NCI Protocol #: *N/A.*

DF/HCC Protocol #: 17-164

TITLE: A Phase 2 Study of Daratumumab in Patients with Relapsed or Refractory Waldenström Macroglobulinemia.

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Agent: Daratumumab (Darzalex®)

IND #:134092
IND Sponsor: Jorge J. Castillo, MD

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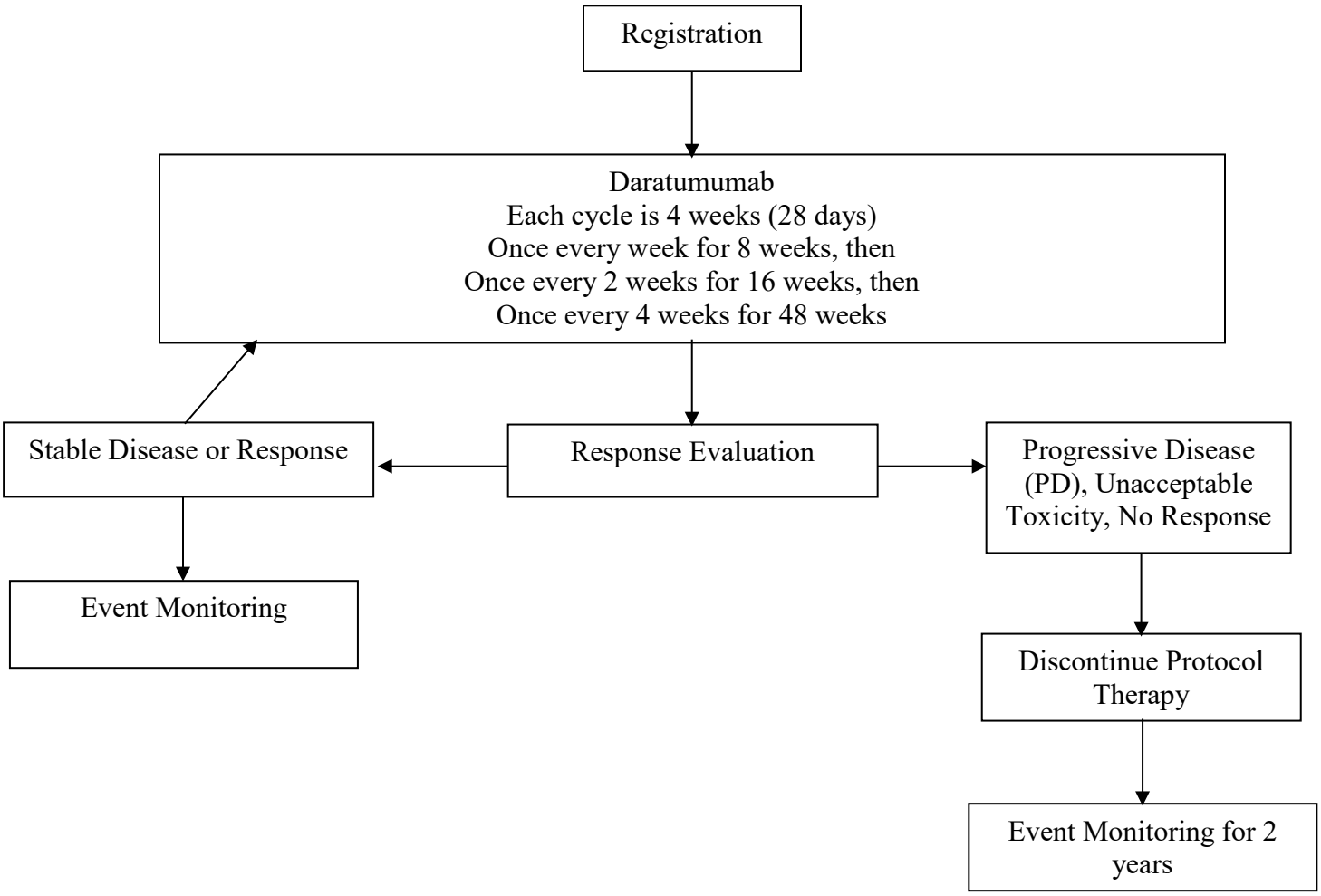
SCHEMA


Registration
Daratumumab
Each cycle is 4 weeks (28 days)
Once every week for 8 weeks, then
Once every 2 weeks for 16 weeks, then
Once every 4 weeks for 48 weeks
Stable Disease or Response
Response Evaluation
Progressive Disease (PD), Unacceptable Toxicity, No Response
Event Monitoring
Discontinue Protocol Therapy
Event Monitoring for 2 years

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1. OBJECTIVES

1.1 Study Design

This is a Phase 2, multi-center study designed to evaluate the efficacy of single agent daratumumab in relapsed or refractory WM patients.

A Screening visit will be conducted within 30 days of Day 1 of Cycle 1. If the Screening visit and screening laboratories are done within 14 days of Cycle 1, Day 1, then a separate visit and laboratories will not be required on Cycle 1, Day 1, though may be done at the investigator's discretion. At the Screening visit, a medical history will be obtained, and a complete physical examination will be performed including vital signs and an ECOG performance status. A bone marrow aspirate and biopsy may be performed within 90 days prior to Cycle 1 Day 1, and CD38 expression (by flow cytometry and/or immunohistochemistry), and MYD88 and CXCR4 mutation status will be determined. CT scanning of the chest, abdomen and pelvis with intravenous contrast, if possible, may be performed within 90 days prior to Cycle 1 Day 1. If a participant has known extramedullary disease outside of the chest, abdomen, or pelvis, then imaging of the lesion should be conducted by investigator-determined modality. The same modality should be used throughout the study. Clinical laboratory tests including a complete blood count plus differential, comprehensive chemistry panel (electrolytes, BUN, creatinine, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase), beta 2-microglobulin, serum and protein electrophoresis with quantification of immunoglobulins (IgM, IgG, IgA) and immunofixation studies, indirect antiglobulin testing, and serum pregnancy tests for women of child-bearing potential will also be performed at the Screening visit.

Participants who meet the eligibility requirements will be enrolled on study and initiated on daratumumab. Daratumumab will be administered in three phases: Induction, consolidation and maintenance. The duration of each cycle is 28 days. During induction, participants will receive daratumumab on days 1, 8, 15 and 22 of each 28-day cycle for 2 cycles for a total of 8 infusions or 8 weeks of therapy. Consolidation will start 2 weeks +/- 3 days after completing induction. During consolidation, daratumumab will be administered on days 1 and 15 of each 28-day cycle for 4 cycles for a total of 8 infusions or 16 weeks of therapy. Maintenance will start 4 weeks +/- 7 days after the 8^{th} infusion of consolidation is completed. During maintenance, daratumumab will be administered on day 1 of each 28-day cycle for a total of 12 cycles or 48 weeks of therapy. Every effort should be made to keep subjects on the planned dosing schedule. However, doses given within 3 days of the scheduled dose are permitted as long as the interval between doses is at least 5 days. Daratumumab will be administered for a total of 28 infusions or until progression, unacceptable toxicity, or decision to withdraw from the trial. Dose reductions due to daratumumab-related toxicity will not be permitted. The total duration of therapy is approximately 72 weeks (1.5 years). Participants will remain on study as long as they do not have unacceptable toxicity or demonstrate progressive disease.

Response criteria updated at the Sixth International Workshop on Waldenström macroglobulinemia (Owen 2013) will be used to assess response, stable disease, and progressive disease.

An interim safety analysis will be performed once at least 10 patients had received the first 4 weekly doses of daratumumab.

1.2 Primary Objectives

- To assess the best overall response rate (ORR) (>25% reduction in disease burden) to single agent daratumumab in relapsed or refractory WM patients at any point on therapy.

1.2.1 Secondary Objectives

- To assess the minor, partial, very good partial and complete response rate to single agent daratumumab in relapsed or refractory WM patients.
- To determine Progression Free Survival (PFS) following daratumumab in relapsed or refractory WM patients
- To evaluate the safety profile of daratumumab in patients with relapsed or refractory WM patients.

1.2.2. Exploratory objectives

- To observe differences (if any) in overall and major responses (PR or better) attainment, and time to response based on tumor CD38 expression, and MYD88 and CXCR4 genotype.

2. BACKGROUND

2.1 Study Disease

Waldenström macroglobulinemia is a malignant B-cell lymphoma associated with the accumulation of clonal lymphoplasmacytic cells and monoclonal IgM secretion. Whole genome sequencing has revealed activating somatic mutations in MYD88 (L265P) and the C-terminal domain of CXCR4 in Waldenström macroglobulinemia (Treon et al, NEJM 2012; Hunter et al, Blood 2014). In tumor cells, $MYD88^{L265P}$ triggers NFkB activation via two divergent pathways involving Bruton tyrosine kinase (BTK) and IRAK1/IRAK4 (Yang et al, Blood 2013). Ibrutinib is an orally administered, small molecule inhibitor of BTK, which triggers apoptosis of $MYD88^{L265P}$ expressing Waldenström macroglobulinemia cells. In a multicenter prospective study, 63 symptomatic Waldenström's macroglobulinemia patients with a median of 2 (range 1-9) prior therapies, 40% of whom were refractory to their prior therapy received ibrutinib (420 mg PO once daily) until progression or unacceptable toxicity (Treon et al, NEJM 2015). Post-therapy, median serum IgM levels declined from 3,520 to 880 mg/dL; hemoglobin rose from 10.5 to 13.8 g/dL, and bone marrow involvement declined from 60% to 25% ($p<0.01$ for all comparisons). The median response time was 4 weeks. Overall and major response rates were 90.5% and 73.0%, and were highest in patients with $MYD88^{L265P}CXCR4^{Wild\text{-}Type\ (WT)}$ (100% and 91.7%), followed by $MYD88^{L265P}CXCR4^{WHIM}$ (85.7% and 61.9%), and $MYD88^{WT}CXCR4^{WT}$ (60% and 0%) (Treon et al, NEJM 2015b). No complete responses were observed. Ten patients achieved a VGPR (15.8%), 8 of whom had $CXCR4^{WT}$ disease. Patients with $MYD88^{L265P}CXCR4^{WHIM}$ showed delayed major response kinetics in comparison to patients with the $MYD88^{L265P}CXCR4^{WT}$ genotype (Treon et al,

NEJM 2015).

Given the impact of $CXCR4^{WHIM}$ mutations on ibrutinib responses and response kinetics, we sought to address the functional significance of WHIM-like mutations in CXCR4 that are present in up to 40 percent of WM patients, and represent the first reporting of CXCR4 somatic mutations in cancer. We showed that $CXCR4^{WHIM}$ mutations conferred decreased receptor down-regulation, as well as enhanced and sustained AKT and ERK activation following treatment with SDF-1a, the ligand for CXCR4 (Cao et al, Leukemia 2014; Cao et al, BJH 2015). Use of the CXCR4 antagonist AMD3100 blocked SDF-1a triggered AKT and ERK activation in $CXCR4^{WHIM}$ expressing WM cells. The central finding of these studies was that the CXCR4 WHIM-like mutations conferred resistance to ibrutinib triggered apoptosis in WM cells, a finding that was associated with persistent AKT and ERK activation. The finding that enhanced AKT and ERK activity following SDF-1a is present in $CXCR4^{WHIM}$ expressing cells, and that inhibition of these targets potentiated ibrutinib killing provides support for a potential explanation for the clinical results obtained in WM patients treated with ibrutinib. Consistent with these *in vitro* findings, robust pAKT staining was observed in tumor samples from $CXCR4^{WHIM}$ patients, which contrasted against marginal pAKT staining in tumor samples from $CXCR4^{WT}$ patients (Cao et al, Leukemia 2014). Importantly, pAKT staining remained robust despite continuous ibrutinib therapy for 6 months in $CXCR4^{WHIM}$ patients, and continued to be marginal in $CXCR4^{WT}$ patients. Conversely, low level pERK staining was observed at baseline, and following ibrutinib therapy in bone marrow samples, without any discernible differences between $CXCR4^{WT}$ and $CXCR4^{WHIM}$ patients. These findings depict constitutive AKT activity, which functions as a powerful survival factor in WM, as being relevant to *in vivo* $CXCR4^{WHIM}$ signaling, and likely in view of the aggregate findings of this study as a likely contributor to clinical resistance to ibrutinib. The additional finding that SDF-1a protected against apoptosis triggered by other WM relevant therapeutics including bendamustine, fludarabine, bortezomib, and idelalisib in WM cells engineered to express the $CXCR4^{WHIM}$ mutation is of great interest, and suggests the relevance of these findings against a broader array of agents used to treat WM (Cao et al, BJH 2015).

2.2 Daratumumab

Daratumumab is an IgG1κ human monoclonal antibody that targets CD38. Potential mechanisms of action have been investigated in both in vitro and in vivo studies. The results denote that complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) are major mechanisms of action for daratumumab. Half-maximal killing of myeloma cells in vitro by CDC and ADCC occurred at antibody levels of approximately 0.1 μg/mL and 0.03 μg/mL, respectively. Trials in the xenograft lymphoma model in severe combined immunodeficiency mice have shown that daratumumab potently inhibits the in vivo growth of CD38-expressing tumor cells at concentrations from 0.5 mg/kg.

In November 2015, the FDA granted accelerated approval for daratumumab to treat patients with multiple myeloma who have received at least 3 prior treatments. Daratumumab is not approved for the treatment of Waldenström Macroglobulinemia. Daratumumab is the first monoclonal antibody approved for treating multiple myeloma. The safety and efficacy of daratumumab were demonstrated in 2 open-label studies. In a phase I/II multicenter study, 104 patients with multiple myeloma were exposed to daratumumab (Lokhorst et al NEJM 2015). In the group that received

16 mg/kg IV doses, the ORR was 36%, including 2 patients with CR and 2 with VGPR. The median PFS was 5.6 months and 65% of the patients who responded did not have progression at 12 months. In a multicenter randomized phase II study, 106 patients received 16 mg/kg doses (Lonial et al Lancet 2016). The ORR was 29% with 3% stringent CR and 9% with VGPR. The median time to first response was 1 month, the median duration of response was 7.4 months and the median PFS was 3.7 months.

2.3 Rationale

CD38 surface expression is present on many cell types in different tissues including subsets of B and T-lymphocytes. Marked expression of CD38 has been demonstrated on plasma cells. Interestingly, no CD38 expression has been detected on pluripotent (early) CD34+ stem cells, while more mature (intermediate) CD34+ cells do express CD38. In WM, a substantial component of the malignant clone (40-70%) expresses CD38 (21-23). Results from in vitro trials of daratumumab show ADCC and CDC activity against fresh tumor cells (myeloma) and inhibition of the CD38 enzyme activity. CD38 catalyzes production of second messengers that affect calcium mobilization. Furthermore, daratumumab prevents in vivo tumor growth in a prophylactic (murine) xenograft model. Recent data supports that daratumumab therapy was associated with expansion of CD4+ T-helper as well as CD8+ cytotoxic cells, and increase in clonality of the T-cell receptor repertoire, which could enhance cytotoxic T-cell responses. Such finding is supported by the observation than responders to daratumumab have increased T-cell responses to viral and alloantigens suggesting an upregulation of antitumor immune response. Such changes in T-cell expansion were more evident in responders than in non-responders to daratumumab.

2.4 Correlative Studies Background

MYD88 L265P is a recently identified somatic mutation present in >90-95% of WM patients. MYD88 L265P supports growth and survival of WM cells by activation of Bruton tyrosine kinase (BTK), as well as IRAK1/4 (Yang et al, Blood 2013). Based on these findings, a clinical trial using the BTK inhibitor ibrutinib was investigated in 63 patients with relapsed or refractory WM (Treon et al, NEJM 2015). The study showed ibrutinib to be safe and effective, and supported the approval of ibrutinib by the US FDA, EMA, and Health Canada. Both MYD88 and CXCR4 tumor mutation status impacted responses to ibrutinib. Absence of MYD88 mutations, and presence of CXCR4 mutations were associated with lower response rates to ibrutinib. Moreover, responses were delayed by 6-12 months in subjects harboring CXCR4 mutations. In most WM patients, CXCR4 mutations are subclonal with an estimated median cancer cell fraction of 40-50%, though transcriptional signature remains relatively homogeneous (Hunter et al, Blood 2016; Xu et al, BJH 2016). Transduction of WM cells with CXCR4 WHIM receptors, results in enhanced activation of the growth factors pAKT and pERK (Cao et al, Leukemia 2014; Cao et al, BJH 2015).

Bone marrow aspirate (approximately 30 cc) will be collected at baseline, at initiation of maintenance, and within 4 weeks following completion of maintenance. Samples will be evaluated for the presence of MYD88 and CXCR4 mutations, as well as CD38 expression by flow cytometry and/or immunohistochemistry.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Clinicopathological diagnosis of Waldenström Macroglobulinemia (Owen et al. 2003), and meeting criteria for treatment using consensus panel criteria from the Second International Workshop on Waldenström macroglobulinemia (Kyle et al. 2003)

3.1.2 Bone marrow at screening positive for CD38 expression by flow cytometry and/or immunohistochemistry

3.1.3 At least one previous treatment for WM with either documented disease progression or no response (stable disease) to the most recent treatment regimen

3.1.4 Measurable disease, defined as presence of serum immunoglobulin M (IgM) with a minimum IgM level of >2 times the upper limit of normal of each institution is required

3.1.5 Participants with symptomatic hyperviscosity or serum IgM >5,000 mg/dL to undergo plasmapheresis prior to treatment initiation

3.1.6 Age ≥18 years

3.1.7 ECOG performance status ≤2 (see Appendix A)

3.1.8 Participants must have preserved organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,000/mcL
- Platelets ≥ 50,000/mcL
- Hemoglobin ≥ 8 g/dL
- Total bilirubin ≤ 1.5 mg/dL or < 2 mg/dL if attributable to hepatic infiltration by neoplastic disease
- AST/ALT ≤ 2.5 × institutional upper limit of normal
- EGFR ≥ 30 ml/min

3.1.9 Not on any active therapy for other malignancies with the exception of topical therapies for basal cell or squamous cell cancers of the skin. Participants progressing on ibrutinib therapy (or other BTK inhibitor) may continue on therapy through screening, stopping at least 1 day prior to Cycle 1 Day 1.

3.1.10 Females of childbearing potential (FCBP) must agree to use two reliable forms of contraception simultaneously or have or will have complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) while participating in the study; and 2) for at least 90 days after discontinuation from the study. FCBP must be referred to a qualified provider of contraceptive methods if needed. FCBP must have a negative serum pregnancy test at screening.

3.1.11 Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.

3.1.12 Able to adhere to the study visit schedule and other protocol requirements.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

3.2.1 Any serious medical condition, laboratory abnormality, uncontrolled intercurrent illness, or psychiatric illness/social condition that would prevent study participation.
3.2.2 Concurrent use of any other anti-cancer agents or treatments or any other investigational agents.
3.2.3 Any condition, including the presence of laboratory abnormalities, which places the participant at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
3.2.4 Known CNS lymphoma.
3.2.5 New York Heart Association classification III or IV heart failure.
3.2.6 Known history of Human Immunodeficiency Virus (HIV).
3.2.7 Active infection with Hepatitis B Virus (HBV) including participants with positive HBsAg testing at screening. Participants with evidence of resolved infection (i.e. 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 are excluded. EXCEPTION: Participants 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.
3.2.8 Active infection with Hepatitis C Virus (HCV) (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
3.2.9 Lactating or pregnant women.
3.2.10 Grade $\geq$2 toxicity (other than alopecia) continuing from prior anti-cancer therapy.
3.2.11 History of non-compliance to medical regimens.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Study Coordinator. All sites should call the Study Coordinator 617-632-5598 or 617-582-8667 to verify dose level availabilities.
Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse and/or data manager, and faxed (617-632-6752) or e-mailed (kirsten_meid@dfci.harvard.edu) to the Study Coordinator:

- Copy of serum protein electrophoresis, CBC, CMP, CT of the chest, abdomen and pelvis, and bone marrow biopsy report
- Screening visit note
- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist

The Eligibility Checklist should be filled out by a clinical study staff member and the "Screening Staff" section must be signed by them. Study staff at the Coordinating Center will review the eligibility documentation and sign as the "Enrollment Monitor."

The research nurse or data manager at the participating site will then call [617-632-5598 or e-mail [kirsten_meid@dfci.harvard.edu] the Project Manager to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration (SOP #: REGIST-101B) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the

participant's malignancy.

5.1 Treatment Regimen

Daratumumab will be administered in three phases: Induction, consolidation and maintenance. The duration of each cycle is 28 days. During induction, participants will receive daratumumab on days 1, 8, 15 and 22 of each 28-day cycle for 2 cycles for a total of 8 infusions or 8 weeks of therapy. Consolidation will start 2 weeks +/- 3 days after completing induction. During consolidation, daratumumab will be administered on days 1 and 15 of each 28-day cycle for 4 cycles for a total of 8 infusions or 16 weeks of therapy. Maintenance will start 4 weeks +/- 7 days after the 8th infusion of consolidation is completed. During maintenance, daratumumab will be administered on day 1 of each 28-day cycle for a total of 12 cycles or 48 weeks of therapy. Every effort should be made to keep subjects on the planned dosing schedule. However, doses given within 3 days of the scheduled dose are permitted as long as the interval between doses is at least 5 days. Daratumumab will be administered for a total of 28 infusions or until progression, unacceptable toxicity, or decision to withdraw from the trial. Dose reductions due to daratumumab-related toxicity will not be permitted. The total duration of therapy is approximately 78 weeks (1.5 years).

Regimen Description					
Agent	**Premedications; Precautions Approximately 60 minutes before daratumumab infusion**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Daratumumab	Pre-medications will be given as per section 5.4.1	16 mg/kg	IV	Induction: 2 cycles of weekly infusions Consolidation: 4 cycles of every other week infusions Maintenance: 12 cycles of monthly infusions	28 days (4 weeks)

Reported adverse events and potential risks are described in Section 7.

5.2 Pre-Treatment Criteria

Cycle 1, Day 1 results do not need to meet eligibility parameters. Day 1 chemistry and hematology laboratories must be reviewed prior to treatment.

Participants must meet the following criteria on treatment days of all cycles:

- No grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment within 7 days,
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue or asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab
- Neutrophil count ≥ 500/μL (growth factor permitted, including on day of treatment)

- No Febrile neutropenia of any grade
- Platelet count ≥ 50,000/μL in the presence of bleeding (platelet transfusion permitted, including on day of treatment)
- Platelet count ≥ 25,000 μL without bleeding (platelet transfusion permitted, including on day of treatment)

Daratumumab treatment should be resumed when the toxicity has resolved to ≤Grade 2. If the daratumumab administration does not commence within the pre-specified window of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

5.3 Agent Administration

Daratumumab 16 mg/kg will be administered per the Table 5.3.1. Participants should be observed for 30 minutes after the completion of the infusion.

Table 5.3.1. Daratumumab infusion instructions

	Dilution volume	**Initial rate (first hour)**	**Rate increment**	**Maximum rate**
First infusion	1000 mL	50mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hour of the first infusion.

[b] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥ 100 mL/hr in the first two infusions.

Vital signs (blood pressure, temperature, heart rate, respiratory rate) will be obtained before infusion, every 60 minutes (± 10 minutes) during the infusion period, and at 30 minutes (± 5 minutes) after the completion of infusion.

5.3.1 Infusion Related Reactions

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab as outlined below:

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate (Table 5.3.1).

- Grade 3 (severe): If the intensity of the reaction decreases to Grade 2 or lower, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 5.3.1. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.

- Grade 4 (life threatening): Permanently discontinue daratumumab treatment

Product description and storage information is described in Section 8.

5.4 General Concomitant Medication and Supportive Care Guidelines

Participants will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the participant about any new medications he/she is or has taken after the start of the study drug.

5.4.1 Prophylactically Prescribed Medication

All prophylactic premedication administration is mandatory. An antiviral should be prescribed for herpes zoster prophylaxis, with the participant initiating treatment within one week prior to starting Daratumumab and continuing for 3 months after treatment ends.

Premedications[1]:	**1st & 2nd Daratumumab Infusion**	**3rd & Subsequent Infusions***
60 minutes before daratumumab infusion	1. Acetaminophen 975mg PO 2. Diphenhydramine 25-50mg IV or PO 3. Methylprednisolone 100mg IV 4. Famotidine 20 mg IV 5. Montelukast 10mg PO 6. Fexofenadine 60mg PO	1. Acetaminophen 975mg PO 2. Diphenhydramine 25-50mg IV or PO 3. Methylprednisolone 60mg IV
2 hours after start of the infusion (Daratumumab infusion to be paused at this point)	1. Methylprednisolone 40mg IV 2. Famotidine 20mg IV 3. Diphenhydramine 25 mg IV	n/a
Post infusion	1. Methylprednisolone 20mg PO 24 & 48 hours after infusioncompletion 2. Albuterol Nebulizer solution 2.5mg Q6hours PRN wheezing**	1. Methylprednisolone 20mg PO 24 & 48 hours after infusion completion 2. Albuterol Nebulizer solution 2.5mg Q6hours PRN wheezing **

*If patient has not experienced any infusion reaction. Otherwise, continue with the 1st and 2nd infusion premedication schedule until 2 consecutive infusions given without infusion reaction
** The Albuterol Nebulizer is only for patients with a higher risk of respiratory complications. It can be administered for the first 4 infusions and after that, if there is no reaction, it can be discontinued.
[1]Sites outside DF/HCC may follow their internal standard practice for daratumumab premedications.

Methylprednisolone may be dose reduced per investigator discretion for participants who cannot tolerate the higher dose. Post infusion methylprednisolone may be discontinued per investigator discretion.

5.4.2 Permitted Treatments

Subjects may receive DVT prophylaxis (if needed) with LMWH, warfarin, or similar. All anticoagulants, and/or aspirin should be held in case the platelet count is <50,000 mm^3.

The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Colony stimulating factors, erythropoietin, and transfusion of platelets and red cells;
- It is important to prevent constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed);
- Plasmapheresis to prevent and/or treat IgM flare and symptomatic hyperviscosity

5.4.3 Avoidance of Medications

- Subjects taking oral or parenteral corticosteroids should be tapered off this medication for 5 half-lives prior to the first dose of daratumumab and must remain discontinued from all oral and parenteral corticosteroids while participating in the study (unless used for treatment of infusion reactions, rash, antiemetic prophylaxis or as part of the protocol chemotherapy regimen or subjects on low-dose corticosteroids (≤20 mg prednisone or equivalent) for chronic conditions. Investigators should discuss individual cases with the medical monitor.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 18 cycles or until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s).
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements.
- Participant decides to withdraw from the protocol therapy.

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the PI, Jorge J. Castillo at 617-632-3352.

5.6 Duration of Follow Up

Participants will be followed for up to 24 months after discontinuation from protocol therapy or start of new therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays will be made as indicated in the following table(s). No dose modification will be allowed. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.). All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted. If administration of daratumumab must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or missed according to rules described in below.

Dosing will be held for any of the following drug-related conditions:

- Grade 3 or higher non-hematologic toxicities with the following exceptions:
    - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment within 7 days,
    - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
    - Grade 3 fatigue or asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab
- Neutrophil count < 500/μL (growth factor permitted)
- Febrile neutropenia of any grade
- Platelet count < 50,000/μL in the presence of bleeding
- Platelet count < 25,000 μL without bleeding

Participants can be retreated according to the following guidelines once non-hematological toxicity has resolved to ≤ Grade 2, ANC ≥500/ μL, and/or platelets are ≥25,000/ μL without bleeding. If the toxicity has not resolved within 28 days, patients should discontinue treatment, unless allowed to continue by PI discretion.

Daratumumab treatment should be resumed when the toxicity has resolved to ≤ Grade 2. If the daratumumab administration does not commence within the pre-specified window (+/- 3 days and at least 5 days between doses) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up. If participants require a dose delay for plasmapheresis then the dose can be given up to 1 week later. This would not be considered a missed dose. If more than 2 consecutive planned doses of daratumumab are missed due to AEs, treatment continuation should be discussed with the overall PI before resumption of therapy.

Potential for IgM flare

Abrupt increases in serum IgM levels following administration of anti-CD20 monoclonal antibodies and intravenous immunoglobulin are well recognized in WM patients (Treon et al, Ann Oncol 2004; Ghobrial et al, Cancer 2004; Yang et al, ASH 2010; Furman et al, ASH 2011). Such abrupt increases can prompt symptomatic hyperviscosity in patients with high serum IgM levels, i.e. >5,000 mg/dL and can contribute to worsening of IgM related morbidity such as cryoglobulinemia, cold agglutinemia, and demyelinating neuropathy. Plasmapheresis is therefore used to treat symptomatic IgM flares, as well as prophylax in patients with high serum IgM levels. Following plasmapheresis, serum IgM levels will return to steady state in 5 weeks. As such, WM patients who undergo plasmapheresis will be non-evaluable for response purposes within 4 weeks of last plasmapheresis. It is recommended that patients with symptomatic hyperviscosity or a pre-treatment serum IgM level >5,000 mg/dL undergo plasmapheresis before treatment with daratumumab. Treatment with daratumumab may be delayed for up to one week if plasmapheresis

is warranted. Close serial monitoring of serum IgM levels (at least weekly) is recommended for all participants during cycles 1 and 2. After cycle 2, monitoring would be per protocol on Days 1 & 15 of Cycles 3-6, and Day 1 of Cycles 7-18 unless directed otherwise by treating physician.

6.1 Management of Hepatitis B Virus Reactivation

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 see Section 10.

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.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List

7.1.1.1 Adverse Event List(s) for Daratumumab

Among the subjects treated with a therapeutic dose of daratumumab 16 mg/kg administered intravenously as monotherapy:

- 6 subjects (4%) discontinued daratumumab treatment due to a treatment emergent adverse event (TEAE), none of which were considered by the investigator to be related to daratumumab.
- 3 subjects (2%) died due to TEAEs; no deaths due to daratumumab-related TEAEs were reported.
- The most frequently reported TEAEs were fatigue (40%); nausea and anemia (28% each); back pain (26%); neutropenia (23%); pyrexia (22% each), upper respiratory tract infection (22%) and thrombocytopenia (21%).
- SAEs were reported in 33% of subjects, the most frequently reported SAEs were pneumonia (6%) and pyrexia, hypercalcemia, and general physical health deterioration (3% each).
- Grade 3 or 4 AEs were reported in 56% of subjects; most commonly these were anemia (17%), thrombocytopenia (14%), neutropenia (12%), lymphopenia (6%), leukopenia, pneumonia, and hypertension (5% each).
- Infusion-related reactions (IRRs) were reported in 48% of subjects. Of the subjects who

experienced an IRR, 95% experienced an IRR at the first infusion; 11% had an IRR at more than one infusion. Bronchospasm was reported in 3% of subjects. Grade 3 IRRs were reported in 3% of subjects, no Grade 4 or 5 IRRs were reported. Grade 3 IRRs included bronchospasm (reported in 2 subjects [1%]); the remaining Grade 3 IRRs of dyspnea, hypoxia, and hypertension were reported in 1 subject (0.6%) each.

- AEs of infections were reported in 59% of subjects. The most frequently reported were upper respiratory tract infection (22%), nasopharyngitis (15%), pneumonia (9%), sinusitis (7%), and urinary tract infection (6%). Grade 3 or higher TEAEs of infections or infestations were reported in 10% of subjects and 1% of subjects, respectively.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the NCI web site http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

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)

7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, all grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.3.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
Investigations	Platelet count decreased	4	No	Related	If hospitalization required, must be reported to DFCI IRB and PI
Investigations	Neutrophil count decreased	4	No	Related	If hospitalization required, must be reported to DFCI IRB and PI

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to Janssen

7.5.1 Overview

As the sponsor of the Study, PRINCIPAL INVESTIGATOR shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The PRINCIPAL INVESTIGATOR will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

7.5.2 Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: DARZALEX™ (daratumumab).

7.5.3 Definitions

7.5.3.1 Adverse Event (AE)

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.

7.5.3.2 Adverse Events of Special Interest

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
- Tumor lysis syndrome
- Other malignancies
- Intravascular hemolysis – all grades

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.**

7.5.3.3 Individual Case Safety Report (ICSR)

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

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- 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)
- Janssen protocol ID

7.5.3.4 Product Quality Complaint (PQC)

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

7.5.3.4.1 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) 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.

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 or 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.

7.5.3.5 **Serious Adverse Event (SAE), Adverse Events of Special Interest and Special Reporting Situations (see section 7.5.3.2)**

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 English **within 24-hours of becoming aware of the event(s).**
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, Adverse Event of Special Interest, serious ADR or special situation is required.

- The PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 10 within **24 hours of such report or correspondence being sent to applicable health authorities.**

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.

7.5.3.5.1 **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.]

7.5.3.5.2 **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.

7.5.3.5.3 **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.

7.5.3.6 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.

7.5.3.7 Special Reporting Situations

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.**

7.5.3.8 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.

7.5.3.9 Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs)

SAE Email Address: IIS-BIO-VIRO-GCO@its.jnj.com

SAE Facsimile Number: 1-866-651-0219

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Janssen (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Daratumumab

8.1.1 Description

Daratumumab, a CD38 antagonist, is being developed for the treatment of multiple myeloma and other malignancies. The active ingredient, daratumumab, is a human immunoglobulin G1 kappa

(IgG1κ) monoclonal antibody (mAb) that binds CD38 expressing cells with high affinity in a variety of hematological malignancies, including myeloma, lymphomas, and leukemias, as well as other cell types and tissues with various expression levels.

8.1.2 **Form**

The active ingredient, daratumumab, of the IMP is a human mAb that specifically recognizes CD38 protein expressed on the surface of plasma cells, but also other cell types and tissues with various levels of CD38 expression. It is produced in a mammalian CHO suspension culture and purified by affinity and ion exchange chromatography (IEC), as well as by specific viral clearance procedures.

Daratumumab consists of the known structure of an IgG1κ mAb, which includes 2 peptide heavy chains and 2 peptide light chains. The 2 heavy chains are connected to each other by 2 interchain disulfide bonds, and 1 light chain is attached to each heavy chain by a single interchain disulfide bond. The light chain has 2 intrachain disulfide bonds and the heavy chain has 4 intrachain disulfide bonds. The IgG1κ antibody has an isoelectric point at approximately 8.4 – 9.0 as determined by imaging capillary isoelectric focusing.

The molecular weight (MW) of the antibody is approximately 148 kDa as determined by MALDI-TOF-MS. Using SDS-PAGE under reducing condition the MW of the light chain was found to be 26 kDa and the MW of the heavy chain to be 53 kDa.

The mAb is N-linked glycosylated at Asn302. The antibody glycosylation profile predominantly contains bi-antennary core fucosylated glycans with varying amounts of terminal galactose.

Daratumumab drug product is formulated as a concentrate of 20. mg/mL ± 2. mg/mL in an isotonic buffer consisting of sodium acetate, sodium chloride, mannitol and polysorbate 20 at pH 5.5.

8.1.3 **Storage, Stability and Handling**

The daratumumab vials should be stored in the original carton in a refrigerator at 2ºC to 8ºC and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Since daratumumab does not contain preservatives, any unused portion remaining in the vial must be discarded. Daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration.

8.1.4 **Compatibility, Preparation and Administration**

Daratumumab 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 20 mL, respectively. It is administered by the intravenous (IV) route after dilution in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) provided by the investigation site.

Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP),

polyethylene (PE), or polylefin blend (PP+PE).

Following dilution, the infusion bag/container may be stored for up to 24 hours in a refrigerator at 2 ºC to 8 ºC (36 ºF to 46 ºF), protected from light. Infusion should be completed within 15 hours. Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Polyurethane (PI), polybutadiene (PBD), PVC, PP, or PE administration sets must be used.

8.1.5 **Availability and Ordering**

Daratumumab will be provided free of charge by Janssen Scientific Affairs, LLC as 400mg/20ml vials. Biologics, Inc. will provide drug distribution services for the study. In the event that 400mg/20mL vials are not available, Janssen Scientific Affairs, LLC will provide an equivalent formulation of daratumumab in 100mg vials as a substitute.

Biologics, Inc. contact details for drug ordering:
Fax: 919-256-0794
Email: CRSOrders@biologicsinc.com

Throughout the course of the study, a Biologics, Inc. clinical hotline support, staffed with clinical pharmacists, is made available 24/7/365 in the event an investigator or site coordinator has a question. **Hotline phone**: 1-800-693-4906

8.1.6 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.7 **Destruction and Return**

The Drug Accountability Log will contain the date and amount of study drugs received and dispensed. All used and partially used study drug will be destroyed by the site, in accordance with the site's standard operating procedures (SOPs). All expired drug and any unused drug remaining once all patients are off study treatment will be destroyed on site in accordance with the site's standard operating procedures (SOPs).

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

9.1.1 Laboratory Correlative Studies

Bone marrow aspirate (approximately 30 cc in 2 heparinized syringes & 1 purple top or 3 purple tops for outside sites) will be collected at baseline, prior to administration of cycle 7, and within 4 weeks following completion of therapy. At each time point, the samples will be genotyped for MYD88 and CXCR4 by the Bing Center for WM laboratory. The samples will be used until depletion. All samples from sites other than DFCI will be shipped ambiently priority overnight Monday-Thursday by a qualified carrier to:

Christopher Patterson
Administrative Director
Dana-Farber Cancer Institute, Harvard Medical School Bing Center for Waldenstrom's Macroglobulinemia
450 Brookline Avenue, Mayer 548
Boston, MA 02215
Ph: 617-632-6285
Fx: 617-632-4862
cpatterson@partners.org

10. STUDY CALENDAR

	Screening* ≤ 30 days from study entry	**Treatment Phase**							**Off Treatment Assessment** Within 4 weeks of completion or removal from study ± 2 weeks	**Follow-Up Phase** Post Treatment; Every 12 ± 2 weeks for 24 months or until next therapy
		Induction Cycles 1 and 2 (+/- 3 days)				**Consolidation** (Beginning 2 weeks +/- 3 days after C2 completion) Cycles 3 to 6		**Maintenance** (Beginning 4 weeks +/- 7 days after C6 D15) Cycles 7 to 18		
		Day 1	Day 8 (+/- 3 days)	Day 15 (+/- 3 days)	Day 22 (+/- 3 days)	Day 1 (+/- 3 days)	Day 15 (+/- 3 days)	Day 1 (+/- 3 days)		
Physical exam[1], weight, height	X	X				X		X	X	X
Medical History	X									
ECOG performance status (see Appendix A)	X	X				X		X	X	X
CT of the chest & abdomen / pelvis[2]	X							X[2]	X[2]	X (if applicable)
Bone marrow biopsy and aspiration[3]	X							X[3]	X[3]	X (if applicable)
Serum immuno-electropheresis & Response assessment	X	X				X		X	X	X
Serum IgM	X	X	X	X	X	X	X	X	X	X
Serum IgA, IgG	X	X				X		X	X	X
Complete Blood Count plus differential[1]	X	X	X	X	X	X	X	X	X	X
Coagulation profile: PT, PTT, PT-INR	X									
Chemistry including: Electrolytes, Renal (BUN, Creatinine) and Hepatic function testing [ALT, AST, Alk phos, total Bilirubin], albumin, total protein	X	X	X	X	X	X	X	X	X	X
Vital signs (Temp, HR, RR, BP)**	X	X	X	X	X	X	X	X		
Beta-2 microglobulin, Von Willebrand screening	X									
Pregnancy Test[4]	X									
HBsAg, HBsAb, HBcAB	X	X[6]				X[6]		X[6]		
HCV Ab	X									
Indirect antiglobulin testing	X									
Daratumumab administration		X	X	X	X	X	X	X		
Adverse event monitoring[5]		X				X		X	X	X

* Physical exam, laboratory tests, vital signs, and weight do not need to be repeated if Cycle 1, Day 1 is within 14 days of Screening. Cycle 1, Day 1 labs, if drawn, do not need to re-confirm eligibility prior to administering first dose.

**Vital signs (Blood pressure, heart rate, respiratory rate, temperature) should be taken prior to infusion, and every 60 minutes during the infusion period (± 10 minutes), and 30 minutes (± 5

minutes) after the completion of the infusion.

[1]More frequent visits may be required at the discretion of the treating physician.

[2]**If CT scans of the chest, abdomen and pelvis have been collected and done within 90 days of Cycle 1 Day 1 they will not be required at the screening visit. If the participant has known extramedullary disease outside the chest, abdomen, or pelvis, imaging should be performed with investigator-preferred modality.** Scans will be **repeated just before Cycle 7 and at End of Treatment for participants with extramedullary disease at baseline** defined as adenopathy >1.5 cm in any axis, and splenomegaly >15 cm in the craniocaudal axis**.** If participant has disease only outside chest, abdomen, and pelvis, only the affected area will need to be re-imaged with the same modality as at screening. Scans will also be repeated to confirm a complete response, if the participant has no detectable monoclonal protein and had extramedullary disease at baseline and at the discretion of the investigator.

[3] **If bone marrow aspirate and biopsy had been collected within 90 days of Cycle 1 Day 1 they will not be required at the screening visit.** Bone marrow biopsy and aspiration will be performed just before cycle 7 and at the end of treatment. Bone marrow aspiration and biopsy may also be done at the investigator's discretion, and at any time to confirm a complete response, if the participant has no detectable monoclonal protein.

[4]For women of childbearing potential only: Serum pregnancy test is required at screening.

[5]Please refer to Section 6 for Dose Delays.

[6]Participants who have serologic evidence of HBV exposure at screening but are HBsAg negative and do not have active HBV infection are allowed to enroll on study. Participants with resolved infection (ie, 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. Participants who have unclear interpretation (HBsAg negative and anti-HBc positive and anti-HBs negative) must also be screened using real-time PCR and those who are PCR positive will be excluded. Retesting of HBV DNA only should be done every three months while on therapy for any participants with evidence of prior HBV exposure at screening.

11. MEASUREMENT OF EFFECT

11.1 Definitions

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response: Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Response will be assessed on Day 1 of each cycle starting with Cycle 2 unless the participant has undergone plasmapheresis within the previous 4 weeks. Participants discontinuing BTK inhibitors might not be evaluable for response due to IgM rebound until Cycle 4 Day 1 (Gustine JN, et al. Ibrutinib discontinuation in Waldenstrom macroglobulinemia. Am J Hematol 2018; 93:511-517). These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

11.2 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): is defined as ≥90% reduction in serum IgM levels, or normalization of serum IgM levels.

Partial Response (PR): Partial response (PR) is defined as achieving a ≥50% reduction in serum IgM levels.

Minor Response (MR): A minor response (MR) is defined 25-49% reduction in serum IgM levels.

Progressive Disease (PD): Progressive disease (PD) is defined as occurring when a greater than 25% increase in serum IgM level occurs with an absolute increase of at least 500 mg/dL from the lowest attained response value, or progression of clinically significant disease related symptom(s). Reconfirmation of the initial IgM increase is required when IgM is the sole criterion for progressive disease confirmation. Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event. An increase of 1 cm in any axis for adenopathy, or 2 cm in the craniocaudal axis of the spleen will be considered evidence of progression of extramedullary disease. Development of Bing Neel syndrome, or other extramedullary disease manifestations, as well as disease transformation will be considered as progressive events.

Stable Disease (SD): Stable disease is defined as having < 25% change in serum IgM levels, in

the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM.

Overall Response Rate (ORR): Includes patients who achieved MR, PR, VGPR and CR. The best overall response rate will be at any point on therapy.

11.3 Time-to-event definition

- Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression (including initiation of new therapy or death).

11.4 Relapsed/Refractory definitions

Refractory disease: Disease that is non-responsive (failure to achieve minimal response or development of progressive disease (According to the Sixth International Workshop on WM) while on therapy), or progresses within 60 days of last therapy.

Relapsed disease: Previously treated disease that progresses (According to the Sixth International Workshop on WM) while on therapy) and requires initiation of new therapy that does not meet criteria for refractory.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review

toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Collaborative Agreements Language

Not applicable

13. STATISTICAL CONSIDERATIONS

This is a phase II single-arm, open-label prospective study aimed at evaluating the efficacy of daratumumab, an anti-CD38 monoclonal antibody, in patients with relapsed and/or refractory WM. With a double-sided alpha of 0.04 and power of 0.92, a sample size of 30 patients would suffice to show a statistical difference between the alternative hypothesis of obtaining an ORR of 70% versus the null hypothesis of obtaining an ORR of 40%. If 18 patients or more obtain a response, then daratumumab will continue further evaluation. If 17 patients or less obtain a response, then daratumumab should not continue further evaluation. The critical value of 18 means to include 70% as the upper level of the 95% CI, while the critical value of 6 patients means to exclude 40% as the upper level of 95% CI based on a exact binomial estimate (STATA SE 13.1). In addition, assuming that an adverse event associated with study drug has a true incidence of 10%, with an estimated sample size of 30 patients, the likelihood of observing at least 1 adverse event would be at least 95%

13.1 Study Design/Endpoints

This is a phase II single-arm, open-label prospective study aimed at evaluating the efficacy and

safety of daratumumab in patients with relapsed and/or refractory WM. With a double-sided type I error of 4% and power of 92%, a sample size of 30 patients would suffice to show a statistical difference between the alternative hypothesis of obtaining an ORR (see section 1.2) of 70% versus the null hypothesis of obtaining an ORR of 40%. If 18 patients or more obtain a response, then daratumumab will continue further evaluation. If 17 patients or less obtain a response, then daratumumab should not continue further evaluation. The primary endpoint is ORR. Secondary endpoints include MR, PR, VGPR, CR and PFS.

13.2 Sample Size, Accrual Rate and Study Duration

A total of 30 patients will be accrued. Accrual time will be approximately 1 year, at a rate of 2-3 patients per month. The individual study duration will be approximately 1.5 years. Patients will then be followed up for 2 years after completion or discontinuation of therapy or until death, whichever occurs first. The total study duration will be approximately 4.5 years (1 year of accrual, 1.5 years of therapy and 2 years of follow-up). The individual study duration will be approximately 3.5 years (1.5 years of therapy and 2 years of follow-up).

Accrual Targets						
Ethnic Category	**Sex/Gender**					
	Females		**Males**		**Total**	
Hispanic or Latino	1	+	4	=	5	
Not Hispanic or Latino	5	+	20	=	25	
Ethnic Category: Total of all subjects	6 (A1)	+	24 (B1)	=	30 (C1)	
Racial Category						
American Indian or Alaskan Native		+		=		
Asian		+	1	=	1	
Black or African American	1	+	1	=	2	
Native Hawaiian or other Pacific Islander		+		=		
White	5	+	22	=	27	
Racial Category: Total of all subjects	6 (A2)	+	24 (B2)	=	30 (C2)	
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

13.3 Stratification Factors

No stratification factors will be applied to any analysis.

13.4 Interim Monitoring Plan

Please refer to section 13.1 and 13.2.

13.5 Analysis of Primary Endpoints

Primary analysis will be performed in the Full Analysis Set (FAS) for the primary assessment of efficacy. The FAS will include those participants who have received at least one dose of therapy. The primary analysis will include calculating the proportion of patients having at least a 25% reduction in serum IgM (minor response or better) at any point on therapy. Confidence intervals (95%) around these point estimates will be presented.

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13.6 Analysis of Secondary Endpoints

Secondary analyses will be performed in the FAS. Time to progression (TTP) will be estimated using Kaplan Meier methodology with median time plus 25th and 75th percentile along with 95% confidence intervals, as appropriate.

Minor, partial, very good partial, and complete response rates will be estimated in the FAS population by calculating the proportion of patients having those responses and calculating the 95% confidence intervals around these point estimates.

All participants who receive at least one dose of daratumumab during the study will be included in the safety analysis.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All participants who receive at least one dose of any test material during the study will be included in the safety analysis.

13.7.2 Evaluation of the Primary Efficacy Endpoint

All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned a response category based on the response criteria in Section 9.1.2. According to section 11.1.2, patients who underwent plasmapheresis less than 4 weeks prior to response assessment will be deemed non-evaluable, according to Section 11.1.2.

All participants who met the eligibility criteria and were enrolled in the trial will be included in the main analysis of the response rate. All conclusions will be based on all eligible participants.

14. PUBLICATION PLAN

Interim study results will be presented at a major scientific meeting (American Society of Hematology and/or the International Workshop on Malignant Lymphoma) once all patients complete 6 months of therapy. A full report that will include primary and secondary endpoints will be published in a peer-reviewed journal that meets the requirements of the International Committee of Medical Journal Editors within 24 months of reaching the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER OVERSIGHT PLAN AND DATA AND SAFETY MONITORING PLAN VERSION 2 8.2.2017

DFCI IRB Protocol #:17-164

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15. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

15.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

15.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol

document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

16. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

16.1 DF/HCC Sponsor

The DF/HCC Sponsor, **Jorge J. Castillo** will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol. A current CV will be collected at study initiation.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol, as well as current Investigator Brochure or product information.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed. All site Principal Investigators will sign protocol signature pages at study initiation and each protocol version change.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable. Any delegated Sponsor/Investigator responsibilities (i.e. to CROs, drug distribution

vendor, etc) will be documented and the appropriate regulatory authority will be informed.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

16.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:
- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring. Source data will be maintained and Case Report Forms (CRFs) will be verified with source data, as applicable.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

16.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements as listed in the IP Management Plan
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

17. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

17.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

17.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

17.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research. Informed consent will be explained to each study participant and signed and dated by the participant prior to participation. The consent will be retained by the investigator.

17.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.

- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

17.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

17.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

17.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

17.7 DF/HCC Multi-Center Protocol Registration Policy

17.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed (617-632-6752) or e-mailed (kirsten_meid@dfci.harvard.edu) to the Coordinating Center

- Copy of serum protein electropheresis, CBC with diff, Chemistries, CT C/A/P, bone marrow biopsy
- Screening visit note
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

17.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

17.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

17.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case

number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

17.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

17.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

17.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

17.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

17.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

17.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

17.10 Data Management

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for all eCRF users.

17.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

18. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section *8.*

Participating Institutions should order their own agent regardless of the supplier. (i.e., NCI or a pharmaceutical company.) Daratumumab will be supplied by Janssen Scientific Affairs, LLC and a drug distribution vendor will be utilized for shipment to each institution.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

19. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

19.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Additionally, regular and ongoing communication with Participating Institutions will be accomplished by holding all site teleconferences at quarterly until enrollment is completed and the last participant in has been on study for at least 6 months. After this there will be teleconferences every 6 months until all participants are off treatment. Additional teleconferences will take place as needed for significant events (i.e. change in accrual, event involving participant, etc.) The Lead Institution will keep in close touch with the Participating Institutions via email and phone. Source documents from Participating Institutions, will be collected at specific data points that support the primary and or secondary endpoints.

Remote Monitoring

Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. Each participant's initial consent and eligibility will be reviewed within 30 days of enrollment. Study visits and corresponding CRFs will be reviewed every 6 months for protocol compliance, AEs, SAEs, study drug administration, dose modifications, and follow-up of action items. Pharmacy records will be remotely reviewed every 6 months.

On-Site Monitoring

Participating Institutions will have annual on-site visits to for a Pharmacy site review, Regulatory binder review, and to meet with the site PI (if available).

Closeout Monitoring

Closeout monitoring will be done remotely at the end of the study.

19.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. Monitoring logs will also be maintained to document monitoring activities. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable

to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

19.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. Due to the small patient population, the accrual minimum requirement is at least 1 patient every two years.

20. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

20.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

20.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

20.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

20.4 Participating Institution Performance

The DF/HCC Sponsor and the DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX C: INVESTIGATIONAL PRODUCT MANAGEMENT PLAN

A Phase 2 Study of Daratumumab in Patients with Relapsed or Refractory Waldenström Macroglobulinemia.

Overall Principal Investigator: Jorge J. Castillo, MD
Coordinating Center: Dana-Farber Cancer Institute

Version 4
Version Date January 11, 2018

1. IP Forecasts

1.1 IP projections for the duration of the IIS

Patients will be treated with daratumumab at a dose level of 16mg/kg on the following schedule:

Cycle	Dosing Schedule
Cycle 1-2	Days 1, 8, 15, 22
Cycle 3-6	Days 1, 15
Cycle 7-18	Day 1

Dosing will be an IV infusion following the guidance for commercial daratumumab administration outlined in the United States Package Insert as well as according to site policy. Each cycle will be 28 days.

With an expected patient accrual of 30 who can each receive a maximum of 28 doses of daratumumab, the projections are below for 400mg vials:

- Assuming 4 vials per dose per patient, and patient weight of 100kg:400mg vials
- 4 vials of 400mg daratumumab X 28 doses X 30 patients= 3,360 vials

With an expected patient accrual of 30 who can each receive a maximum of 28 doses of daratumumab, the projections are below for 100mg vials:

- Assuming 16 vials per dose per patient, and patient weight of 100kg:100mg vials
- 16 vials of 100mg daratumumab X 28 doses X 30 patients= 13,440 vials

Drug	Vials/ dose (400mg vials)	Total Doses	# Patients	Vials/ Patient	Total Vials	10% Overage	20% Overage
Daratumumab	4	28	30	112	3360	3696	4032

Drug	Vials/ dose (100mg vials)	Total Doses	# Patients	Vials/ Patient	Total Vials	10% Overage	20% Overage
Daratumumab	16	28	30	448	13440	14784	16128

1.2 Overall plan per Quarter for IP requirements (inclusive of each participating site, over-all subject enrollment rate, current inventory and expiring IP at each site)

The team anticipates accrual at 2 patients/month to complete accrual of 30 patients in 15 months. Each patient will be dispensed study drug at the timepoints described in section 1.1 of this IP

Management Plan. Each subsite will be allowed to maintain IP dispensation and accountability records per their individual site SOPs. Dana-Farber Cancer Institute, as the coordinating center will review each sites SOPs to ensure they comply with GCP and ICH guidelines. Each subsite will maintain drug destruction records per their sites individual SOPs. Dana-Farber Cancer Institute, as the coordinating center, will collect all pharmacy records at the completion of the study.

1.3 Process to re-evaluate IP requirements (inclusive of all participating sites)

DFCI will submit monthly enrollment updates to Janssen Scientific Affairs, LLC. The study team will inform the pharmacy when a new patient is enrolled. Biologics, Inc., the drug distribution center, will provide monthly dispensing and accountability reports to Janssen Scientific Affairs, LLC and Dana-Farber Cancer Institute.

2 Inventory Control

2.1 Record of receipt and disposition of IP

Biologics, Inc.,the drug distribution center, will receive and check all incoming shipments with proper documentation, enter into a 21CFR Part 11 compliant system, and place in proper and monitored storage. Upon destruction, or return of study drug, all documents are completed, accountability logs are signed off on and closed, and drug is disposed of or returned properly.

Biologics, Inc. will ship the study drug to each participating site. All study drug will be shipped in original manufacturer's packaging with a protocol-specific label adhered to the outer packaging. Study Drug is shipped in a Biologics branded package with appropriate materials to maintain temperature stability. All drug orders are shipped via *FedEx for Priority Overnight* delivery for shipments to US sites.

Each shipment includes a label on the Ziploc bags with the following information:

- The Study Number
- IND caution statement and/or local regulatory statements
- Drug identification
- Lot Number
- Expiration date
- Dosing instructions (i.e., "Administer as Directed per Protocol")
- Storage instructions (i.e., "Store at controlled refrigerated temperature, 2-8°C")
- Emergency contact instructions

For all shipments from Biologics:

- A complete accountability record including date of dispense, site name, quantity dispensed, and balance forward will be recorded. Study accountability records are documented in electronic 21 CFR format and are kept in a secured area for duration of the study.

- Provide a Pharmacist review; a licensed pharmacist checks off package for accuracy of contents, authorizing order via 21 CFR compliant trial accountability log.
- Enclose a packing slip that includes the quantity of drug provided with a section to be completed once received by the site coordinator. This section includes confirmation of drug receipt, verification of package contents, and instruction to fax the completed packing slip to Biologics.
- Process and ship authorized and completed orders "same day" of receipt if received before 2:00 p.m. ET Monday through Thursday. Authorized and completed orders received after 2:00 pm ET Monday through Thursday will be processed and shipped the next business morning.
- Packages are tracked until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator for all shipments.

DFCI will receive and check all incoming shipments with proper documentation. DFCI keeps the shipping receipt and records the disposition of the drug. DFCI will receive and check all incoming shipments with proper documentation, and place in proper and monitored storage. Upon destruction all documents are completed, accountability logs are signed off on and closed, and drug is disposed.

Each participating sub-site will maintain records of drug accountability and destruction according to their local SOPs, which will be reviewed by the coordinating center for compliance with GCP and ICH guidelines.

2.2 Periodic review and documentation of current supply of all IP

Biologics will effectively manage inventory to reduce waste due to expiration issues through strict adherence to FIFO inventory procedures, just in time inventory management, and end of day and monthly audits.

Each day Biologics will perform an end of day audit for all trial specific drugs that were dispensed on that particular day. The end of day audit reconciles the physical shelf inventory to accountability records. During the monthly inventory report Biologics personnel will compare shelf inventory against the balance as stated on the drug accountability report. Perpetual inventory audits are documented via 21 CFR Part 11 compliant accountability records throughout the duration of the study and with oversight by the Director of Clinical Trial Services.

The DFCI pharmacy routinely reviews the amount of IP on site and re-orders as needed based on current enrollment.

2.3 Plan for resupply of IP based upon overall IIS use and/or expiration of IP

Biologics, Inc. will request resupply as needed based on inventory level and expiry dates from

Janssen Scientific Affairs. The coordinating center will liaise with the drug distribution center as needed based on drug supply levels via telephone or email to review currently supply and expiry dates. Each individual sub-site will measure drug supply levels and forecast needed drug supply based on local practice.

2.4 System to quarantine and control expired or recalled IP

All study product that requires quarantine will immediately be recorded in the accountability record, moved from general storage, placed into a secure quarantined area separate from other study drug. Janssen Scientific Affairs, LLC will be notified and the supply will be handled as required.

3 Storage

3.1 IP storage conditions

All participating sites are required to maintain adequate accountability and storage of investigational agents as specified in the study protocol and the study data safety monitoring plan. Each individual sub-site may store IP per their local SOP for storage procedures for investigational drug supply.

Biologics, Inc. will store the study drug in secure temperature and humidity controlled storage for the duration of the study. Drug and the accountability log is reviewed and signed off by the qualified personnel as outlined in Biologics operating procedures. This quality check is documented via Clinical Trial Material Accountability/Quality Assurance Log (Receipt) and the document is then stored in the trial files for the duration of the study. All study drugs will be stored at controlled temperatures until shipment with access limited to essential personnel only.

Daratumumab will be stored at controlled refrigerated temperatures of 2-8°C. Biologics will assume receipt of one study drug supply on at least a quarterly basis. Temperature and humidity monitoring that is 21 CRF Part 11 compliant is provided 24/7/365 throughout the duration of the study. During non-operational hours, electronic surveillance alerts Biologics after-hour's response personnel to out of range fluctuations in temperature and humidity. Biologics will provide temperature monitoring reports upon request. Temperature excursions will be communicated to the manufacturer & Coordinating Center to provide an assessment of affected drug supplies.

Biologics will maintain separate inventories for protocol-specific drug supplies.

Inventory Maintenance includes:

- Separate physical locations with shelf labeling
- Study, Drug, Strength, Expiration shelf labeling
- Inventory management within Biologics information system
- Inventory reports on agreed fields submitted on agreed schedule

DFCI will store the study drug in secure temperature and humidity controlled storage for the duration of the study. All study drugs will be stored at controlled temperatures with access limited to essential personnel only.

3.2 Plan for maintaining documentation of proper storage conditions according to the package insert/IP guidelines

Biologics, Inc. will include proper storage and drug usage information on packing slips and auxiliary documents in all shipments sent to the study sites.

Proper storage and drug usage information is contained in section 8 of the protocol. All participating sites are required to maintain adequate accountability and storage of investigational agents as specified in the study protocol and the study data safety monitoring plan.

Each individual sub-site may follow their local SOP for maintaining documentation of drug supply. Each sites SOP will be reviewed by the coordinating center to ensure it complies with GCP and ICH guidelines.

3.3 IP storage separate from non-clinical material, in secure location and limited access

Prior to distribution, the IP will remain separate from other study drugs and will be stored in a secure facility at the drug distribution center, Biologics, Inc., as described in the drug distribution center's SOPs.

All drug is received in dry dock and then sent to the DFCI Pharmacy. Once the packages are opened the packing slip is examined. Proper documentation of the Janssen specific protocol number is required on the packing slips. The pharmacy technicians identify the received drug as investigational and the drug is transferred to the investigational pharmacy for receipt and acknowledgement. Investigational drug is stored according to the DFCI protocol number in research refrigerators, separated from non-research material.

Each individual sub-site will be allowed to utilize their local SOP for investigational product once the SOP is reviewed by the coordinating center for compliance with GCP and ICH guidelines.

3.4 Temperature excursions

Biologics, Inc. should follow their standard of practice as well as the guidance from the protocol document regarding temperature excursions.

DFCI pharmacy refrigerators record temperatures continuously and are attached to an alarm for any excursion. If an excursion happens after hours a pharmacist is on call to answer the alarm. Investigational product is then quarantined according to the requirements per protocol.

Each individual sub-site should follow their local standard of practice as well as the guidance from the protocol document regarding temperature excursions. The coordinating center will review each SOP to ensure that it complies with GCP and ICH guidelines.
Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze or shake. Protect from light. This product contains no preservative. If the storage temperature falls outside of the range noted

above per institutional SOP, this is considered a temperature excursion. When a temperature excursion occurs, each individual sub-site must quarantine the product and inform the coordinating center as soon as possible. The coordinating center is responsible for liaising with Janssen Scientific Affairs, LLC for guidance on continued use of the product and will inform sites whether the product is suitable for continued use.

4 IP Accountability

4.1 IP use in accordance with this IIS

Biologics, Inc. will include pertinent information on all packing slips and include auxiliary documents to inform sites of instructions for use. In all communications with the sites prior to shipment, the drug distribution center can review this information with the receiver.

Each supply of investigational product will come equipped with a packing slip from Janssen Scientific Affairs, LLC. This packing slip will have the Janssen Scientific Affairs, LLC study number. Each participating site will be informed during the Site Initiation Visit that investigational product should only be used for the IIS.

4.2 Process for maintaining IP transaction logs

All participating sites are required to maintain adequate accountability and storage of investigational agents. As outlined in the study protocol and study data safety monitoring plan.

5 IP Destruction

5.1 Confirmation of each site's SOP to destroy IP at site

Because of their participation in studies using DFCI-supplied investigational drug, all DFCI institutions have the capability of either destroying Study Product at their site or have an SOP for return of the Study Product to the distributor for destruction.

5.2 Confirmation that documentation of each site's SOP for IP destruction will be retained

A copy of the sub-site drug destruction SOP will be filed in the Trial Master File.

5.3 Confirmation that each site will retain documentation of IP destruction

Drug destruction and/or pharmacy records will be kept current and reviewed during routine monitoring visits and prior to study closeout at all participating sites, as outlined in the study protocol and study data safety monitoring plan.

6 IP Distribution

6.1 Shipping information contacts at S-I site or at drug distribution supplier for sites participating in the IIS

Biologics, Inc. and the coordinating center will provide drug ordering instructions to all participating sites.

Biologics, Inc. contact details for drug ordering:
Fax: 919-256-0794
Email: CRSOrders@biologicsinc.com

Throughout the course of the study, a clinical hotline support, staffed with clinical pharmacists, is made available 24/7/365 in the event an investigator or site coordinator has a question.
Hotline phone: 1-800-693-4906

During the approval and activation process, the coordinating center will inform Janssen Scientific Affairs, LLC and the drug distribution center of any new site prior to activation of said site and prior to any IP shipment to said site.

6.2 Confirmation that all necessary documents are in place prior to shipment to any participating site

Biologics, Inc. and DFCI will execute a contract prior to study launch. DFCI will execute any agreements required with the sub-sites prior to the activation of said site. DFCI has existing process in place for confirmation of local IRB review prior to patient registration. Each site will be unable to request shipment until IRB approval centrally at the coordinating center is received and all regulatory documents (e.g. CVs, MLs, DOA, etc.) have been filed in the Trial Master File.

6.3 Distribution/coordination plan for shipping IP to participating sites

In general, a minimum of a three-month forecasted supply of study drug will be shipped to each participating site to ensure that drug shipments do not occur more frequently than once a quarter to each site. Exceptions to this rule of thumb should be reviewed with DFCI.

6.4 Confirmation that S-I or IP distribution supplier will record and maintain shipping documentation of IP to participating sites

Biologics, Inc. will record a complete accountability record including date of dispense, site name, quantity dispensed, and balance forward will be recorded. Study accountability records are documented in electronic 21CFR format and are kept in a secured area for the duration of the study.

Each individual sub-site will maintain a record of shipment according to their local SOPs for maintaining documentation of IP shipment. This SOP will be reviewed by the coordinating center for compliance with GCP and ICH guidelines.

7 Packaging and Labeling

7.1 IP should be clearly identified to be used only for the specified IIS

Biologics, Inc. will include a disclaimer that IP is to be used only for the specified IIS on the packing slip, or on auxiliary documentation that is placed on the study product prior to dispense to the study site.

Janssen Scientific Affairs, LLC will include the Janssen protocol number clearly on the packing slip or auxiliary documentation in the shipment of study drug to Biologics, Inc.

The coordinating center will ensure a yearly monitoring review of pharmacy drug accountability records. The drug accountability record and the drug destruction log will be collected at the end of the study per DFCI SOPs.

7.2 Any additional participating sites' labeling requirements per institution's policy/SOP and/or local and/or country regulations

Biologics, Inc. will create, submit, and agree upon the shipping label with DFCI prior to study launch and any requirements at specific study sites will need to be discussed during this process. Shipping and handling from the drug distribution vendor to each site will follow the drug distribution vendor's standards of practice. The practices will meet all GCP and ICH guidelines as appropriate.