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TITLE: ***A Phase 1/2 Study of Ulocuplumab And Ibrutinib in symptomatic patients with mutated CXCR4 Waldenstrom's Macroglobulinemia.***

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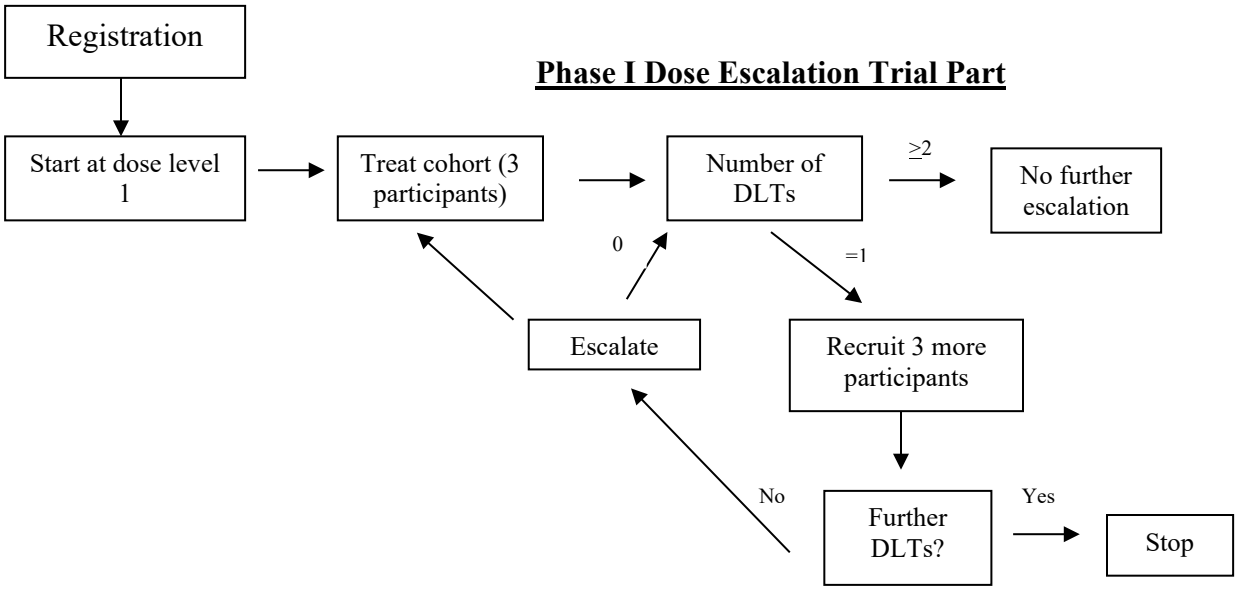
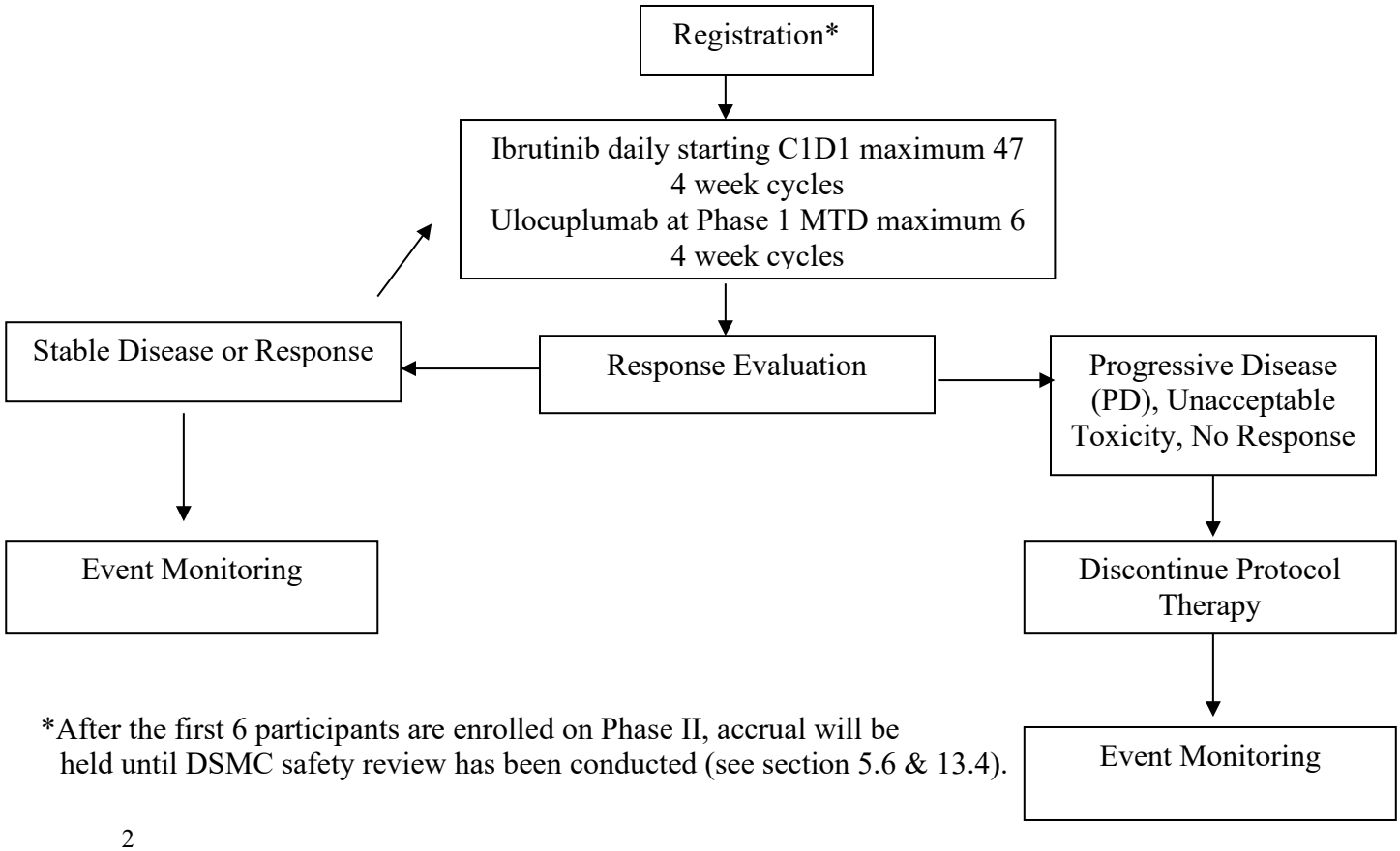


Phase II Single Arm Trial Part



*After the first 6 participants are enrolled on Phase II, accrual will be held until DSMC safety review has been conducted (see section 5.6 & 13.4).

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1. OBJECTIVES

1.1 Study Design

This is a Phase I/II, single center study designed to evaluate the safety and efficacy of ulocuplumab combined with ibrutinib in symptomatic patients with CXCR4 mutated WM. The phase I part of the study is designed to identify the maximum dose or maximum tolerated dose (if a dose-limiting toxicity is identified) of ulocuplumab to be combined with ibrutinib. The dose of ulocuplumab will be escalated during the Phase I portion, and the fixed FDA approved dose of ibrutinib (420 mg/day) for treatment of symptomatic WM patients will be used. The Phase I part of the study will be followed by a phase II part designed to assess in an expanded population of patients the clinical safety, tolerability, and efficacy of uloculplumab using the maximum dose or maximum tolerated dose (if a dose-limiting toxicity is identified) derived from the Phase I portion of the study and ibrutinib at 420 mg/day.

Treatment will be comprised of ibrutinib administered orally starting day 1 of cycle 1 for 47 cycles, along with ulocuplumab administered intravenously weekly during Cycle 1, and then every other week for Cycles 2-6. A 3+3 Phase I design will be employed for 3 dose levels, and 20 additional patients will be recruited at the maximum dose or maximum tolerated dose (if a dose-limiting toxicity is identified) for the Phase II dose expansion. After the first six participants are accrued to the Phase II cohort, enrollment will be held to conduct a DSMC safety analysis of the first two cycles of treatment.

A Screening visit will be conducted within 30 days prior to 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 will be performed during screening, and MYD88 and CXCR4 mutation status will be determined. Research samples to determine CXCR4 expression on WM cells will also be obtained at the screening visit or within 90 days prior to Cycle 1 Day 1. CT scanning of the chest, abdomen and pelvis must 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, SGOT (AST), SGPT (ALT), alkaline phosphatase), magnesium, beta 2-microglobulin, von Willebrand panel, coagulation profile, serum and protein electrophoresis with quantification of immunoglobulins (IgM, IgG, IgA) and immunofixation studies, 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 ulocuplumab based on a 3+3 Phase I study design shown in Figure 1, with expansion to Phase II with recruitment of 20 additional participants. Three dose levels of ulocuplumab will be evaluated (Table 1). Three patients will be enrolled into the initial dose cohort. If no dose limiting toxicity

(DLT) is observed after cycle 1 & 2 in any of these subjects, the trial will proceed to enroll additional subjects into the next higher dose cohort. If one subject develops a DLT at a specific dose, an additional three subjects will be enrolled into that same dose cohort. Development of DLTs in more than 1 of 6 subjects in a specific dose cohort will be deemed that the MTD has been exceeded, and further dose escalation will not be pursued. All patients will receive ibrutinib at 420 mg orally per day beginning day 1 of cycle 1 for 47 cycles.

Ulocuplumab will be administered on day 1 $\pm$ 2 days weekly for cycle 1 (Days 1, 8, 15, 22), then day 1 $\pm$ 2 and day 15 $\pm$ 2 for cycles 2-6. Participants will be evaluated for tolerance and response on the first day they receive treatment for each cycle beginning with cycle 2, at the end of treatment which will occur 4 weeks $\pm$ 1 week after the last administered therapy, and every 12 weeks $\pm$ 1 week thereafter as long as the participant remains on study. Participants will be eligible to continue therapy and remain on study so long as they do not have unacceptable toxicity or demonstrate progressive disease.

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

Bristol-Myers Squibb, the study supporter and manufacturer of ulocuplumab, terminated the development of ulocuplumab on 3/29/19. Due to this, the Phase 2 portion of this study was never opened. BMS continued to supply drug for this study until 7/1/2020. The Sponsor-Investigator halted enrollment on this study after the 3rd participant in the Phase 1 cohort #3 was accrued. All participants enrolled were able to complete planned ulocuplumab dosing, and participants then continued on commercial ibrutinib monotherapy.

The Sponsor-Investigator has decided to discontinue all study therapy and follow-up procedures for all participants remaining on the study as of 12/31/22.

1.2 Primary Objectives

- Phase I: To determine the maximum dose or maximum tolerated dose (if a dose-limiting toxicity is identified) of ulocuplumab with ibrutinib in symptomatic patients with CXCR4 mutated WM.
- Phase II: To determine the major response rate (>50% reduction in disease burden) in patients with CXCR4 mutated WM.

1.3 Secondary Objectives

- Phase II: To determine the time to minor and major response, as well as time to progression (TTP) in symptomatic patients with CXCR4 mutated WM.
- Phase II: To determine the best overall response rate (ORR) (>25% reduction in disease burden) and Very Good Partial Response (>90% reduction in disease burden)/Complete Response (VGPR/CR) of ibrutinib combined with ulocuplumab in symptomatic patients with CXCR4 mutated WM.

2. BACKGROUND

2.1 Study Disease

Waldenström's macroglobulinemia (WM) 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 and the C-terminal domain of CXCR4 in WM (Treon et al, 2012; Hunter et al, 2014; Treon et al, 2015a). In WM cells, mutated MYD88 triggers NFkB activation via two divergent pathways involving Bruton's tyrosine kinase (BTK) and IRAK1/IRAK4 (Yang et al, 2013). Ibrutinib is an orally administered, small molecule inhibitor of BTK, which triggers apoptosis of mutated MYD88 expressing WM cells. In a multicenter prospective study, 63 symptomatic previously treated WM patients received single agent ibrutinib. The median prior therapies for these patients was 2 (range 1-9), and 40% were refractory to their prior therapy. Patients received ibrutinib (420 mg) until progression or unacceptable toxicity (Treon et al, 2015b). Post-therapy, at best response, median serum IgM levels (used to measure disease burden) declined from 3,520 to 880 mg/dL; hemoglobin rose from 10.5 to 13.8 g/dL; and the bone marrow disease involvement declined from 60% to 25% ($p<0.01$ for all comparisons). The median time to a minor response ($\geq$25% reduction in serum IgM) was 4 weeks, and to a major (>50% reduction in serum IgM) was 8 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, 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 (>6 months) in comparison to patients with the $MYD88^{L265P}CXCR4^{WT}$ genotype (Figure 1; Treon et al, 2015b).

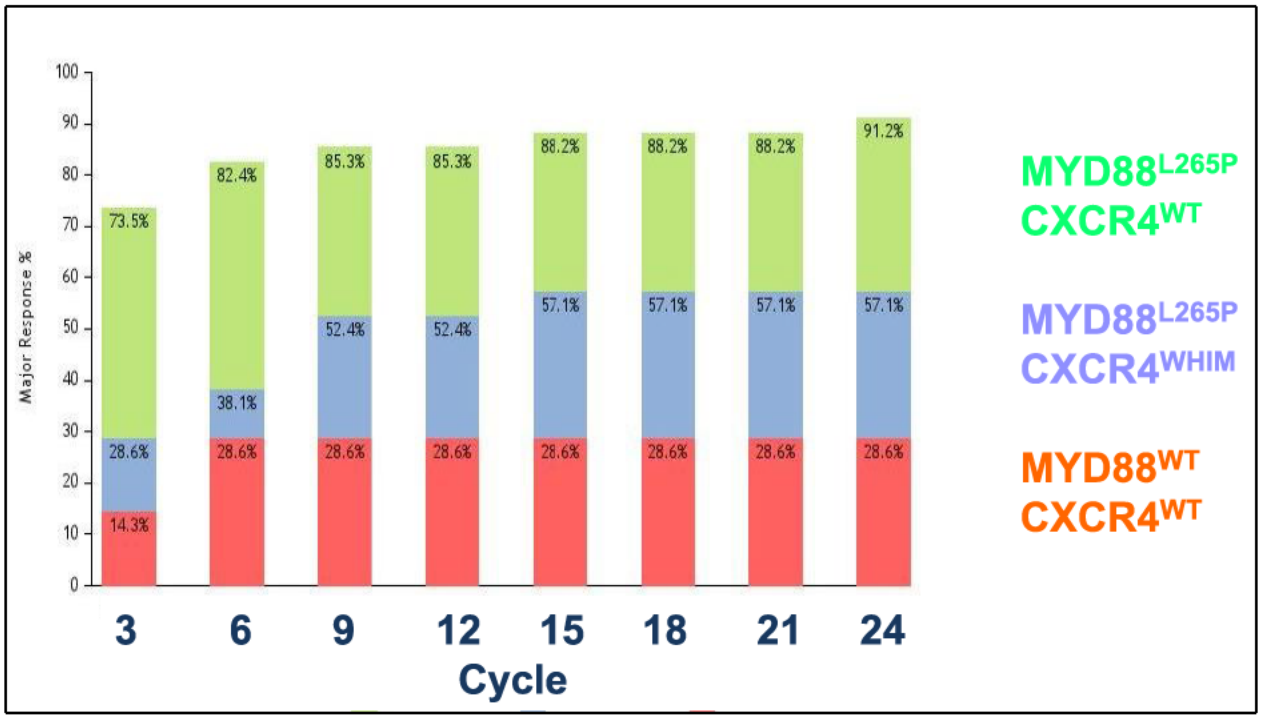


Figure 1. Kinetics of response to single agent ibrutinib in previously treated WM patients stratified by MYD88 and CXCR4 mutation status. Taken from Treon et al, 2015b.

High levels of overall (90%) and major (71%) response rates were also observed in a multicenter study that administered ibrutinib to heavily pre-treated rituximab refractory WM patients (Dimopoulos et al, 2016). Patients with *CXCR4* mutations showed delayed responses, including reductions in serum IgM and hemoglobin levels (Figure 2; Dimopoulos et al, 2016). The only patient with wild-type *MYD88* included also did not respond to ibrutinib. At a median follow-up of 18.1 months, the 18-month progression-free and overall survival rates in its study were 86% and 97%, respectively.

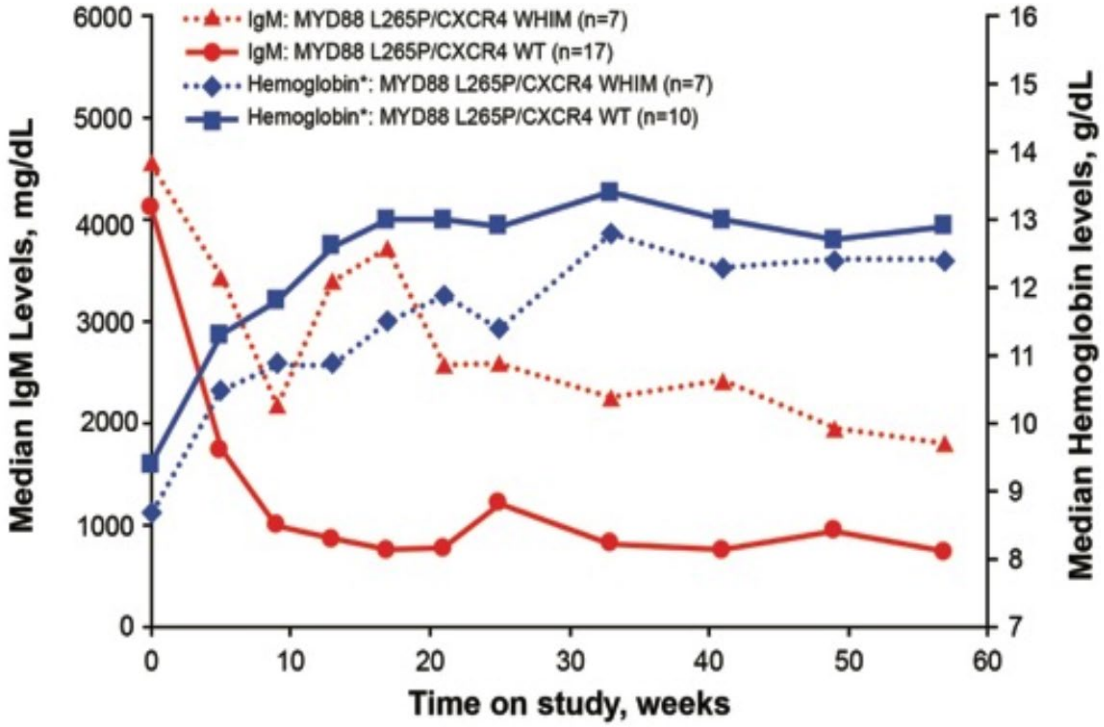


Figure 2. Impact of MYD88 and CXCR4 mutation status on serial serum IGM and hemoglobin levels in previously treated, rituximab-refractory WM patients. Taken from Dimopoulos et al, 2016.

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, 2014; Cao et al, 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, 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, 2015). While our studies addressed intracellular signaling mediated by $CXCR4^{WHIM}$ mutations, an impact on cell migration, adhesion and a protective microenvironment may also be relevant since the CXCR4 blocking antibody ulocuplumab protected mice inoculated with $CXCR4^{S338X}$ expressing WM cells (Rocarro et al, 2014). Therefore, combination strategies utilizing CXCR4 inhibitors with other chemotherapeutics could potentially be beneficial in WM patients carrying $CXCR4^{WHIM}$ mutations. The use of CXCR4 antagonists like ulocuplumab may therefore offer a targeted approach to therapy of WM patients with WHIM-like somatic mutations.

2.2 IND Agent Ulocuplumab

Ulocuplumab (BMS- 936564) is a first in class, fully human IgG4 monoclonal anti-CXCR4 antibody that inhibits the binding of CXCR4 to CXCL12. Ulocuplumab induces apoptosis of $CXCR4^{+}$ multiple myeloma cell lines and has single agent activity in vivo in MM tumor xenograft models. It is thus hypothesized that ulocuplumab may improve overall and major responses, and kinetics of response to ibrutinib therapy and possibly other WM related therapies.

CXCR4 is expressed on > 75% of human cancers and cell surface expression of CXCR4 is associated with poor prognosis and survival. CXCR4 plays a role in multiple fundamental aspects of cancer, including proliferation, migration, adhesion, invasion, metastasis, angiogenesis, and survival. Blockade of cellular recruitment via CXCR4 inhibition may also facilitate the release and mobilization of leukemic cells from their "safe" environment in the bone marrow or lymphoid tissues, thereby making them more susceptible to chemotherapy. Thus, antagonists to CXCR4 may potentially intervene in malignancies where CXCR4 is highly expressed and may also improve survival when used in combination with chemotherapy.

In a study at the Dana-Farber Cancer Institute, Ghobrial et al (2014) examined the safety, tolerability, pharmacokinetics, pharmacodynamics and clinical activity of ulocuplumab alone and in combination with lenalidomide plus low-dose dexamethasone (Len-Dex), or in combination with bortezomib plus dexamethasone (Bor-Dex) in subjects with rel/ref MM. Ulocuplumab (i.e., 1, 3 and 10 mg/kg) was dose escalated with a 3-plus-3 design with doses of Len-Dex orBor-Dex to identify the maximum tolerated dose. For Cycle 1, ulocuplumab was administered as monotherapy on Days 1 and 8. Starting on Day 15, ulocuplumab was administered in combination

with lenalidomide [25 mg/d/21 days of a 28 day cycle] plus low dose dexamethasone [40 mg/week] and monitored for incidence of dose limiting toxicities (DLTs) within Cycle 1 (42 Days) of study treatment. For the Bor-Dex group, also starting on Day 15, ulocuplumab was administered in combination with bortezomib (1.3 mg/m2 on Days 1, 4, 8, 11 of a 21 day cycle] plus dexamethasone [days 1,2,4,5,8,9,11,12] and monitored for incidence of DLT(s) within Cycle 1 (35 Days) of study treatment. For the expansion phase, subjects received 10mg/kg ulocuplumab monotherapy on Days 1 and 8 followed by weekly doses in combination with Len-Dex (28-day cycles). Subjects were assessed at day 14 and after every cycle by IMWG criteria.

Forty-four subjects were evaluated on this study (median age, 59.5 yrs; range, 44-77). The median number of prior therapies was 4, (range, 1-9), with 76% of subjects having received ≥ 3. Subjects had received bortezomib in 93% of the cases, lenalidomide in 86%, thalidomide in 30%, carfilzomib in 20% and pomalidomide in 11%. Thirty subjects in escalation received ulocuplumab alone and in combination with Len-Dex : One subject in the U-Bor-Dex group experienced a DLT in which there was delayed platelet recovery to ≤ Grade 1 or baseline which resulted in a delay of dosing of ≥ 21 days. Ulocuplumab was escalated to a maximum of 10 mg/kg without reaching MTD in monotherapy or in combination therapy. Twenty-one subjects were treated in expansion phase. There were no grade 4 toxicities with ulocuplumab monotherapy and Grade 3 toxicities with monotherapy included thrombocytopenia (6.5%), anemia (4.3%), respiratory infections (4.3%), femur fracture (4.3%), lymphopenia (2.2%), neutrophil count decreased (2.2%), platelet count decreased (2.2%) and cerebrovascular accident (2.2%). The safety profile of ulocuplumab with Len-Dex or Bor-Dex was similar to either combination alone. Two subjects (4.5%) presented reversible G2 infusion reactions. The overall response rate (≥ PR) for all subjects in escalation and expansion was 50% (22/44), including 1 CR, 6 VGPR and 15 PR. The ORR by group was 55.1 % (16/29) and 40% (6/15) for U-Len-Dex and U-Bor-Dex, respectively. Furthermore, the ORR in expansion with 10 mg/kg U-Len-Dex was 57% (12/21) with 4 VGPRs and 8 PRs. Eight subjects in this expansion group had at least SD with a mean duration of 159 days (range, 46-437 days), resulting in 95% of subjects with clinical benefit. A median 2-fold mobilization of leukocytes into the peripheral circulation was reported after each infusion of ulocuplumab at 3 and 10 mg/kg. Samples showed rapid mobilization of leukocytes at 2 hours post-ulocuplumab with a partial decrease at 3-4 days post-administration without reaching baseline. Mobilization of plasma cells was also documented in some subjects. The results of this study showed that the blockade of the CXCR4-CXCL12 axis by ulocuplumab was safe and associated with a high response rate in combination with Len-Dex in patients with relapsed/refractory myeloma who previously received lenalidomide and bortezomib.

2.3 Other Agent Ibrutinib

Ibrutinib is a selective, irreversible inhibitor of Bruton's Tyrosine Kinase (BTK) that is approved by the U.S. FDA and the European Medicines Agency for the treatment of symptomatic WM. Activated BTK binds to MYD88, and triggers NFkB signaling. Ibrutinib potently inhibits BTK with a median inhibitory concentration of 0.5 nM. Ibrutinib also potently inhibits HCK at a median inhibitory concentration of 5 nM, a SRC family member that is triggered by mutated MYD88 and transactivates BTK, AKT, and ERK1/2 that support the growth and survival of WM cells (Yang et al, 2016).

Ibrutinib (IMBRUVICA®) is approved by the U.S. Food and Drug Administration (FDA) for the

treatment of : 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate, 2) chronic lymphocytic leukemia (CLL) including patients with17p deletion or a TP53 mutation, and 3) patients with symptomatic WM (Treon et al, 2015).

Ibrutinib pharmacokinetics

Following oral administration of ibrutinib at doses of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function

Clinical experience with ibrutinib

Ibrutinib is an orally administered agent. The first human Phase 1 study (PCYC-04753) was designed to evaluate the initial safety, tolerability, and pharmacokinetic and pharmacodynamic properties of ibrutinib in participants with recurrent B cell lymphoma. In this clinical setting a useful adverse event profile was obtained.

PCYC-04753 Study

PCYC-04753 was a multicenter Phase 1 study that included subjects with CLL, MCL and WM and constituted the first in-human trial of ibrutinib. The objectives included studying the safety profile of ibrutinib, identifying the maximum tolerated dose and optimal dosing schedule, and characterizing efficacy, pharmacokinetics, and pharmacodynamics. A minimum of 6 subjects per cohort received 1 of 5 escalating dose levels of ibrutinib between 1.25 and 12.5 mg/kg for 28 consecutive days in a 35-day cycle, with the objective of escalating 3 dose levels above that which achieved full BTK occupancy based on the fluorescent probe assay. Two additional cohorts received a continuous ibrutinib dose of 8.3 mg/kg without a 7-day rest and a fixed continuous dose of 560 mg/day.

Summary of Safety Data from PCYC-04753 and Monotherapy Trials

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below. The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071) as summarized below.

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

For more detailed information refer to the current version of the IB.

Clinical Efficacy

The outcome of patients with B-cell malignancies on ibrutinib has been published (Advani et al, 2012). Responses have been observed in all histologies dosed to date, including CLL/SLL, MCL, ABC DLBCL and WM patients who received ibrutinib treatment at dose of up to 560 mg a day. Among 50 evaluable subjects across all B-cell histologies, Advani et al (2012) reported an overall response rate of 60%, with 7 complete responses (CRs) and 23 partial responses (PRs). A fluorescent probe assay demonstrated complete active-site occupancy of BTK by ibrutinib in subjects given doses of 2.5 mg/kg or higher.

A multicenter, prospective study of single agent ibrutinib investigated the safety and efficacy of ibrutinib in relapsed or refractory WM patients (Treon et al, 2015b). The median number of prior therapies for these patients was 2 (range 1-9), and 40% of patients were refractory to their previous therapy. Seventy-eight percent of patients had a moderate-high WM IPSS prognostic score. Post therapy, the median serum IgM levels for all 63 patients declined from 3,520 to 880 mg/dL at best response ($p<0.01$). Pre-therapy, 46/63 (73.0%) patients had a serum IgM $\geq$3,000 mg/dL; following treatment, at best response, 6/63 (9.5%) patients had a serum IgM $\geq$3,000 mg/dL ($p<0.01$). Median BM involvement decreased from 60% to 25% ($p<0.01$), while hemoglobin increased from a median of 10.5 to 13.8 g/dL at best response ($p<0.01$). Responses included very good partial response (n=10); partial response (n=36); and minimal response (n=11) for overall and major responses of 90.5% (95% CI 80.4%-96.4%) and 73.0% (95% CI 60.3-83.4%), respectively. The median time to at least minor and partial responses were 4 and 8 weeks, respectively. Overall responses were similar regardless of baseline age (<65 vs. $\geq$65 years), ECOG status (0 vs. $\geq$1), pre-therapy Waldenström's macroglobulinemia International Prognostic Scoring System (IPSS) score, serum β_2-microglobulin levels (<3.0 vs. >3.0 mg/L), hemoglobin (<11 vs. >11 g/dL), serum IgM (<4,000 vs. $\geq$4,000 mg/dL), BM disease involvement (<50% vs. $\geq$ 50%), prior relapsed or refractory status, and prior lines of therapy (1-3 vs. >3), as well as for major responses across most of the baseline subgroups (Treon et al, 2015b). 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, 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 (>6 months) in comparison to patients with the

$MYD88^{L265P}CXCR4^{WT}$ genotype (Figure 1; Treon et al, 2015b).

CT-defined adenopathy (≥1.5 cm) was present in 37 patients at baseline. Serial imaging for 35 patients showed decreased or resolved (n=25; 67.6%); stable (n=9; 24.3%); or increased (n=1; n=2.9%) adenopathy. Two patients came off study before repeat imaging was required. Among 7 patients with CT-defined splenomegaly (≥15 cm), spleen size was decreased (n=4; 57.1%), stable (n=2; 28.6%), or not evaluable (n=1; 14.3%) following elective splenectomy. Nine patients (14.3%), 3 with positive anti-MAG antibodies, received ibrutinib for progressive IgM-related peripheral sensory neuropathy. All responded, and subjective improvements in peripheral sensory neuropathy occurred in 5, and remained stable in 4 during the treatment course. Symptomatic hyperviscosity related to progressive disease that required plasmapheresis prompted start of ibrutinib in 4 patients. All responded, and none required additional plasmapheresis by the end of Cycle 2. One patient required plasmapheresis for acquired Factor VIII deficiency. He responded, and did not require further plasmapheresis. The spontaneous bleeding events that prompted therapy also resolved. With a median on treatment duration of 19.1 (range 0.5-29.7) months, 43 patients (68.3%) remained on therapy. Reasons for treatment discontinuation included non-response (n=1); progressive disease (n=7); treatment-aggravated thrombocytopenia (n=1); hematoma after BM biopsy (n=1); prolonged drug hold for infection unrelated to ibrutinib (n=1); myelodysplasia/acute myeloid leukemia associated with baseline 5q- deletion related to prior therapies (n=1); disease transformation possibly related to prior nucleoside analogue therapy (n=2); antineoplastic therapy for rectal carcinoma (n=1); ibrutinib incompatible medication (n=1), patient decision to use commercially sourced ibrutinib (n=2), travel difficulties (n=1), and alternative therapy (n=1). The estimated progression-free and overall survival at 24 months was 69.1% (95% CI 53.2%-80.5%) and 95.2% (95% CI 86.0-98.4%), respectively. For patients with progressive disease, the median time to progression was 9.6 (range: 3.5 – 19.4) months if transformation cases were censored, and 9.5 (range: 3.5 – 19.4) months if transformation events were included. Subset analysis showed that >3 prior lines of therapy, high pre-therapy IPSS score, and $MYD88^{WT}CXCR4^{WT}$ mutation status associated with inferior progression-free survival.

In a prospective, multicenter, open-label substudy within a randomized, placebo-controlled, phase 3 study of ibrutinib and rituximab in WM (PCYC 1127, see below), 31 WM patients refractory to rituximab and requiring treatment received oral ibrutinib 420 mg daily until progression or unacceptable toxicity (NCT02165397). Endpoints included progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and hemoglobin. The median age was 67 years (range 47-90); 42% had high-risk disease per the International Prognostic Scoring System Waldenström Macroglobulinemia, median number of prior therapies was 4 (range 1-7), and all were rituximab-refractory. At a median follow-up of 18.1 months, the ORR was 90% (major response rate, 71%), and estimated 18-month PFS and OS rates were 86% and 97%, respectively. Rapid clinical improvement was observed after four weeks of ibrutinib, with a median IgM decrease of 48% and median hemoglobin increase from baseline of >1g/dL, improving further over time. These clinical outcomes correlated with improvements in validated patient-reported outcomes. Common grade ≥3 adverse events (AEs) included neutropenia (13%), hypertension (10%), anemia, thrombocytopenia, and diarrhea (6% each). No IgM flare, atrial fibrillation, or major bleeding was observed. Five (16%) patients discontinued ibrutinib: 3 due to progression and 2 due to AEs (gastrointestinal AL amyloidosis and diarrhea); while 84% continued on ibrutinib at the time of reporting (Dimopoulos et al, 2016).

In an ongoing phase III randomized study (PCYC 1127; NCT02165397), 181 symptomatic WM patients that included treatment naïve, and previously treated patients were randomized in a 1:1 ratio to receive the monoclonal antibody rituximab at 375 mg/m^2 IV weekly for 4 weeks, followed by a second 4-weekly course 3-months later, and either ibrutinib 420 mg daily or matching placebo until progressive disease (PD) or unacceptable toxicity. Key inclusion criteria include WM with documented PD or no response (stable disease) to last treatment if previously treated; symptomatic disease requiring treatment per the 2ndInternational Workshop on WM; and adequate hematologic, hepatic, and renal function. Exclusion criteria include CNS involvement and clinically significant cardiovascular disease. The primary endpoint is progression-free survival assessed by an independent review committee. Secondary endpoints are ORR, overall survival, hematologic improvement, time to next treatment, and safety. Enrollment is complete and study results are awaited.

2.4 Rationale

CXCR4 is expressed on WM cells (Ngo et al, 2008, Rocarro et al, 2014) and dysregulation of CXCR4 path signaling is common in WM (Hunter et al, 2016). Up to 40% of WM patients harbor a somatic activating mutation that supports tumor growth and survival, as well as drug resistance against many agents used to treat WM in response to its ligand CXCL12 (Hunter et al, 2014; Cao et al, 2014; Rocarro et al, 2014; Cao et al, 2015). CXCR4 mutations are almost always expressed in WM patients with mutated MYD88, and are associated with loss of genes that regulate MYD88 signaling (Hunter et al, 2016). Gene overexpression of CXCL12 has also been observed in WM cells regardless of CXCR4 mutation status, and contributes to enhanced CXCR4 signaling (Hunter et al, 2016). The use of CXCR4 antagonists may therefore offer a targeted approach to therapy of WM patients with WHIM-like somatic mutations. It is thus hypothesized that ulocuplumab will improve overall and major responses, and response kinetics to ibrutinib in symptomatic patients with CXCR4 mutated WM.

2.5 Correlative Studies Background

In most WM patients, CXCR4 mutations are subclonal with an estimated median cancer cell fraction of 40-50%, though the transcriptional signature remains relatively homogeneous despite the subclonal nature of CXCR4 mutations in WM (Hunter et al, 2016; Xu et al, 2016). CXCR4 mutated patients also show loss of regulatory genes that regulate MYD88 signaling (Hunter et al, 2016). Furthermore, the presence of CXCR4 WHIM mutations confers enhanced activation of AKT and ERK (Cao et al, 2014; Cao et al, 2015). Bone marrow aspirate (approximately 45cc) will therefore be collected at the baseline screening visit, on day 1 of cycle 2 (phase 1 participants only), at the completion of cycle 6 following the last ulocuplumab infusion, at year 1, and thereafter every year until study completion. Bone marrow lymphoplasmacytic cells will be genotyped for MYD88 and CXCR4 at baseline to determine eligibility, and at every BM sampling for the cancer cell fraction of mutated CXCR4 cells determined by next generation (whole exome) sequencing; ii) wild-type and mutated CXCR4 transcriptional signature determined by transcriptome analytsis; and iii) CXCR4, CXCR7 cell surface expression, pAKT, and pERK determined by multicolor flow cytometry.

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 Waldenstrom's Macroglobulinemia and meeting criteria for treatment using consensus panel criteria from the Second International Workshop on Waldenstrom's macroglobulinemia (Kyle et al, 2003) or have high risk disease with an serum IgM level of 6,000 mg or higher (Gustine et al, 2016).

3.1.2 MYD88 and CXCR4 mutated disease (determined by Treon laboratory or molecular diagnostics laboratory).

3.1.3 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.

3.1.4 Age ≥ 18 years

3.1.5 ECOG performance status ≤2 (see Appendix A.).

3.1.6 To establish eligibility, participants must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,000/uL independent of growth factor support within 7 days of screening
- Platelets ≥ 75,000/uL independent of platelet transfusions within 7 days of screening
- Hemoglobin ≥ 8 g/dL
- Total bilirubin ≤ 1.5 mg/dL or < 2 mg/dL if attributable to hepatic infiltration by neoplastic disease or Gilbert's syndrome
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional upper limit of normal
- Creatinine ≤ 2 mg/dL

3.1.7 Not on any active therapy for other malignancies with the exception of topical therapies for basal cell or squamous cell cancers of the skin.

3.1.8 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 28 days after discontinuation from the study. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. FCBP must be referred to a qualified provider of contraceptive methods if needed. FCBP must have a negative serum pregnancy test at screening.

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

3.1.10 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 Treatment with strong CYP3A4/5 inhibitors or inducers

3.2.4 Prior exposure to ibrutinib or ulocuplumab

3.2.5 With the exception of low-dose aspirin, subjects enrolled in this study should not take concomitant medications that durably inhibit platelet function including marine oil tablets. For such medications a wash-out period of ≥ 7 days is required prior to starting treatment. Agents which inhibit platelet function transiently or inhibit coagulation by other mechanisms are restricted (e.g. use with caution). Medications that directly and durably inhibit platelet function include aspirin containing combinations, clopidogrel, dipyridamole, tirofiban, epoprostenol, eptifibatide, cilostazol, abciximab, ticlopidine, cilostazol.

3.2.6 Participants should not take drugs that directly and durably inhibit coagulation with the exception of warfarin (coumadin) and heparin including low-molecular-weight heparin (LMWH), including enoxaparin, tinzaparin, etc.

3.2.7 Participants enrolled in this study should not take concomitant medications that are considered to have a risk of Torsades de Pointes (category 1 on http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists). For such medications a wash-out period of >7 days is required prior to starting treatment.

3.2.8 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.

3.2.9 Known CNS lymphoma.

3.2.10 New York Heart Association classification III or IV heart failure.

3.2.11 Known history of Human Immunodeficiency Virus (HIV), active infection with Hepatitis B Virus (HBV), and/or Hepatitis C Virus (HCV).

3.2.12 Lactating or pregnant women.

3.2.13 Grade > 2 toxicity (other than alopecia) continuing from prior anti-cancer therapy.

3.2.14 Inability to swallow capsules

3.2.15 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

N/a

4.4 Registration Process for Other Investigative Sites

N/a.

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

Treatment will be administered in four-week cycles. Treatment will be comprised of ibrutinib administered orally starting day 1 of cycle 1 for 47 cycles, along with ulocuplumab administered intravenously weekly during Cycle 1, and then every other week for Cycles 2-6. A 3+3 Phase I design will be employed for 3 dose levels, and 20 additional patients will be recruited at the maximum dose or maximum tolerated dose (if a dose-limiting toxicity is identified) for the Phase II dose expansion.

Bristol-Myers Squibb, the study supporter and manufacturer of ulocuplumab, terminated the development of ulocuplumab on 3/29/19. Due to this, the Phase 2 portion of this study was never opened. BMS continued to supply drug for this study until 7/1/2020. The Sponsor-Investigator halted enrollment on this study after the 3rd participant in the Phase 1 cohort #3 was accrued. All participants enrolled were able to complete planned ulocuplumab dosing, and participants then continued on commercial ibrutinib monotherapy.

The Sponsor-Investigator has decided to discontinue all study therapy and follow-up procedures for all participants remaining on the study as of 12/31/22.

Each cycle is four weeks. Ibrutinib will be administered continuously for 47 cycles. Ulocuplumab will be administered weekly on days 1, 8, 15, and 22 (± 2 days for each dose) for Cycle 1, then every other week on days 1 and 15 (± 2 days) for Cycles 2-6. For the Phase I portion, a 3+3 design will be used following the dosing schema in Table 1.

Table 1. Cohort dosing

Dose Level	Ibrutinib	Ulocuplumab Cycle 1	Ulocuplumab Cycles 2-6
Cohort 1 –Starting dose	420mg PO DQ	400 mg weekly	800 mg every other week
Cohort 2	420mg PO DQ	800 mg weekly	1200 mg every other week
Cohort 3	420mg PO DQ	800 mg weekly	1600 mg every other week

The MTD or highest administered dose informed from the Phase I portion of the study will be used in Phase II portion of the study.

Participants will be pre-medicated with 10mg of oral dexamethasone and 20mg of oral famotidine (or equivalent for either agent) 8-18 hours prior to each dose of ulocuplumab, in addition to 30-60 minutes before each treatment.

Regimen Description					
***Agent*[1]**	**Premedications; Precautions 30-60 minutes before ulocuplumab infusion**	**Dose**	**Route**	**Schedule**	**Cycle Length**

Ulocuplumab	1. Diphenhydramine 25-50 mg IV or PO 2. Acetaminophen 650 mg orally 3. Corticosteroids (10 mg of IV dexamethasone or equivalent) 4. Famotidine (or equivalent) 20 mg PO or IV*	Refer to Table 1. Cohort Dosing	IV	Cycle: 1 Days 1, 8, 15, and 22 ± 2 days Cycles 2-6: Days 1 and 15 ± 2 days	28 days (4 weeks)
Ibrutinib	Not applicable	420mg	PO	QD (outpatient)	28 days (4 weeks)

[1] The order of administration of Ibrutinib and Ulocuplumab does not matter.
*Oral famotidine or equivalent may be given in the event of drug shortages or formulary changes.

Reported adverse events and potential risks are described in Section 7. Dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Pre-Treatment Criteria

C1D1 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 Day 1 of all cycles:

- No grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy)
- No non-hematologic grade 3 toxicities
- Neutrophil count ≥ 750/uL (growth factor permitted to retreat)
- Platelet count ≥ 50,000 uL (platelet transfusion permitted to retreat)
- Hemoglobin ≥ 8 g/dL

5.3 Treatment Administration

5.3.1 Ulocuplumab

Ulocuplumab (400mg, 800mg, 1200mg, or 1600mg flat dose) will be administered as a single 60 minute intravenous infusion. Participants should be observed for one hour after the completion of every infusion.

Ulocuplumab will be administered 30-60 minutes after pre-medications on Day 1, 8, 15, and 22 of Cycle 1 (± 2 days for each dose), and Days 1 and 15 for Cycles 2-6 (± 2 days for each dose).

Vital signs (blood pressure, temperature, heart rate, respiratory rate) will be obtained before infusion, every 15 minutes (± 5 minutes) during the infusion period, and at 15, 30, and 60 minutes (± 5 minutes) after the completion of infusion.

Since ulocuplumab contains only human protein sequences, it is unlikely to be immunogenic and to induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it

might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo or hypertension, bronchospasm, or other symptoms.

For Grade 1 symptoms, i.e. mild reaction for which infusion interruption is not indicated, and intervention is not indicated:

Patient will remain at the clinic and monitored until there is recovery from symptoms. Continuation of infusion as before can proceed until infusion is completed. Information on prophylactic pre-medications is provided in Section 5.7.1.

For Grade 2 symptoms, i.e. moderate reaction that requires infusion interruption, and that necessitates intervention such as antihistamines, non-steroidal, or anti-inflammatory agents (NSAIDs), narcotics, corticosteroids, or intravenous fluids. Patients will remain at the clinic and monitored until there is recovery from symptoms. Infusion may be restarted at 50% of the original infusion rate when symptoms resolve. If no further complications occur after 30 minutes, the rate may be increased to 100% of the original infusion rate. Subject should be monitor closely at this time. If symptoms recur, then the infusion will be stopped and no further ulocuplumab will be administered at that visit. The amount of study drug infused must be recorded on the case report form (CRF). Patient will be monitored until recovery from symptoms.

For prolonged Grade 3 or Grade 4 symptoms, i.e. severe reactions that are severe or not rapidly responsive to symptomatic medication and/or interruption of infusion, or recurrence of symptoms following initial improvement, study drug should be terminated. An intravenous infusion of normal saline, and support as follows can be considered by the treating clinician: bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration, 0.3 mg of a 1:1,000 solution for intramuscular administration, or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. The subject should be monitored until the treating clinician is comfortable that symptoms will not recur. Ulocuplumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis, and treating clinician should if possible remain at bedside and monitor the subject until recovery from symptoms.

In the case of late occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

Product description and storage information is described in Section 8.

5.3.2 **Ibrutinib Administration**

Ibrutinib 420 mg will be prescribed per the FDA package label, administered orally once daily for 47 cycles. The capsules should be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the

study (see section 5.7.3).

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible within 6 hours, with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.
Participants will be treated with ibrutinib for 47 cycles or until progression, unacceptable toxicity, or decision to withdraw from the trial. Dose reductions due to toxicity will be permitted on information seen in Section 6.

Ibrutinib will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken. Participants will be instructed to take the study drug at approximately the same time each day, ideally at least 30 minutes before eating or at least 2 hours after a low-fat meal. Participants will also be instructed on how to complete the diary. Participants will be reminded that dietary habits around the time of ibrutinib intake should be as consistent as possible throughout the study. If a dose is missed, study drug may be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, ibrutinib should not be taken on that date, and the patient should take the next ibrutinib dose at the scheduled time the next day. The missed dose will not be made up and must be returned at the next scheduled visit. The patient will be instructed to document missed drug doses in the study diary. Furthermore, they will be instructed to call the PI or research nurse if vomiting occurs. If the pills are vomited, this should be noted on the patient diary, but a replacement dose should not be taken that day. All dosages prescribed and dispensed to the participant, and all dose changes during the study must be recorded.

5.4 Definition of Dose-Limiting Toxicity (DLT) for Ulocuplumab (Phase I only)

The following will be considered a DLT if occurring during the 1st & 2ndCycle of Therapy:

- ≥ Grade 4 hematologic toxicity (anemia, neutropenia, or thrombocytopenia)
- Any grade 5 hematologic or non-hematologic toxicity
- Any grade 4 non-hematologic toxicity, including vomiting or diarrhea
- Any other ≥ Grade 3 adverse event not due to underlying disease, except for Grade 3 infection, easily reversible asymptomatic laboratory abnormalities, and nausea, vomiting, or diarrhea controlled by medications.
    - Grade 3 vomiting or diarrhea can only be excluded if the participant does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity resolves to less than grade 3 within 72 hours.
    - Reversible asymptomatic laboratory abnormalities may be excluded only if they are correctable to <grade 3 within 72 hours.

The following will NOT be considered a DLT:

- An IgM flare, which is commonly observed with antibody therapy in WM patients and may require plasmapheresis
- Lymphocytosis, or mobilization of leukocytes which often occurs as a consequence of CXCR4 antagonism
- Lymphopenia, which is an intended consequence of therapy
- A ≤ Grade 2 infusion reaction

Management and dose modifications associated with the above adverse events attributed to ulocuplumab are outlined in Section 6.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
$\geq$2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. 20 additional participants will be entered at the next lowest dose level.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose.

5.5 Definition of Maximum Tolerated Dose (MTD) for Ulocuplumab (from Phase I)

The MTD is defined as the highest combination drug dosage not causing medically unacceptable, dose-limiting toxicity (DLT) in more than 33% of the treated participants in the first cycle and second cycle of treatment. Adverse events and laboratory abnormalities that are considered DLTs are defined in Section 5.4. The MTD or maximum dose from Phase I portion of the study will be used in the phase II part of the study.

5.6 Ulocuplumab Dose for Phase II Part of Study

The MTD or maximum dose from Phase I portion of the study will be used in the phase II part of the study. After the first six participants are accrued to the Phase II cohort, enrollment will be held to conduct a DSMC safety analysis of the first two cycles of treatment. The DSMC will determine if there have been excessive dose reductions or delays which require an amendment to the Phase II ulocuplumab dose level.

5.7 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.

5.7.1 Prophylactically Prescribed Medication

All prophylactic premedication administration is mandatory. Participants will be pre-medicated with 10mg of oral dexamethasone and 20mg of oral famotidine (or equivalent for either agent) 8-18 hours prior to each dose of ulocuplumab. The following premedications should be administered within 30-60 minutes prior to administration of ulocuplumab:

- IV or oral diphenhydramine 25-50 mg
- Acetaminophen 650 mg orally
- Corticosteroids (10 mg of IV dexamethasone or equivalent)
- Famotidine (or equivalent) 20 mg PO or IV

5.7.2 Permitted Treatments

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

5.7.3 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 ulocuplumab 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.
- Medications that are generally considered to have a risk of causing "Torsades de Pointes" (Category 1 on http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists). Subjects must have a washout period of > 7 days prior to first dose of investigational product. Caution is warranted when administering ulocuplumab to subjects taking drugs associated with prolongation of QTc listed in Category 2: Drugs with Possible Risk of Torsades de Pointes.
- Medications that Durably Inhibit Platelet Function:

  With the exception of low-dose aspirin, subjects enrolled in this study should not take concomitant medications that durably inhibit platelet function. For such medications, a wash-out period of ≥ 7 days is required prior to starting treatment. Medications that directly and durably inhibit platelet function include aspirin-containing combinations, clopidogrel, dipyridamole, tirofiban, dipyridamole, epoprostenol, eptifibatide, cilostazol, abciximab, ticlopidine, cilostazol should be avoided.
- Medications that Inhibit Coagulation: With the exception of heparin including low-molecular-weight heparin (LMWH) (enoxaparin, tinzaparin, etc), or Factor X inhibitors, subjects should not take drugs that directly and durably inhibit coagulation.
- Supplements such as fish oils and vitamin E preparations should be avoided.

CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, withhold ibrutinib treatment for the duration of inhibitor use.

- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg PO QD for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A.

- No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

No chronic treatment with systemic steroids (at dosages equivalent to prednisone > 20 mg/day for more than 14 days) or other immunosuppressive agents should be used. Topical or inhaled corticosteroids are allowed.

5.8 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 47 cycles or until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s) based on study team determination.
- Participant demonstrates an inability or unwillingness to comply with treatment administration and/or documentation requirements for ibrutinib.
- 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.
- Unacceptable toxicity requiring discontinuation of Ibrutinib
- Withdrawal of subject consent.

Participants meeting criteria for disease progression but deemed by the investigator to be clinically benefiting from ibrutinib will be permitted to continue on protocol therapy at the PI's discretion. 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. An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the DF/HCC website at http://www.dfhcc.harvard.edu/research/clinical-research-support/document-library-forms-sops-etc/.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Study Chair Steven Treon at 617-470-7064 or the PI, Jorge J. Castillo at 617-632-3352.

The Sponsor-Investigator has decided to discontinue all study therapy and follow-up procedures for all participants remaining on the study as of 12/31/22.

5.9 Duration of Follow Up

Participants will be followed for up to 24 months after completion of protocol therapy, or until termination from study, disease progression, initiation of new anti-neoplastic therapy, or death. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution of the adverse event to at least grade 1 or less, or stabilization of the adverse event. The Sponsor-Investigator has decided to terminate all follow-up as of 12/31/22.

5.10 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
- Study termination as of 12/31/22

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 and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

In the case of toxicity, appropriate medical treatment should be used (including transfuions, cytokine growth factors, anti-emetics, anti-diarrheals, etc.) as medically indicated. 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, treatment interruption(s) and dose adjustment(s) are permitted. Adverse event attribution to ibrutinib, ulocuplumab or both agents should be determined before treatment interruptions and dose adjustments are made. For non-hematologic toxicities attributable to ulocuplumab, but not to ibrutinib, ibrutinib dosing may be continued.

Dosing of ibrutinib and ulocuplumab will both be held for any of the following hematologic conditions:

- Absolute neutrophil count (ANC) <500/uL
- Platelet count <50,000/uL
- Hemoglobin <8 g/dL

Protocol therapy may be re-started as follows:

- Recovery of ANC to ≥750 uL for ulocuplumab, and ≥500/uL for ibrutinib
- Recovery of Platelet count to ≥50,000/uL
- Recovery of Hemoglobin to ≥8 g/dL
- Recovery of non-hematologic toxicity to grade 1 or less

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

- Grade 3 non-hematological toxicity
- Grade ≥2 atrial fibrillation. Consider the risks and benefits of restarting and continuing ibrutinib treatment. If clinically indicated, the use of concomitant antiarrythmics, rate control medications, cardiac ablation, or the use of warfarin, non-warfarin or vitamin k antagonist anticoagulants agents may be considered to prevent or control ibrutinib related atrial fibrillation

If administration of ibrutinib must be interrupted because of unacceptable toxicity, ulucuplomab should also be held. Resumption of ibrutinib treatment should be handled as follows:

- 1st Occurrence: Retreat at dose level 1 (or dose level -1 if in the opinion of the principal investigator this is in subject's best interest).
- 2nd Occurrence: Retreat at Dose level -1
- 3rd Occurrence: Retreat at Dose level -2
- 4th Occurrence: Discontinue ibrutinib

If administration of ibrutinib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 6-1.

Dose re-escalations of ibrutinib will not be permitted once dose reduced to next lower dose level unless done for concurrent treatment with CYP3A inhibitors (section 5.7.3). Dose reductions are permitted down to dose level -2 in Table 6-1 before a patient is taken off study. If a participant requires a dose delay of ibrutinib for > 28 days, then the participant will be taken off study.

Table 6-1. Ibrutinib Dose Modification Guidelines

Dose Level	Dose and Schedule
1	420 mg po qD
-1	280 mg po qD
-2	140 mg po qD

Participants who must permanently discontinue Ibrutinib administration will be removed from protocol therapy.

Ulocuplomab should be held if ibrutinib is held (as noted above). Dosing of ulocuplumab should also be held for any of the following ulocuplumab-related conditions:

- Grade 3 non-hematological toxicity

If administration of ulocuplumab must be interrupted because of unacceptable toxicity, unless only delayed due to ibrutinib associated toxicity, resumption of treatment should be handled as follows:

- 1st Occurrence: Retreat at current dose (or dose level -1 if in the opinion of the principal investigator this is in subject's best interest).
- 2nd Occurrence: Retreat at Dose level -1
- 3rd Occurrence: Retreat at Dose level -2
- 4th Occurrence: Retreat at Dose level -3
- 5th Occurrence: Discontinue ulocuplumab

Dose level reduction(s) or termination for ulocuplumab will follow the rules described in Table 6-2, 6-3, or 6-4.

Dose re-escalations of ulocuplumab will not be permitted once dose reduced to next lower dose level. Dose reductions are permitted per Table 6-2, 6-3, or 6-4 before a patient is taken off study. If a participant requires a dose delay of ibrutinib for > 28 days, then the participant will be taken off study.

If administration of ulocuplumab must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 6-2, 6-3, and/or 6-4. Treatment with ulocuplumab may be delayed and schedules adjusted if holding ulocuplumab is necessary. Ibrutinib therapy can be continued throughout ulocuplumab hold period unless the adverse event may also be related to ibrutinib. In such situations, treatment hold and/or dose modifcations may be made for both drugs per Table 6-1 (for ibrutinib) and Table 6-2, 6-3, & 6-4 (for ulocuplumab).

Dose hold and de-escalation for ulocuplumab for the Phase II portion of the study will follow the rules for the cohort deemed to represent the maximum dose or MTD from the Phase I part of the study and shown in Table 6-2, 6-3, & 6-4. If a participant requires a dose delay of ulocuplumab

for > 28 days, then ulucuplomab will be discontinued. For participants permanently discontinuing ulocuplumab, ibrutinib therapy may be continued alone for study duration.

Table 6-2. Ulocuplumab Dose Modification Guidelines Cohort 1

Cohort dose level 1	Ulocuplumab Dose Level 1	Dose level -1	Dose level -2
Cycle 1	400mg	200mg	STOP
Cycle 2-6	800mg	400mg	200mg

Table 6-3 Ulocuplumab Dose Modification Guidelines Cohort 2

Cohort dose level 2	Ulocuplumab Dose Level 1	Dose level -1	Dose level -2	Dose level -3
Cycle 1	800mg	400mg	200mg	STOP
Cycle 2-6	1200mg	800mg	400mg	STOP

Table 6-4 Ulocuplumab Dose Modification Guidelines Cohort 3

Cohort dose level 3	Ulocuplumab Dose Level 1	Dose level -1	Dose level -2	Dose level -3	Dose Level -4
Cycle 1	800mg	400mg	200mg	STOP	-
Cycle 2-6	1600mg	1200mg	800mg	400mg	STOP

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, 2004, Ghobrial et al, Cancer 2004). Such abrupt increases can prompt symptomatic hyperviscosity in patients with high serum IgM levels and can contribute to worsening of IgM related morbidity such as cryoglobulinemia, cold agglutinemia, and demyelinating neuropathy (Treon et al, 2015). Plasmapheresis is therefore used to treat symptomatic IgM flares, as well as prophylax in patients with high serum IgM levels (>4,000 mg/dL). Following plasmapheresis, serum IgM levels will return to steady state in 4-5 weeks. As such WM patients will be inevaluable for response purposes. It is recommended patients with symptomatic hyperviscosity or a pre-treatment serum IgM level >4,000 mg/dL undergo plasmapheresis before treatment with ulocuplumab. Treatment with ulocuplumab may be delayed for up to two weeks if plasmapheresis is warranted. Close serial monitoring of serum IgM levels (at least weekly) is recommended for all participants during cycle 1, and at least every other week during cycles 2-6. For purposes of dose limiting toxicity, an IgM flare will not count given the expected nature of the flare with antibody therapy in WM patients.

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 Ulocuplumab

Table 5.5.5.1-1: [redacted]

[redacted]

7.1.1.2 Adverse Event List for Ibrutinib

Risks

Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied.

Cardiac

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged, follow the protocol dose modification guidelines (see Section 6).

Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity.

Lymphocytosis and Leukostasis

Leukostasis

There were isolated cases of leukostasis reported in non-WM subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis

typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, >400,000/ul) has been observed in non-WM subjects. Lymphocytosis was uncommon in subjects with WM treated with ibrutinib, and was typically <5,000/ul.

Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in non-WM subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and preexisting kidney abnormalities.

Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD.

Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

Treatment-Emergent Adverse Events in > 10% of Subjects

Treatment-emergent AEs in more than 10% of subjects receiving ibrutinib as monotherapy (N=1071) are summarized in Table 5. The most frequently reported treatment-emergent AEs were diarrhea, fatigue, nausea, cough, anemia, pyrexia, and neutropenia.

Table 5: Treatment-Emergent Adverse Events (any grade) in >10% of Subjects Receiving Ibrutinib Monotherapy including crossover patients (Safety Population)

	Monotherapy Studies
Number of Subjects	1071
Subject with 1 or more events	987 (92.2%)
Preferred Term	
Diarrhoea	429 (40.1%)
Fatigue	315 (29.4%)
Nausea	238 (22.2%)
Cough	199 (18.6%)
Anaemia	188 (17.6%)
Pyrexia	185 (17.3%)
Neutropenia	178 (16.6%)
Arthralgia	159 (14.8%)
Oedema peripheral	159 (14.8%)
Constipation	158 (14.8%)
Thrombocytopenia	158 (14.8%)
Upper respiratory tract infection	147 (13.7%)
Muscle spasms	146 (13.6%)
Vomiting	142 (13.3%)
Dyspnoea	130 (12.1%)
Headache	127 (11.9%)
Pneumonia	127 (11.9%)
Decreased appetite	120 (11.2%)
Contusion	117 (10.9%)
Dizziness	108 (10.1%)

Note: Monotherapy studies includes PCYC-1102-CA, PCYC-1104-CA, PCYC-1106-CA, PCYC-1112-CA, PCYC-1112-CA(crossover only), PCYC-1117-CA, PCYC-1118E-CA, PCYC-04753, PCI-32765-JPN-101, PCI32765MCL2001, and PCI32765CLL3001(crossover only).

[TSFAE01B.RTF] [JNJ-54179060\Z_IB\DBR_IB_2015\RE_IB_2015\PROD\TSFAE01B.SAS] 26JUN2015, 11:43

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.

7.3.2 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.

7.3.3 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 BMS Worldwide Safety

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety.

- The FDA Medwatch form should be used to report SAEs. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs and pregnancies must be reported to BMS within 24 hours of learning of the event regardless of causality. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

a) results in death

b) is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

c) requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)

d) results in persistent or significant disability/incapacity

e) is a congenital anomaly/birth defect

f) is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

g) Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

h) Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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 BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

7.6 Routine AE reporting to BMS

All treatment emergent AEs (including severity grade, action taken, and outcome) will be communicated to BMS on a quarterly basis.

7.7 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.

7.8 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 <u>also</u> 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 Ulocuplumab

8.1.1 Description

[redacted]

[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

[redacted]

[redacted] 2°C to 8°C, protect from light and protect from freezing

[redacted]

8.1.3 Storage and Stability

[redacted]

8.1.4 Compatibility

[redacted]

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

Ulocuplumab is provided as global open label supply, packaged and labeled under the responsibility of Bristol-Myers Squibb Drug Supply Management. Study treatment labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

8.1.7 Preparation

[redacted]

[redacted]

8.1.8 Administration

[redacted]

8.1.9 Ordering (BMS to provide)

In this protocol, investigational product is Ulocuplumab, which will be supplied by BMS, where other preventative medications or SOC medications that are not considered IMP, are not supplied by BMS. Ancillary supplies, such as NSS, syringes, needles, etc will be sourced and supplied locally by the site.

The process for ordering study drug from BMS for the initial shipment and resupply shipments will be managed by the site through completion of a drug shipment request form, which will be provided by BMS.

8.1.10 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.)

8.1.11 Destruction and Return

The Drug Accountability Log will contain the date and amount of study drugs received, and unused vials destroyed. All used and partially used study drug will be destroyed by the site, in accordance with the site's standard operating procedures (SOPs).

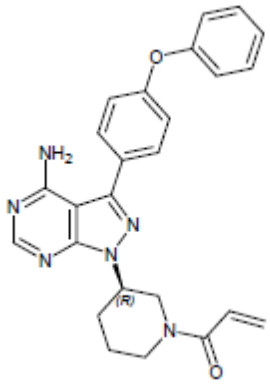
8.2 Ibrutinib

8.2.1 Description

Ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib exhibited 18% to 23% oral bioavailability in rats and 7% to 11% oral bioavailability in dogs. The mean terminal half-life of ibrutinib after oral administration ranged from 1.7 to 3.1 hours in mice, 1 to 4.7 hours in rats, and 3.3 to 6.4 hours in dogs. Preliminary results suggest a 1.5- to 2.5-hour half-life of ibrutinib in humans. The effects of renal and/or hepatic impairment on drug clearance are not known at this time. In vitro studies have indicated that ibrutinib is metabolized extensively by cytochrome P450 (CYP) 3A4.

8.2.2 Form

The structure of ibrutinib is:



Ibrutinib is a white to off-white crystalline solid. Ibrutinib has a single chiral center and is the R-enantiomer. Ibrutinib product is manufactured for Pharmacyclics LLC by a contract manufacturer.

Ibrutinib PO Hard Gelatin Capsule is an oral formulation containing micronized ibrutinib and the following compendial excipients: microcrystalline cellulose (NF); croscarmellose sodium (NF); sodium lauryl sulfate (NF); may contain magnesium stearate (NF). The 140 mg strength contains 140 mg of the active ingredient, ibrutinib, adjusted for water content and purity in a size 0, white, hard gelatin capsule. Capsules are packaged in 60-cc high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle is distributed by Pharmacyclics LLC. The number of capsules per bottle is indicated on the label.

Ibrutinib is also available in tablets in 140mg, 280mg, and 420mg strengths. Each 140mg tablet is a yellow green to green round tablet debossed with “ibr” on one side and “140” on the other side. Each 280mg tablet is a purple oblong tablet debossed with “ibr” on one side and “280” on the other side. Each 420mg tablet is a yellow green to green oblong tablet debossed with “ibr” on one side and “420” on the other side.

8.2.3 Storage and Stability
Ibrutinib should be stored according to the package insert.

8.2.4 Handling
N/a. Ibrutinib will be commercially supplied.

8.2.5 Availability
Ibrutinib is considered standard of care for this patient population. It will be commercially sourced and charged to patient insurance.

8.2.6 Administration
Ibrutinib should be self-administered daily by the participant according to the package insert.

8.2.7 Ordering
Ibrutinib is commercially available.

8.2.8 Accountability
The investigator or designee will comply with all institutional commercial drug SOPs.

8.2.9 Destruction and Return
N/A.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

9.1.1 Laboratory Correlative Studies

Bone marrow aspirate (approximately 45cc) will therefore be collected at the baseline screening visit, on day 1 of cycle 2 (phase I participants only), at the completion of cycle 6 following the last ulocuplumab infusion, at year 1, and thereafter every year until study completion. Bone marrow lymphoplasmacytic cells will be genotyped for MYD88 and CXCR4 at baseline to determine eligibility, and at every BM sampling for the cancer cell fraction of mutated CXCR4 cells determined by next generation (whole exome) sequencing; ii) wild-type and mutated CXCR4 transcriptional signature determined by transcriptome analytsis; and iii) CXCR4, CXCR7 cell surface expression, pAKT, and pERK determined by multicolor flow cytometry.

10. STUDY CALENDAR

	Screening* ≤ 30 days from study entry	**Treatment Phase**							**Off Treatment Assessment[5]** Within 4 ± 2 weeks of completing or coming off study.	**Follow-Up Phase[6]** Post Treatment. Every 12 ± 2 weeks for 24 months, next therapy or death.
		Cycle 1				Cycles 2-6 (+/- 2 days)		Cycles 9,12,15,18,21,24,27,30,33,36,39,42,45		
		Day 1	Day 8 (+/- 2 days)	Day 15 (+/- 2 days)	Day 22 (+/- 2 days)	Day 1 (+/- 2 days)	Day 15 (+/- 2 days)	Day 1 (+/- 14 days)		
Physical exams*[1], weight, height	X	X				X		X	X	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[2]	X (if applicable)
Bone marrow biopsy and aspiration[3]	X					X[3]		X[3]	X	X (if applicable)
Serum immuno-electropheresis	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
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 (SGPT), AST (SGOT), 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	X									
Pregnancy Test[4]	X									
HBsAg, HBsAb, HBcAB	X									
HCV, HIV Ab	X									
Ulocuplumab administration		X	X	X	X	X	X			
Ibrutinib diary review						X		X		

* Physical exam, vital signs, laboratory tests, 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, every 15 minutes during the infusion (±5 minutes), and 15, 30, and 60 minutes post infusion (± 5 minutes).

[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** on days 1 of cycle 12, 24, 36, and off-treatment assessment **for participants who had extramedullary disease at baseline (i.e. lymph nodes 15 mm or greater, spleen ≥15 cm, or other documented extramedullary site of WM disease).** 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. CT scans will also be done at the completion of Cycle 6 on Day 15 (+/- 2 days). Scans will also be repeated to confirm a complete response if the participant has no detectable monoclonal protein and had extramedullary disease (as noted above) at baseline and at the discretion of the investigator.

[3]Bone marrow biopsy and aspiration will be done during the screening visit or within 90 days prior to Cycle 1 Day 1, and on days 1 of cycle 6, 12, 24, 36, and off-treatment assessment. Bone marrow biopsy and aspiration will also be done at the completion of Cycle 6 on Day 15 (+/- 2 days). Up to 45 additional cc of aspirate will be collected (if collectable) at these sampling times for laboratory correlative studies specified in section 9.1.1. A bone marrow aspirate only will be collected on day 1 of cycle 2 for laboratory correlative studies per 9.1.1 from participants on the Phase I part of the study only. Bone marrow biopsy and aspiration may also be performed to confirm complete response, or progression, and study samples may be collected at this time to perform laboratory corollary studies per section 9.1.1

[4]For women of childbearing potential only, a serum pregnancy test is required at screening.

[5]Participants still on commercial ibrutinib as of study termination on 12/31/22 are not required to complete the Off Treatment visit and will not enter follow-up.

[6]All follow-up will be terminated as of 12/31/22.

11. MEASUREMENT OF EFFECT

11.1.1 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. 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.)

11.1.2 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 $\geq$ 90% reduction in serum IgM levels, or normalization of serum IgM levels.

Partial Response (PR): Partial response (PR) is defined as achieving a $\geq$ 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. For participants on active therapy who are on a drug hold for > 7 days, serum IgM levels will be considered unevaluable for response assessment. Patient must be on study drug for >2 consecutive weeks to be considered eligible for serum IgM response assessment. 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.

11.1.1 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).

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

CTRIO/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 CTRIO/ODQ according to the schedule set by the CTRIO/ODQ.

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.

After the first six participants are accrued to the Phase II cohort, enrollment will be held to conduct a DSMC safety analysis of the first two cycles of treatment.

12.3 Multicenter Guidelines

Not applicable.

12.4 Collaborative Agreements Language

Not applicable.

13. STATISTICAL CONSIDERATIONS

This is a phase I/II, dose-escalating, single-arm, open-label prospective study aimed at evaluating the safety of ulocuplumab, an anti-CXCR4 monoclonal antibody, in symptomatic patients with CXCR4 mutated WM. As a phase I study, response and/or survival outcomes will not be taken into account for sample size purposes. Regarding toxicity, assuming that an adverse event associated with study drug has a true incidence of 10%, with an estimated sample size of 38 patients (maximum population to be enrolled), the likelihood of observing at least 1 adverse event would be at least 90%

13.1 Study Design/Endpoints

This is a phase I/II, dose-escalating, single-arm, open-label prospective study aimed at evaluating the safety of ibrutinib combined with ulocuplumab, an anti-CXCR4 monoclonal antibody, in patients with symptomatic CXCR4 mutated WM. Toxicity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0), which is available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The following will be considered a DLT if occurring during the 1st or 2nd Cycle of Therapy

- ≥ Grade 4 hematologic toxicity (anemia, neutropenia, or thrombocytopenia)
- Any grade 5 hematologic or non-hematologic toxicity
- Any grade 4 non-hematologic toxicity, including vomiting or diarrhea
- Any other ≥ Grade 3 adverse event not due to underlying disease, except for Grade 3 infection, easily reversible asymptomatic laboratory abnormalities, and nausea, vomiting, or diarrhea controlled by medications.
    - Grade 3 vomiting or diarrhea can only be excluded if the participant does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity resolves to less than grade 3 within 72 hours.
    - Reversible asymptomatic laboratory abnormalities may be excluded only if they are correctable to <grade 3 within 72 hours.

The following will NOT be considered a DLT

- An IgM flare, which is commonly observed with antibody therapy in WM patients and may require plasmapheresis.
- Lymphocytosis, or mobilization of leukocytes which often occurs as a consequence of CXCR4 antagonism.
- Lymphopenia, which is an intended consequence of therapy.
- A ≤ Grade 2 infusion reaction.

The maximum tolerated dose (MTD) will be the dose below that which produced a DLT or the maximum dose allowed by protocol (1600 mg) if no DLT was observed. The MTD will be then

be used for the phase II portion of the study.
Dose escalation will be as follows, for a maximum accrual of 18 patients:

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. 20 additional participants will be entered at the next lowest dose level.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose.

13.2 Sample Size, Accrual Rate and Study Duration

A maximum of 18 patients will be accrued for the phase I study.

A maximum of 20 evaluable patients will be accrued for the phase II study. To be evaluable for response, patients must have one cycle of therapy. Patients inevaluable for response will be replaced. Assuming an H0 of major response rate of 50% vs. an H1 of 80%, a sample of 20 patients would have a power of 80% with an alpha of 0.04 to detect a difference. If 15 patients or more obtain a major response, then the study would be a success, if 14 patients or fewer obtain a major response, then the study would be a failure and the combination should not continue further evaluation. Sample size and power estimation were obtained using the binomial method (STATA version 13).

Accrual time will be approximately 12-18 months, at a rate of 2-3 patients per month. Patients will be followed for the duration of time on active protocol therapy (47 cycles), and then 2 additional years after completion of cycle 47. Participants will be followed for up to 24 months after completion of protocol therapy, or until termination from study, disease progression, initiation of new anti-neoplastic therapy, or death. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution of the adverse event to at least grade 1 or less, or stabilization of the adverse event.

13.3 Stratification Factors

No stratification factors will be applied for either the Phase I or Phase II portion of the study.

13.4 Interim Monitoring Plan

The study will be monitored by the DFCI Data Safety Monitoring Committee (DSMC). The DSMC will meet at least two times a year and more often if needed (e.g., for safety review). For each meeting, the study will be reviewed for safety and progress toward completion. Copies of the toxicity reports prepared by the DSMC meetings will be distributed to the Principal Investigator. The Principal Investigator will then distribute to subinvestigators. Any DSMC recommendations for changes to the study will be distributed to the Principal Investigator and then circulated to sub-investigators by the Principal Investigator. No interim analysis of the outcome data is planned.

After the first six participants are accrued to the Phase II cohort, enrollment will be held to conduct a DSMC safety analysis of the first two cycles of treatment. The DSMC will determine if there have been excessive dose reductions or delays which require an amendment to the Phase II ulocuplumab dose level.

13.5 Analysis of Primary Endpoints

The primary objective of the Phase I portion of the protocol is to determine the MTD of ulocuplumab combined with ibrutinib. The maximum tolerated dose (MTD) will be the dose that produces a DLT or the maximum dose allowed by protocol (1600 mg) if no DLT is observed (see section 13.1).

Participants from the Phase II portion of the protocol will be included 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.

Primary analyses will be performed in FAS population and will include calculating the proportion of patients having a major response (PR or better). Confidence intervals (95%) around these point estimates will be presented.

13.6 Analysis of Secondary Endpoints

The Per-Protocol Analysis Set (PPS) is defined as all participants from the FAS set who complete the study and are deemed to be protocol-compliant. To be protocol-compiant, a participant must not have any major protocol deviations during the study period. Protocol deviations will be identified prior to database lock and will be listed in the clniical study report. The PPS will be used for secondary assessment of efficacy endpoints.

Secondary analyses will be performed in both the FAS and PPS populations. There are no secondary endpoints for the Phase I portion of the protocol. For the Phase II participants the time to response, both major (PR or better) and minor response will be estimated using Kaplan Meier methodology with median time plus 25th and 75th percentile time to response along with 95% confidence intervals being provided, as appropriate. Time to progression (TTP) will also be estimated using Kaplan Meier methodology. Best overall response and Very Good Partial Response (>90% reduction in disease burden)/ CR (complete response) will be estimated in both

the FAS and PPS populations involving calculating the proportion of patients having an overall response (MR or better). Confidence intervals (95%) around these point estimates will be presented.

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 who have received at least one cycle of therapy are eligible for response assessment. Inevaluable patients for response will be replaced. All conclusions will be based on evaluable participants.

14. PUBLICATION PLAN

Interim study results may be presented at a major scientific meeting (American Society of Hematology, the International Workshop on WM or the International Conference on Malignant Lymphoma) once the Phase I portion of the study is completed. Once the Phase II portion is completed, a final study report will be presented at a major meeting.

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.