TITLE: A Phase II Study of Daratumumab plus Ibrutinib in Patients with Waldenström's Macroglobulinemia.

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Confidentiality Statement

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Protocol Synopsis:

Title: A Phase II Study of Daratumumab plus Ibrutinib in Patients with Waldenstrom's Macroglobulinemia	
Study Drugs:	Daratumumab and Ibrutinib
Indication:	Waldenstrom's Macroglobulinemia
Study Phase:	Phase II

Background and Rationale:

While many treatment options are available for Waldenstrom's macroglobulinemia (WM), ibrutinib remains the only approved therapy in both upfront and salvage settings. Data for effective therapies is derived from published Phase 2 studies utilizing rituximab in combination with alkylating agents, purine analogs or proteasome inhibitors with overall response rates (ORR) ~80-95% [1].

Ibrutinib has demonstrated impressive results as a single agent in previously treated rituximab refractory WM patients with an ORR of 91%, a major response rate of 73%, and a 2 year PFS of 69% [2]. Despite the impressive response rates, the majority of patients only achieve partial responses with the median IgM levels plateauing around 800mg/dL at time of best response. Mutations in genes such as *MYD88*, *CXCR4* and *BTK,* affect response and in the case of *CXCR4* and *BTK*, resistance to ibrutinib [3,4]. When ibrutinib is held for side effects, surgery or other reasons there is a rapid rise in IgM off of the drug, suggesting ibrutinib is having more of an effect on inhibition of IgM secretion than cell death. These observations provide an opportunity to use novel targeted approaches in combination with ibrutinib to further deepen these response rates in hopes to improve both PFS and OS.

Increasing evidence suggests the cell of origin for WM is an activated memory B cell with ~50-70% of cases demonstrating some level of CD38 expression [5-7]. Daratumumab is a monoclonal antibody targeting CD38 currently approved for use in multiple myeloma but not approved to treat WM [8,9]. Using daratumumab in combination with ibrutinib, we seek to target CD38 expression in WM patients both in combination as upfront therapy and as an additive therapy to patients currently on ibrutinib who have reached a response plateau.

Objectives:

Primary Objective:

- To evaluate the safety and toxicity of combination daratumumab and ibrutinib

Secondary Objectives:

- To assess overall response rate in Cohort A
- To evaluate the deepening of response in cohort B.
- To evaluate duration of response (DoR)
- To evaluate time to progression (TTP)
- To assess progression free survival (PFS)
- To assess overall survival (OS)

Exploratory Objectives:

- Specimens will be collected for future unknown use. Anticipated studies will be determined at a future date. Janssen will retain the right to approve the use of samples for exploratory analysis.

Methodology:

We propose a multi-center, two cohort Phase II clinical trial to investigate the effectiveness of adding daratumumab to ibrutinib in WM patients. Cohort A will consist of patients who are ibrutinib naïve and appropriate for ibrutinib based treatment. Cohort B will consist of patients who have achieved a response plateau less than a complete remission (CR) on single agent ibrutinib.

Subjects in Cohort A will be identified by their treating physician and eligible for enrollment if they are treatment naïve or ibrutinib naïve after prior therapy and eligible for ibrutinib based treatment. Subjects in Cohort B will be identified by their treating physician and eligible for enrollment if they have had at least 6 months of exposure to single agent ibrutinib and demonstrate an IgM response plateau defined by two IgM measurements, at least 8 weeks apart that have changed <15% from the previous mark. In Cohort B response assessment will be measured from initial IgM level prior to ibrutinib initiation. Enrolled subjects will be prescribed commercial ibrutinib, 420mg PO daily. The investigational agent, daratumumab will be administered based on FDA approved dosing in multiple myeloma (16mg/kg) with 8 weekly induction treatments during Cycles 1 and 2, followed by every other week dosing for Cycles 3-6, then monthly dosing from Cycle 7 until Cycle 24 at which point they will continue with ibrutinib as monotherapy until Cycle 52 (4 years total) which is the predefined study completion for enrolled subjects at which point they will complete follow-up.

Study visits and response assessments with IgM measurements will occur with each cycle for the first year then every three cycles after cycle 13. Subjects with measureable extramedullary disease will have CT scans every 6 cycles until radiographic CR. Patients will be considered evaluable for response if they completed the initial 8 weeks of daratumumab induction therapy and evaluable for toxicity if receiving one dose of daratumumab. Patients will continue on combination therapy for 2 years or until disease progression or unacceptable toxicities at which point patients will come off trial. Patients achieving a CR after two years of combination therapy will be given an option to continue with single agent commercial ibrutinib.

Subjects to be enrolled	24 total subjects, 12 in Cohort A and 12 in Cohort B
Study Duration	6 years
Accrual period	2 years

Inclusion Criteria:

1. Age ≥18 years of age
2. Ibrutinib naïve or previously treated patients currently on ibrutinib with a plateau in disease

response are eligible to participate:

a. Ibrutinib naïve subjects may be either treatment naïve or previously treated but ibrutinib naive to enter cohort A.

b. Subjects entering cohort B must have a plateau response on ibrutinib defined as ≥ 6 months of ibrutinib treatment with 2 IgM measurements at least 2 months apart with ≤ 15% change from the previous measurement. Subjects with IgM level < 0.7 g/dL will be eligible if their IgM level increases < 0.15 g/dL over two subsequent IgM measurements as defined above.

3. Subjects must have measurable disease defined by a serum IgM level ≥0.5g/dL
4. Eastern Cooperative Oncology Group performance status of 0-2
5. Hematology values must be within the following limits:

   a. Absolute neutrophil count (ANC) ≥ 1000 mm^3 independent of growth factor support for 7 days prior to study entry.

   b. Platelets ≥ 50,000/mm^3 independent of transfusion support within 7 days of study entry. TPO mimetics are not allowed to meet criteria.

   c. Hemoglobin ≥ 8g/dL, independent of transfusion support within 7 days of study entry

6. Biochemical values within the following limits:

   a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN)

   b. Total bilirubin ≤ 2 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

   c. Creatinine clearance (CLcr) ≥ 25 ml/min

7. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.
8. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.
9. Subjects must sign (or their legally-acceptable representatives must sign) an informed consent indicating that they understand the rational of the study and can participate in all study

procedures.

Exclusion Criteria:

1. Subject does not have a recorded IgM level recorded within 3 months prior to ibrutinib initiation.
2. Subject meeting definition of disease progression while on ibrutinib. Subjects with IgM levels < 0.7gdL are given special consideration. Please see inclusion criteria for 2b.
3. Subjects in cohort B experiencing ongoing non hematologic toxicities attributable to ibrutinib > Grade 1 will be excluded from study entry.
4. Major surgery or a wound that has not fully healed within 4 weeks of enrollment.
5. Evidence of disease transformation at time of enrollment.
6. Evidence of or known central nervous system involvement.
7. Evidence of or known amyloidosis.
8. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
9. Requires anticoagulation with warfarin or equivalent vitamin K antagonists.
10. Requires chronic treatment with strong CYP3A inhibitors. Subjects that required strong CYP3A inhibitors can be considered for enrollment after a washout period of 14 days prior to study drug administration.
11. Requires strong CYP3A inducers. Subjects that required strong CYP3A inducers but completed a course of treatment can be considered for enrollment after a washout period of 14 days prior to study drug administration.
12. Patients with history of Chronic Obstructive Pulmonary Disease or Reactive Airway disease must have pulmonary function tests. If the subject has a FEV1 ≤ 50% of predicted normal they will be excluded.
13. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.
14. Vaccinated with live, attenuated vaccines within 4 weeks of randomization.
15. Seropositive for human immunodeficiency virus (HIV)
16. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects

with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

17. Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
18. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.
19. Active malignancy not treated with curative intent within 2 years of study entry with exception of nonmelanomatous skin cancers and cervical carcinoma in situ.

Treatment Phases:

Treatment will consist of induction, continuation, and maintenance phases. Induction will be defined as the first 2 cycles of combination treatment. The consolidation phase will include treatment with daratumumab on day 1 and day 15 of each cycle starting with cycle 3 through cycle 6. Starting at cycle 7 subjects will enter the maintenance phase with monthly daratumumab infusions until Cycle 24 day 1 (two years) at which point they will complete their combination treatment with daratumumab. Cycle 25 and beyond patients will continue on ibrutinib monotherapy.

Subjects will have doctor visits on each day of treatment with daratumumab but required study visits will only occur monthly for the first year followed by every 3 cycles for the remainder of the study. On non-study visits during induction, subjects will have baseline labwork considered to be standard of care obtained at the discretion of the investigator followed by daratumumab infusions. Subjects will take three, 140mg capsules of ibrutinib orally, daily starting on the same day as infusion and continue daily through all cycles.

Treatment Administration:

Treatment will be administered on an outpatient basis.

Ibrutinib will be administered as a single dose 420mg tablet daily for a total daily dose of 420mg. Ibrutinib naïve subjects, will have a one month lead-in Cycle -1, with ibrutinib monotherapy prior to initiating combination induction. Subjects in Cohort A who experience any Grade 3 or greater toxicity must have that toxicity resolve to Grade 1 or less prior to daratumumab combination therapy. Subjects will be asked to take a single tablet of ibrutinib orally with or without food. Subjects will take the tab on a continuous daily basis with one cycle of treatment consisting of 28 days. Subjects enrolled on the ibrutinib naïve Cohort A, will take their first dose of ibrutinib before or after their daratumumab infusion. On days in which they do not receive a daratumumab infusion they will be asked to take their ibrutinib tablet at the same time each day. Subjects will continue daily dosing of ibrutinib until disease progression, toxicities, or study completion whichever comes first.

Daratumumab will be administered per the current package insert. Subjects will receive 16mg/kg weekly for 8 total doses during induction. They will then receive 16mg/kg of daratumumab on day 1 and day 15 starting on cycle 3 through cycle 6. Starting with Cycle 7 through cycle 24 subjects will receive daratumumab 16mg/kg on day 1 until disease progression, toxicities or study completion whichever comes first.

Subjects will be premedicated with 100mg of methylprednisolone intravenously (IV), 650mg of acetaminophen PO, and 25-50mg of diphenhydramine IV all given 30 minutes prior to infusions with daratumumab. Methylprednisolone dosing may be reduced to 60mg IV with subsequent doses after the first infusion if no adverse events are recorded. Subjects will be asked to take 20mg of methylprednisolone PO for two days after each infusion and this can be eliminated at the discretion of the investigator after completion of the first cycle.

Evaluation of Efficacy and Safety

Response will be assessed by the investigator, based on laboratory values, physical examinations, CT scans (or MRI if CT scan is medically contraindicated), bone marrow examinations.

All measurable disease must be documented at screening by physical examination, laboratory testing, CT scan (or MRI if CT is medically contraindicated), and bone marrow. During the study, each study visit by a physical examination and laboratory testing. Clinical disease assessments will take place at baseline, monthly for the first 12 months and then every 3 months until disease progression, death or study removal for any other reason. Additional radiographic studies will be performed every 6 months on study for patients with baseline extramedullary disease. For consistency, the same method of imaging should be performed for a subject throughout the study.

Safety Assessment:

Safety will be assessed by physical examinations, Eastern Cooperative Oncology Group (ECOG) criteria for performance status, laboratory tests, adverse events, and concomitant medication usage. The following adverse events (including laboratory abnormalities reported as adverse events) that occur between the first dose of either study drug through 30 days after the last dose of either study drug will be collected:

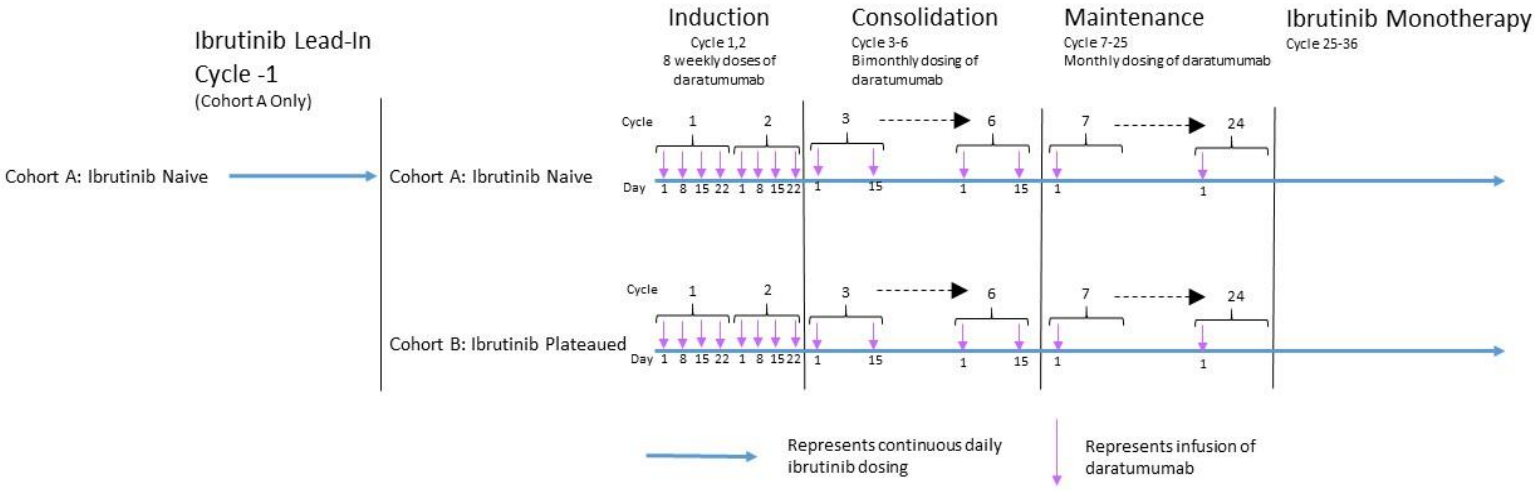
• Treatment-emergent serious adverse events

• Grade ≥3 adverse events

• Adverse events of special interest, and any adverse event resulting in ibrutinib or daratumumab dose interruption, reduction or discontinuation

Any laboratory assessments associated with the above adverse events should be collected in the CRF. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Schema


Ibrutinib Lead-In
Cycle -1
(Cohort A Only)
Induction
Cycle 1,2
8 weekly doses of daratumumab
Consolidation
Cycle 3-6
Bimonthly dosing of daratumumab
Maintenance
Cycle 7-25
Monthly dosing of daratumumab
Ibrutinib Monotherapy
Cycle 25-36
Cohort A: Ibrutinib Naive
Cohort A: Ibrutinib Naive
Cycle 1 2 3 6 7 24
Day 1 8 15 22 1 8 15 22 1 15 1 15 1 1
Cohort B: Ibrutinib Plateaued
Cycle 1 2 3 6 7 24
Day 1 8 15 22 1 8 15 22 1 15 1 15 1 1
Represents continuous daily ibrutinib dosing
Represents infusion of daratumumab

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1. Study Objectives

Ibrutinib is an effective treatment strategy for Waldenström's macroglobulinemia (WM) achieving major response rates of approximately 70% in rituximab refractory patients. Unfortunately these responses are generally partial responses (PR) and rapid elevations of IgM occur when the drug is held. This suggests an inability of ibrutinib to address the source of the disease. It is not yet clear whether long-term health risks of persistently elevated IgMs exist and thus we hypothesize we can deepen response rates and increase durability by adding daratumumab to ibrutinib in both treatment naïve and previously treated WM patients who have achieved a disease response plateau on ibrutinib.

We propose a multi-center, two cohort, Phase II clinical trial to investigate the effectiveness of adding daratumumab to ibrutinib in WM patients. Subjects in Cohort A will be identified by their treating physician and eligible for enrollment if they are treatment naïve or relapsed after 1 prior therapy but remain naïve to ibrutinib or BTK inhibitors and appropriate for ibrutinib based treatment. Subjects in Cohort B will be identified by their treating physician and eligible for enrollment if they have had at least 6 months of exposure to single agent ibrutinib and demonstrate an IgM response plateau defined by two IgM measurements, at least 8 weeks apart that have changed <15% from the previous mark. Enrolled subjects will be prescribed commercial ibrutinib, 420mg PO daily. The investigational agent, daratumumab will be administered based on FDA approved dosing in multiple myeloma (16mg/kg) with 8 weekly induction treatments, followed by every other week dosing for cycles 3-6, then monthly dosing, cycle 7-24. Cycle 25 and beyond subjects will continue on single agent ibrutinib. Patients will be premedicated with 100mg of methylprednisolone, 650mg of acetaminophen and 25-50mg IV of diphenhydramine 30 minutes prior to all infusions of daratumumab. Methylprednisolone dosing may be reduced to 60mg with subsequent doses after the first infusion. Subjects will be asked to take 20mg of methylprednisolone for two days after each infusion which can be eliminated after the first cycle at the discretion of the investigator.

Study visits and response assessments with IgM measurements will occur day 1 of each cycle through cycle 13 then day of 1 every three cycles after the first year on treatment. Subjects with measureable extramedullary disease will have CT scans every 6 months while on study or until radiographic CR at which point they will occur at the discretion of the investigator. Patients will be considered evaluable for response if they completed the initial 8 weeks of daratumumab induction therapy. Response assessment in Cohort B will be measured from the IgM level recorded prior to ibrutinib initiation. Subjects will continue on combination therapy for 2 years until disease progression or unacceptable toxicities at which point patients will stop daratumumab therapy and come off study. All subjects will be followed for 1 year after completing combination therapy unless they come off study early for other reasons. Subjects achieving a CR will be given an option to continue with single agent commercial ibrutinib or stop all therapy.

1.1. Primary Objectives

- To evaluate safety and toxicity of combination daratumumab and ibrutinib.

1.2. Secondary Objectives

- To assess major response rate with combination daratumumab and ibrutinib cohort A
- To evaluate deepening response rates in Cohort B after daratumumab addition
- To evaluate duration of response (DoR)
- To evaluate time to progression (TTP)
- To assess progression free survival (PFS)
- To assess overall survival (OS)

1.3. Exploratory Objectives

There are no prespecified exploratory studies planned. However, samples will be collected at specifi time points as outlined in Section 9 and will be available for future unknown use. Janssen will retain the right to approve the use of banked specimens for correlative analysis even if not the primary scientific collaborator performing the analysis.

2. Waldenström's Macroglobulinemia Background

Waldenström's Macroglobulinemia is defined as a IgM producing lymphoplasmacytic lymphoma (LPL) characterized by small B lymphocytes, plasmacytoid lymphocytes and differentiated plasma cells usually infiltrating the bone marrow[10]. It is considered a rare indolent lymphoma with affecting 3 out of 1 million people in the United States yearly with median survival of approximately 8-9 years [11,12].

Upon diagnosis, patients are commonly observed until development of IgM related complications such as peripheral neuropathy, cold agglutinins, or cryoglobulinemia and constitutional symptoms, bulky extramedullary disease or cytopenias due to infiltration of bone marrow by tumor cells [1].

Historically upfront management for fit patients with WM has been with chemo-immunotherapy (CIT) regimens when treatment was indicated. Phase 3 data comparing bendamustine/rituximab (BR) to rituximab/cyclophosphamide/doxorubicin/prednisone (RCHOP) for indolent lymphomas included 41 patients with WM [13]. Overall response rates were high in both groups but there was less toxicity with improved progression free survival (PFS) was noted in subjects receiving BR. Additionally, dexamethasone/rituximab/cyclophosphamide (DRC) has been studied demonstrating it was safe and effective with 83% of patients responding [14].

Novel agent containing therapies have since been established as safe, effective, and chemotherapy free options for older unfit patients with comparable response rates and durability compared to standard the CIT regimens previously published. Outcomes with bortezomib/dexamethasone/rituximab (BDR) has recently been updated with 6 year minimum

follow-up of 59 previously untreated patients demonstrating 85% ORR with median PFS of 43 months and median duration of response (DoR) of 64.5 months [15].

Anti-CD20 therapy has been a mainstay as an initial treatment for unfit low tumor burden patients with both rituximab and ofatumumab demonstrating impressive response rates [16-18]. While anti-CD20 therapy is a great option for moderately symptomatic patients it should be used with caution in patients with elevated IgM levels or symptoms of hyperviscosity as an IgM flare has been noted which can cause an exacerbation of the patient's symptoms [19].

Ibrutinib has now garnered approval in both upfront and salvage settings for previously treated patients with WM after it demonstrated impressive response rates in rituximab refractory patients with an ORR of 90.5% with a major response rate of 73% [2]. 2 year PFS and overall survivals (OS) were 69.1% and 95.2% respectively in which it received accelerated approval.

Genomic alterations leading to WM development have been identified and can impact on clinical presentation and response to novel therapies. In 2012, Treon et al identified *MYD88* L265P mutations in 91% of LPL samples with subsequent downstream activation of NF kappa B signaling. These studies also identified WHIM-like *CXCR4* mutations as impaciting on lymphomagenesis and response to ibrutinib [20,21]. Since those seminal publications, a host of other relevant genes have been identified as recurrently mutated and playing a role in pathogenesis including genes such as *ARID1A*, *ARIDA1B*, *CD79B*, *MLL2*, *TP53*, *MYBBP1A*, *HIVEP2*, and *LYN* [3].

In 2015, Treon et al published response rates to ibrutinib based on mutational status of these two genes [2]. The authors showed that patients with mutated *MYD88* and wild type (wt) *CXCR4* had the best response compared to those with both mutated *MYD88* and *CXCR4*, major response rates of 91.7% vs. 61.9% respectively. The patients who were wt for both mutations had the worst response rates demonstrating a major response rate of only 28.2%. While responses for ibrutinib can be durable[22], most remain as only partial responses (PR) and resistance to ibrutinib has been documented requiring novel therapeutic combinations to overcome or prevent disease resistance and deepen responses.

3. Rationale

Ibrutinib a potent inhibitor of Bruton's tyrosine kinase (BTK) has been approved by the Federal Drug Administration (FDA) for patients with untreated and relapsed WM [2]. Despite an impressive ORR of 90.5%, the majority of patients only achieve partial responses (PRs) with the median IgM nadir at approximately 800mg/dL at time of best response demonstrating a 2 year progression free survival (PFS) of 69.1% [2]. Additionally, when ibrutinib dosing is interrupted there is a rapid rise in IgM off of the drug suggesting ibrutinib's dominant impact is upon the inhibition of IgM secretion rather than elimination of the malignant clone.

As long as the malignant clone persists, the patient remains at risk for rapid return of the disease with any interruption of treatment or upon developing resistance to ibrutinib. In addition, given

the current paradigm of continuous therapy patients remain at risk to developing toxicities related to long term treatment. As a result, additional therapeutic options are required. As WM is a disease characterized by intra-clonal differentiation, any therapy to be highly effective has to be able to attack lymphocytes, plasmacytoid lymphocytes, and plasma cells. Ibrutinib's efficacy in other low grade B cell malignancies and lack of efficacy in myeloma would suggest its greatest effect is on the lymphocyte population and not on the plasmacytoid or plasma cell populations.

Increasing evidence suggests the cell of origin for WM is an activated memory B cell with ~50-70% of cases demonstrating some level of CD38 expression [5-7]. Cell lines models of WM also have demonstrated to have high expression of CD38 [23]. Daratumumab is a monoclonal antibody targeting CD38 and is currently FDA approved for use in multiple myeloma [8,9]. Importantly, there is recent evidence that by targeting CD38 with daratumumab, B cell receptor signaling can be attenuated enhancing the activity of ibrutinib in preclinical models (Paulus ASH 2017).

The hypothesis of the study is that combination therapy with ibrutinib and daratumumab in patients with WM will be safe, effective, and result in deeper responses with improved durability over that seen historically with ibrutinib monotherapy. This study will provide the scientific community with preliminary evidence of activity of this novel combination in WM and provide a platform for future studies investigating this combination.

4. Risk/Benefit Assessment

The benefits of treatment and knowledge gained from this study outweigh risk of combination therapy to subjects. Daratumumab is currently an FDA approved therapy for multiple myeloma that has been safely combined with multi-modality treatments with good safety profile with outstanding effects on disease control. Ibrutinib is a well tolerated and effective FDA approved therapy for WM and has been safely combined with rituximab and CIT regimens in other histologies such as CLL.

5. Correlative Studies

Samples will be collected at prespecified time points as outlined in Section 9. All baseline correlative samples will be collected during screening upon a subject's signing of informed consent. Samples will be collected for study specific use and will be retained for future unknown testing. Samples will be protected from patient identifiers and coded with subject ID numbers that will be generated upon consenting to the protocol. Only qualified researchers who have been approved and deemed collaborators by the principal investigator will be allowed access to deidentifed patient samples to perform correlative assays. Samples will be collected and shipped within 1 business day and stored in collaboration with laboratories at Mayo Clinic-Jacksonville. All specimens collected for future use will be shipped to:

Aneel Paulus, M.D.
Mayo Clinic
4500 San Pablo Rd.
Griffin Building Room 132
Jacksonville, FL 32224

6. Investigational Agents

6.1. Ibrutinib

Ibrutinib is a first-in-class, potent, orally administered covalently binding small-molecule inhibitor of Bruton's tyrosine kinase (BTK) currently under investigation as an anti-cancer agent in various B-cell malignancies, AML and in solid tumors. It has garnered FDA approvals in mantle cell lymphoma, chronic lymphocytic lymphoma, Waldenstrom's macroglobulinemia and most recently marginal zone lymphoma and chronic GVHD.

6.1.1. Mechanism of Action

Bruton's tyrosine kinase is an integral protein that mediates downstream signaling of the B cell receptor (BCR). In WM, BTK is constitutively activated and directly interacts with *MYD88* L265P mutants resulting in robust BTK activity. Inhibition of BTK with ibrutinib decreases *MYD88* L265P mediated complexing, resulting in decreased Nf Kappa B activation and increased apoptotic activity and cell death after exposure to ibrutinib[24].

6.1.2. Nonclinical Studies-Ibrutinb

Ibrutinib has been evaluated in vitro for its ability to inhibit purified BTK and other members of Tec family kinases. B cell receptor signaling has been demonstrated to be inhibited via inhibition of BTK autophosphorylation at an inhibitory concentration (IC_{50}) of 11nM [25]. Ibrutinib inhibited the proliferation of cell lines derived from patients with DLBCL at concentrations of 1-2nM. Studies performed with primary CLL cells, ibrutinib reduced proliferation at concentrations of 500-1000nM. In Waldenstrom's cell lines, ibrutinib reduced cell growth but only at 1uM and was dose dependent. Exposure to ibrutinib did not affect cellular proliferation or viability. Ibrutinib was able to completely abrogate BTK autophosphorylation but that phosphorylation by upstream LYN/SYK was actually augmented. In WM cell lines ibrutinib was able to inhibit ERK phosphorylation but AKT activation was not abrogated which is not the case in CLL or MCL cell lines. Lastly it was demonstrated that the BCR signalosome is not critical for CXCL12 induced responses in WM and only affect BCR controlled integrin adhesion thus mobilizing malignant cells from the protective niches of the lymphoid organs [26].

6.1.3. Nonclinical Pharmacokinetics and Metabolism-Ibrutinib

Ibrutinib is metabolized by CYP3A. In both animals and humans, ibrutinib was metabolized primarily by hydroxylation of the phenyl moiety, opening of the piperidine with reduction to a

primary alcohol or carboxylic acid, and epoxidation of the acrolein moiety. In vitro studies indicate ibrutinib is a weak inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Both ibrutinib and its main metabolite are at most weak inducers of CYP450 thus it is unlikely to involve drug-drug interactions with other drugs involving CYP450 enzymes.

In rats, dogs and humans excretion of ibrutinib-related radioactivity occurred principally via feces with less than 3.3% of administered radioactivity recovered in the urine of rats and dogs. Biliary excretion was confirmed as the major route of elimination in rats.

6.1.4. Toxicology-Ibrutinib

The maximum nonlethal dose of ibrutinib following administration by oral gavage was 2000mg/kg for mice, 400mg/kg for female rats and 1000mg/kg for male rats. The no observed adverse effect level (NOAEL) was found to be 100mg/kg/day for males and 50mg/kg/day for female rats. Clinical histologic signs of toxicity included adverse effects on body weight (weight gain), diarrhea, lymphoid depletion, intestinal inflammation and acinar atrophy of the pancreas. With recovery periods up to 6 weeks partial or complete resolution of all histopathologic changes occurred in the specific tissues. There was no evidence of genotoxicity in any of the assays used to assess this parameter.

6.1.5. Clinical Studies-Ibrutinib

In WM, 2 pivotal trials have been completed and reported. In 2015, Treon et al reported on the initial efficacy in a Phase II study enrolling 63 rituximab refractory WM subjects [2]. In this report the median serum IgM level decreased from 3520mg/dL to 880 mg/dL at time of best response. An overall response rate (ORR) 90.5% with major responses defined as, partial response (PR), very good partial response (VGPR) or complete response (CR), of 73%. Mutational genotypes were associated with responses with mutated *MYD88* L265P only subjects with 91.2% achieving a major response. Subjects with mutated *MYD88* and mutated *CXCR4* had a major response rate of 61.9% and those with wt sequences had a major response rate of only 28.6%. At 24 months the estimated rate of PFS was 69.1% and the OS was estimated at 95.2%

Safety analysis revealed 15% of patients experienced grade 3 or greater neutropenia, 13% experienced grade 3 or greater thrombocytopenia. Grade 3 or greater nonhematologic toxicity was rare with the vast majority of toxicities considered Grade 2 or less. The most common Grade 2 toxicities were related to gastrointestinal disorders and infections with up to 6% of patients experiencing grade 2 reflux or pneumonias. Grade 2 or greater atrial fibrillation was noted in 5% of patients with only 2% of patients experiencing post procedural bleeding.

In 2017, the iNNOVATE investigators published a sub study analysis reporting on the efficacy and safety of single agent ibrutinib in relapsed refractory WM patients. The study is a currently ongoing international randomized Phase 3 study accruing patients with relapsed rituximab refractory disease. The study randomized patients to 3 arms; rituximab plus ibrutinib, rituximab plus placebo, or ibrutinib alone. The published data focused on the results from the ibrutinib only

arm. In total 31 patients were accrued to the ibrutinib only arm between August 2014 and February 2015. Thirteen (42%) of the 31 patients had high-risk disease per the International Prognostic Scoring System Waldenström Macroglobulinemia. At a median follow-up of 18.1 months, the overall response rate was 90% with 71% of patients attaining a major response. The estimated 18 month PFS was 86% and the 18 month OS was 97%. Baseline hemoglobin of 10.3 g/dL increased to 11.4 g/dL after 4 weeks of treatment. Grade 3 or greater adverse events were neutropenia (13%), hypertension (10%), and anemia, thrombocytopenia, and diarrhea (6%) each. Serious adverse events occurred in 10 patients (32%) and most often related to infections. Five patients discontinued ibrutinib; 3 due to progression and 2 due to adverse events.

Given the results of the Phase II data the Federal Drug Administration (FDA) gave accelerated approval for the treatment of patients in both treatment naïve and relapsed refractory settings.

6.1.6. Clinical Pharmacokinetics and Metabolism-Ibrutinib

The absolute bioavailability of ibrutinib administered in capsule formulation after 560mg oral dose was found to be 2.9%. Ibrutinib absorption from the GI tract is complete as there is minimal fecal excretion of unchanged ibrutinib in combination with high levels of oxidative metabolites. Plasma protein binding of ibrutinib in human plasma is 97.3% and 91.0% respectively with a volume of distribution of 683L after an IV dose of 100ug of ibrutinib.

The drug is extensively metabolized by CYP3A mediated metabolic pathways mainly epoxidation of the acryloyl moiety and hydroloysis to form the dihydrodiol. Excretion is predominantly via the feces with approximately 80% recovered mostly within 2 days with only 8% excreted in the urine. The half-life of ibrutinib is 4 to 6 hours.

6.1.7. Clinical Safety-Ibrutinib

Based on available data, ibrutinib has an acceptable safety profile as both monotherapy and when combined with chemo immunotherapy among the B cell malignancies studied. The most frequently treatment emergent adverse events in > 10% of patients were diarrhea, fatigue and nausea. The most common serious treatment adverse events in >1% of subjects were pneumonia and atrial fibrillation.

6.2. Daratumumab

Daratumumab is a human immunoglobulin G1 kappa monoclonal antibody that binds CD38 expressing cells with high affinity in several hematologic malignancies.

6.2.1. Mechanism of Action-Daratumumab

Daratumumab is a human IgG mAb immunotherapy with high binding affinity to CD38 which induces cell death through multiple mechanisms of action. Complement-dependent cytotoxicity (CDC), antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis as well as direct cytotoxicity by induction of apoptosis Fc gamma receptor

crosslinking. Daratumumab eliminates Tregs, B regs and leads to expansion of both CD4 and CD8 helper T cells.

6.2.2. Nonclinical Studies-Daratumumab

In mouse xenograft models, daratumumab reduced tumor growth in both preventative and therapeutic settings. In vitro studies using bone marrow mononuclear cells from patients with multiple myeloma demonstrated increased killing of tumor cells when combined with lenalidomide or bortezomib. In WM daratumumab can exert direct lethal effect on cell lines and ADCC not CDC appears to be the dominant mechanism of action. ADCC mediated toxicity was contingent on CD38 expression and that ibrutinib resistant clones can down regulate CD38 expression [27].

6.2.3. Nonclinical Pharmacokinetics and Metabolism-Daratumumab

The half-life increased from 36 to 132 hours over the course of 6 weekly at 5mg/kg and increased from 103 to 586 hours at 25mg/kg. Dosing gave rise to a more than dose proportional exposure suggestive of target mediated disposition.

6.2.4. Nonclinical Toxicology-Daratumumab

Two primary toxicities observed in primate studies were infusion related reactions and thrombocytopenia. Infusion reactions occurred during the first but not subsequent infusions. The thrombocytopenia was reversible upon clearance of the drug and the drug has a 15 fold increased affinity for chimpanzee platelets over human platelets.

6.2.5. Clinical Studies-Daratumumab

Daratumumab currently has 3 FDA approved indications to treat patients with multiple myeloma. Daratumumab is indicated as monotherapy in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double refractory to a PI and IMiD, in combination with pomolidamide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a PI, and in in combination with lenalidomide and dexamethasone who have received at least one prior therapy. No clinical studies with daratumumab have been performed today in patients with WM.

6.2.6. Clinical Pharmocokinetics and Metabolism-Daratumumab

The half-life of daratumumab is both concentration and time dependent. After the first dose of 16mg/kg of daratumumab the half-life was 9 days and is expected to be 18 days with repeated dosing. Exposure efficacy analyses on the data from combination therapies suggest that maximum clinical benefit on progression free survival, duration of response and overall response rate has been attained for the majority of the subjects with an acceptable safety profile at the recommended dose, 16mg/kg. Despite decreasing concentration of daratumumab over time the

current dosing schedule was adequate to produce the concentration level that can maintain the level of target saturation at Q4W dosing interval. Daratumumab peak and trough concentrations at similar timepoints across monotherapy and combination studies have had no impact on the concentration of daratumumab.

6.2.7. Clinical Safety-Daratumumab

Grade 3 or 4 treatment emergent adverse events (TEAE) were reported in 56% of sujects treated with 16mg/kg. The most frequently reported Grade 3 or 4 TEAE were anemia (17%), neutropenia (12%), lymphopenia (6%), leukopenia, pneumonia and hypertension (5% each). Serious adverse events were reported in 33% of subjects treated with 16mg/kg. Most frequently noted were pneumonia (6%), pyrexia, general health debilitation, hypercalcemia (3%). In the 16mg/kg group, 14 subjects (9%) died 11 dying from progressive disease the remaining due to TEAE though none were felt related to daratumumab.

7. Subject Selection

7.1 Study Population

Subjects with a diagnosis of WM and meeting requirements for active therapy as defined by the 2nd International Workshop on Waldenstrom's Macroglobulinemia [28] and meet the inclusion and exclusion criteria will be eligible for participation in this study. See **Appendix A** for indications for therapy.

7.2. Inclusion Criteria

1) Subjects must have a diagnosis of WM and meet the requirements for active therapy as defined by the 2nd International Workshop on Waldenstrom's Macroglobulinemia (see **Appendix A** for indications for therapy).
2) Age ≥18 years of age
3) Ibrutinib naïve or previously treated patients currently on ibrutinib with a plateau in disease response are eligible to participate.
   a) Ibrutinib naïve subjects may be either treatment naïve or previously treated but ibrutinib naïve to enter cohort A.
   b) Subjects entering cohort B must have a plateau response on ibrutinib defined as ≥ 6 months of ibrutinib treatment with 2 IgM measurements at least 2 months apart with ≤ 15% change from the previous measurement. Subjects with IgM level < 0.7 g/dL will be eligible if their IgM level increases < 0.15 g/dL over two IgM measurements as defined above.
4) Subjects must have measurable disease defined by a serum IgM level ≥0.5g/dL
5) Eastern Cooperative Oncology Group performance status of 0-2
6) Hematology values must be within the following limits:

a. Absolute neutrophil count (ANC) ≥ 1000/mm^3 independent of growth factor support for 7 days of study entry if cytopenias are due to marrow involvement.

b. Platelets ≥ 50,000/mm^3 independent of transfusion support within 7 days of study entry. TPO mimetics are not allowed to meet eligibility criteria.

c. Hemoglobin ≥ 8g/dL, independent of transfusion support within 7 days of study entry

7) Biochemical values within the following limits:

d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN)

e. Total bilirubin ≤ 2 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

f. Creatinine clearance (CLcr) > 25 ml/min

8) Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.

9) Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.

Subjects must sign (or their legally-acceptable representatives must sign) an informed consent indicating that they understand the rational of the study and can participate in all study procedures.

7.3. Exclusion Criteria

1) Subject does not have a recorded IgM level recorded within 3 months prior to ibrutinib initiation.

2) Subject meeting definition of disease progression while on ibrutinib. Subjects with IgM levels < 0.7gdL are given special consideration. Please see inclusion criteria for 2b.

3) Subjects in cohort B experiencing ongoing non hematologic toxicities attributable to ibrutinib > Grade 1 will be excluded from study entry.

4) Major surgery or a wound that has not fully healed within 4 weeks of enrollment.

5) Evidence of disease transformation at time of enrollment.

6) Waldenstrom's complicated by amyloidosis

7) Known central nervous system lymphoma.

8) History of stroke or intracranial hemorrhage within 6 months prior to randomization.

9) Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).

10) Requires chronic treatment with strong CYP3A inhibitors. Subjects that required strong CYP3A inhibitors but completed a course of treatment can be considered for enrollment after a washout period of 14 days prior to study drug administration.

11) Requires strong CYP3A inducers. Subjects that required strong CYP3A inducers but completed a course of treatment can be considered for enrollment after a washout period of 14 days prior to study drug administration.

12) Patients with history of Chronic Obstructive Pulmonary Disease or Reactive Airway disease must have PFTs with FEV1 calculated. Patients with a FEV1 ≤ 50% of predicted normal will be excluded.

13) Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.

14) Vaccinated with live, attenuated vaccines within 4 weeks of randomization.

15) Seropositive for human immunodeficiency virus (HIV)

16) Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

17) Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

18) Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.

19) Active malignancy not treated with curative intent within 2 years of study entry. Nonmelanomatous skin cancers and cervical carcinoma in situ are excluded.

8. Registration Procedures

8.1. Patient Registration

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

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

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

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

9. Study Procedures

Eligible subjects will be identified by the treating investigator and be recommended for the study based on potential to meet eligibility criteria. Identified subjects will be brought to clinic to initiate the informed consenting process. Once a subject agrees to participate they will be provided an informed consent form detailing the study design, investigational agents, risks, benefits and subject and investigator responsibilities prior to obtaining their signature.

Once consented, subjects will enter the screening phase which will last up to 28 days, during which time confirmation of eligibility and baseline evaluations will take place. Subjects meeting eligibility will then be assigned to one of two cohorts depending on their treatment history. Cohort A subjects will be ibrutinib naïve patients and cohort B will be subjects currently on ibrutinib who have reached a response plateau. Twelve patients will be enrolled into each cohort.

Subjects will then enter the treatment phase with initial induction followed by the maintenance

phase as defined by the protocol. Subjects will be followed by clinical exams, laboratory investigations and imaging until disease progression unacceptable toxicity or completion of 2 years of therapy. After completion of combination therapy, subjects will be followed for an additional year on single agent ibrutinib.

9.1. Schedule of Evaluations

Table 1. Schedule of events

Study Procedure	Screening	Cycle -1 Day -28 (Cohort A only prior to daratumumab dosing)	Cycle 1				Cycle 2			
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
			Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22
Daratumumab Administration[k]			X	X	X	X	X	X	X	X
Informed consent	X									
Demographics	X									
Medical history	X	X	X				X			
Concurrent meds	X	X	X				X			
Physical exam	X	X	X	X	X	X	X	X	X	X
Vital signs, height, weight	X	X	X	X	X	X	X	X	X	X
CBC w/differential	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X
SIFE+[b]	X									
Immunoglobulin M		X	X				X			
Bone marrow biopsy/aspirate[c]	X									
HIV and Hepatitis Ab screening[d]	X									
EKG	X									
Pulmonary Function Testing (FEV1 calculation)	X									
Blood Type and Screen	X		X							
Research sample (aspirate)[c]	X									
Research sample (peripheral blood)[j]	X									
Adverse event evaluation		Continuously and at each treatment or study visit								
Radiologic evaluation[e]	X	Radiologic measurements should be performed on Day 1 Cycle 7, 13, 19, 25, 31, 37 day 1 evaluation (+15 day window after Day 1 is allowed)								
B-HCG	X[f]									

Study Procedure	Cycles 3-6		Cycles 7-13 Day 1	Cycles 14, 15, 17, 18, 20, 21, 23, 24 Day 1 (non-study visits)	Cycles 16, 19, 22 Day 1 (study visits)	Cycles 25, 28, 31, 34 Day 1 (study visits)	EOT Cycle 37 Day 1 visit or 28 days after coming off-study
	Day 1	Day 15					
Daratumumab Administration[k]	X	X	X	X	X		
Informed consent							
Demographics							
Medical history	X		X	X	X	X	X
Concurrent meds	X		X	X	X	X	X
Physical exam	X		X	X	X	X	X
Vital signs, height, weight	X	X	X	X	X	X	X
CBC w/differential	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X
SIFE+[b]	X[g]		X[h]		X	X	
Immunoglobulin M	X	X	X	X			X
Bone marrow biopsy/aspirate[c]	X[i]						X[i]
HIV and Hepatitis Ab screening[d]	X[d]		X[d]		X[d]	X[d]	X[d]
EKG							
Pulmonary Function Testing (FEV1 calculation)							
Blood Type and Screen							
Research sample (aspirate)[c]	X[i]						X[i]
Research sample (peripheral blood)[j]			X[j]				X[j]
Adverse event evaluation	Continuously and at each treatment or study visit						
Radiologic evaluation[e]	Radiologic measurements should be performed on Day 1 Cycle 7, 13, 19, 25, 31, 37 day 1 evaluation (+15 day window after Day 1 is allowed)						
B-HCG							

a. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

b. SIFE+ should include serum protein electrophoresis, immunofixation, serum immunoglobulin G, A, M levels, free kappa light chains, free lambda light chains.

c. Bone marrow biopsy will be performed at baseline and then to confirm complete remission as is standard of care. At baseline, 1 green top tube and 1 lavender top tube will be collected for research.

d. Hepatitis ab screening should include Hepatitis A IgG with reflex to IgM, Hepatitis B surface Ag, Hepatitis B surface ab, Hepatitis B core ab, Hepatitis C ab. If Hepatitis B surface or core ab, or Hepatitis C ab are positive, reflex testing with PCR for either HBV DNA or HCV RNA should be performed. HBV serology testing does not need to be repeated if performed within three months prior to first dose. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. Subjects with a history of HBV infection will be monitored for reactivation by HBV DNA by PCR every 3 cycles during treatment (e.g. Cycle 4, 7, 10, etc.), at end of daratumumab treatment (e.g. Cycle 25), and for up to 6 months post-daratumumab therapy (e.g. Cycle 28 and 31).

e. Radiologic evaluation is defined as CT chest, abdomen and pelvis with contrast. For patients ineligible for contrast CT chest non con with MRI abdomen and pelvis is default.

f. Serum pregnancy test (women of childbearing potential).

g. SIFE+ will only be required Cycle 4 D1, the remaining cycles serum IgM will be recorded only.

h. SIFE+ will only be required for Cycle 7 D1, Cycle 13 D1, the remaining cycles serum IgM will be recorded only.

i. Research biopsy and aspirate at Cycle 4 Day 1 (+ 15 day window) and then again at progression; 1 green top tube and 1 lavender top tube will be collected.

j. Peripheral blood samples (2 lavender top tubes) will be collected at screening, Cycles 7, 13, 19, and 25, and at EOT.

k. Required study visits include screening, Day 1 of Cycle -1, 1-13, and every three cycles thereafter through Cycle 37/EOT. Non-study visits for daratumumab administration include Days 8, 15, and 22 of Cycle 1-2, Day 15 of Cycles 3-6, and Day 1 of Cycles 14, 15, 17, 18, 20, 21, 23, and 24. See Section 8.5 for more information.

9.2. Screening Phase

- Informed consent
- Demographic collection
- Medical history
- Concurrent medication reconciliation
- Physical exam
- Vital signs (including height and weight)
- ECG
- Pulmonary Function Testing with FEV1 measurement (only required for subjects with known history of Chronic Obstructive Pulmonary Disease or Reactive Airway Disease)
- CBC with differential
- Serum chemistry as outlined in Table I (CMP, LDH, phosphorus)
- Serum pregnancy test (women of childbearing potential only)
- Serum protein electrophoresis and immunofixation with free light chain analysis
- Hepatitis and HIV screening
    - HBV serology testing does not need to be repeated if performed within three months prior to first dose.
    - If Hepatitis B surface or core ab or Hepatitis C ab are positive, reflex testing with PCR for either HBV DNA or HCV RNA should be performed. Subjects with serologic findings suggestive of vaccination (anti-HBs positivity as the only serologic marker) and known history of vaccination do not need HBV DNA PCR.
- Blood typing
- Bone marrow biopsy and aspirate collection (2 Research tubes 1 green top and 1 lavender top)
- Peripheral blood research tube (2 lavender top from peripheral blood)

9.3. Treatment Phases

Treatment will consist of the following phases:

- Ibrutunib Lead-in (Cohort A only)
- Induction Phase
- Continuation Phase
- Maintenance Phase
- Ibrutinib Monotherapy Phase

Ibrutinib Lead-In (Cohort A only)

The ibrutinib lead-in will apply to subjects in **Cohort A only** and will consist of one cycle of continuous daily ibrutinib monotherapy (Cycle -1) prior to beginning combination treatment as part of the induction phase.

Induction Phase

The induction phase will consist of two cycles of continuous ibrutinib daily dosing in combination with eight weekly doses of daratumumab. Daratumumab dosing can occur within a window of ±3 days. Induction will be defined as the first 8 weeks of combination treatment.

Subjects in Cohort A will begin the induction phase after the one cycle ibrutinib lead-in. Subjects in Cohort B will begin overall study treatment with Cycle 1 of the induction phase.

Continuation Phase

The continuation phase will consist of four cycles of continuous ibrutinib daily dosing in combination with bimonthly dosing of daratumumab (Day 1 and 15 of each cycle [±3 days]). Subjects from both cohorts will begin this phase after the induction phase.

Maintenance Phase

The maintenance phase will consist of 23 cycles of continuous ibrutinib daily dosing in combination with monthly dosing of daratumumab (Day 1 of cycle [±3 days]). Subjects from both cohorts will begin this phase after the continuation phase.

Ibrutinib Monotherapy Phase

The ibrutinib monotherapy phase will consist of 12 cycles of continuous ibrutinib daily dosing. Subjects from both cohorts will begin this phase after the maintenance phase.

Study Visit Schedule

Day 1 of Cycles -1 (Cohort A only), Cycles 1 – 13 and every 3 cycles thereafter (e.g. 16, 19, 22, 25, etc.), and End of Treatment will be considered required study visits at which all procedures and labs listed below and in Table 1 will be performed.

Subjects will also have doctor visits on each day of treatment with daratumumab that does not coincide with a required study visit (i.e. Days 8, 15, and 22 of Cycle 1-2, Day 15 of Cycles 3-6, and Day 1 of Cycles 14, 15, 17, 18, 20, 21, 23, 24 – referred to as non-study visits) at which the procedures and labs listed below and in Table 1 should be

performed prior to daratumumab administration in accordance with standard of care and per investigator discretion.

9.3.1. Ibrutinib Lead-In (Cohort A only, Cycle -1) and Induction Phase (Cycles 1 and 2)

Cycle -1 D1 **Cohort A Only**

- Medical history
- Adverse event evaluation
- Concurrent medications
- Physical exam
- Vital signs (including height and weight)
- CBC with differential
- Serum Chemistry (CMP, LDH, Phosphorus)
- Immunoglobulin M measurement
- Blood samples for research use

Cycle 1 and 2 Day 1

- Medical history
- Concurrent medications
- Physical exam
- Vital signs (including height and weight)
- CBC with differential
- Serum chemistry (CMP, LDH, phosphorus)
- Immunoglobulin M measurement
- Blood type and screen **(Cycle 1 only)**
- Adverse event evaluation
- Daratumumab infusion

Cycle 1 and 2 Days 8, 15, and 22 (non-study visits)

- Physical exam
- Vital signs (including height and weight)
- CBC with differential
- Serum chemistry (CMP, LDH, phosphorus)
- Adverse event evaluation
- Daratumumab infusion

9.3.2. Continuation phase (Cycles 3-6)

The continuation phase will consist daratumumab infusions every other week starting from Cycle 3 Day 1 through Cycle 6. During this period, study visits will occur on day 1 of each cycle. On non-study visits (i.e. Day 15 of each cycle), subjects will have daratumumab infusions, routine office visits, as well as routine lab work at the discretion of the investigator. On study visits, the listed labs and procedures below will occur.

Cycle 3-6 Day 1

- Medical history
- Concurrent medications
- Physical exam
- Vital signs (including height and weight)
- CBC with differential
- Serum chemistry (CMP, LDH, phosphorus)
- SIFE+ **(Cycle 4 only)**
- Immunoglobulin M measurement
- **Research** bone marrow biopsy/aspirate (1 green top and 1 lavendar top tube) **(Cycle 4 only [+15 day window])**
- Daratumumab infusion.
- HBV DNA PCR if at risk for reactivation **(Cycle 4 only)**

Cycle 3-6 Day 15 (non-study visits)

- Vital signs (including height and weight)
- CBC with differential
- Serum chemistry (CMP, LDH, phosphorus)
- Immunoglobulin M measurement
- Adverse event evaluation
- Daratumumab administration

9.3.3. Maintenance phase (Cycles 7-24)

The maintenance phase will consist of daratumamb infusions every 28 days starting Cycle 7 Day 1 study visits will occur every 28 days through Cycle 13 day 1. Subjects will be treated with daratumumab on all study visit days. From Cycle 13 day 1 up and through Cycle 24 day 1, daratumumab infusions will be given monthly but study visits will only occur every 3 cycles. On study visits the below listed labs and procedures will occur.

Cycles 7 – 13, 16, 19, and 22

- Medical history
- Concurrent medications
- Physical exam

- Vital signs (including height and weight)
- CBC with differential
- Serum chemistry (CMP, LDH, phosphorus)
- SIFE+ **(cycles specified in schedule of events)**
- Immunoglobulin M measurement **(cycles specified in schedule of events)**
- Peripheral blood research tube (2 lavendar top tubes) **(Cycle 7, 13, 19, and 25 only)**
- Adverse event evaluation
- Daratumumab infusion
- Radiographic evaluation **(C7, C13, C19, day 1 only [+15 day window])**
- HBV DNA PCR if at risk for reactivation **(Cycle 7, 10, 13, 16, 19, and 22 only)**

Cycles 14, 15, 17, 18, 20, 21, 23, and 24 (non-study visits)

- Medical history
- Concurrent medications
- Physical exam
- Vital signs (including height and weight)
- CBC with differential
- Serum chemistry (CMP, LDH, phosphorus)
- Immunoglobulin M measurement
- Adverse event evaluation
- Daratumumab infusion

9.3.4. Ibrutinib Monotherapy phase

The ibrutinib monotherapy phase will occur after patients have completed 24 cycles of combination therapy. After Cycle 24, study visits will still occur every 3 months but no daratumumab infusions will be given. On study visits, the below listed labs and procedures will occur.

Cycles 25, 28, 31, and 34

- Medical history
- Concurrent medications
- Physical exam
- Vital signs (including height and weight)
- CBC with differential
- Serum chemistry (CMP, LDH, phosphorus)
- SIFE+
- Peripheral blood research tube (2 lavendar top tubes) **(Cycle 25 only)**
- Adverse event evaluation

- Radiographic evaluation **(Cycle 25 and 31 day 1 only [+ a 15 day window])**
- HBV DNA PCR if at risk for reactivation **(Cycle 25, 28, and 31 only or every 12 weeks for up to 6 months post-daratumumab therapy)**

9.3.5. End of Treatment or Progression

Subjects that complete 3 years of therapy will then come off study. At C37D1, subjects will have EOT procedures collected. Additionally any subject that comes off for therapy early for toxicity, or progression will be required to return 28 days later for EOT procedures.

EOT (to be done at Cycle 37 or at time of treatment discontinuation)

- Medical history
- Concurrent medications
- Physical exam
- Vital signs (including height and weight)
- CBC with differential
- Serum chemistry (CMP, LDH, phosphorus)
- Immunoglobulin M
- **Research** bone marrow biopsy/aspirate (at time of progression (1 green top and 1 lavendar top)
- Peripheral blood research tubes C37D1 (2 lavendar top tubes)
- Adverse event evaluation
- Radiographic evaluation **(Cycle 31 day 1 only [+ a 15 day window])**

10. Treatment Administration

Treatment will be administered on an outpatient basis. Appropriate dose modifications for daratumumab and ibrutinib are described in Section 6.

Ibrutinib will be administered as 3, 140mg capsules daily for a total daily dose of 420mg. Subjects will be asked to take the capsules orally with or without food. Subjects will take the pills on a continuous daily basis with once cycle of treatment consisting of 28 days. Subjects will take their first dose of ibrutinib before or after their daratumumab infusion. On days in which they do not receive a daratumumab infusion, they will be asked to take their ibrutinib capsules at the same time each day. Subjects will continue daily dosing of ibrutinib until disease progression, toxicities, or study completion whichever comes first.

Daratumumab will be administered per the current package insert. Subjects will receive 16mg/kg weekly for 8 total doses. They will then receive 16mg/kg of daratumumab every other week starting on Cycle 3-6. From Cycle 7-24, subjects will receive daratumumab 16mg/kg on an every 4 week basis until disease progression, toxicities or study completion whichever comes first. Subjects will be premedicated with 100mg of methylprednisolone intravenously (IV), 650mg of

acetaminophen PO, and 25-50mg of Benadryl IV all taking 30 minutes prior to infusions with daratumumab. Methylprednisolone dosing may be reduced to 60mg IV with subsequent doses after the first infusion if no adverse events are recorded. Subjects will be asked to take 20mg of methylprednisolone PO for two days after each infusion and this can be eliminated after completion of the first cycle at the investigators discretion if no adverse events are recorded.

10.1. General Concomitant Medication and Supportive Care Guidelines

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted and patient should receive full supportive care during study participation (including fluids and electrolyte replacement, and antibiotics when appropriate). Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy. Transfusions may be given in accordance with institutional policy. After consultation with the Sponsor the following may be considered; localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies. Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

10.2. Medications to be Used with Caution with Ibrutinib

Ibrutinib is metabolized primarily by CYP3A4. The co-administration with strong CYP3A or moderate CYP3A inhibitors may increase ibrutinib concentrations which may increase the risk of drug-related toxicity. Dose modifications of ibrutinib are recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Avoid grapefruit and seveille oranges.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction. In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp).

A list of common CYP3A inhibitors and inducers is provided in **Appendix B**. Please see table II for dose modification guidelines for ibrutinib if CYP3A inhibitors are required.

See below Table 2 for dose modification based on CYP3A inhibitor used.

Table 2. Dose modifications based on CYP3A inhibitor usage.

Co Administered Druge	Recommended Ibrutinib dose
• Moderate CYP3A inhibitor • Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100mg twice daily, or 200mg twice daily	140mg once daily
• Posaconazole suspension 200mg three times daily or 400mg twice daily • Posaconazole IV injection 300mg once daily • Posaconazole delayed release tablets, 300mg once daily.	70 mg once daily
• Other stronger CYP3A inhibitors	Avoid concomittant use

10.2.1. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

10.2.2. Management of Minor Surgical Procedures

For minor procedures such as (central line placement, needle biopsy, lumbar puncture, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and not restarted until 3 days after the procedure. Bone marrow biopsies may be performed while on ibrutinib.

10.2.3. Management of Major Surgical Procedures

For any surgery or procedure that will require sutures or staples for closure, ibrutinib should be held for at least 7 days prior to the planned intervention and restarted at least 7 days after the procedure at the discretion of the investigator. For emergent surgical interventions, ibrutinib should be held immediately and until the site is healed or for at least 7 days whichever is longer.

10.2.4. Prohibited Concomitant Medications on Study

Any non-study protocol related chemotherapy, anti-cancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment. Corticosteroids for the treatment of the underlying malignancy are prohibited (Refer to Section 9.1 for further guidance).

11. Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s) greater than 4 weeks from scheduled dose, combination treatment may continue for 2 years with 1 year of ibrutinib monotherapy or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

11.1. Duration of Follow Up

The anticipated duration of patients on study will be 3 years. Patients will be followed for 1 year after completion of combination treatment, or for 28 days after removal from study, or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event even if that period is longer than 28 days.

12. Dosage and Administration of Study Drugs.

12.1. Study Drug Administration Overview

Daratumumab and ibrutinib is to be administered as described in the Schedule of Events Table 1. Each cycle is 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur +/- 3 days of the scheduled day in order to accommodate the schedule of the site or the subject with Day 1 of each subsequent cycle adjusted accordingly to maintain the 28 day cycle duration. During weeks 1-24 daratumumab will be given weekly or bi weekly +/- 3 days in order to accommodate the schedule of the site or subject. During Screening and prior to daratumumab infusion on C1D1 blood type and screening

should be collected.

12.1.1. Daratumumab Administration

Daratumumab (16mg/kg) will be administered by IV infusion to subjects initially once weekly for 8 weeks, then every other week for 16 weeks, followed by infusion every 4 weeks thereafter until disease progression, unacceptable toxicity, or completion of 2 years of therapy.
Each dose will be calculated based on the subject's actual weight rounded to the nearest kilogram. Dosing will be based off the screening weight unless it changes +/- 10% at which point doses will be recalculated. All infusions will be performed as outpatient visits with vital sign monitoring to occur per institutional infusion guidelines.

12.1.2. Daratumumab Preinfusion Medications

Preinfusion medications are required for subjects on days they receive daratumumab infusions and will receive the following medications prior to each infusion:

- Acetaminophen 650mg orally no more than 1 hour prior to daratumumab infusion
- Diphenhydramine 25-50mg intravenous or orally 30 minutes prior to infusion.
- Methylprednisolone 100mg intravenous 30 minutes prior to infusion. If patients tolerate the infusion without reactions, a lower dose of 60mg methylprednisolone may be substituted for subsequent infusions.

12.1.3. Daratumumab Postinfusion Medications

Subjects will be asked to take 20 mg of methylprednisolone or glucocorticoid equivalent dose for 2 days post infusion. Consideration should be given to provide short acting beta adrenergic receptor agonists to provide supportive care should bronchospasm occur after returning home from the clinic. If there are no reactions after 4 doses then post-infusion medications may be waived at the investigator's discretion.

12.2. Management of Infusion-Related Reactions

Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, and a defibrillator) must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an infusion-related reaction develops, then the infusion should be paused. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

If an infusion is paused, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

12.2.1. Infusion-Related Events of Grade 1 or Grade2

If the investigator assesses an adverse event to be related to the daratumumab infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the subject experiences a Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from the onset, then the subject must be withdrawn from treatment.

12.2.2. Infusion-Related Reactions of Grade3 or Higher

For infusion-related adverse events that are Grade 4, the infusion should be stopped and treatment with daratumumab will be discontinued for that subject.

For infusion-related adverse events that are Grade 3, the daratumumab infusion must be stopped, and the subject must be observed carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion. If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion.
Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject.

12.3. Ibrutinib Administration

Ibrutinib 420 mg (1m 420mg tablet) is administered orally once daily. The tablet is to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The tablet

should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. During treatment days with daratumumab combination dosing, ibrutinib should be taken 0-2 hours prior to daratumumab with 8 ounces of water.

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be dispensed to anyone.

12.3.1. Ibrutinib Overdose

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

12.4. Dose Delays and Dose Modification

Dose modification of daratumumab is not permitted, but dose delay remains the primary method for managing daratumumab-related toxicities. Ibrutinib and daratumumab therapy should be held until recovery upon the onset of any of the following toxicities:

- Grade 4 hematologic toxicity
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
    - Grade 3 nausea that responds to anti-emetics within 7 days
    - Grade 3 vomiting that responds to anti-emetics within 7 days
    - Grade 3 diarrhea that responds to anti-diarrheal within 7 days
    - Grade 3 fatigue that was present at baseline or that lasts for <7 days.
    - Grade 3 asthenia that was present at baseline or that lasts for less than 7 days after.

Supportive care should be provided, and growth factor support should be applied as outlined in

Section 5.3.

If the investigator feels the toxicities outlined above, are likely attributed to ibrutinib dosing, daratumumab dosing may continue without being held after discussion with the study monitor. Upon recovery of ≤ Grade 2, ibrutinib dosing should be the initial drug restarted. Daratumumab infusions should restart at least 7 days after ibrutinib dosing has resumed and there has been no recurrence of the toxicity.

12.4.1. Daratumumab Dose Delay Management

If dosing is delayed for either toxicity or other non-toxicity related issue then the following schedule should be followed during the specific phases of daratumumab treatment.

During the induction phase (Cycles 1 and 2) if the dose is delayed >3 days then that week's dose will be considered missed and treatment will commence the following week. If a missed dose occurs during induction, then that dose will not be made up and subjects will remain on schedule.

During the consolidation phase (Cycles 3-6) if a dose is held greater than 1 week, then the next dose given should be the scheduled Day 15 dose.

During the maintenance phase Cycle 7 and beyond if a dose is delayed greater than 2 weeks then it should be resumed with the subsequent cycle on day1.

12.4.2. Ibrutinib Toxicity Management

For toxicities outlined in Section 12.4 the following dose modifications are to be taken:

- First Occurrence: Withhold ibrutinib until recovery to Grade 1 or less and restart at the original dose level
- Second Occurrence: Withhold ibrutinib until recovery to Grade 1 or less, restart at 280mg/day
- Third Occurrence: Withhold ibrutinib until recovery to Grade 1 or less, restart at 140mg/day
- Fourth Occurrence: Discontinue ibrutinib.

13. Pharmaceutical Information

13.1. Investigational Agent-Daratumumab

Daratumumab as a drug product is a colorless to yellow liquid concentrate. It is presented at a target concentration of 20 mg/mL in a 6R or 25R vial with a nominal fill volume of 5 mL or 20 mL, respectively. It is intended for administration by the IV route after dilution in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) provided by the investigation site. The

diluent will be a commercially available product approved by the competent authority of the relevant country.

13.2. Availability of study drugs

Daratumumab is an investigational agent supplied to investigators by Janssen. The study drug will be open-label with labeling fulfilling all requirements specified by governing regulations. Ibrutinib will be used per its FDA labeling and will be obtained through commercial mechanisms via the subject's insurance.

13.3. Daratumumab Accountability

Daratumumab Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents received from Janssen on a Drug Accountability Record Form (DARF).

14. Measurement of Effect

During this study, participants will be evaluated every 4 weeks +/- 1 week for Cycles 1-12 and then every 12 weeks +/- 2 weeks for Cycles 13-26 during combination treatment to complete 2 years of treatment. Subjects that complete combination treatment will be evaluated on single agent ibrutinib every 12 weeks +/- 2 weeks for an additional 1 year until study completion. Subjects will be assessed for efficacy according to the response criteria in Section 9.1 adopted by the Third International Workshop on WM.

14.1. Response Criteria

Subjects will be evaluable for a response if they have completed 2 Cycles of combination induction treatment (Weeks 1-8). See **Appendix C** for summary of response criteria.

Complete Response (CR): A complete response (CR) is defined as having resolution of WM related symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. A complete response requires reconfirmation demonstrating normal serum IgM levels, and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later.

Very Good Partial Response (VGPR): ≥90% reduction in serum IgM levels, or normalization of serum IgM levels.

Partial Response (PR): ≥ 50% reduction in serum IgM levels

Minor Response (MR): 25-49% reduction in serum IgM levels

Progressive Disease (PD): >25% increase in serum IgM level occurs with an absolute increase of at least 500mg/dL from the lowest attained response value, or progression of clinically significant disease related symptoms. Reconfirmation of the initial IgM increase is required when the IgM is the sole criterion for progressive disease. For participants on active therapy who are on a drug hold for > 7 days an increase in serum IgM will not be considered progression if in the investigators opinion it is secondary to the drug hold. Subjects will be allowed reinitiation of drug. If after four consecutive weeks on active therapy there is no decrease in IgM, subjects will be considered to have progressive disease. If there is clinical benefit continuation on trial will be considered. Cases such as this should be discussed with the study sponsor. An increase of 1cm in any axis for adenopathy or 2 cm in the craniocaudal axis of the spleen will be considered progression. Development of central nervous system or transformation will be considered progressive events.

Stable Disease (SD): <25% change in serum IgM levels in the absence of new or increasing adenopathy, splenomegaly or other signs of active WM.

Overall Response: Includes MR, PR, VGPR, CR
Major Response: Includes PR, VGPR, CR

14.2. Time to Event Definitions

Duration of Response (DoR): The duration of overall response is measured from the time measurement criteria are met for Minor response or better until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest IgM measurements recorded since the treatment started).

Progression-Free Survival (PFS): PFS is defined as the duration of time from start of treatment to time of progression or death.

Overall Survival (OS): OS is defined as the duration of time from start of treatment to time of death or last follow-up.

Time to Progression (TTP): TTP is defined as the time to tumor progression as defined in Section 9.1. If the subject has not progressed, then data will be censored at the last study visit at which a tumor assessment was performed.

Evaluation of toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Daratumumab.

Evaluation of response. All patients included in the study will be assessed for response to treatment if they have completed Cycle 2.

15. Data Reporting / Regulatory Considerations

15.1. Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients.

15.2. REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group-based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

15.3. Regulatory Considerations

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

16. Statistical Considerations

Because this is a pilot study, no formal sample size/power calculation is required. However, with 12 patients each cohort, an exact binomial (Clopper-Pearson) 95% confidence interval for the toxicity proportion (i.e., primary endpoint) can be constructed to have a width of approximately 45.0% (1.6%, 46.5%) (i.e., separate confidence interval for each cohort). This calculation assumes that the toxicity proportion for the incidence of non-hematologic Grade ≥ 3 events will be no greater than 15% in either cohort. Secondary endpoints include major response (PR/VGPR/CR), percentage of patients with deepening of response in Cohort B, duration of response, and time to progression. Given this is a pilot study with low subject enrollment and lack of power, analysis of outcomes will remain descriptive without comparison analyses between cohorts. The toxicity and major response proportions will be calculated for each cohort along with exact binomial (Clopper-Pearson) 95% confidence intervals. Duration of response and time to progression will be descriptively reported for each cohort. Assuming adequate follow-up time, Kaplan-Meier survival analysis will be used to assess progression-free survival (PFS) and overall survival (OS) in each cohort. All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for 1) the toxicity proportion, 2) the major response proportion, and 3) median PFS/OS-time and PFS/OS proportions, will be calculated to assess the precision of the obtained estimates. All analyses will

be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and Stata Version 15.0 (StataCorp, College Station, TX).

17. Reporting and Exclusions

17.1. Adverse Events and Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

17.2. Adverse Event Definition

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

17.3. Adverse Events of Special Interest for Daratumumab (DARZALEX®)

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- HBV Reactivation
- Visual Disturbance
- Other malignancies

Any Adverse Event of Special Interest that is to be reported to the COMPANY should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of knowledge of the event.**

17.4. Adverse Events of Special Interest for Ibrutinib (Imbruvica®)

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- *Major Hemorrhage*

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

- *Intracranial Hemorrhage*

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

- *Other Malignancies*

In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

Any Adverse Event of Special Interest that is to be reported to the COMPANY should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of knowledge of the event.**

17.5. Individual Case Safety Report

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender

- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)

17.6. Product Quality Complaint

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

17.7.Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

17.7.1. Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]
- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

17.7.2. Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

17.8.Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

For DARZALEX™ (daratumumab),the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure

18. Special Reporting Situations

SAE's include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Reporting of SAE to IRB

- All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: https://research.weill.cornell.edu/sites/default/files/immediate_reporting_policy.pdf

Reporting of SAE to FDA [For protocols where WCMC is the Sponsor-Investigator]

- If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA. The investigator must notify the FDA of any SAE's as soon as possible but no later than 7 calendar days after the initial receipt of the information

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

18.1.Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

19. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

20. Procedures for Reporting Safety Data and Product Quality Complaints for Janssen Medicinal Products to Janssen Scientific Affairs, LLC

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

20.1.SAEs, Adverse Events of Special Interest and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The PRINCIPAL INVESTIGATOR will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 15,Transmission Methods, in English within 24-hours of becoming aware of the event(s).

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE, Adverse Events of Special Interest or pregnancy exposure report to Janssen Scientific Affairs, LLC.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, within 24 hours becoming aware, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, serious ADR or special situation is required.

20.2.Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

20.3.PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected for any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.
If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

21. Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

22. Data and Safety Monitoring Plan (DSMP)

Monitoring activities will be commensurate with the nature, size and complexity of the trial in accordance with institutional policies and will be determined after IRB and Data Safety Monitoring Board (DSMB) review of the protocol immediately prior to study activation. For this study we will utilize a Weill Cornell Medicine DSMB.

We will evaluate safety of combination therapy after 12 subjects have been enrolled onto the protocol and completed 8 weeks of combination induction therapy. The study team will review all subject data at this specified time point and provide a written report to the DSMB for review. Stopping rules will be employed in this study based on observed toxicities from monotherapy trials in subjects with multiple myeloma receiving daratumumab or WM subjects receiving monotherapy ibrutinib. For purposes of this safety analysis, each subject will be assessed individually and toxicities tabulated. Only toxicities occurring within the first 8 weeks of combination treatment will be considered for potential study termination.

In monotherapy daratumumab or ibrutinib studies, Grade 3 or greater non hematologic toxicities were rare with the most common event being pneumonia noted in 6% of subjects respectively for daratumumab and ibrutinib (data from prescribing inserts). Grade 3 or greater hematologic toxicities when restricted to anemia, thrombocytopenia, or neutropenia were noted in up to 20% of subjects treated with daratumumab monotherapy and up to 19% in subjects treated with ibrutinib monotherapy.

Based on these observed events we will stop the study if 5 of the first 12 subjects enrolled experience a Grade 3 or greater, toxicity (heme or non-heme) which leads to a study drug hold greater than 28 days or leads to either study drug discontinuation within the first two months of treatment. Any drug hold that occurs within the first 8 weeks but extends beyond the initial 8 week monitoring period will be followed for a full 28 days. For a toxicity to be included in this analysis, the toxicity must be considered due to the study drug per investigator assessment. Accrual will be held upon enrollment of the 12th evaluable subject until they have been observed through induction and the study team in consultation with the DSMB have made a determination regarding additional enrollment, this study hold is anticipated to last approximately 3 months.

- Type, severity, frequency, duration, and relationship to study drug of any AEs or abnormalities of laboratory tests, SAEs, or AEs leading to discontinuation will be recorded.
- Monthly IgM serum levels and every 6 month CT scans will be recorded and used to assess efficacy.
- Subjects may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a subject from the study:
    - Non-compliance
    - Withdrawal of consent by the subject
    - Erroneous inclusion into the study
    - Development of defined exclusion criteria
    - Intolerable toxicity or adverse event
    - Pregnancy
    - Termination of the study by the sponsor

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Appendix A: Treatment indications for patients entering study.

Clinical and laboratory indications for initiation of therapy
• Recurrent fever, night sweats, weight loss, fatigue
• Hyperviscosity
• Lympadenopathy which is either symptomatic or bulky (≥5cm in maximum diameter)
• Symptomatic hepatomegaly and/or splenomegaly
• Symptomatic organomegaly and/or organ or tissue infiltration
• Peripheral neuropathy due to WM
• Symptomatic cryoglobulinemia
• Cold agglutinin anemia
• Immune hemolytic anemia and/or thrombocytopenia
• Nephropathy related to WM
• Amyloidosis related to WM
• Hemoglobin ≤10g/dL
• Platelet count $<100x10^9$/L

Appendix B: Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below.

Inhibitors of CYP3A	**Inducers of CYP3A**
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbituarates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
beceprevir	St. John's Wort
telaprevir	troglitazone
troleandomycin	
posaconazole	
Moderate Inhibitors:	
aprepitant	
amprenavir	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole[b]	
imatinib	

Source: http://medicine.iupui.edu/clinpharm/ddis/main-table/

a. Based on PBPK simulations, up to 9.7-fold increase in AUC and 6.2-fold increase in C_{max} could be observed. If ibrutinib needs to be administered with posaconazole, 140 mg ibrutinib will be dosed.

b. Based on internal data, 140 mg ibrutinib dosed with voriconazole produces ibrutinib exposures similar to 560 mg ibrutinib dosed alone. Therefore, for this study, if ibrutinib needs to be administered with voriconazole, 140 mg ibrutinib will be dosed.

Appendix C: Consensus-based uniform response criteria for WM developed by the International Workshop on WM ,updated in the Sixth IWWM and published by Owen et al.

Response category Definition	
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline* Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but<90% reduction in serum IgM level from baseline* Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but<50% reduction in serum IgM level from baseline* No new signs or symptoms of active disease
Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline* No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	≥25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

*Sequential changes in IgM levels may be determined either by M-protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

**An absolute increase of >5 g/L (0.5 g/dL) is required when the increase of IgM component is the only applicable criterion.