}^3$.
- All other non-hematologic toxicity (except alopecia) must have resolved to \leq Grade 2 or to the patient's baseline condition
- If ANC is less than 500, dosing should be delayed a week until resolution. Pegfilgrastim or filgrastim daily is encouraged
- If ANC is between 500 and 1000, pegfilgrastim 6 mg (preferred) or filgrastim 300-400 mg should be administered to maintain dose intensity.

If the patient fails to meet these criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet these criteria, delay therapy and continue to re-evaluate. The maximum delay before treatment should be discontinued will be 4 weeks or at the discretion of the Principal Investigator.

For dosing recommendations upon recovery, refer to Table 7-3 and Table 7-4.

Table 7-1 A IXAZOMIB Dose Reduction Steps:

Once ixazomib is reduced for any toxicity, the dose may not be re-escalated.

Dose Level	Dose (mg)	Schedule
Dose Level 3	4.0 mg	Days 1, 8, 15
Dose Level 2	3.0 mg	Days 1, 8, 15
Dose Level 1	2.0 mg	Days 1, 8, 15
Dose Level -1	1.0 mg	Days 1, 8, 15
Dose Level -2	1.0 mg	Day 1 only

	Table 7-1 B LENALIDOMIDE Dose Reduction Steps
Starting Dose If CrCl 30-60 start dose level -2	20 mg daily on Days 1-21 every 28 days
Dose Level – 1	15 mg daily on Days 1-21 every 28 days
Dose Level – 2	10 mg daily on Days 1-21 every 28 days
Dose Level – 3	5 mg daily on Days 1-21 every 28 days
Dose Level – 4	5 mg on alternate days on Days 1-21 every 28 days

Lenalidomide 5 mg daily on alternate days on days 1-21 every 28 days is the minimum lenalidomide dose. Discontinue lenalidomide in patients who cannot tolerate this dose.

Table 7-2 Dose Modifications for Intra-cycle Hematologic Toxicity	
NCI CTC Toxicity Grade	Dose Modification Instructions for Cycle 1 Only
Grade 3 neutropenia associated with fever (temperature $\geq 38.5^{\circ}$ C) or Grade 4 neutropenia	<ul style="list-style-type: none"> • Hold (interrupt) lenalidomide and ixazomib dosing. For cycle 1, day 8 and/or 15 rituximab should be held. • Follow CBC weekly. • Consider G-CSF to improve neutropenia. • When neutropenia has resolved to \leq grade 2 prior to day 21 of the current cycle, restart both lenalidomide and ixazomib either at the same dose level or 1 dose level lower at the discretion of the investigator. Continue at this dose level until day 21.
Thrombocytopenia \geq Grade 3 (platelet count $< 50,000/\text{mm}^3$)	<ul style="list-style-type: none"> • Hold (interrupt) lenalidomide and ixazomib dosing. • Follow CBC weekly. • If thrombocytopenia resolves to \leq grade 2 prior to Day 21 of the current cycle, restart lenalidomide and ixazomib at current 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 and ixazomib by 1 dose level at the start of the next cycle. Omitted doses are not made up. • Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count recovers to \leq grade 2.

Dosage Adjustments for Hematologic Toxicity

Table 7-3 Dose Modifications in Subsequent Treatment Cycles 2+ for Hematologic Toxicity

Criteria	Action
<p>ANC < 0.5 x 10⁹/L, platelet count < 75 x 10⁹/L, or other non-hematologic toxicities > Grade 1 (except for the AEs noted in table 7-4) or not to the patient's baseline condition</p>	<ul style="list-style-type: none"> • Hold ixazomib and lenalidomide until neutropenia and/or thrombocytopenia is ≤ grade 2. • Consider G-CSF to improve neutropenia. • Resume ixazomib and lenalidomide at same dose level or 1 dose level lower at the discretion of the investigator. • The maximum delay before treatment should be discontinued will be 4 weeks or at the discretion of the PI.
<p>ANC between 0.5 x 10⁹/L and 1.0 x 10⁹/L, platelet count < 75 x 10⁹/L, or other non-hematologic toxicities > Grade 1 or not to the patient's baseline condition</p>	<ul style="list-style-type: none"> • Recommend administration of G-CSF. • Resume lenalidomide and ixazomib at same dose level or 1 dose level lower at the discretion of the investigator.

Treatment modifications due to treatment-related non-hematologic AEs (Table 7-4).

Table 7-4: Dose Modifications for Non-Hematologic Toxicity	
NCI CTC Toxicity Grade	Dose Modification Instructions
Non-blistering rash: Grade 1-2 Grade 3 Grade 4	<ul style="list-style-type: none"> Grade 1-2, symptomatic intervention; no change in dosing. If Grade 3, hold (interrupt) lenalidomide and ixazomib. Follow weekly. If the toxicity resolves to \leq 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 rituximab, lenalidomide and ixazomib. Remove patient from study.
Desquamating (blistering) rash: Any Grade	<ul style="list-style-type: none"> Discontinue rituximab, lenalidomide and ixazomib. Remove patient from study.
Peripheral Neuropathy: Grade 1 Grade 1 with pain or Grade 2 Grade 2 with pain or Grade 3 Grade 4	<ul style="list-style-type: none"> If grade 1, without pain, no change in dosing If Grade 1 with pain or Grade 2, hold lenalidomide and ixazomib until resolves to \leq grade 1 without pain, restart with one dose level reduction in ixazomib If Grade 2 with pain or Grade 3, hold (interrupt) lenalidomide and ixazomib dose. Follow at least weekly. If the toxicity resolves to \leq grade 1 prior to Day 21 of the current cycle, restart lenalidomide and ixazomib 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 and ixazomib by 1 dose level at the start of the next cycle. Omitted doses are not made up. If Grade 4, discontinue lenalidomide and ixazomib. Remove patient from study.
Venous thrombosis/ embolism: \geq Grade 3	<ul style="list-style-type: none"> Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate. Restart lenalidomide at investigator's discretion (maintain dose level).
Hyperthyroidism or hypothyroidism	<ul style="list-style-type: none"> Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
Other non-hematologic toxicity : \geq Grade 3	<ul style="list-style-type: none"> Hold (interrupt) lenalidomide and ixazomib dosing. Follow at least weekly. If the toxicity resolves to \leq grade 2 prior to Day 21 of the current cycle, restart lenalidomide and ixazomib 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 or ixazomib, reduce the both lenalidomide and ixazomib dose by 1 dose level when restarting treatment.

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.2 and 8.3).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.1 Adverse Events and Potential Risks

8.1.1 Ixazomib

See Tables 1-1 and 1-2 for a comprehensive list of reported adverse events and potential risks.

8.1.2 Lenalidomide

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.

Patients with lymphoma have a higher risk of developing a second new cancer when compared to people without lymphoma. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with lenalidomide as induction therapy (treatment for several cycles to reduce number of cancer cells) and/or bone marrow transplant followed by prolonged lenalidomide administration compared to patients treated with induction therapy and/or bone marrow transplant then placebo. Whether this will occur in patients with lymphoma is not known.

8.1.2.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (CC-5013, NSC 703813)

The Comprehensive Adverse Events and Potential Risks List (CAEPR) provides a thorough and detailed list of reported and/or potential adverse events associated with the agent below. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR below, as well as the investigator's brochure, package insert or protocol can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS. Frequency is provided based on 4081 patients. Below is the CAEPR for lenalidomide (CC-5013).

Version 2.5, July 16, 2014¹

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n=4081]		
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
ENDOCRINE DISORDERS		
	Hypothyroidism	
GASTROINTESTINAL DISORDERS		
Constipation		
Diarrhea		
	Nausea	
		Pancreatitis
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
	Fever	
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis
		Immune system disorders – Other (graft vs. host disease) ²
INFECTIONS AND INFESTATIONS		
	Infection ³	
INVESTIGATIONS		
		Lipase increased
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Musculoskeletal and connective tissue disorders – Other (muscle cramp/muscle spasm)	
	Myalgia	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n=4081]		
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)		
		Leukemia secondary to oncology chemotherapy ⁴
		Myelodysplastic syndrome ⁴
		Neoplasms benign, malignant and unspecified (incl. cysts and polyps) – Other (tumor flare) ⁵
		Treatment related secondary malignancy ⁴
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Leukoencephalopathy
PSYCHIATRIC DISORDERS		
	Insomnia	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
	Skin and other subcutaneous tissue disorders – Other (pyroderma gangrenosum)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
VASCULAR DISORDERS		
	Thromboembolic event ⁶	

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol, and the agent should be included in the email.

²Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

³Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

⁴There has been an increased frequency of secondary malignancies (including AML/MDS) in multiple myeloma patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant.

⁵Serious tumor flare reactions have been observed in patients with Chronic Lymphocytic Leukemia (CLL) and lymphoma.

⁶Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

⁷Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

⁸Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

⁹Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere[®]), prednisone, and zoledronic acid (Zometa[®]).

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a development monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Also reported on lenalidomide (CC-5013) trials but with the relationship to lenalidomide (CC-5013) still undetermined due to low frequency (i.e., <3%):

BLOOD AND LYMPHATIC SYSTEM DISORDERS – Blood and lymphatic system disorders – Other (eosinophilia); Blood and lymphatic system disorders – Other (monocytosis); Blood and lymphatic system disorders – Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Spleen disorder

CARDIAC DISORDERS – Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders – Other (cardiovascular edema); Cardiac disorders – Other (ECG abnormalities); Chest pain – cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS – Tinnitus

ENDOCRINE DISORDERS – Cushingoid; Hyperthyroidism

EYE DISORDERS – Blurred vision; Conjunctivitis; Dry eye; Flashing lights; Retinopathy

GASTROINTESTINAL DISORDERS – Abdominal distension; Abdominal pain; Anal mucositis; Ascites; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders – Other (Crohn’s Disease aggravated); Gastrointestinal disorders – Other (diverticulitis); Gastrointestinal disorders – Other (pale feces); Gastrointestinal hemorrhage⁷; Gastrointestinal obstruction⁸; Ileus; Mucositis oral; Rectal mucositis; Small intestinal mucositis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – General disorders and administration site conditions – Other (edema NOS); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain

HEPATOBIILIARY DISORDERS – Cholecystitis; Hepatic failure

IMMUNE SYSTEM DISORDERS – Allergic reaction; Immune system disorders – Other (angioedema)

INFECTIONS AND INFESTATIONS – Infections and infestations – Other (Opportunistic infection associated with \geq grade 2 lymphopenia)

INJURY, POISONING, AND PROCEDURAL COMPLICATIONS – Bruising; Fall; Fracture; Hip fracture; Vascular access complication

INVESTIGATIONS – Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations – Other (hemochromatosis)

METABOLISM AND NUTRITION DISORDERS – Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – Arthritis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders – Other (rhabdomyolysis); Neck pain; Osteonecrosis of jaw⁹; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCL. CYSTS AND POLYPS) – Tumor pain

NERVOUS SYSTEM DISORDERS – Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Edema cerebra; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Myelitis; Nervous system disorders – Other (hyporeflexia); Nervous system disorders – Other (spinal cord compression); Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor

PSYCHIATRIC DISORDERS – Agitation; Anxiety; Confusion; Depression; Psychosis

RENAL AND URINARY DISORDERS – Renal and urinary disorders – Other (chromaturia); Urinary frequency; Urinary incontinence; Urinary tract pain.

REPRODUCTIVE SYSTEM AND BREAST DISORDERS – Reproductive system and breast disorders – Other (hypogonadism); Vaginal hemorrhage

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS – Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS – Alopecia; Dry skin; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders – Other (Sweet’s Syndrome); Urticaria

VASCULAR DISORDERS – Hot flashes; Hypertension; Hypotension; Phlebitis; Vascular disorders – Other (hemorrhage NOS)

NOTE: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Please refer to the package insert for the comprehensive list of adverse events.

8.1.3 Rituximab

8.1.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Rituximab (NSC 687451)

The Comprehensive Adverse Events and Potential Risks List (CAEPR) provides a thorough and detailed list of reported and/or potential adverse events associated with the agent below. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR below, as well as the investigator’s brochure, package insert or protocol can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS. Frequency is provided based on 986 patients. Below is the CAEPR for Rituximab (NSC 687451).

Version 2.1, March 19, 2010¹

Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n=986]		
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Blood and lymphatic system disorders – Other (Hyperviscosity: Waldenstrom’s)	

	Febrile neutropenia	
Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n=986]		
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)
CARDIAC DISORDERS		
	Myocardial infarction	
	Sinus tachycardia	
	Supraventricular tachycardia	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Diarrhea	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Chills		
	Edema limbs	
	Fatigue	
Fever		
Infusion related reaction		
	Pain	
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis
	Serum sickness	
INFECTIONS AND INFESTATIONS		
	Infection ²	
	Infections and infestations – Other (Activation of Hepatitis B, C, CMV, parvovirus B19, JC virus, varicella zoster, herpes simples, West Nile virus)	
	Infections and infestations – Other (Infection in HIV Positive Patients)	
INVESTIGATIONS		
Lymphocyte count decreased		
	Neutrophil count decreased	
	Platelet count decreased	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Hyperglycemia	
	Hypocalcemia	
	Hypokalemia	
		Tumor lysis syndrome

Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n=986]		
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Myalgia	
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)		
	Tumor pain	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
	Lethargy	
		Nervous system disorders – Other (progressive multifocal leukoencephalopathy)
	Seizure	
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS		
		Adult respiratory distress syndrome
	Allergic rhinitis	
	Bronchospasm	
	Cough	
	Dyspnea	
	Hypoxia	
	Pneumonitis	
	Sore throat	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
	Skin and other subcutaneous tissue disorders – Other (angioedema)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
	Urticaria	
VASCULAR DISORDERS		
	Flushing	
	Hypertension	
	Hypotension	

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol, and the agent should be included in the email.

²Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

³Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

⁴Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

Also reported on rituximab trials but with the relationship to rituximab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS – Bone marrow hypocellular; Hemolysis

CARDIAC DISORDERS – Atrial fibrillation; Atrial flutter; Cardiac disorders – Other (cyanosis); Left ventricular systolic dysfunction; Sinus bradycardia; Ventricular fibrillation

EYE DISORDERS – Conjunctivitis; Eye disorders – Other (ocular edema); Uveitis; Watering eyes

GASTROINTESTINAL DISORDERS – Constipation; Dyspepsia; Dysphagia; Gastrointestinal obstruction³; Gastrointestinal perforation⁴; Mucositis oral

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – Flu like symptoms; Non-cardiac chest pain

INFECTIONS AND INFESTATIONS – Infections and infestations – Other (Opportunistic infection associated with \geq Grade 2 Lymphopenia)

INJURY, POISONING, AND PROCEDURAL COMPLICATIONS – Fracture

INVESTIGATIONS – Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Investigations – Other (hyperphosphatemia); Investigations – Other (LDH increased); Weight loss

METABOLISM AND NUTRITION DISORDERS – Anorexia; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hyponatremia; Hypernatremia; Hyperuricemia; Hypoglycemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – Arthritis

NERVOUS SYSTEM DISORDERS – Nervous system disorders – Other (Cranial Neuropathy NOS); Peripheral motor neuropathy; Peripheral sensory neuropathy; Pyramidal tract syndrome; Reversible posterior leukoencephalopathy syndrome; Syncope

PSYCHIATRIC DISORDERS – Agitation; Anxiety; Depression; Insomnia

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS – Epistaxis; Pharyngolaryngeal pain; Pleural effusion; Pulmonary edema; Respiratory, thoracic, and mediastinal disorders – Other (bronchiolitis obliterans)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS – Alopecia; Skin and subcutaneous tissue disorders – Other (paraneoplastic pemphigus)

VASCULAR DISORDERS – Phlebitis; Thromboembolic event; Vasculitis

NOTE: Rituximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Please refer to the package insert for the comprehensive list of adverse events.

8.2 Definitions

8.2.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

8.2.2 Significance of an Adverse Event

External adverse events are adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Institutional Review Board has jurisdiction. **Internal adverse events** are adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicentre or single-center research projects. The significance of AEs is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe, or life threatening). Based on the National Cancer Institute Guidelines for Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

- **Grades 1** are mild adverse events (e.g., minor event requiring no specific medical intervention, asymptomatic laboratory findings only, marginal clinical relevance).
- **Grades 2** are moderate adverse events (e.g., minimal intervention, local intervention, non-invasive intervention, transfusion, elective interventional radiological procedure, therapeutic endoscopy or operation).
- **Grades 3** are severe and undesirable adverse events (e.g, significant symptoms requiring

hospitalization or invasive intervention, transfusion, elective interventional radiological procedure, therapeutic endoscopy or operation).

- **Grades 4** are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, haemorrhage, sepsis, life-threatening physiologic consequences, need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).
- **Grades 5** are fatal adverse events resulting in death.

8.2.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm³ to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.2.4 Expectedness

Adverse Events can be Expected or Unexpected.

- An **expected** adverse event is an event previously known or anticipated to result from

participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

- An **unexpected** adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

8.2.5 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

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

8.3 Procedures for Reporting All Adverse Events

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) and to Celgene Drug Safety from the first dose of study drug through 30 days after administration of the last dose of study drug. Any SAE that occurs at any time after completion of study treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee) and to Celgene Drug Safety. In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee) and to Celgene Drug Safety.

Adverse Event Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

Since this is an investigator-initiated study, the principal investigator, Dr. Brian Hill, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported in English to Millennium Pharmacovigilance (or designee):

- **Fatal and Life Threatening SAEs** within 24 hours of the sponsor-investigator's observation or awareness of the event
- **All other serious (non-fatal/non-life threatening) events** within 4 calendar days of the sponsor-investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance and to Celgene Drug Safety.

The sponsor-investigator must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at <http://ctep.cancer.gov/reporting/ctc.html>.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.
- **Attribution:** Attribution is the relationship between an adverse event or serious adverse event and the study drug. For this study, relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Follow-up information on the SAE may be requested by the sponsors of the study.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at <http://ctep.cancer.gov/reporting/ctc.html>.

Sponsor-investigator must also provide Millennium Pharmacovigilance and Celgene Drug Safety with a copy of all communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information

MILLENNIUM

Fax Number: 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

CELGENE

Celgene Corporation
Global Drug Safety and Risk Management

Fax: (908) 673-9115

E-mail: drugsafety@celgene.com

Suggested Reporting Form:

- SAE Report Form (provided by Millennium)
- US FDA MedWatch 3500A:
<http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>
- Any other form deemed appropriate by the sponsor-investigator

Institutional Review Board Reporting Requirements:

Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.3) and to Celgene Drug Safety. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.3) and to Celgene Drug Safety. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (provided by Millennium or Celgene)

8.5 Data Safety Toxicity Committee

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that ALL serious adverse events are reported to the Case Comprehensive Cancer Center's Data Safety Toxicity Committee. This submission is simultaneous with their submission to the Sponsor or other Regulatory body.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.6 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0.

Agents are listed in alphabetical order.

9.1 Ixazomib

Chemical Name: 2,2'-{2-[(1R)-1-1{[(2,5-dichlorobenzoyl)amino]acetyl}amino]-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diyl}diacetic acid

Other Names: MLN9708

Classification: proteasome inhibitor (as the boronic acid)

Molecular Formula: C₂₀H₂₃BCl₂N₂O₉

Mode of Action: proteasome inhibitor

Metabolism: hydrolysis, hydroxylation, dehydrogenation and N-dealkylation

Product Description: capsule

Solution Preparation: NA

Storage Requirements: The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle.

Route of Administration: oral

Drug Procurement: Ixazomib will be supplied for this study by Millennium, a Takeda corporation.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug

shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9.2 Lenalidomide

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

Other Names: NA

Classification: Immunomodulatory agent

Molecular Formula: C₁₃H₁₃N₃O₃

Mode of Action: Immunomodulatory agent

Metabolism: rapidly absorbed following oral administration; approximately two-thirds is eliminated unchanged through urinary excretion

Product Description: Capsules

Solution Preparation: NA

Storage Requirements: Room temperature

Stability: Not defined

Route of Administration: Oral

Drug Procurement: Lenalidomide will be supplied for this study by Celgene.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9.3 Rituximab

Other Names: Rituxan ®; MabThera ®, IDEC-C2B8

Classification: Monoclonal antibody

Mode of Action: Binding to CD20

Product Description: chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma)

Solution Preparation: diluted to a concentration of 1 to 4 mg/mL in polyvinylchloride or polyolefin IV bags containing normal saline or 5% dextrose

Stability: Intact vials of rituximab are stored refrigerated at 2 – 8°C (36 - 46°F). Protect vials from direct sunlight. Once diluted as above, stable for up to 24 hr. at 2 – 8°C, and at room temperature for an additional 12 hrs. after refrigeration (for a maximum period of 36 hrs.) if protected from light.

Route of Administration: Intravenous slow infusion

Drug Procurement: Rituximab must be obtained from commercial sources.

Commercially available: Preservative-free injection 10mg/mL, in 10 and 50 mL single-unit vials. Please see Package Insert for further information.

The cost of this agent will be the subject's responsibility, often covered by medical insurance.

10.0 CORRELATIVE / SPECIAL STUDIES

10.1 Tissue Microarray

10.1.1 Background and Rationale

Predictive biomarkers for response and resistance to biologically targeted agents should improve our ability to personalize therapy by selecting agents most likely to be effective based on the biomarker. No such validated biomarkers exist for indolent non-Hodgkin's Lymphoma, iNHL, treated with the agents in this study. A set of tissue samples from patients enrolled in this study will be stored on glass slides (tissue microarray or TMA) for future processing for appropriate studies focused on biomarker development simultaneously for DNA, RNA, or protein targets. TMA provides an ideal method of storing fixed tissue samples so that they can be processed at a future time when more information on prognostic and predictive factors becomes available.

10.1.2 Collection of Specimens

Formalin-fixed, paraffin embedded (FFPE) diagnostic tissue biopsies from all patients for whom these are available will have a core removed from the FFPE tissue block and placed into the TMA, by standard procedures in the Tomsich Pathology Laboratory. The site should prepare the patient block, provide the de-identified number for the study and ship as soon as readily available. Shipment of these samples at ambient temperature is satisfactory.

The pathology procedure is to perform an H&E stain to order to identify the tumor tissue in the block and have it marked by the pathologist. Tumor cores of 1 mm size will be taken from the marked area(s) by the research tech. For the TMA and duplicate TMA, 4 cores would be required because each TMA would also include a duplicate core. Additional 2-4 cores, depending on the tissue size, would also be collected and saved in a labeled Eppendorf tube for future molecular

studies. The TMA will be gradually built and the core locations mapped in a TMA schematic as the tissue specimens arrive in the laboratory.

Any remaining block can be returned to the site. Please contact Dr. Ondrejka or the research laboratory (Lisa Durkin) with any questions regarding the collection of the specimen:

Dr. Sarah Ondrejka, M.D. Ph. 216-445-1662 Fax 216-445-7253 Email: ondrejs@ccf.org
Lisa Durkin Ph. 216-445-9452 Email: durkinl@ccf.org

The site is instructed to ship to the address and label as shown below. Include the name of the study, CASE 1414 on the shipping label. About 24 hours prior to shipment, provide the shipping information to Lisa Durkin, durkinl@ccf.org, and Dr. Ondrejka's medical secretary, Linda Rosa, lrosa@ccf.org.

Cleveland Clinic 2119 East 93rd. Street Desk L15 Cleveland, OH 44106 Attn: Durkin/Rosa/Ondrejka

10.1.3 Handling of Specimens

TMA will be stored in the Tomsich Pathology Laboratory in a secure ambient temperature monitored location. All patient tissue must be de-identified prior to placing in the TMA.

10.1.4 Correlative Methods

Precise plans for analysis of TMA by immunohistochemistry and/or macromolecule isolation will depend on future knowledge. This correlative is simply to store samples in usable form at this time.

10.2 Flow Cytometry on Peripheral Blood

10.2.1 Background and Rationale

Flow cytometry is commonly used to identify and quantitate normal and abnormal circulating lymphocytes. It is sensitive and specific for detecting small numbers of circulating lymphoma cells, as well as providing insight into the host immune response of normal lymphocyte subsets.

Baseline evaluation of blood lymphocytes subsets may be a marker of nodal immune response, and the molecular signature of tumor infiltrating cells in lymph node biopsies of patients with follicular lymphoma does provide prognostic information while nodal T-lymphocyte subset evaluation predicts prognosis independently of the Follicular Lymphoma International Prognostic Index (FLIPI). Specifically, CD4+ T-cells and interfollicular CD68+ cells (macrophages) are associated with a poor outcome, while FOXP3+ cells, CD8+ cells, and programmed death 1 (PD-

1) + cells are associated with a good prognosis. We have shown that absolute NK cells at baseline are a prognostic factor in follicular lymphoma. In this study, we will use the immunodeficiency panel as standardly performed in the Tomsich laboratory to assess lymphocyte subsets at baseline and end of treatment. This measures CD3, CD4 and CD8 T cells, NK cells and CD19+ B cells.

Serial quantitation of remaining circulating lymphoma cells may be an indicator of systemic response and outcome. Minimal residual disease (MRD) refers to submicroscopic disease burden remaining in a patient after therapy for a neoplasm. Attaining a state of undetectable MRD has been shown to correlate with longer progression free survival and decreased relapse risk in some diseases. Whether this is merely a marker for those with more responsive disease or whether more therapy aimed at eradicating MRD is beneficial is not always clear.

Some patients will achieve a state of no MRD after therapy; however, as time from end of therapy lengthens MRD may become detectable. Theoretically it is possible to react and treat a patient much earlier before the disease burden increases and the patient becomes more difficult to treat.

There are several methods of monitoring MRD. Molecular techniques using polymerase chain reaction can be applied if there is a stable molecular abnormality in the disease, like t(14;18) in follicular lymphoma. In the absence of a recurring translocation, the patient specific clonal V-D-J immunoglobulin gene rearrangement can be assessed, though this is labor and cost intensive. Also it is not clear that the detection of the molecular abnormality with PCR correlates clinically with outcomes. Newer NexGen sequencing methods can also be used to quantitate residual clonal cells (Adaptiv LymphoSight® assay). Another method of evaluating for MRD is multicolor flow cytometry to detect clonal B cells using cell surface antigens unique to the malignant clone. The ability to evaluate for multiple antigens on the cell allows for accurate identification of a malignant cell in a population of mainly normal cells. Standard flow assays can be adapted for this and validated, but are not routinely done in pathology labs, including at CCF. Standard lymphocyte analysis by flow measures the percentage of B cells, from which an absolute number of B cells can be calculated.

In this study we will evaluate residual B cells pre- and post-treatment as potential biomarkers. We will extract and store DNA from these samples for possible future NexGen sequencing assessment of MRD.

10.2.2 Collection of Specimens

Blood samples will be drawn into anti-coagulated tubes (see Appendix VI) as per standard procedures. All such samples will be at the time of clinically indicated blood sampling so no extra venipunctures are needed.

10.2.3 Handling of Specimens

Blood samples will be sent to the flow cytometry lab of the Tomsich Pathology Laboratory (see Appendix VI) for processing and fluorescent staining and flow cytometric analysis by standard procedures.

10.2.4 Correlative Methods

Patients whose blood has no detectable B cells (MRD negative status) will be compared with those in whom B cells remain detectable in terms of PFS and OS to determine if this can be an early marker of outcome for patients with iNHL treated with the treatment regimen in this protocol.

Baseline T cell subset levels will be correlated with outcome as before.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters and Schedule of Events

Parameter	Pre-study ¹	Day 1 of Every Cycle (+/- 3 days)	Cycle 1-3 Day 8	Cycle 1-3 Day 15	Cycle 1-3 Day 22	Restaging ¹² and Follow-up ¹⁴
Assignment of FLIPI scores ²	X					
Notation of GELF criteria ²	X					
History and Physical examination	X	X				X
Performance Status	X	X				X
Tumor Measurements by Physical Exam (if applicable)	X	X				X
CBC and Differential	X ³	X	X ⁴	X ⁴	X ⁴	X
Serum Chemistries (electrolytes, AST, ALT, total bilirubin, direct bilirubin ⁵ , creatinine, glucose, alkaline phos, and calcium)	X ⁷	X	X	X		X
LDH	X	X	X	X		X
Beta-2-microglobulin	X					
HIV testing	X					
Uric acid	X	X Cycles 3-6 only if > ULN prior cycle	X	X		
Monoclonal protein determination ¹³	X	X ¹³				X ¹³
Bone marrow aspirate biopsy If not known to be involved	X (up to 90 days)					After cycle 12 if in CR ⁶
Pregnancy test (for women of child-bearing potential) ⁷	X ⁷					
Hepatitis B surface antigen and core antibody testing ⁸	X ⁸					

T4, TSH	X	Day 1 Cycle 7 only				X ¹⁵
Immunodeficiency Panel ¹⁶	X	Day 1 cycle 7 only				After cycle 12
Creatinine clearance	X	calculated				
CT Chest, Abdomen, and Pelvis; Neck (if involved)	X ⁹					After cycles 3 and 6 ¹⁰
PET/CT Scan	X ⁹					After cycle 12 ¹¹
Baseline Symptoms/AE Evaluation ¹⁷	X	X	X	X		X

On rituximab treatment days 8 and 15 of cycle 1, patients will be assessed by a nurse for toxicity, and CBC, serum chemistries, LDH and uric acid will be performed. Pre-study parameters can be up to 30 days prior to start of treatment, except bone marrow aspirate and biopsy can be up to 90 days, if not known to be positive for lymphoma

1. Cycles are every 28 days. Patients may be evaluated in the office more frequently at the physician's discretion.
2. Yes/No should be entered for each criterion of GELF and FLIPI, as well as absolute calculation of FLIPI-1 and FLIPI-2. (See Appendix V).
3. At baseline: please record the absolute lymphocyte count.
4. Cycles 2 and 3 for dose escalation cohorts *only* : CBC and differential is required on Days 8, 15 and 22. Other labs (chem, LDH, UA) should be done days 8, 15 of cycle 1 only, not in cycles 2-3
5. Direct bilirubin is required only if total bilirubin is elevated.
6. Repeat bone marrow biopsy core and aspirate only if positive at baseline and otherwise meets criteria for CR.
7. Within 2 weeks of start of induction treatment. For definition of woman of childbearing potential (WOCBP) see lenalidomide (Revlimid®)REMS program. Before starting lenalidomide: WOCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative. Female subjects will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. During study participation and for 28 days following discontinuation from the study: WOCBP with regular cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study

discontinuation, and at days 14 and 28 following discontinuation from the study. In addition to the required pregnancy testing, the Investigator must confirm with WOCBP that she is continuing to use two reliable methods of birth control at each visit. Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood. Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation. If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, study drug must be immediately discontinued.

8. Patients must be tested for hepatitis B surface antigen within 6 weeks of randomization. Liver function tests and quantitative PCR assay for HBV levels in serum to be performed monthly until 6 months following last rituximab dose for HBcAb positive patients. Further, consideration should be given to treat such patients with anti-viral prophylaxis (e.g., lamivudine 100mg po QD) prior to, during, and for 6 months after completion of the last dose of rituximab. Patients who are positive for HBsAg (surface antigen) are not allowed to enroll on study.
9. If PET/CT scan has been done, do not need separate diagnostic quality CT unless the only measurable disease is in the mesentery and not measurable without oral contrast, in which case CT abdomen/pelvis with oral/IV contrast should be done prior to treatment.
10. CT scans (chest/abdomen/pelvis; neck if involved) should be done to evaluate response between days 22 – 29 after cycle 3 and after cycle 6. If a PET/CT is done, then CT does not need to be done, unless the only initially measurable disease was in the mesentery and not measurable without oral contrast, in which case CT abdomen/pelvis with oral/IV contrast should be done.
11. Once patient enters PET negative complete remission, then only CT's (chest/abdomen/pelvis, include neck if previously involved) need to be done in follow-up
12. Restaging will be 8 - 12 weeks after day 1 cycle 12 (or after day 1 of last cycle of treatment if stopped early). Repeat bone marrow only if it was involved prior to treatment and patient otherwise meets criteria for CR.
13. Monoclonal protein (M-protein) blood determination includes: serum immunofixation, quantitative IgG, IgA, IgM,. If M-protein is detected, the abnormal value will be checked every other cycle beginning with cycle 2, and during follow-up at months 6, 12, 24, 36, 48 and 60 (each \pm 30 days) or until the patient comes off the study
14. FOLLOW-UP: per clinical standards, generally every 3 months for 2 years or as clinically indicated, with: History and Physical examination, Performance Status, Tumor Measurements by Physical Exam (if applicable), CBC and Differential, Serum Chemistries and LDH. CT [Chest, Abdomen, and Pelvis, Neck if previously involved] at months 6, 12, and 24 (each \pm 30 days). Follow-up visit and CT schedule should count from end of treatment restaging scan. Once the patient has disease

progression or otherwise meets criteria for treatment failure, patient can be followed for survival by telephone or other contact without in-person visit or protocol-mandated CT scans.

15. Thyroid functions at baseline, pre- cycle 7, at re-staging and once 6 months later
16. Immunodeficiency Panel: One anti-coagulated (prefer purple-top) tube sent to Tomsich Flow laboratory. See Appendix VI for details. Draw at baseline, before cycle 7 and again at
17. Baseline Symptoms and AE assessments should be done on days 8 and 15 for Cycle 1 only. For Cycles 2 and 3, assessments will be performed on Day 1.

12.0 MEASUREMENT OF EFFECT

Non-Hodgkin Lymphoma Response Criteria

NOTE: These criteria are based on the Revised Response Criteria for Malignant Lymphoma, (Cheson et al., Journal of Clinical Oncology, 2007, 25:579-586).

The criteria use the following categories of response as described by the working group: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks.

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant.
- If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features: a) they should be clearly measurable in at least two perpendicular measurements; b) they should be from as disparate regions of the body as possible; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required.
- The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1 cm, 2.2 cm, etc.)
- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.

12.1 Complete Response (CR)

Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

12.1.1 In patients with a typically FDG-avid lymphoma with no pre-treatment PET scan, or for lymphomas for which the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.

12.1.2 For variably FDG-avid lymphomas without a pretreatment PET scan, or if a pretreatment PET scan was negative: all lymph nodes and extranodal masses must have regressed on CT to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and >1.0 cm in their short axis prior to treatment must have decreased to < 1 cm in their short axis after treatment.

12.1.3 The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination, and nodules related to lymphoma should disappear. However, no normal size can

be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.

- 12.1.4** If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

NOTE: Complete Remission/unconfirmed (CRu): Using the above definition for CR and that below for PR eliminates the category of CRu.

12.2 Partial Response (PR)

The designation of PR requires all of the following:

- 12.2.1** A $\geq 50\%$ decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; (b) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- 12.2.2** No increase in the size of other nodes, liver or spleen.
- 12.2.3** Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified, e.g. large-cell lymphoma or small cleaved cell lymphoma.
- 12.2.4** No new sites of disease.
- 12.2.5** For a typically FDG-avid lymphoma with no pretreatment PET scan or one that was PET-positive prior to therapy, the post-treatment PET should be positive at any previously involved sites.
- 12.2.6** For variably FDG-avid lymphomas/FDG-avidity unknown, without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT scan criteria should be used.
- 12.2.7** Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
- 12.2.8** When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

12.3 Stable Disease (SD)

12.3.1 Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease (see below).

12.3.2 Typically FDG-avid lymphomas: The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

12.3.3 For variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pretreatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

12.4 Progression (PD) and Relapse

For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes $< 1 \times 1$ cm will not be considered as abnormal for relapse or progressive disease.

Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single PET scan without histologic confirmation.

12.4.1 Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

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

12.4.2 At least a 50% increase from nadir in the SPD of any previously involved nodes or extranodal masses, or in a single involved node or extranodal mass, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node or extranodal mass with a diameter of the short axis of less than 1.0 cm must increase by $> 50\%$ and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.

12.4.3 At least a 50% increase in the longest diameter of any single previously identified node or extranodal mass more than 1 cm in its short axis.

12.4.4 Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

12.4.5 Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by

imaging studies or physical examination, it is found to be histologically negative.

12.5 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).

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

12.6 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.7 Time to Treatment Failure

Time to treatment failure (event-free survival) is defined as the time from study entry to first event of disease progression, discontinuation of treatment for any reason, initiation of new treatment, or death.

12.8 Overall Survival

Overall survival is defined as the date of study entry to the date of death.

13.0 RECORDS TO BE KEPT / REGULATORY CONSIDERATIONS

ADMINISTRATIVE REQUIREMENTS

Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
Phone: 1-877-N1-POINT (1-844-617-6468)
E-mail: GlobalOncologyMedInfo@takeda.com
FAX: 1-800-881-6092
Hours: Mon-Fri, 9 a.m. – 7 p.m. ET(US)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 8.3). Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The Overture and OnCore™ Databases will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. Overture and OnCore™ are Clinical Trials Management Systems housed on secure servers maintained at Case Western Reserve University. Access to data through Overture and OnCore™ is restricted by user accounts and assigned roles. Once logged into the Overture or OnCore™ system with a user ID and password, Overture and OnCore™ define roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

Overture and OnCore™ are designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the Overture database. A calendar of events and required forms are available in Overture and OnCore™.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed Consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Accessing Electronic Medical Records for University Hospitals Health System: NA

13.2.4 Retention of Records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.5 Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics

CASE1414 RIXAR

Protocol Version 8, 4/11/2022

Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

14.0 STATISTICAL CONSIDERATIONS

14.1 Populations for Analysis

Patients in Phase 1B considered evaluable for toxicity to determine MTD will include those that complete the first 4 week cycle or those removed for DLT in cycle 1.

Patients evaluable for response will be those who complete 3 cycles of therapy and at least one post-baseline response assessment or those who are taken off study for progressive disease.

14.2 Methods

Phase 1 B consisted of up to three dose levels (See Section 6). 12 patients total were enrolled and the MTD was determined to be at DL3.

Phase 2 will follow as one expansion cohort treated at the MTD which was determined to be DL3. It will comprise of 18 patients evaluable for response, with follicular lymphoma. A maximum of 24 patients will be available for this portion of the analysis, 18 from expansion cohorts, and 6 who were treated at the RP2D.

14.3 Efficacy Analysis

Response criteria are outlined in Section 12.

14.4 Early Stopping Toxicity

If 2 of the first 6 patients treated at the RP2D experience an SAE, or if subsequently the fraction of patients experiencing SAE exceeds 1/3, accrual to the trial will be halted and trial continuation reassessed with the Case Comprehensive Cancer Center's Data Safety Toxicity Committee in concert with the Millennium Pharmacovigilance and Celgene Drug Safety Departments.

REFERENCES

1. Gupta, N., et al., *Clinical Pharmacokinetics of Intravenous and Oral MLN9708, An Investigational Proteasome Inhibitor: An Analysis of Data From Four Phase 1 Monotherapy Studies*. in 52nd ASH Annual Meeting and Exposition, 2010. **116**(21): p. abstr 1813.
2. Gupta, N., M. Saleh, and K. Venkatakrishnan. *Flat-Dosing Versus BSA-Based Dosing for MLN9708, An Investigational Proteasome Inhibitor: Population Pharmacokinetic (PK) Analysis of Pooled Data From 4 Phase-1 Studies* in 53rd ASH Annual Meeting and Exposition. 2011. San Diego, CA; p. abstr 1433
3. Chow, L.Q., et al. *MLN9708, an investigational proteasome inhibitor, in patients with solid tumors; Updated phase 1 results in Head and Neck Symposium*. 2012. Phoenix, AZ
4. Assouline, S., et al. *Once-weekly MLN9708, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma: results of a phase 1 dose-escalation study in 17th EHA Annual Congress*. 2012. Amsterdam, the Netherlands.
5. Lonial, S., et al. *Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM)* in ASCO Annual Meeting. 2012. Chicago, Illinois.
6. Kumar S, et al. *Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose- Escalation Study* In 53rd ASH Annual Meeting and Exposition; 2011 10-13 Dec; San Diego, CA; p. abstr 816..
7. Merlini, G., et al. *MLN9708, a Novel, Investigational Oral Proteasome Inhibitor, in Patients with Relapsed or Refractory Light-Chain Amyloidosis (AL): Results of a Phase 1 Study* in 54th ASH Annual Meeting and Exposition. 2012. Atlanta, Georgia.
8. Kumar, S. et al. *A Phase 1/2 Study of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM)* in 54th ASH Annual Meeting and Exposition. 2012. Atlanta, Georgia.
9. Richardson, P.G., et al. *MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in previously untreated multiple myeloma patients (pts): Evaluation of weekly and twice-weekly dosing* in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands.
10. San Miguel, J., et al. *Oral MLN9708, an an investigational proteasome inhibitor, in combination with melphalan and prednisone in patients with previously untreated multiple myeloma: a phase 1 study* in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands.
11. Richardson P, Baz R, Wang L, Jakubowiak A, Berg D, Liu G, et al. *Investigational Agent MLN9708, An Oral Proteasome Inhibitor, in Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (MM): Results From the Expansion Cohorts of a Phase 1 Dose-Escalation Study* In: 53rd ASH Annual Meeting and Exposition; 2011 10-13 Dec; San Diego, CA; p. abstr 301.
12. Lonial S, Baz R, Wang M, Talpaz M, Liu G, Berg D, et al. *Phase I study of twice weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM)*. J Clin Oncol (ASCO Meeting Abstracts) 2012;30(15 suppl):abstr 8017.
13. Kumar S, Bensinger W, Reeder C, Zimmerman T, Berenson J, Berg D, et al. *Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with*

- Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose-Escalation Study* In: *53rd ASH Annual Meeting and Exposition*; 2011 10-13 Dec; San Diego, CA; p. abstr 816.
14. Kumar S, Bensinger W, Reeder C, Zimmerman T, Berenson J, Liu G, et al. *Weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed/refractory multiple myeloma (MM): A phase I study*. *Journal of Clinical Oncology 2012 ASCO Annual Meeting Proceedings 2012:Abstract 8034*.
 15. Kumar S, Niesvizky R, Berdeja J, Bensinger W, Zimmerman T, Berenson J, et al. *Safety and Pharmacokinetics of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, Alone and in Combination*. *Clinical Lymphoma Myeloma and Leukemia 2013;13(Supplement 1):S154; abstr P-230*
 16. *Common Terminology Criteria for Adverse Events (CTCAE)*. 2010.

APPENDICES:

Appendix I Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
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)
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.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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

Appendix II Cockcroft-Gault Equation

Creatinine Clearance = CrCl

For males:

$$\text{CrCl} = \frac{(140 - \text{age [years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

For females:

$$\text{CrCl} = \frac{0.85 (140 - \text{age [years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Appendix III List of Potential Medication Interactions Affected by CYP3A4 Systems of Enzymes

Potential Medication Interactions Affected by CYP3A4 Systems of Enzymes

List of Known CYP3A4 Inhibitors		
Indinavir	Erythromycin	Diethyldithiocarbamate
Nelfinavir	Fluconazole	Fluvoxamine
Ritonavir	Grapefruit Juice	Gestodene
Clarithromycin	Verapamil	Imatinib
Itraconazole	Diltiazem	Mibefradil
Ketaconazole	Cimetidine	Mifepristone
Nefazodone	Amiodarone	Norfloxacin
Saquinavir	Chloramphenicol	Norfluoxetine
Suboxone	Boceprevir	Starfruit
Telithromycin	Ciprofloxacin	Telaprevir
Aprepitant	Delaviridine	Voriconazole

List of Known CYP3A4 Inducers	
Efavirenz	Phenobarbital
Nevirapine	Phenytoin
Barbiturates	Pioglitazone
Carbamazepine	Rifabutin
Glucocorticoids	Rifampin
Modafinil	St. John's Wort
Oxcarbazepine	Troglitazone

Appendix IV Patient Pill Diary

Subject Number: _____

Subject Initials: _____

Cycle # _____

Case1414 Daily Pill Diary

Dear Subject / Legal Guardian,

Thank you for participating in this clinical research study. As part of this research study, we are asking that each day you record in this diary information about the date and time of each dosing of study medication. Bring this diary with you to each appointment until the diary is collected by the study site staff.

INSTRUCTIONS FOR TAKING LENALIDOMIDE (DAYS 1-21 OF EACH 28-DAY CYCLE)

- Take your medication at approximately the same time in the morning every day.
- Swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules.
- 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.

INSTRUCTIONS FOR TAKING IXAZOMIB (DAYS 1, 8, 15 OF EACH 28-DAY CYCLE)

- Swallow ixazomib capsules whole, with water. Do not break, chew, or open the capsules.
- Ixazomib should be taken on an empty stomach (no food or drink) at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.
- Missed doses can be taken as soon as you remember if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If you vomit after taking a dose, do not repeat the dose. Resume dosing at the time of the next scheduled dose.

GENERAL INSTRUCTIONS

- If you did not take your daily dose, please write down why in the space provided.
- If you experience side effects, please write these down in the space provided as well.
- Call your nurse if you have any questions about taking either medication.

Name of Site Contact: _____

Phone Number: _____

- Return this diary at the end of every cycle to site staff.

Day	Date			Time Pills Taken		Dose Taken mg	Indicate Which Pill Taken (Place "X" in Corresponding Box)		Comments/Side Effects Reason for missed doses or any side effects you have when taking the medications.
	Month	Day	Year	AM	PM		Lenalidomide	Ixazomib	
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
21									
22	No study medication taken on this day.								
23	No study medication taken on this day.								
24	No study medication taken on this day.								
25	No study medication taken on this day.								
26	No study medication taken on this day.								
27	No study medication taken on this day.								
28	No study medication taken on this day.								

Appendix V Risk Factors: GELF tumor burden criteria and FLIPI score GELF

To meet GELF criteria, patient must have at least one criterion:

- Nodal or extranodal mass > 7 cm
- At least 3 nodal masses: each > 3.0 cm in longest dimension
- Systemic symptoms due to lymphoma or B symptoms
- Splenomegaly with spleen > 16 cm by CT scan
- Evidence of compression syndrome (e.g., ureteral, orbital, gastrointestinal) or pleural or peritoneal serious effusion due to lymphoma (irrespective of cell content)
- Leukemic presentation ($> 5.0 \times 10^9/L$ malignant circulating follicular cells)
- Cytopenias (absolute neutrophil count $< 1.0 \times 10^9/L$, hemoglobin $< 10 \text{ gm/dL}$, and/or platelets $< 100 \times 10^9/L$).

FLIPI

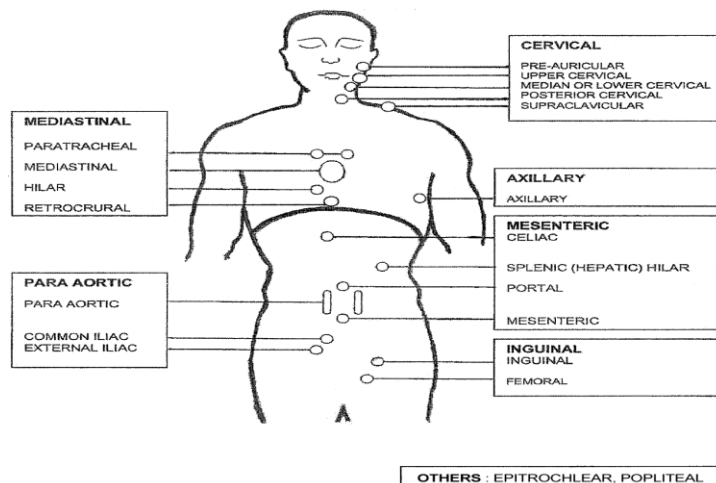
Each patient should be assessed for the presence or absence of the following 5 adverse prognostic factors (adverse factor in italics):

- 1) Age (*> 60 years* vs. 60 years or less)
- 2) Ann Arbor stage (*III-IV* vs. I-II)
- 3) Hemoglobin level (*< 120 g/L* vs. 120 g/L or higher)
- 4) Number of nodal areas ≥ 5 or less; see figure below)
- 5) Serum LDH level (*above normal* vs. normal or below)

Each patient should then be assigned into one of the following 3 risk groups:

- low risk (0-1 adverse factor)
- intermediate risk (2 factors)
- poor risk (3 adverse factors)

Nodal map according to FLIPI model.



Solal-Celigny P, et al. Blood 2004; 104:1258-1265; and Buske C, et al. Blood. 2006;108:1504-150

FLIPI-2

An updated analysis of the FLIPI was reported (FLIPI-2). This analysis was completed on 832 follicular lymphoma patients treated from 2003 through 2005, of who the majority received rituximab-based therapy. Five clinical factors were identified as being correlated with survival. Three of the parameters were different than the original FLIPI (FLIPI-1), while two were similar (i.e., anemia and older age).

Each patient should be assessed for the presence or absence of the following 5 adverse prognostic factors (adverse factor in italics):

- 1) Age (*> 60 years* vs. 60 years or less)
- 2) Hemoglobin level (*< 120 g/L* vs. 120 g/L or higher)
- 3) β 2-microglobulin (*above normal* vs. normal or below)
- 4) Largest involved lymph node (*> 6 cm* vs. 6cm or lower)
- 5) Bone marrow (*involved* vs. not involved)

Federico M, et al. J Clin Oncol 2009; 2.

Appendix VI: Blood Specimen Handling

One tube of EDTA anti-coagulated blood (purple top) will be drawn at baseline, with day 1 cycle 7 lab draw and at re-staging after cycle 12, at a regularly scheduled venipuncture time. The tube will be labeled with the patient information and a study specific requisition will be attached to the specimen. The specimen will be delivered to the Tomsich Reference Laboratory. The blood specimen and requisition form must be received and processed within 48 hours by the Tomsich flow cytometry lab, available Monday through Friday.

If drawn at Cleveland Clinic, samples will be sent by the same mechanism as for standard blood tests.

If drawn at University Hospitals, tubes can be sent with the regularly scheduled Cleveland Clinic daily lab pick up at 2085 Adelbert Road Cutting Room 231(Andrew Wing of Bishop) which runs Monday through Friday. Samples need to be at the designated pick-up spot by 2:45pm. If missed Monday through Thursday, samples will be picked up the next day. If delivered after 2:45pm on Friday, samples will not be able to be run.

The Immunodeficiency (CDC) Panel will be run and reported in SunQuest.