Study Numbers: NU 14H06
PCI-32765MCL2003

Initial version: September 24, 2014
AMD 11: ver. date 08.06.2022

A Phase II Clinical Trial Evaluating Ibrutinib Maintenance Following Intensive Induction for Patients with Previously Untreated Mantle Cell Lymphoma (MCL)

Principal Investigator:
Reem Karmali, MD, MS
Northwestern University Feinberg School of Medicine
676 North St. Clair Street, Suite 850
Chicago, IL 60611-2927
Phone: (312) 695-0990
Fax: (312) 695-1144
reem.karmali@nothwestern.edu

NU Sub-Investigator(s):
Leo I Gordon, MD
Jane N Winter, MD
Shuo Ma, MD, PhD
Valerie Nelson, MD, MBA

Participating Sites:

Dana Farber d/b/a Massachusetts General Hospital
Jeremy Abramson, MD
jabramson@mgh.harvard.edu

University of Utah
Deborah M. Stephens, DO
deborah.stephens@hci.utah.edu

Biostatistician:
Xinlei Mi, PhD
xinlei.mi@northwestern.edu

Study Drug: Ibrutinib

IND Status: Exempt

Funding Source: Janssen Scientific Affairs, LLC

Version Date: August 8, 2022 (Amendment 11)

Sponsor:
Northwestern University
Robert H. Lurie Comprehensive Cancer Center
Clinical Trials Office
676 N. St. Clair Street, Suite 1200
Chicago, IL 60611

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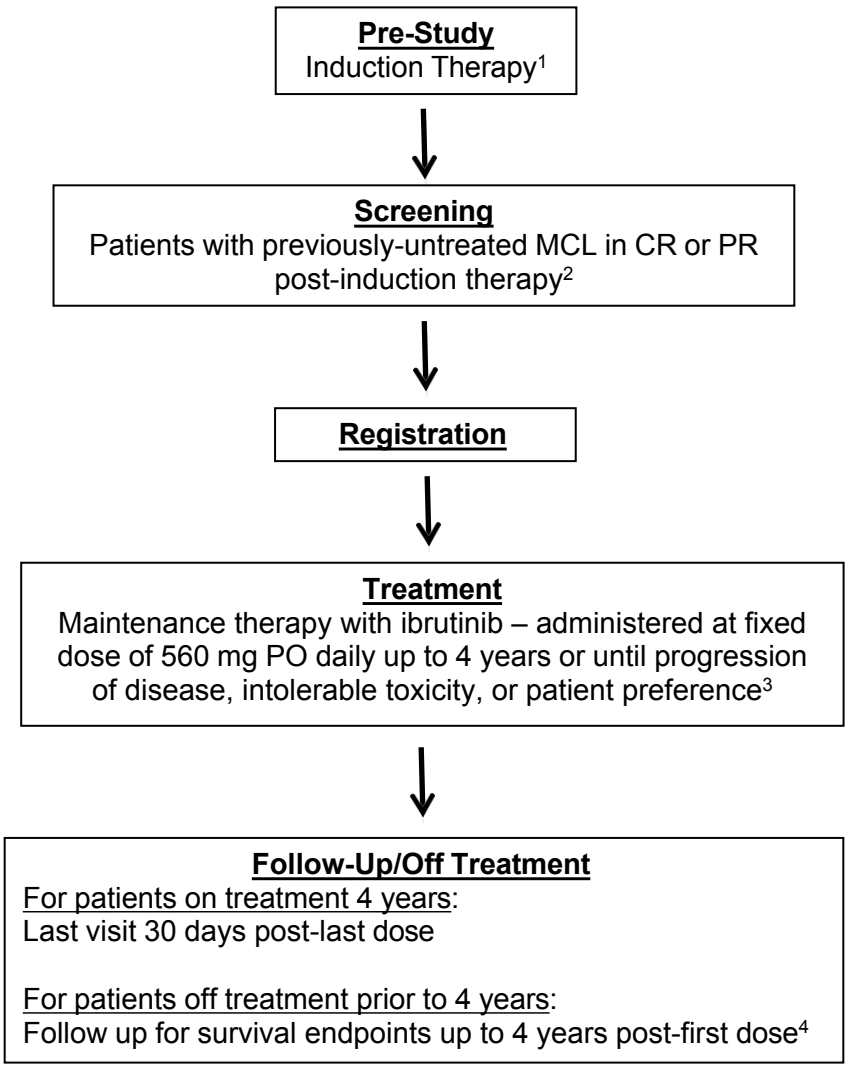
LIST OF ABBREVIATIONS

Examples Include:

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphocytic Leukemia
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IV (or iv)	Intravenously
MCL	Mantle Cell Lymphoma
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PCF	Pathcore Facility
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



[1]Patients must receive at least 4 cycles of induction chemotherapy with or without auto-SCT, including R-CHOP (with or without alternating R-DHAP), R-Hyper-CVAD, or R-bendamustine.

[2]Per Cheson 2007 criteria.

[3]During treatment, 1 cycle = 28 days. Patients will be evaluated (and drug will be dispensed) prior to each cycle for the first 6 months, then every 3 cycles thereafter for the remainder of treatment. See section 4.2 for the provision of 6-month visits after 2 years.

[4]Follow-up schedule for patients off-treatment will be every 3 months up to 2 years post-first dose, then every 6 months up to 4 years post-first dose. Date of progression will be documented as well.

STUDY SUMMARY

Title	A Phase II Clinical Trial Evaluating Ibrutinib Maintenance Following Intensive Induction for Patients with Previously Untreated Mantle Cell Lymphoma (MCL)
Version Date	August 8, 2022 (Amendment 11)
Phase/Design	Phase II, single-arm, multicenter, open-label study
Study Center(s)	Lead site: Northwestern University Participating sites:, University of Michigan, University of Utah, and Dana Farber d/b/a Massachusetts General Hospital
Objectives	Primary objective: Determine the 3-year PFS in patients with previously-untreated MCL who achieve response to intensive induction therapy and then receive maintenance Ibrutinib. Secondary objectives: • Toxicity • Rates of conversion from PR to CR • Median overall survival at 4 years Exploratory objectives: Monitor MRD results by PCR and correlate with PFS and OS.
Sample Size	36 *evaluable* patients (patients who receive < 1 complete cycle of therapy will not be considered evaluable for efficacy endpoints and will be replaced; we estimate this to represent 3 or fewer subjects)
Diagnosis and Main Inclusion Criteria	1. Histologically confirmed MCL. 2. Disease response (either CR or PR), without known progression, to one (1) prior systemic chemotherapy regimen, with or without consolidative auto SCT. The options are: a. R-CHOP (with or without cytarabine-containing cycles, including “Nordic” [1] and MCL-NET protocols [2]) with or without auto SCT b. R-Hyper-CVAD with or without auto SCT c. R-Bendamustine with or without auto SCT 3. Prior radiotherapy is permissible. 4. Age ≥ 18 years. 5. ECOG performance status ≤ 2.
Treatment Plan	Ibrutinib will be given at a fixed dose of 560 mg PO daily throughout the study, to patients who have completed at least 4 cycles of intensive induction chemotherapy (with or without ASCT). The dose is based upon safety and efficacy data. For the purposes of this study, one cycle will be defined as 28 days. This will be continued up to 4 years in the absence of progression of disease, intolerable toxicity, or patient preference (including withdrawal of consent).

Statistical Methodology	The primary endpoint is three-year PFS. Our null hypothesis is that ibrutinib maintenance will yield no improvement upon the 60% three-year PFS observed in studies described above. We consider an observed three-year PFS of 80% both feasible and of significant clinical improvement. The study will have 10% Type I error and 90% power to detect an effective treatment using a one-stage design based on the true proportion of patients achieving 3-year PFS is at least 80% versus the null hypothesis that the true complete response rate is at most 60%. Based upon these parameters, our sample size will be 36 evaluable patients. For the final analysis, if 25 or fewer patients are alive and without progression from among all 36 evaluable patients accrued, we will consider this regimen ineffective for this patient population. If, on the other hand, 26 or more patients are alive and without progression, this will be considered sufficient evidence that this treatment may be recommended for further testing in subsequent studies, particularly in a randomized setting.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background & Current Therapies

Mantle cell lymphoma (MCL) is an uncommon B-cell non-Hodgkin lymphoma (NHL) that carries a poor overall prognosis in spite of high response rates to induction chemotherapy [3, 4]. It accounts for about 6% of all NHL cases in the Western world. At the molecular level, MCL is uniquely characterized by overexpression of the cell cycle regulator protein cyclin D1. This is due to the chromosomal translocation t(11;14)(q13;q32), which puts the cyclin D1 gene, B-cell leukemia/lymphoma 1 (bcl-1), under the control of the immunoglobulin heavy chain enhancer with subsequent overexpression of cyclin D1 [5-7].

Although there is no consensus as to the ideal frontline therapy for MCL, aggressive multi-agent chemoimmunotherapy combinations such as R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone) have been advocated. More intensive regimens, such as Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine) or other regimens that incorporate high-dose cytarabine [1, 2], may improve outcomes, though this has not been clearly shown and toxicity with such regimens is clearly increased[8]. Younger patients with good performance status are frequently considered for more intensive induction therapy followed by consolidation therapy with autologous stem cell transplant (ASCT); however, this degree of intensive therapy is not an option for most patients with MCL because of their age and comorbidities[9, 10].

Multiple prospective and retrospective trials have demonstrated patterns of continuous response over many months and years, suggesting that all patients are at risk for eventual relapse [3, 4, 11]. Once the disease has progressed after first-line therapy, the prognosis is dismal.

The best estimates of 3-year progression-free survival (PFS) in patients with MCL treated with R-Hyper-CVAD (Rituximab-Hyper-CVAD) in multicenter studies are 58-64% [11]. Likewise, consolidation with high-dose therapy (HDT) and ASCT after R-CHOP also seems to improve depth and duration of responses as compared to R-CHOP, but does not clearly improve overall survival. Interestingly, an retrospective analysis of patients treated at National Comprehensive Cancer Network (NCCN) Centers suggested that patients treated with Hyper-CVAD had similar outcomes to those treated with R-CHOP followed by HDT-ASCT, but that HDT-ASCT did not improve outcomes when used as consolidation after induction with R-Hyper-CVAD [11].

Maintenance strategies have previously been studied in patients with MCL. For example, a phase III European study randomized patients with previously untreated MCL, who achieved a response to R-CHOP, to maintenance treatment of either rituximab or interferon, and showed improved median PFS and OS among those on the rituximab arm [12].

Ibrutinib is a selective BTK inhibitor that has demonstrated profound activity in patients with relapsed/refractory MCL, with an overall response rate (ORR) of 68% and median PFS of 13.9 months [13]. Ibrutinib was approved by the Food

and Drug Administration (FDA) in November 2013 as single agent treatment for patients with MCL who have received at least one prior therapy. It has since been approved for CLL/SLL, CLL/SLL with 17p deletion, and Waldenström's macroglobulinemia. The drug is well tolerated, with neutropenia and gastrointestinal disturbances as its chief adverse effects. Ibrutinib is now the focus of multiple combination treatment trials. However, there is no reported data for the role of ibrutinib as maintenance therapy after response to other treatment.

1.2 Ibrutinib Background and Toxicities

Ibrutinib, an irreversible inhibitor of BTK, has been shown to have potent inhibitory and anti-proliferative activity, in cell line as well as in vivo mouse xenograft models of B-cell malignancies such as ALL and CLL. Inhibition of BTK activity interrupts cellular signaling processes that control cell division in B-cells. The pharmacology and toxicology of ibrutinib in animal models are detailed in the Investigator's Brochure.

In an open-label drug-drug interaction study of 18 men, ibrutinib was administered alone at a 120 mg dose or in combination with ketoconazole at a 40 mg dose. Preliminary results demonstrated a mean 25-fold increase in ibrutinib area under the plasma concentration-time curve (AUC) and a 29-fold increase in Cmax following co-administration with ketoconazole. Terminal half-life was not increased. Ibrutinib single-dose administration was well-tolerated. No drug-related adverse events were reported. No Grade 3 or 4 toxicities or serious adverse events were reported.

1.2.1 Preclinical & pharmacokinetic data

1.2.1.1 Mechanism of Action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

1.2.1.2 Pharmacodynamics

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥2.5 mg/kg/day (175 mg/day for average weight of 70 kg).

1.2.1.3 Pharmacokinetics

<u>Absorption</u>

Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC observed in patients at 560 mg is

(mean ± standard deviation) 953 ± 705 ng/mL. Administration with food increases ibrutinib exposure approximately 2-fold compared with administration after overnight fasting.

Distribution
Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The apparent volume of distribution at steady state (Vd,ss/F) is approximately 10000 L.

Metabolism
Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.

Elimination
Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [14C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

1.2.2 Clinical efficacy data

Efficacy results from two separate studies demonstrate that ibrutinib has robust activity as a single-agent in the treatment of subjects with relapsed or refractory MCL. As of October 2011, 60 subjects with MCL (9 from study PCYC-04753 and 51 from study PCYC-1104-CA) had been evaluated for response to treatment with ibrutinib; despite the poor-risk nature of the MCL population on these 2 studies, the ORR was 70% (42/60); this is very favorable in comparison to historical data with bortezomib in a less heavily pretreated relapsed MCL population.

In the PCYC-04753 study (a phase I, multicenter, dose escalation study of 56 patients with a variety of B-cell malignancies) all 9 subjects with MCL were evaluable for response. Of these, 7 achieved an objective response by the Revised Response Criteria for Malignant Lymphoma [14], including 3 CRs and 4 PRs; in addition there was 1 SD and 1 PD. All of the subjects responding to treatment achieved response at the time of the first response assessment (after 2 cycles of treatment). Of the 3 subjects who achieved a CR, 2 subjects did so upon initial response assessment and 1 was a PR initially who converted to CR after 8 cycles (28-days cycle duration) of therapy. Responses have been durable; 5

subjects who entered a long-term follow-up study and continued to receive study treatment achieved duration of response ranging from 10.5 to 27.5 months from treatment initiation.

The safety and efficacy of ibrutinib in patients with MCL who have received at least one prior therapy were evaluated in an open-label, multi-center, single-arm trial of 111 previously treated patients. The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were Caucasian. At baseline, 89% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplant. At baseline, 39% of subjects had at least one tumor >/= 5 cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening. Ibrutinib was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Efficacy results indicated an ORR of 65.8% (95% CI 56.2-74.5; 69% by IRC), including CR rate of 17.1% and PR rate of 1548.6%. The median DOR was 17.5 months, and median time to response 1.9 months.

1.2.3 Toxicity data

The data described below reflect exposure to ibrutinib in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months. The following risks are discussed in more detail in the full prescribing information:

- Hemorrhage (5%)
- Infections (25%)
- Myelosuppression (41%)
- Renal Toxicity (67%)
- Second Primary Malignancies (5%)

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite. The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

An evaluation of the safety data across 5 clinical studies (sponsored by Pharmacyclics & Janssen Scientific Affairs) including 392 subjects found moderate toxicities associated with ibrutinib treatment. The most common (> 10%) treatment-emergent adverse events (AEs) were diarrhea

(40.4%), fatigue (32.1%), nausea (24.0%), cough (17.6%), and peripheral edema (16.7%). These AEs are classified as grade 1 or 2 in severity and were not dose-limiting. Grade 3 or 4 adverse events were noted in about 45.8% of the patients, which were typically hematologic in nature (anemia 5.8%, thrombocytopenia 5.1%, and neutropenia 4.5%). Serious adverse events (SAEs) were experienced by 35.9% of subjects, which included pneumonia (4.5%), febrile neutropenia (3.2%), and atrial fibrillation (2.9%).

Hemorrhagic AEs have been reported following ibrutinib treatment, either as monotherapy or in combination with other agents. Out of 392 subjects, 6 (1.5%) experienced subdural hematoma; in 5 of these 6 the event was reported as serious, and in 2 it was determined to be possibly related to ibrutinib. Additional serious hemorrhagic events have included hematuria (2 subjects), cerebrovascular accident with intracerebellar hemorrhage, GI hemorrhage, hematoma, and hemorrhagic enterocolitis (1 subject each). Non-serious bleeding events have included contusion, ecchymosis, petechiae, epistaxis, retinal hemorrhage, hematuria, hemoptysis, and hematochezia. These events have generally resolved.

Although in vitro studies have found that ibrutinib can inhibit platelet function, the clinical significance of this effect is not clear. An expert review of the hemorrhagic SAEs that have occurred in clinical studies seemed to conclude that the incidence of subdural hematoma was unlikely to be related to the platelet inhibitory activity of ibrutinib. Other potential risk factors for subdural hematoma may have included age, any history of fall, or concomitant use of anti-coagulants such as warfarin.

Across all ibrutinib studies—monotherapy and combination treatment—32 (8.2%) of the 392 subjects discontinued treatment due to an AE, including 12 for reasons related to infection or its complications (e.g., pneumonia, sepsis, bacteremia, pyrexia, neutropenia with or without fever, etc.).

Refer to the investigator's brochure for additional toxicity information.

1.3 Rationale for the Current Study

There is an unmet medical need for developing new therapeutic options to treat patients with MCL. Ibrutinib is currently the focus of several mono and combination-treatment studies, in a variety of B-cell malignancies. However, the role of single-agent ibrutinib in a maintenance therapy setting for previously-untreated MCL patients has not been explored. We therefore propose a phase II trial to assess the role of ibrutinib as maintenance therapy for MCL patients who have achieved response to induction with either R-Hyper-CVAD, R-CHOP (with or without cytarabine-containing cycles [1, 2]), or R-Bendamustine, with or without auto transplant. The study population would therefore involve patients with histologically confirmed MCL who have achieved either CR or PR after intensive induction systemic chemotherapy.

Ibrutinib will be given as maintenance therapy at a daily dose of 560 mg taken orally (1 cycle = 28 days). In the PCYC-1104-CA study, ibrutinib was administered to relapsed/refractory MCL patients as a fixed dosage of 560

mg/day; in this study, 96% of the patients retained steady-state ibrutinib AUC values >160 ng·h/mL, indicating that the vast majority of patients who received a dose of 560 mg/day achieved exposures yielding full BTK active-site occupancy. This dose in relapsed or refractory MCL patients showed an acceptable toxicity profile. Based on these data, the oral daily 560 mg dose has been selected for this study. Treatment will continue up to 4 years in the absence of progression of disease or intolerable toxicity, or patient preference. We also plan to collect whole blood samples from all patients in order to monitor MRD results by PCR; samples will be collected at four time-points: baseline (pre-treatment), after 1 month and 6 months of treatment, and approximately 18-24 months post-first dose of treatment.

2.0 STUDY OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

The primary objective will be to determine the progression-free survival (PFS) rate after 3 years.

Progression-free survival (PFS) will be defined as the absence of disease progression or death from any cause. The rate of PFS will be calculated after 3 years.

2.2 Secondary Objectives & Endpoints

Secondary objectives will include the following:

2.2.1 Assess toxicity.
Adverse events will be defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The occurrence and severity of each will be recorded.

2.2.2 Determine rates of conversion from PR to CR.
The rate of conversion from PR to CR will be calculated based on Cheson 2007 criteria.

2.2.3 Determine median overall survival (OS) after 4 years.
Patients will be evaluated monthly for the first 6 months on treatment, then every 3 months thereafter. Patients who go off treatment will continue to be followed for survival up to a maximum of 4 years post-first dose. Follow-up will occur every 3 months (up to 2 years after the first dose of treatment) and then every 6 months thereafter (up to 4 years post-first dose). Median OS after 4 years will be calculated.

2.3 Exploratory Objectives & Endpoints

Compare MRD results overtime by PCR and correlate these with PFS and OS.

We will obtain archived tissue (FFPE slides) from a previous biopsy from all patients for baseline clone identification; in addition, we will collect peripheral whole blood samples at baseline, 1 month after first dose, 6 months after first dose, and approximately 18-24 months after first dose. MRD analysis will be

conducted using PCR methods and results will be compared over time and correlated with PFS and OS.

3.0 SELECTION OF SUBJECTS

The target population for this phase II study is patients with histologically confirmed (previously untreated) mantle cell lymphoma (MCL) who have achieved response (CR or PR) to intensive induction systemic chemotherapy (with or without ASCT). This will be a multicenter trial conducted at Northwestern University. Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include University of Utah, and Dana Farber d/b/a Massachusetts General Hospital.

A total of 36 *evaluable* subjects will be needed for this trial (defined as having received ≥ 1 complete cycle of treatment). Approximately 5 potentially eligible patients are seen per month, and it is anticipated that at least 2 per month will be accrued *once the protocol is open and enrolling at all sites*. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University or to the local PI at each participating site.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11.4 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically confirmed MCL
Please note: Measureable disease is not required, but will be followed if it exists.

3.1.2 Patients must have received 4 or more cycles of one of the following prior systemic induction chemotherapy regimens:

- R-CHOP (with or without cytarabine-containing cycles, including "Nordic" and MCL-NET protocols) [1, 2]) with or without auto SCT
- R-Hyper-CVAD with or without auto SCT
- Bendamustine + rituximab with or without auto SCT

Please note:

- *Patients are allowed to receive combinations of the above regimens*
- *At the time of registration, patients must be at least 14 days out from last dose of cytotoxic chemotherapy, but no more than 120 days. If a patient underwent auto SCT, he/she must demonstrate engraftment (per treating investigator's discretion) and meet all other hematological requirements as outlined in 3.1.8 below.*
- *Patients who progress during induction therapy are not eligible to enroll in this study.*

3.1.3 Patients must have achieved a response to induction chemotherapy (either CR or PR by Cheson 2007 criteria) and be without known progression.

3.1.4 Patients *may* have received prior radiotherapy.

3.1.5 Patients must be age ≥ 18 years.

3.1.6 Patients must exhibit an ECOG performance status ≤ 2.

3.1.7 Patients must demonstrate adequate organ and marrow function (as defined below) documented within 14 days of registration:

- ANC ≥ 1000/mm^3, independent of growth factor support
- Platelets ≥ 100,000/mm^3, or ≥ 50,000 in cases of ongoing bone marrow involvement *(In either case, these must be independent of transfusion support)*
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- AST(SGOT)/ALT(SPGT) ≤ 3 x ULN
- Creatinine clearance ≥ 25 ml/min (using the Cockcroft-Gault Equation – See Appendix III)

Please note: Patients who do not meet the above criteria because of Gilbert's Syndrome are still eligible.

3.1.8 Women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (see below 'NOTE" for details) prior to study entry and for the duration of study participation (see timelines below for women and men). In addition, men must agree not to donate sperm during and after study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

NOTE: For female patients, these restrictions apply for 1 month after the last dose of study drug. For male patients, these restrictions apply for 3 months after the last dose of study drug.

NOTE: A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not undergone a hysterectomy or bilateral oophorectomy; or*
- Has not *been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).*

NOTE: 'Adequate contraception' is defined as a method that has a low failure rate (i.e., less than 1% per year) when used consistently and correctly and includes implants, injectables, birth control pills with two hormones, some intrauterine devices (IUDs), sexual abstinence (which is defined as refraining from all aspects of sexual activity) or a sterilized partner. If using hormonal contraceptives, such as birth control pills or devices, a second barrier method of contraception (e.g., condoms) must be used.

Men must notify the study staff if their partner becomes pregnant while on study treatment or within 3 months of last dose. Women must notify the

study staff if they become pregnant while on study treatment or within 1 month of last dose of ibrutinib, and must immediately stop taking the study treatment.

3.1.9 Female patients must have a negative pregnancy test (blood or urine) within 14 days prior to registration.

3.1.10 Patients must be willing and able to avoid consuming food and beverages containing grapefruit, Star fruit or Seville oranges (as these contain certain ingredients that inhibit CYP3A4/5 enzymes) while on ibrutinib study therapy.

3.1.11 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

3.2.1 Patients who have received ≥ 7 days of prior ibrutinib or any prior treatment with another BTK inhibitor are not eligible.

3.2.2 Patients receiving ongoing treatment with any other investigational agents are not eligible.

3.2.3 Patients receiving live/attenuated vaccinations within 4 weeks prior to registration are not eligible.

3.2.4 Patients with a *known* CNS involvement of lymphoma are not eligible (CNS staging not required).

3.2.5 Patients who have undergone major surgery within 4 weeks prior to registration are not eligible.

3.2.6 Patients who have had a prior allogeneic stem cell transplant are not eligible.
NOTE: If a patient underwent auto SCT, he/she must demonstrate engraftment (per treating investigator's discretion) and meet all other hematological requirements as outlined in 3.1.8 above.

3.2.7 Patients diagnosed or treated for malignancy other than MCL are not eligible unless they meet one of the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for ≥3 years before registration and felt to be at low risk for recurrence by the treating physician.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated cervical carcinoma in situ without evidence of disease.
- Malignancy is not considered life-threatening in the opinion of the investigator and does not require treatment (for example, low risk

prostate cancer undergoing active surveillance or low-risk myelodysplastic syndrome not requiring therapy).

3.2.8 Patients with a history of stroke or intracranial hemorrhage within 6 months prior to registration are not eligible.

3.2.9 Patients who require anticoagulation with warfarin or equivalent vitamin K antagonists are not eligible.

3.2.10 Patients who require chronic treatment with strong CYP3A4/5 inhibitors ≤ 14 days prior to registration are not eligible.

NOTE: See Appendix I for examples of such medications. Patients who are currently on treatment with strong CYP3A4/5 inhibitors may be eligible if they are able to be switched to an alternative therapy that is not a strong CYP3A4/5 inhibitor prior to registration on study.

3.2.11 Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib are not eligible.

3.2.12 Patients with uncontrolled intercurrent illness including, but not limited to, any of the following are not eligible:

- Ongoing or active systemic infection
- Symptomatic congestive heart failure
- Myocardial infarction within 6 months prior to registration
- Unstable angina pectoris
- Uncontrolled or symptomatic cardiac arrhythmias
- Any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification
- Psychiatric illness/social situations that would limit compliance with study requirements.

3.2.13 Patients who have any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at risk are not eligible.

3.2.14 Patients with a *known* HIV infection are not eligible (HIV testing not required).

3.2.15 Patients with a *known* JC virus infection and/or progressive multifocal leukoencephalopathy (PML) are not eligible.

3.2.16 Patients with clinically active hepatitis A, B, or C infections are not eligible. Note: Patients with a history of hepatitis may be eligible if they have a normal titer. Such cases should be approved by the study PI.

3.2.17 Female patients who are pregnant and/or lactating are not eligible.

NOTE: It is not known whether ibrutinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibrutinib, breastfeeding should be discontinued during ibrutinib treatment.

4.0 TREATMENT PLAN

4.1 Overview

Induction therapy will not be part of the protocol-specified treatment. Patients must have received four (4) or more cycles of R-CHOP (with or without alternating R-DHAP), R-Hyper-CVAD, or bendamustine + rituximab (all with or without auto SCT), with documented PR or CR by Cheson 2007 criteria. Within 14 days of study registration, patients will begin treatment with ibrutinib at a fixed dose of 560 mg PO daily. One cycle will be defined as 28 days. Patients may continue to receive cycles of ibrutinib therapy up to 4 years in the absence of progression of disease or intolerable toxicity, or patient preference (including withdrawal of consent).

4.2 Administration

Ibrutinib will be administered orally at a dose of 560 mg daily. Patients will be instructed to take 4 140mg capsules for a dose of 560 mg. Ibrutinib is to be taken in the morning (around the same time each day) with approximately 8 ounces (240 mL) of water. All 4 capsules should be taken at the same time and the capsules should remain intact. Subjects should not attempt to open capsules or dissolve them in water.

Subjects should avoid consuming food and beverages containing grapefruit, Star fruit, or Seville oranges for the duration of the study due to CYP 3A4/5 inhibition. The study drug should be taken at roughly the same time each day. If a dose is missed, it can be taken anytime later that same day, with a return to the normal schedule the following day. In general, vomited doses should not be made up, however patients should contact their physician to discuss such cases.

Subjects will be given a study calendar on which to record all taken, missed, or skipped doses for the first 6 cycles of study treatment. The calendar will be returned for review with a member of the study team at scheduled visits to assess compliance in addition to pill counts. During the first 6 cycles, ibrutinib will be dispensed at the beginning of each 28-day cycle. Subjects will be provided with 2 days overage (30 days' worth total) each time study drug is dispensed to allow for delays in scheduling of return visits. After the initial 6 cycles of treatment, visits will be conducted every 3 months and a sufficient drug supply will be dispensed at each visit to last until the next visit. If after 2 years a patient is clinically stable without significant adverse events and lives far from the study site, he or she may elect to be seen by the study investigator every 6 cycles with local clinic visits every 3 cycles in between. In such cases, a 6-month drug supply may be dispensed, however this supply should be given in moderation only for patients who live far away or are otherwise inconvenienced by quarterly study visits. Patients will continue maintaining a study calendar/pill diary for the duration of treatment.

Study staff will instruct subjects on how to store ibrutinib for at-home use as indicated for this protocol (e.g. in a secure location, away from children).

4.3 Toxicity Management & Dosing Holds/Dose Modifications

4.3.1 Dose Holds

At each study visit (see section 5.0 for schedule), the subject will be evaluated for possible drug toxicities. All previously established or new toxicities observed at any time are to be recorded in the appropriate electronic case report form (eCRF) and managed as described below. The lead principal investigator and QAM should be contacted regarding any unmanageable toxicity.

Study drug may be held for a maximum of 28 consecutive days. Once the ibrutinib dose is reduced, it cannot be re-escalated. When a dose is missed or held, it will not be made up, regardless of duration. Observations and scheduled assessments will continue regardless of amount of drug the patient has had and should always be based on time from C1D1. (For example, if a patient is held on C2D14 for a week, the day they re-start will be C2D21, and the patient will still have scheduled assessments as planned on C3D1) Please contact QA if you have any questions on timing of holds or study assessments.

See section 4.4.3 for subjects requiring the initiation of anticoagulants while receiving study drug and for instructions on dose modifications or temporary hold during concomitant administration of CYP3A4/5 inhibitors or inducers. For guidance on dose hold during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study drug please see section 4.4.4.

4.3.2 Dose Modifications

The actions described below should be followed for the indicated drug- related toxicities per Table 4-1:

- Grade 3 (ANC <1000/mm^3) or Grade 4 neutropenia (ANC <500/mm^3)
- Grade 3 thrombocytopenia (platelets <50,000/mm^3) in the presence of significant bleeding
- Grade 4 thrombocytopenia (platelets <25,000/mm^3)
- Grade 3 or 4 neutropenia with infection or fever
- All other Grade 4 hematological toxicities
- Grade 3 or Grade 4 non-hematological toxicities including nausea, vomiting or diarrhea (if persistent despite optimal antiemetic or antidiarrheal therapy), exceptions noted below for cardiac related toxicities (see Sections 4.3.2.1 & Section 4.3.2.1.1)
- Grade 2 cardiac failure
- Any unmanageable Grade 2 or Grade 3 drug-related toxicities. The PI should be contacted in these cases.

Table 4-1 Dose Modification Actions	
Occurrence	**Action[1]**
First	Hold ibrutinib until recovery to ≤ Grade 1 or baseline; restart at 420 mg dose
Second	Hold ibrutinib until recovery to ≤ Grade 1 or baseline; restart at 280 mg dose
Third	Discontinue ibrutinib

[1] When ibrutinib doses are held they will not be made up – study assessments will continue as originally scheduled. Ibrutinib may be held for a maximum of 28 consecutive days at a time. Study treatment should be permanently discontinued in the event of a toxicity lasting >28 days. Once the ibrutinib is reduced it cannot be re-escalated.

4.3.2.1 Dose Modifications for Grade 3 Cardiac Arrhythmias

The actions described below should be followed for the indicated following drug-related toxicities (Table 4-2):

- Grade 3 cardiac arrhythmias

Table 4-2 Dose Modification Actions for Grade 3 Cardiac Arrhythmias	
Occurrence	**Action[1]**
First	Hold ibrutinib until recovery to ≤ Grade 1 or baseline; restart at 420 mg dose
Second	Discontinue ibrutinib

[1] When ibrutinib doses are held they will not be made up – study assessments will continue as originally scheduled. Ibrutinib may be held for a maximum of 28 consecutive days at a time. Study treatment should be permanently discontinued in the event of a toxicity lasting >28 days. Once the ibrutinib is reduced it cannot be re-escalated.

4.3.2.1.1 Dose Modifications for Grade 3 and higher Cardiac Failure & Grade 4 Cardiac Arrhythmias

Ibrutinib is to be discontinued if the following drug related toxicities occur:

- Grade 3 or 4 cardiac failure
- Grade 4 cardiac arrhythmias

4.3.3 Lymphocytosis

Upon initiation of ibrutinib, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute count 5,000/mcL) occurred in 33% of relapsed/refractory MCL treated with ibrutinib in the MCL registration trial (PCYC1104). This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks. Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability and headache. However, some of these cases

were in the setting of disease progression.

4.4 Concomitant Medications/Treatments

All concomitant therapies must be recorded in the appropriate eCRF and source documents throughout the study, beginning with the time of written informed consent up to 30 days after the last dose of study drug.

4.4.1 Permitted Concomitant Medications/Treatments

- Standard supportive care therapies (e.g., antiemetics, loperamide) needed for the management of symptoms are permitted, as clinically indicated.
- Hematopoietic growth factors may be administered according to institutional guidelines
- Hormonal birth control is permitted.

4.4.2 Prohibited Concomitant Medications/Treatments

The following medications are prohibited during the study:

- Any chemotherapy
- Anticancer immunotherapy
- Chronic use of systemic corticosteroids above prednisone 10mg p.o. daily (or equivalent dose of other corticosteroid)
- Experimental therapy
- Radiotherapy

4.4.3 Concomitant Medications/Treatments Requiring Special Precautions

4.4.3.1 CYP3A4/5 Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4/5. The clinical significance of the potential drug-drug interaction with strong CYP3A4/5 inhibitors in oncology subjects is currently not known. Due to this potential increase in ibrutinib exposure, concomitant use of strong CYP3A4/5 inhibitors (such as, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, ketoconazole, itraconazole, and nefazodone; see Appendix I for a comprehensive list of such medications) should be avoided while the subject is receiving treatment and at least 14 days prior to registration. Moderate CYP3A4/5 inhibitors (aprepitant, erythromycin, fluconazole, verapamil, and diltiazem) should be used with caution. Grapefruit juices, Star fruit, and Seville oranges may also increase ibrutinib plasma concentrations and should be avoided for the duration of ibrutinib treatment.

If use of a strong CYP3A inhibitor is indicated, selection of an alternate concomitant medication with less potent enzyme inhibition potential is strongly recommended. If ibrutinib must be administered with a strong or moderate CYP3A inhibitor, refer to Table 4-3 for recommended dose modifications for ibrutinib, and notify the PI and NU Quality Assurance Monitor (QAM). Subjects should be monitored closely for potential treatment-related toxicities. After discontinuation of the CYP3A inhibitor, the same dose of ibrutinib that was administered prior to the temporary hold may be given upon reinitiation of ibrutinib.

Table 4-3: Dose Modifications for Use with CYP3A Inhibitors

Patient Population	Coadministered Drug	Recommended Ibrutinib Dose
B-Cell Malignancies	• Moderate CYP3A inhibitor	280 mg once daily Modify dose as recommended per Table 4-1, Table 4-2 and Section 4.3.2.1.1.
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily Modify dose as recommended per Table 4-1, Table 4-2 and Section 4.3.2.1.1.
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily Interrupt dose as recommended per Table 4-1, Table 4-2 and Section 4.3.2.1.1..
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib.
Chronic Graft versus Host Disease	• Moderate CYP3A inhibitor	420 mg once daily Modify dose as recommended per

		Table 4-1, Table 4-2 and Section 4.3.2.1.1..
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	280 mg once daily Modify dose as recommended per Table 4-1, Table 4-2 and Section 4.3.2.1.1..
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	140 mg once daily Modify dose as recommended per Table 4-1, Table 4-2 and Section 4.3.2.1.1..
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib.

Coadministration of ibrutinib with strong CYP3A4/5 inducers (such as carbamazepine and rifampin) may decrease ibrutinib plasma concentrations and should be avoided. A comprehensive list of inhibitors, inducers, and substrates is provided in a link in Appendix I.

4.4.3.2 Antiplatelet Agents and Anticoagulants

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis and petechiae; and major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Also, patients with congenital bleeding diathesis have not been studied.

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be withheld at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section prohibitions and restrictions).

Ibrutinib should be used with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. It is possible that treatment with ibrutinib may increase the risk of bruising or bleeding, particularly in subjects receiving antiplatelet agents or anticoagulants. Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding and ibrutinib should be held in the event of major bleeding events defined as adverse event of special interest (Section 7.2.5).

4.4.4 Precautions & Restrictions Regarding Surgical Interventions or Procedures

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any planned surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and at least 7 days after the procedure, and restarted at the discretion of the treating investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor planned procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis), ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure.
- For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, per the appropriate procedural guidelines above.

4.6 Duration of Therapy

Patients may continue on ibrutinib maintenance therapy up to 4 years in the absence of disease progression or development of unacceptable toxicity; or patient preference (withdrawal of consent). Clinical suspicion of progressive disease (PD) or loss of response should be investigated radiographically, and will result in removal of active therapy if confirmed by clinical investigation.

4.7 Duration of Follow Up

Patients who complete 4 years of maintenance therapy with ibrutinib will have one final follow-up study visit approximately 30 days post-last dose. Patients who discontinue study therapy prior to this point will be followed up to a maximum of 4 years (post-first dose of treatment) for survival endpoints (including date of progression). Follow-up will occur every 3 months (up to 2 years after the first dose of treatment) and then every 6 months thereafter (up to 4 years post-first dose.

4.8 Removal of Patients from Therapy and/or Study as a Whole

Patients can be removed from the study treatment (follow-up permitted) and/or from the study as a whole (no follow-up permitted) at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from *treatment* (follow-up continues)
- Patient withdraws *consent* (termination of treatment *and* follow-up)
- Patient is *unable to comply* with protocol requirements (termination of treatment, follow up continues)
- Patient demonstrates *disease progression* (termination of treatment, follow-up continues). Clinical suspicion of progressive disease (PD) or loss of response should be investigated radiographically, and will result in removal of active therapy if confirmed by clinical investigation.

- Patient experiences *toxicity* that makes continuation in the protocol unsafe (termination of treatment, follow up continues)
- Treating physician determines that continuation on the study would *not be in the patient's best interest* (termination of treatment, follow up continues)
- Patient becomes *pregnant*, see section 7.2.6 for reporting timeframe (termination of treatment, but follow up continues)
- Patient develops a second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study (termination of treatment, but follow up continues). NOTE: Patients who stop treatment in order to receive other anti-cancer therapy for a second malignancy *may*, on a case-by-case basis and upon approval of PI and DMC, be considered for possible re-start of study medication once other anti-cancer therapy is complete. See Section 4.3.1 for more details.

5.0 STUDY PROCEDURES

Table: Schedule of Events

		Screening	On-Treatment[2]		Off-Treatment	
Test/Assessment	**Pre-Study**	**Baseline Tests[6]**	**Cycles 1-6[9]**	**Cycles 7+[10]**	**EOT[11]**	**Follow-Up[11]**
Documentation of induction chemotherapy[1]	X					
Informed consent		X				
Medical history		X				
Concomitant medications		X	X	X		
Physical exam[12]		X	X	X	X	
ECOG status		X	X	X		
Hematology[3]		X	X	X	X	
Chemistries[4]		X	X	X	X	
Pregnancy test[5]		X				
Hep B & C serologies[15]		X				
Tissue for research[18]		X				
Research blood samples[17]			X	X		
CT scan (C/A/P) or MRI[7]		X	X	X[7]		
Peripheral blood for flow cytometry[17]			X	X		
Bone marrow biopsy[13]		X		X		X[13]
EGD/Colonoscopy[14]		X		X		X[14]
Drug administration & accountability[8]			X			
Adverse events[16]		X	X	X	X	X
Survival					X	X

[1]Must include at least 4 cycles of R-CHOP (with or without alternating R-DHAP), R-Hyper-CVAD, or bendamustine + rituximab (all with or without auto SCT). Last dose of cytotoxic chemotherapy must be at least 14 days prior to registration (but no more than 120 days prior). Patients who underwent auto SCT must show engraftment and meet all required baseline hematological parameters.

[2]While on treatment, one cycle will be defined as 28 days (+/- 2 days). Assessments will occur on day 1 of each cycle (± 2 days, for the first 6 months), then every 3 cycles (± 10 days, up to 4 years). If after 2 years a patient is clinically stable and lives far from the study site, he or she may elect to be seen every 6 cycles (±10 days), with a sufficient drug supply, as detailed in section 4.2. Labs should be resulted prior to treatment to assess the need for dose modifications (see section 4.3 for details). When a dose is missed or held, it will not be made up, regardless of duration. Observations and scheduled assessments will continue regardless of amount of drug the patient has had, and should always be based on time from C1D1. Please contact QA if you have any questions on timing of holds or study assessments.

[3]CBC with platelets/differential

[4]Comprehensive chemistry panel, Mg, and LDH. Comprehensive chemistry panel includes glucose, calcium, albumin, ALT, AST, sodium, potassium, total bilirubin, alk phos, creatinine.

[5]If applicable for WOCBP (urine or serum).

[6]Baseline/screening tests required to be completed as follows: within 90 days prior to registration for imaging, bone marrow biopsy and EGD/Colonoscopy (if applicable) and within 14 days prior to registration for all other baseline assessments (except informed consent, which can be signed within 30 days prior to registration).

[7]Imaging should be performed at baseline, after cycles 3 and 6, every 6 months/cycles for the first 2 years, once at 3 years, and as clinically indicated thereafter (including EOT, as clinically appropriate, for patients who complete 4 years of therapy, or patients that come off study treatment early for a reason other than progression). In general, it is *preferred* that imaging be CT-based; at a minimum, the same modality should be used consistently for each patient.

[8]Ibrutinib will be administered at a dose of 560 mg PO daily throughout the course of treatment unless a dose reduction occurs (see section 4.3.2 for details). Patients will be asked to keep a study calendar for the duration of treatment See section 4.2 for details on dispensing and visit frequency.

[9]Patients will be evaluated on Day 1 of each cycle (±2 days) for the first 6 cycles (prior to the start of each cycle). NOTE: Cycle 1 Day 1 should begin within 14 days after registration, however Day 1 labs (hematology and chemistry tests) need only be repeated if screening labs were performed >7 days prior to C1D1.

[10]Patients will be evaluated every 3 cycles (on Day 1, ±10 days) beginning with cycle 7. After 2 years on therapy, patients will continue to be seen *clinically* every 3 cycles, however collection of data for study purposes will only be required every 6 cycles (approximately every 6 months) for the remainder of study treatment.

[11]**Patients who complete 4 years** of maintenance therapy with ibrutinib will have one final follow-up study visit approximately 30 days post-last dose. **Patients who discontinue study therapy prior to this point** will be followed up to a maximum of 4 years (post-first dose of treatment) for survival endpoints only (no labs or physical exam are required), including date of progression. Follow-up will occur until progression at the following times: every 3 months (±10 days) up to 2 years after the first dose of treatment and then every 6 months (±10 days) thereafter up to 4 years after the first dose of treatment.

[12]Physical exam includes height (baseline only), weight, 12-point symptom assessment and vitals (bp, heart rate, temperature)

[13]Bone marrow biopsy is only required (within 90 days of registration) for those with documented bone marrow involvement of MCL at time of last bone marrow biopsy. These patients should have repeat bone marrow biopsy after 6 cycles of therapy, in order to judge efficacy of treatment, then as clinically indicated during the period of follow up. If no previous bone marrow biopsy was obtained (e.g. at time of diagnosis), or if disease involvement was resolved as of most recent bone marrow biopsy, then none is required for trial entry, however it may be done at the discretion of the treating investigator.

[14]Only required (within 90 days of registration) for those with documented involvement of MCL by EGD and/or colonoscopy, at time of last EGD/colonoscopy. These patients should have repeat EGD/colonoscopy with biopsy after 6 cycles of therapy, in order to judge efficacy of treatment, then as clinically indicated during the period of follow up. If no previous EGD/colonoscopy was obtained (e.g., at time of diagnosis), or if disease involvement was resolved as of most recent EGD/colonoscopy with biopsy, then none is required for trial entry, however it may be done at the discretion of the treating investigator.

[15] At screening, patients will have HepBcAb, HepBsAg, and HepC Antibody. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for several months following ibrutinib treatment. Specifically, those with negative HBsAg and undetectable viral load should have these parameters rechecked approximately every 2-3 months while on ibrutinib and until 6 months after stopping ibrutinib. Any emerging HBsAg positivity, or rising viral load, should prompt interruption of drug and consultation with hepatology. Those with positive HBsAg and/or detectable viral load at time of enrollment should be seen by a hepatologist prior to starting study therapy, and HBV prophylaxis should be strongly considered.

[16]Adverse events will be tracked from time of signed informed consent until completion of the last study-related procedures (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days beyond cessation of study treatment. AE's resulting in discontinuation will be followed until resolution, or until patients start subsequent therapy, whichever comes first.

[17]Peripheral blood samples for exploratory studies (1 x 10 ml EDTA tube) will be collected cycle 1 day 1 (pre-dose), cycle 2, and cycle 7, and at approximately 18-24 months post-first dose of study drug. A second peripheral blood sample should be obtained at the same time as each research sample, and sent for flow cytometry, as standard of care, to be performed at the treating institution. Another sample (1 x 6mL EDTA tube) will be collected and stored for future use at each time point. Please see Section 9.0 for further details.

[18]Tissue (3-5 unstained FFPE slides) from a prior biopsy will be obtained at baseline from all patients (for whom such tissue is available – lack of availability will not disqualify patients from participating, but it is not *optional* for those who do have available tissue). See Section 9.0 for more details.

6.0 ENDPOINT ASSESSMENT

6.1 Primary Endpoint

The primary endpoint will be progression-free survival (PFS) at 3 years. PFS will be measured from start of treatment to time of progression or death from any cause. Progression-free survival will be defined as the absence of either progression or death from any cause. Progression will be evaluated using Cheson 2007 criteria (Revised Response Criteria for Malignant Lymphoma, modified – please see Appendix II). Evidence of clinical progression will be documented by imaging (CT scan or MRI) for patients who have measurable disease. Any patient who receives at least one dose of study treatment will be evaluable for this endpoint.

6.2 Secondary Endpoints

6.2.1 Toxicity

All patients who receive at least one dose of ibrutinib will be evaluable for toxicity (including those who are replaced for efficacy endpoints). The study will use the CTCAE version 4.03 (see appendices for link) for reporting of adverse events. The occurrence and severity of each will be recorded.

After the study has been opened for 18 months, patients will be evaluated for an interim safety analysis. The PI along with the Northwestern Lymphoproliferative Disorders disease team and Quality Assurance will assess data to ensure there are no unexpected safety signals that have been observed at this time. See section 10.3.4 for details on the safety analysis.

6.2.2 Rate of conversion from PR to CR

Progression will be evaluated using Cheson 2007 criteria (Revised Response Criteria for Malignant Lymphoma, modified). Patients must have already achieved either PR or CR during induction chemotherapy prior to enrolling in this study. Patients with measureable disease at time of enrollment will have it followed with imaging. Only patients who had a PR at the time of registration and who complete ≥ 1 complete cycle of ibrutinib maintenance therapy will be evaluable for this endpoint. Please refer to appendices for a summary of Cheson criteria.

6.2.3 Median overall survival at 4 years

Overall survival (OS) will be defined as the duration of time from start of treatment up to 4 years from the start of study treatment.

6.3 Exploratory Endpoints

We will collect archived tissue (FFPE slides) from a prior biopsy as well as peripheral whole blood samples from all patients. Peripheral blood samples will be collected at baseline, after 1 month of treatment, 6 months of treatment, and approximately 18-24 months post-first dose. MRD analysis will be conducted using PCR methods and results over time will be compared and correlated with PFS and OS. Please see section 9.0 for details.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to the protocol page in NOTIS for additional information). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations and as required by the NCI AdEERS Reporting Guidelines.

This study has been designated as an interventional study. As such, all adverse events and special situations, including pregnancies and product quality complaints, will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of the product under the study within the study. Adverse events that result in treatment discontinuation will be followed until resolution or until the patient starts subsequent therapy, whichever comes first.

For the purposes of this study, the Janssen medicinal product is: Ibrutinib (Imbruvica)

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents.

Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. All adverse events (regardless of severity) will be recorded in the appropriate eCRF throughout the study.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death occurs.

7.2 Definitions & Descriptions

7.2.1 Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the *reason* for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions

that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event *leading to* the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v. 4.03 is available at http://ctep.cancer.gov/reporting/ctc.html.

If no CTCAE grading is available, the severity of an AE is graded as follows:

- **Mild (grade 1):** the event causes discomfort without disruption of normal daily activities.
- **Moderate (grade 2):** the event causes discomfort that affects normal daily activities.
- **Severe (grade 3):** the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- **Life-threatening (grade 4):** the patient was at risk of death at the time of the event.
- **Fatal (grade 5):** the event caused death.

7.2.3 Serious adverse events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence. Additional expedited or routine reporting may be required, depending on the nature of the SAE (as outlined in 7.3 below). A "serious" adverse event or reaction is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death***.
  If death results from (progression of) the disease, the disease should be reported as the event (SAE) itself.
- **Is *life-threatening***.
  The patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- **Requires *in-patient hospitalization or prolongation of existing hospitalization* for ≥ 24 hours**.
  NOTE: Hospitalizations that do not meet the criteria for SAE reporting include:
  - *Hospitalizations required for drug administration, study-required testing*
  - *Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)*
  - *Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]*
- **Results in *persistent or significant disability*** *(a substantial disruption of the ability to conduct normal life functions)* ***or incapacity***.
- **Results in a *congenital anomaly/birth defect***.
- **Results in *suspected transmission of infectious agents by a medicinal product*.**
- **Is an *important medical event***.

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

Examples: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unexpected* (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied
- Is *related or possibly related* to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places human subjects or others at *a greater risk of harm* (including physical, psychological, economic, or social harm)

than was previously known or recognized, even if no harm has actually occurred.

7.2.5 Adverse Events of Special Interest

Adverse events of special interest are any events that Janssen Scientific Affairs (the company providing the drug) is actively monitoring as a result of a previously identified signal (even if non-serious). They should be recorded on a Serious Adverse Event Report Form and reported to Janssen Scientific Affairs, LLC within 24 hours of becoming aware of the event. The AEs of special interest for this protocol include:

- **Major hemorrhage** – Defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following:
  - intraocular bleeding causing loss of vision,
  - the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood
  - hospitalization, or prolongation of hospitalization
- **Intracranial hemorrhage** – Any intracranial hemorrhage AE (of any grade severity) including:
  - subdural hematoma/hemorrhage
  - epidural hematoma/hemorrhage
  - intracerebral hemorrhage
- **Other malignancies** – All new malignant tumors (including solid tumors, skin malignancies, and hematologic malignancies) are to be reported for the duration of study treatment and during any protocol-specified follow-up periods (including during post-progression follow-up for overall survival).

7.2.6 Pregnancy

Men must notify the study staff if their partner becomes pregnant while on study treatment or within 3 months of last dose. Women must notify the study staff if they become pregnant while on study treatment or within 1 month of last dose of ibrutinib and must immediately stop taking the study treatment.

All initial reports of pregnancy must be reported to Scientific Affairs, LLC within 24 hours of knowledge of the event. Abnormal pregnancy outcomes (e.g., spontaneous abortion, stillbirth, and congenital anomaly) are considered SAEs and must be reported as SAEs. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study should be reported within 24 hours of knowledge of the event. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required on a case-by-case basis.

7.2.7 Individual Case Safety Report (ICSR)

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

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

7.2.8 Product Quality Complaint (PQC)

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

Examples of PQC include but not limited to:

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

7.2.9 J&J Medicinal Product:

A J&J medicinal product is defined as the specific J&J drug under study and any other J&J medicinal product.

7.2.10 Special Reporting Situations

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

- overdose of a J&J medicinal product
- pregnancy exposure (maternal and paternal)
- exposure to a medicinal product from breastfeeding
- suspected abuse/misuse of a medicinal J&J product
- inadvertent or accidental exposure to a medicinal J&J product
- any failure of expected pharmacological action (i.e., lack of effect) of a J&J medicinal product
- unexpected therapeutic or clinical benefit from use of a J&J medicinal product
- medication error involving a J&J product (with or without patient exposure to the product, e.g., name confusion)
- suspected transmission of any infectious agent via a medicinal product.

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

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

7.3 Adverse Event Reporting

7.3.1 Routine reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted on the protocol page in NOTIS. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Steps to determine if expedited reporting is required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.

4) Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current protocol;
- the drug package insert
- the current Investigator's Brochure.

For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.
https://www.imbruvicahcp.com

7.3.3 Expedited reporting of SAEs & Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM (croqualityassurance@northwestern.edu) within 24 hours of becoming aware of the event. Completion of the NU CTO SAE Form and Medwatch Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)
- Country of incidence

All SAEs will be reported to, and reviewed by, the DMC per the Data and Safety Monitoring Plan (DSMP).

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University) and to participating sites whom have reporting responsibilities to Northwestern University. Participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to Northwestern University and to the NU IRB within 5 working days of notification.
- Information pertaining to an NU subject that fits into any of the categories listed on the Reportable New Information

page will be reported to the NU IRB within 5 business days of knowledge or notification.

For further information regarding the NU IRB policies and requirements for SAE reporting, please reference their website at: http://irb.northwestern.edu/process/when-things-go-wrong/reporting-requirements-timeframes.

7.3.3.3 Reporting to Janssen Scientific Affairs

In general, Janssen Scientific Affairs, LLC must be notified within 24 hours of becoming aware of any events that qualify as SAEs, AEs of Special Interest, Special Reporting Situations, pregnancies, and PQCs (whether or not considered drug related – see section 7.2 for definitions and descriptions of these terms). At a minimum, on a quarterly basis and at the end of the study, Scientific Affairs, LLC will provide to the PI and QAM a listing of all SAEs reported to Janssen Scientific Affairs. The PI and QAM will review this listing and provide any discrepancies to the Janssen Scientific Affairs.

Study endpoints that are SAEs (e.g., all-cause mortality) will be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to Janssen Scientific Affairs. Upon request, the PI (with assistance from the QAM) shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

For each subject, AEs, SAEs, and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

- SAEs or Special Reporting Situations must be reported from time of signed informed consent, through 30 days after the last administration of study drug (whether receiving study drug or not).
- SAEs or Special Reporting Situations that are ongoing at the time a subject completes his/her participation in the study should be followed until any of the following occurs:
    - the event resolves or stabilizes
    - the event returns to baseline condition or value (if available)
    - the event can be attributed to other agents(s) or factors unrelated to study conduct.
    - It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

At a minimum, at the end of the treatment as well as the end of the follow-up phases of the study, Northwestern University shall provide a report containing all AEs, both serious and non-serious. However, in certain circumstances more frequent review of the safety data may be necessary, (e.g. to fulfill a regulatory request), and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs' request. *Reporting timeframes for non-serious AEs should be outlined in the Research Funding Agreement section entitled Reporting of Data.*

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

- Electronically via Janssen SECURE Email service (preferred; please contact the Janssen assigned Trial Manager for access at IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional:
    - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report: 866-451-0371
    - If fax is non-functional, contact assigned Janssen Trial Manager

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

The FDA Medwatch Form will be used for reporting to Janssen Scientific Affairs; study teams will submit the NU CTO SAE and Medwatch form (as outlined above) to the NU QAM (note: the Northwestern study team should submit the Medwatch form directly to Janssen). Reports should include the PI's determination of whether the event was caused by a J&J product. All available clinical information relevant to the evaluation of an SAE, AEs of Special Interest, and Special Reporting Situations including pregnancy reports (with or without an AE) including paternal exposure are required.

- The PI is responsible for ensuring that these cases from clinical studies are complete and if not are promptly followed-up. This includes ensuring the reports are fully investigated and thoroughly documented, and that follow-up information is summarized (e.g. hospital records, coroner's reports, autopsy results) and recorded on the appropriate forms.
- A study case is not considered complete until all clinical details needed to interpret the case are received and the event has resolved, or otherwise explained, or the patient is lost to follow-up. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all SAEs, irrespective of association with the Study Drug

in the course of the Study, by facsimile within 24 hours of such report or correspondence being sent to applicable health authorities.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PI **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PI must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.
Janssen Scientific Affairs will provide to the PI IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports generated by the Janssen Scientific Affairs for the study drug as they become available until all subjects in the have completed their last Study visit according to the study parameters (i.e. Last Subject Last Visit has occurred).

1. **Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products**

   For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the PI should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible

8.0 DRUG INFORMATION

8.1 Ibrutinib

8.1.1 Other names

Ibrutinib (IMBRUVICA™) or JNJ 54179060 is 1-[(3R)-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).

8.1.2 Classification – type of agent

Ibrutinib is a selective BTK inhibitor.

8.1.3 Mode of action

Ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity [15]. In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of BTK,

phosphorylation of BTK's physiological substrate, phospholipase-Cγ (PLCγ), and phosphorylation of a further downstream kinase, extracellular signal-regulated kinase (ERK). Ibrutinib also inhibited the growth of a subset of B-cell lymphoma derived cell lines, with 50% growth inhibition (GI50) values ranging from 0.1 to 5.5 μM.

8.1.4 Storage and stability

The recommended storage condition for ibrutinib capsules is controlled room temperature (20°C to 25°C). Excursions are permitted between 15° and 30°C.

8.1.5 Protocol dose specifics

Ibrutinib will be administered orally at a dose of 560 mg daily. Patients will be instructed to take four (4) 140mg capsules for a dose of 560 mg. Please refer to Section 4 for dose modifications. A 30-day supply of Ibrutinib 140 mg capsules will be dispensed prior to the start of each cycle for the first 6 months of treatment. Thereafter patients will be given a 3 month supply of ibrutinib 140mg capsules every 3 cycles.

8.1.6 Preparation

Ibrutinib is a white to off-white crystalline solid that is supplied in 140 mg capsules. Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib USPI for a list of excipients.

8.1.7 Protocol administration

Ideally ibrutinib will be taken around the same time each day with approximately 8 ounces (240 mL) of water. All 4 capsules should be taken at the same time and the capsules should remain intact. Subjects should not attempt to open capsules or dissolve them in water. The daily self-administered home treatment is to be continuous (without interruption). Please refer to section 4 for further details and instructions.

8.1.8 Incompatibilities

Ibrutinib may be incompatible with certain agents. Please refer to Section 4.4 for complete details and instructions regarding the concomitant use of ibrutinib and CYP3A4/5 inhibitors and inducers and antiplatelet and anticoagulant agents, as well as instructions regarding surgical interventions and procedures while on study treatment.
Patients should also be instructed to avoid grapefruit juice, Star fruit and Seville oranges while on study treatment.

8.1.9 Availability and supply

Ibrutinib will be provided by Janssen Scientific Affairs and distributed as an investigational agent through the Investigational Pharmacy at Northwestern Memorial Hospital (NMH). Supply for patients at outside participating sites will be shipped from the NMH Investigational Pharmacy to each local site. To order drug, the drug order form located in NOTIS can be submitted following the instructions listed on the form. The ibrutinib capsules are packaged in opaque high-density polyethylene

(HDPE) plastic bottles containing 120 capsules with labels bearing the appropriate label text as required by governing regulatory agencies. All bottles will utilize child resistant packaging (caps will be child resistant). Unused ibrutinib, dispensed during previous visits, must be returned and drug accountability records updated per institutional standards. Returned capsules must be discarded and cannot be re-used in this study or outside the study. Please refer to the Drug Management Plan for further details about drug supply and accountability.

8.1.10 Side effects

Refer to the current investigator's brochure for toxicity information.

9.0 EXPLORATORY STUDIES

MRD analysis will be conducted using PCR methods and results will be compared over time (four time-points total). In addition, we will correlate results with PFS and OS. At Northwestern University, the Pathology Core Facility (PCF) Clinical Trials staff will be responsible for procuring, processing, and shipping all samples (tissue and peripheral blood) for exploratory studies. Participating sites should use whatever local services they have available to handle this aspect.

9.1 Sample Collection & Processing Guidelines

9.1.1 Tissue

Archived tissue from a previous biopsy will be obtained from all patients who have it available at baseline (lack of available tissue for exploratory studies will not preclude patients from participating in this study – however it is not *optional* for those who do have tissue available). Approximately 3-5 unstained FFPE slides (from diagnosis or time of high disease load) will be procured. Each slide should be 5-10 microns (or equivalent) in thickness; slides may be stored at ambient temperature until shipment.

9.1.2 Peripheral Blood

Three peripheral blood samples for exploratory studies will be collected at baseline (prior to treatment on Cycle 1 Day 1), after 1 month of treatment, 6 months of treatment, and approximately18-24 months post-first dose of treatment. All study blood samples will be collected at the same time as blood is being drawn for routine care/tests. Two samples will be collected using lavender-top EDTA Vacutainer® sample collection tube. Label the tube with the date of the draw, patient ID number, and patient initials. Using the labeled, lavender-top EDTA Vacutainer® sample collection tube, approximately 10cc of blood will be drawn. Tubes should be gently inverted 8 times to ensure adequate mixing of the anticoagulant. Blood samples may be stored at ambient temperature for up to 24 hours.

Within 24 hours of sample collection, perform cell preparation using Ficoll protocol on one of the EDTA tubes. Isolate peripheral blood mononuclear

cells (PBMCs). Store PBMCs at -80C until shipment (see lab manual for details).

For the second sample of peripheral blood, flow cytometry will be performed, as standard of care at the treating institution. The results of the flow cytometry will be interpreted as positive or negative per the treating investigator and recorded for comparison with simultaneous results of MRD testing by PCR.

A third optional sample will be collected in a 6mL EDTA tube for future research that involves evaluating the treatment response by analyzing changes in the proportion of tumorigenic clones within the patient's blood as compared to the initial biopsy. These samples will be stored in PCF Clinical Trials Unit (CTU). Such future research must be reviewed and approved by Janssen prior to use of the samples.

9.2 Shipping Instructions

See separate lab manual for instructions on shipping both tissue and peripheral blood samples.

9.3 Assay Methodology

Baseline tissue slides will be used to identify clones. All peripheral blood samples will undergo MRD analysis testing using PCR methods. Analysis will be performed by an outside laboratory that is contracted for these services (see separate lab manual for details).

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

10.1.1 Primary Endpoint

Progression-free survival (PFS) will be defined as the absence of disease progression or death from any cause. The rate of PFS will be calculated after 3 years.

10.1.2 Secondary Endpoints

Adverse events will be defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The occurrence and severity of each will be recorded. The rate of conversion from PR to CR will be calculated. Overall survival (OS) will be assessed after 4 years.

10.1.3 Exploratory Endpoints

Minimum residual disease (MRD) will be quantified as being either categorical or continuous.

10.2 Sample Size and Power Calculations

The primary endpoint is three-year PFS. Our null hypothesis is that ibrutinib maintenance will yield no improvement upon the 60% three-year PFS observed in

studies described above. We consider an observed three-year PFS of 80% both feasible and of significant clinical improvement. The study will have 10% Type I error and 90% power to detect an effective treatment using a one-stage design based on the true proportion of patients achieving 3-year PFS is at least 80% versus the null hypothesis that the true complete response rate is at most 60%.

Based upon these parameters, our sample size will be 36 evaluable patients. For the final analysis, if 25 or fewer patients are alive and without progression from among all 36 evaluable patients accrued, we will consider this regimen ineffective for this patient population. If, on the other hand, 26 or more patients are alive and without progression, this will be considered sufficient evidence that this treatment may be recommended for further testing in subsequent studies, particularly in a randomized setting.

10.3 Planned Analyses

10.3.1 Primary Objective

The primary objective will be to determine the progression-free survival (PFS) rate after 2 and 3 years. This will be done in two ways. First, the proportion of patients alive and progression-free at 2 and 3 years will be calculated, along with an exact 90% confidence interval, both two-sided as well as a lower 90% confidence limit. The number of patients alive and progression-free at 2 and 3 years will be used to address the primary hypothesis as indicated in section 10.2 above. In addition, a Kaplan-Meier curve will be calculated to obtain the actuarial estimate of two-year progression-free survival.

10.3.2 Secondary Objectives

To assess toxicity, all adverse events will be summarized as to type, severity, frequency, timing and attribution. Descriptive frequencies and proportions will be used for this analysis.

To determine rates of conversion from PR to CR, only patients who had a PR at the time of registration and who complete ≥ 1 complete cycle of ibrutinib maintenance therapy will be evaluable for this endpoint. These rates will be calculated as a proportion together with exact 90% confidence limits.

To determine median overall survival (OS) after 4 years, Kaplan-Meier curves will be determined for overall survival and the five-year point on this curve, along with 90% confidence limits, will be determined. Patients will be evaluated monthly for the first 6 months on treatment, then every 3 months thereafter. Patients who go off treatment will continue to be followed for survival up to a maximum of 4 years post-first dose. Follow-up will occur every 3 months (up to 2 years after the first dose of treatment) and then every 6 months thereafter (up to 4 years post-first dose).

10.3.3 Exploratory Objectives

To compare MRD results over time by PCR , correlational analyses such as McNemar's test, Pearson and Spearman correlations and Lin's concordance statistics will be used, depending on the metric for MRD (as detected by either flow cytometry or by PCR) used in the analysis. To correlate MRD with either PFS or OS, proportional hazards regression with a time dependent covariate (MRD) will be used.

10.3.4 Interim Analysis

Patients will be formally evaluated for an interim safety analysis as described below after 15, 20 and 25 patients have been observed. The PI along with the Northwestern Lymphoproliferative Disorders disease team and Quality Assurance will assess data to ensure there are no unexpected safety signals that have been observed at this time.

Serious adverse event (SAE, Section 7.2.3) assessment will be done using a Pocock-type boundary [16]. With 36 patients, if the **drug-related** SAE rate is **25%**, and there is a 5% probability of detecting an excess of SAEs when the SAE rate at most 25%, then the number of SAEs that need to be observed as the trial progresses in order to detect an excess of SAEs are 9 SAES/15 patients, 10/20 or 12/25. The boundary can be calculated for any interim sample size.

With 36 patients, if the drug-related Grade 5 SAE rate is 1%, and there is a 5% probability of detecting an excess of Grade 5 SAEs when the SAE rate is at most 1%, then using the Pocock-type boundary, the number of Grade 5 SAEs that need to be observed as the trials progresses in order to detect an excess of Grade 5 SAEs are at least 2 if the current sample size is 26 or less, and at least 3 if the current sample size is between 27 and 36.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient

will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

Amendments to the protocol will be initiated and maintained by the assigned Medical Writer. Requests for revisions may come from multiple sources, including but not limited to the Principal Investigator, study team, drug company, or FDA. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Janssen Scientific Affairs. Amendments will be distributed by the lead institution (Northwestern) to all participating sites upon approval by the Northwestern University IRB.

11.3 Subject Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Trials Office at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CTO website for additional instructions on registering a patient.

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.
- A copy of the official IRB approval letter for the protocol and informed consent.
  NOTE: Informed consent form should be submitted to the Clinical Trials Office for review/approval prior to submission to the local IRB.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to the protocol page of NOTIS for additional information). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. The assigned Quality Assurance Monitor, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to NOTIS for additional data submission instructions.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the

change, and Janssen Scientific Affairs must be notified in parallel. The QAM must be notified within 24 hours of such a change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the Institutional Review Board (IRB). Protocol deviations must be reported according to the policies and procedures of the IRB of record.

A protocol deviation may be considered an instance of Promptly Reportable Non-Compliance (PRNC) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has compromised the rights and welfare of the research subject.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

All protocol deviations will be documented by the study team on eCRFs in NOTIS, as they occur. At NU, deviations will be reviewed during research meetings by the PI, with PI review and responses being documented and entered into the appropriate eCRF. Other participating sites will follow local procedures or SOPs for PI review of deviations. For all sites deviations should be entered into the eCRF in real time with regular PI review, and immediate routing to QA after PI review. Deviation reports (with appropriate documentation of PI review) will be made available to the assigned QAM on request, during monitoring visits and at time of audit.

11.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician, Janssen Scientific Affairs and QAM gives final approval, the publication may be submitted to external publisher.

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APPENDIX I – Lists of Concomitant Medications/Treatments Requiring Special Precautions

A list of drugs that may affect the CYP3A system (and other CYP variants) can be found at:

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Appendix II – Cheson 2007 Criteria

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Appendix III

The following equations should be used to calculate creatinine clearance.

For males:

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

OR

$$\frac{(140 - \text{age [years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

For females:

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

OR

$$\frac{0.85\,(140 - \text{age [years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

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

Appendix IV- Protocol History of Changes

Amendment 1 –May 06, 2015 *Approved by Scientific Review Committee- May 06, 2015*			
Sections(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Title page, Study Summary Table, & 3.0	Tufts and Cleveland Clinic listed as participating sites	Cleveland Clinic removed, Duke University, University of Michigan, Dana Farber added as sites	Administrative
Study Summary table & 3.1.2 (Inclusion Criteria)	"Patients must have received 4 or more cycles of one of the following prior systemic induction chemotherapy regimens: R-CHOP (with or without **alternating R-DHAP**) with or without auto SCT."	Revised to "Patients must have received 4 or more cycles of one of the following prior systemic induction chemotherapy regimens: R-CHOP (with or without **cytarabine-containing cycles**, **including "Nordic" and MCL-NET protocols**) with or without auto SCT."	Revised for clarification
Study Summary table, 1.1, 2.1, 6.1, 10.1.1, 10.2, 10.3.1	"The primary objective will be to determine the progression-free survival (PFS) rate after 2 years."	"The primary objective will be to determine the progression-free survival (PFS) rate after **3** years."	Correction of clerical error
5.0 "Study Procedures"	"Induction Chemotherapy"	Revised to "**Documentation of** Induction Chemotherapy"	Revised for clarification
5.0 (Study Procedures)	Footnote 17: "Peripheral blood samples for exploratory studies (1 10 ml EDTA tube) will be collected at baseline..."	"X" removed from screening baseline column and footnote 17 revised to "Peripheral blood samples for exploratory studies (1 10 ml EDTA tube) will be collected **cycle 1 day 1…"** rather than at baseline.	Revised for clarification
5.0 "Study Procedures", 9.1.2	n/a	Added line in table for "Peripheral blood for flow cytometry" and added to footnote 17 "A second tube of peripheral blood should be obtained at the same time as each research sample, and sent for flow cytometry, as standard of care, to be performed at the treating	Revised for clarification

		institution."	
10.3.3 (Exploratory Objectives)	"To compare MRD results over time by PCR , correlational analyses such as McNemar's test, Pearson and Spearman correlations and Lin's concordance statistics will be used, depending on the metric for MRD used in the analysis."	Revised to "To compare MRD results over time by PCR , correlational analyses such as McNemar's test, Pearson and Spearman correlations and Lin's concordance statistics will be used, depending on the metric for MRD **(as detected by either flow cytometry or by PCR)** used in the analysis.	Revised for clarity
Amendment 2 – July 21, 2015 *Approved by Scientific Review Committee – July 21, 2015*			
Sections(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Title page, Version Date	May 6, 2015	July 21, 2015	Updated version date
Study Schema Study Summary 1.1 Disease background & Current Therapies 1.3 Rationale for Current Study 3.1.2 Inclusion Criteria 4.1 Overview 5.0 Study Procedures: Footnote 1 	Hyper-CVAD	R-Hyper-CVAD	To update hyper-CVAD to R-Hyper-CVAD (R=Rituximab)
<u>Amendment 2 – November 18, 2015</u>			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover-page, 3.0 (Selection of Subjects), 4.3.1 (Dose Delays)	Adam Petrich listed as Principal Investigator	Adam Petrich has been removed as PI and Jason Kaplan has been added; contact information and IND Holder Name have been updated appropriately	Administrative – Dr. Petrich has left the institution and will no longer serve as the study PI; Dr. Kaplan will take over role of PI
Cover-page	n/a	Adds Barbara Pro as a Sub-Investigator	Administrative – Dr. Pro is a new faculty member who will be involved with this study
Cover-page	Lists Tufts University and Duke University as participating sites	Removes Tufts University and Duke University as participating sites and adds University of Utah	Administrative – Tufts and Duke will no longer participate, and University of Utah has been added to the contract
Signature Page	Includes Signature	Removes Signature Page	Administrative – NU

	Pages		protocol template no longer includes a signature page
4.1 (Treatment Plan Overview),	n/a	Adds language to specify that patients will start treatment with ibrutinib within 14 days of study registration	Clarification
4.2 (Administration)	States that ibrutinib should be taken at least 30 minutes before eating or 2 hours after a meal	Removes fasting language	Update to match Investigator's Brochure
4.2 (Administration)	n/a	"In general, vomited doses should not be made up. Patients should contact their physician to discuss options in the event of a vomited dose."	Clarification on dosing instructions
4.4.3 (Concomitant Medications/Treatments requiring Special Precautions)	"If ibrutinib must be administered with a strong or moderate CYP3A4/5 inhibitor, the medical monitor at Janssen should be consulted before use, and a dose reduction of ibrutinib to 140 mg daily or a temporary hold of ibrutinib should be considered."	"If ibrutinib must be administered with a strong or moderate CYP3A4/5 inhibitor, a dose reduction of ibrutinib to 140 mg daily or a temporary hold of ibrutinib should be considered. The PI, Janssen Medical Monitor, and the NU Quality Assurance Monitor (QAM) must be notified as well."	Clarification – allows investigator autonomy
5.0 (Study Procedures – Peripheral blood for flow cytometry), 9.1.2 (Peripheral blood)	Flow cytometry marked as required during screening	"X" removed from procedure table for flow cytometry at Screening; it is only required at C1D1. Clarification added to footnote 17 and section 9.1.2.	Clarification - streamlines sample collection at C1D1
7.0 (Adverse Events),	n/a	Adds language from Janssen defining AE's, SAE's, and reporting timelines	Updated to align with Janssen's new reporting template
7.2.3 (Serious Adverse Events),			
7.2.7 (Individual Case Safety Report),			
7.2.8 (Product Quality Complaint),			
7.2.10 (Special Reporting Situations),			
7.3.3.3 (Reporting to Janssen Scientific Affairs)			
8.1.10 (Ibrutinib Side Effects)	n/a	Includes additional side effects of ibrutinib	Updated to align with risk language in new investigator's brochure

Amendment 3 – March 15, 2016
Approved by Scientific Review Committee –

Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Abbreviations	n/a	Adds the following abbreviations: PCF = Pathcore Facility CTU = Clinical Trials Unit	Administrative
3.0 (Selection of Subjects)	Trial is conducted at Northwestern Medicine Developmental Therapeutic Instituted (NMDTI) of Northwestern University	Removes NMDTI. States that the trial will be conducted at Northwestern University	Not all patients are seen in NMDTI
3.1.2 (Inclusion Criteria)	Referring to induction chemotherapy options: "Patients who received combinations of the above regimens are not eligible"	"Patients are allowed to receive combinations of the above regimens"	PI feels that a combination of the listed regimens is appropriate and should not preclude a patient from entering the study
3.1.10 (Inclusion criteria), 4.2 (Administration), 4.4.3.1 (CYP3A4/5 Inhibitors/Inducers), 8.1.8 Incompatibilities	Patients should avoid consuming Grapefruit and Seville orange products for the duration of the study	Adds that patients should also avoid consuming Star fruit for the duration of the study	Updated safety information
3.2.9 (Exclusion Criteria); 4.4.3.1 (CYP3A4/5 Inhibitors/Inducers)	n/a	Refers to Appendix I for a list of CYP3A4/5 inhibitors	Clarification
3.2.15 (Exclusion Criteria)	Patients with clinically active hepatitis A, B, or C infections are not eligible.	Adds the following note: "Patients with a history of hepatitis may be eligible if they have a normal titer. Such cases should be approved by the study PI."	PI feels that a normal titer would make the patient an appropriate study candidate
4.2 (Administration)	Instructed patients not to make up missed doses, and also to contact their physician to discuss other options	Clarifies that while vomited doses should generally not be made up, patients should still contact their physician to discuss such cases.	Clarification – since vomited doses are a rare occurrence, it is appropriate for patients to contact their physician
4.2 (Administration), 5.0 (Study Table, #8)	Study calendars were not required after 6 months of treatment	Patients must continue maintaining a study calendar for the duration of treatment	QA requirement for appropriate drug accountability
4.3.1 (Dose Delays)	• PI should be contacted regarding unmanageable toxicity • Study drug could be restarted after 28 days on a case-by-	• PI and QAM should be contacted regarding unmanageable toxicity • Removes language about restarting drug. Any patient who is held for 28 days must come	• QAM needs to be involved in toxicity and dose management • QA request – allows for more streamlined

	case basis	off study	management of patient dosing
4.3.2 (Dose Modifications)	n/a	The PI should be contacted for dose modifications due to a Grade 4 or unmanageable Grade 3 drug-related toxicity	Provides guidance since such toxicities are open-ended
4.4.2 (Prohibited Concomitant Meds/ Treatment)	Chronic use of systemic corticosteroids was prohibited unless reviewed and approved by the PI	Chronic use of systemic corticosteroids above prednisone 10mg po daily (or equivalent) is prohibited	Provides more concrete instruction
4.4.4 (Precautions & Restrictions Regarding Surgical Interventions or Procedures)	Ibrutinib should be held until the surgical site is healed or at the discretion of the investigator	Removes the option for investigator's discretion and instead refers to procedural guidelines for specific surgical procedures	Clarification
4.6 (Duration of Therapy), 4.8 (Removal of Patients)	n/a	Adds language: "Clinical suspicion of progressive disease (PD) or loss of response should be investigated radiographically, and will result in removal of active therapy if confirmed by clinical investigation."	PI wants to ensure investigator discretion and clinical investigation is permitted before taking a patient off treatment; stopping Ibrutinib may result in
5.0 (Study Table)	#1: Prior chemo can be no more than 90 days from study treatment #2: n/a #4: Chemistry panel includes comprehensive chemistry, Mg, LDH #6, 13, 14: Window for screening procedures was 14 days and 90 days for imaging	#1: Prior chemo can be no more than 120 days from study treatment #2: Adds that labs should be resulted prior to treatment to assess the need for dose modifications in 4.3 #4: Lists specific labs within a comprehensive chem panel #6, 13, 14: Window for screening window includes 90 days for bone marrow biopsy and EGD/colonoscopy	#1: To clarify discrepancy from 3.1.2 #2: Treatment clarification #4: Clarification – affiliates may have a different comprehensive panel #6, 13, 14: Clarification – BMBX and EGD were previously falling under "imaging"
5.0 (Study table, Footnote 17), 9.1.2 (Peripheral blood)	n/a	Adds a third correlative sample (6mL EDTA) to be collected for future research	Dr. Kaplan has a grant pending that will allow analysis of extra blood samples. In the meantime, blood will be collected for future use.
6.1 (Primary Endpoint)	"Progression will be documented by imaging (CT scan)"	"Progression will be documented by imaging (CT scan or MRI)"	Clarification of discrepancy
7.0 (Adverse Events)	Adverse events were to	Adverse events will now	Clarification per

	be reported from the time of consent until 30 days from the last dose of study drug	be reported from the time of consent until completion of the subject's last study related procedures (which may include contact for follow up safety). Note clarifies that follow-up will only apply to patients who discontinue for reasons other than PD.	Janssen request.
7.2.5 (Adverse Events of Special Interest)	n/a	Adds the following sentence re AE's of special interest: "They should be recorded on a SAE Report Form and reported to Janssen Scientific Affairs, LLC within 24 hours of becoming aware of the event"	Clarification per Janssen request.
7.2.6 (Pregnancy)	Pregnancy outcomes must be followed	Pregnancy outcomes must be followed "on a case-by-case basis"	Janssen does not have a specific timeline for reporting pregnancy outcomes, but we agreed to report on a case-by-case basis
7.3.3 (Expedited reporting of SAE's & Other Events)	Study coordinators were to complete the NU CRO SAE form	Study coordinators must complete the Medwatch and NU CRO SAE form	Administrative - Janssen needs the Medwatch form
7.3.1 (Routine Reporting), 11.5 (Data Management and Monitoring/Auditing), Appendices	Included Data Collection & Submission Guidelines as Appendix I	Removes Appendix I and replaces any submission guideline appendix references with NOTIS references; Renumbers remaining Appendices and corresponding references in protocol	Administrative - aligns with current departmental SOP's
7.3.3.3 (Reporting to Janssen Scientific Affairs)	n/a	Includes contact information for gaining access to Janssen's Secure email service and faxing SAE reports	Administrative
8.1.9 (Availability and Supply)	n/a	Adds the number of capsules (120) included in each bottle of ibrutinib	Clarification
Updated Amendment 3 Prior to IRB Submission – April 5, 2016			
Study Summary, 3.0 (Selection of Subjects)	Listed affiliate sites as: Tufts, Duke, University of Michigan, and Dana Farber	Removes Tufts and Duke as affiliate sites and adds University of Utah	Administrative change to update affiliates
4.4.2 (Prohibited	Prohibited "Chronic use	Prohibits "Chronic use of	Clarification to provide

Concomitant Medications)	of systemic corticosteroids, unless reviewed and approved by the PI"	systemic corticosteroids above prednisone 10mg po daily (or equivalent dose of other corticosteroid)	more specific medication guidelines
8.1.7 (Protocol administration)	Ibrutinib was to be taken "preferably 30 minutes before eating or at least 2 hours after a meal"	Removes language	Janssen request – these prandial conditions are not required
8.1.10 (Side Effects)	n/a	Adds language for the following side effects: • Effects on the heart • Infections • Decreased blood counts • Allergic reactions • Tumor Lysis Syndrome (TLS) • Liver Failure • Interstitial Lung Disease	Janssen added language to align with updated ibrutinib safety information
Amendment 4 – November 3, 2016 *Approved by Scientific Review Committee – November 17, 2016*			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Cover Page	n/a	Adds Valerie Nelson as sub-Investigator at Lake Forest	Lake Forest would like to participate in the study
Cover Page; 3.0 (Selection of Subjects)	Listed University of Michigan is a participating site	Removes University of Michigan as site	University of Michigan will no longer participate
Study Summary	Included short title of protocol	Removes short title	To align with new NU protocol template – no longer required
1.1 (Disease Background and Current Therapies)	n/a	Updates FDA-approval status for ibrutinib – "It has since been approved for CLL/SLL, SLL with 17p deletion, and Waldenström's macroglobulinemia."	To align with current regulatory status of ibrutinib
2.2.1 (Secondary Objectives); 6.2.1 (Toxicity); 7.2.2 (Severity of AE's); 7.3.2 (Steps to determine if expedited reporting is required); 10.1.2 (Secondary Endpoints)	CTCAE version 4.0	CTCAE version 4.03	Administrative
3.1.2 (Inclusion Criteria)	n/a	Adds note: "Patients who progress during induction therapy are not eligible to enroll in this study."	Clarification
3.1.9 (Inclusion Criteria)	Required pregnancy	Requires pregnancy test	Clarification to

	test within 28 days of registration	within 14 days of registration	address discrepancy in 5.0 footnote 6
3.2.6 (Exclusion Criteria)	n/a	Adds exclusion of prior allogeneic stem cell transplant, and an engraftment stipulation for prior auto SCT	Patients with prior transplant may be more susceptible to side effects from ibrutinib
3.2.7 (Exclusion Criteria)	Patients with a malignancy other than MCL are not eligible unless they meet one of the criteria listed.	Adds exception: "Malignancy is not considered life-threatening in the opinion of the investigator and does not require treatment (for example, low risk prostate cancer undergoing active surveillance or low-risk myelodysplastic syndrome not requiring therapy)."	A non-life-threatening malignancy is not felt to be an interfering factor in study treatment
3.2.10 (Exclusion Criteria); 4.4.3.1 (CYP3A4/5 Inhibitors/Inducers)	n/a	Adds that CYP3A4/5 inhibitors are not allowed ≤14 days prior to registration	Clarification
4.3 (Toxicity Management & Dosing Holds/ Dose Modifications)	Referred to dose "delays"	Changes "delay" to "hold"	To clarify that doses will be skipped rather than delayed
4.3.1 (Dose Holds); 4.3.2 (Dose Modifications); 5.0 (Study Procedures #2)	n/a	"When a dose is missed or held, it will not be made up, regardless of duration. Observations and scheduled assessments will continue regardless of amount of drug the patient has had, and should always be based on time from C1D1. (For example, if a patient is held on C2D14 for a week, the day they re-start will be C2D21, and the patient will still have scheduled assessments as planned on C3D1) Please contact QA if you have any questions on timing of holds or study assessments."	Clarification – previously it was not clear whether doses would be skipped or just delayed
4.8 (Removal of Patients from Therapy)	Patients who stop treatment to receive anti-cancer therapy for a second malignancy may be considered for re-start of study therapy	Adds that approval must be sought from PI and DMC	Clarification – a discussion should take place for such a significant decision
	#2: n/a #8: Ibrutinib is to be	#2: Adds a window of ±2 days for study	#2: Clarification #8: Clarification

	given at 560mg throughout the study #9: "Patients will be evaluated monthly" #10: "Patients will be evaluated every 3 cycles" #11: Follow-up to occur every 3 months #12: Vitals to include respirations #15: n/a	assessments and ±7 days for scans #8: Adds clarification "unless a dose reduction occurs" #9: "Patients will be evaluated on Day 1 of each cycle (±2 days)" #10: "…every 3 cycles (on Day 1, ±7 days) #11: Adds window of ±7 days #12: Removes respirations from vitals and adds "12-point symptom assessment" to physical exam #15: Adds specific hepatitis tests to be performed at screening (HepBcAb, HepBsAg, HepC Antibody)	#9: Clarification #10: Clarification#11: Clarification #12: Clarification #15: Clarification
5.0 (Study Procedures #16); 7.0 (Adverse Events)	AE's were to be followed for 30 days after treatment discontinuation	"Adverse events will be tracked from time of signed informed consent until completion of the last study-related procedures (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days beyond cessation of study treatment. AE's resulting in discontinuation will be followed until resolution, or until patients start subsequent therapy, whichever comes first."	Clarification
6.1 (Primary Endpoint)	"Only patients who complete > 1 complete cycle (28 days) of ibrutinib maintenance therapy" were evaluable for PFS	Changes evaluable patients to "any patient who receives at least one dose of study treatment"	This is to be an intention to treat design, therefore any patient who receives treatment will be included in the analysis
6.2.1 (Toxicity)	n/a	Adds language about an interim safety analysis: "After the study has been opened for 18 months, patients will be evaluated for an interim safety analysis. The PI along with the Northwestern Lymphoproliferative Disorders disease team	Upon request from Janssen

		and Quality Assurance will assess data to ensure there are no unexpected safety signals that have been observed at this time"	
7.3.2 (Steps to determine if expedited reporting is required)	n/a	Updates product information website for Imbruvica	Administrative; new information provided by Janssen
8.1.9 (Availability and Supply)	• n/a • Drug accountability records are to be recorded with unused ibrutinib	• Adds: "To order drug, the drug order form located in NOTIS can be submitted following the instructions listed on the form" • Adds that records should be updated "per institutional standards"	• Clarification for sub-sites • Affiliate request since sites have varying accountability methods
8.1.10 (Side Effects)	• FOCBP and men were to use a high effective method of birth control • n/a	• Adds the requirement of a barrier method for both FOCBP and sexually active men • Updates side effects of ibrutinib to align with latest IB	• Additional safety language provided by Janssen
10.2 (Samples Size and Power Calculations)	References two-year PFS observed in prior studies	Changes to three-year PFS observed in prior studies	Typographical error
Updated Amendment 4 Prior to IRB Submission – November 28, 2016 *Approved by Scientific Review Committee – December 15, 2016*			
6.2.1 (Toxicity); 5.0 (Study Procedures #8)	n/a	References section 10.3.4 for details on the interim safety analysis	Clarification requested by Janssen
10.3.4 (Interim Analysis)	n/a	Expands on exactly how the interim safety analysis will take place. Toxicity will be monitored by the PI and disease team after the study has been opened for 18 months. Specifically, SAE's will be monitored for unexpected safety signals.	Clarification requested by Janssen.
Amendment 5 – May 9, 2017 *Approved by Scientific Review Committee – June 12, 2017*			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Study Schema; 4.2 (Administration); 5.0 (Study Procedures, #2,8)	n/a	Patients should normally have visits every 3 months, however patients can have 6-month study visits (with local clinic visits in between) if after 2 years they are clinically stable and live far from the	To allow flexibility for patients who are inconvenienced by study visits. In patients who are clinically stable a local clinic visit is appropriate.

		study site. Drug may be provided every 6 months in these cases.	
3.1.7 (Inclusion Criteria)	Labs were required within 28 days prior to registration	Labs are required within 14 days prior to registration	To fix discrepancy
4.3.2 (Dose Modifications)	Dose modifications were to take place for any Grade 4 or unmanageable Grade 3 drug-related toxicities	Dose modifications may now take place for Grade 4 or unmanageable **Grade 2** or 3 drug-related toxicities.	To allow for more investigator discretion of unmanageable toxicities.
	At the first occurrence of an AE requiring dose modification, the original dose level was to be resumed.	Adds that drug can be restarted either at the original dose level **or one dose level lower per investigator discretion**.	To allow for more investigator discretion of appropriate ibrutinib dosing
	The table for dose modification actions dictated the exact dose level to adjust to (420mg at the second occurrence, and 280mg at the third occurrence).	Adds dose levels in Table 4-2 (560mg, 420mg, 280mg), and refers to dose levels in Table 4-1, rather than specific doses.	Fixes discrepancy if a patient's dose has already been reduced for a prior toxicity.
5.0 (Study Procedures)	#6: All screening procedures were to take place within 14 days of registration	#6: Adds exception for informed consent, which can be signed within 30 days of registration.	Clarification
	#7: Scans were to take place after cycles 3 and 6 and every6 months thereafter	#7: Scans should take place after cycles 3 and 6, every 6 months for the first 2 years, once at 3 years, and as clinically indicated thereafter.	To align more closely with standard practice and allow more flexibility.
	#7: Scans did not specify an end of treatment time point	#7: "…as clinically indicated thereafter (<u>including EOT, as clinically appropriate, for patients who complete 4 years of therapy, or patients that come off study treatment early for a reason other than progression</u>)"	An EOT scan was felt to be clinically appropriate for patients who fall into these categories; this scan will be highly encouraged but not mandatory.
	#11: Patients who discontinue treatment early will be followed for up to 4 years for survival endpoints"	Adds "…for survival endpoints **only (no labs or physical exam are required**)"	Clarification that no labs will be required in follow-up
	#17: "Another sample will be collected and stored for future use"	#17: "Another sample will be collected and stored for future use <u>at each time point.</u>"	#17: Clarification
7.3.3.3 (Reporting to Janssen Scientific Affairs)	Patricia Corbin was Janssen contact	Removes Patricia Corbin and adds Brooke Ackerman	Administrative staff change

10.3.4 (Interim Analysis)	Section referenced both a one-time interim safety analysis at 18 months, and continuous SAE monitoring using a Pocock-type boundary.	Clarifies that the interim safety analysis will be continuous, with monitoring after 15, 20 and 25 patients have been observed. Updates the numbers of SAEs to be observed for an excess of SAEs.	Clarifications for consistency; the interim analysis needs to be either one-time or continuous, and the PI and statistician have decided that continuous is most appropriate.
Amendment 6 – November 30, 2017 *Approved by Scientific Review Committee – December 12, 2017*			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Cover Page; 3.0 (Eligibility); 4.3.1 (Dose Holds)	Study PI was Dr. Jason Kaplan	Updates study PI to Dr. Barbara Pro	Administrative faculty change due to Dr. Kaplan leaving the institution
Amendment 7 – March 19, 2019 *Approved by Scientific Review Committee – April 5, 2019*			
Section(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
Cover Page	n/a	Adds Reem Karmali as sub-investigator	Administrative update to account for new faculty
Cover Page	Alfred Rademaker was listed as the biostatistician	Replaces Alfred Rademaker with Denise Scholtens	Administrative update to account for new biostatistician
Cover Page; 7.3.3 (Expedited reporting of SAEs & Other Events);	Referenced Northwestern University's Clinical Research Office (CRO)	References Northwestern University's Clinical Trials Office (CTO)	Administrative update
4.4.3.1 (CYP3A4/5 Inhibitors/Inducers)	n/a	Adds Table 4-3 to provide additional instructions for ibrutinib dose modifications for patients who must take moderate/strong CYP3A inhibitors	Updated to align with revised IMBRUVICA™ (ibrutinib) prescribing information
5.0 (Study Procedures; Footnote 11)	Follow up was stated as every 3 months which conflicted with other sections	Follow up is stated as every 3 months up to 2 years and every 6 months thereafter to match other sections	Corrected discrepancy
5.0 (Study Procedures)	The window for visits every 3 cycles and during follow-up was ±7 days, and there was no window for visits every 6 cycles	Updates window to ±10 days for visits both every 3 and 6 cycles; also updates window to for follow-up to ± 10 days	Updated for consistency and to provide more flexibility to patients in a maintenance phase of treatment and follow-up; drug provision has been accounted for
7.0 (Adverse Events)	The timeline for AE reporting referenced the follow-up schedule	Clarifies that AE reporting is to occur for 30 days after the last dose of drug,	Administrative update

		in line with the follow-up schedule	
7.3.2 (Steps to determine if expedited reporting is required)	Referenced link within website www.imbruvicahcp.com to obtain product information	Updates website to www.imbruvicahcp.com	Administrative update
8.1.10 (Ibrutinib Side Effects)	n/a	Includes additional risk/side effects of ibrutinib	Updated to align with revised/new risk language provided by Janssen
9.1.2 (Peripheral Blood); 9.2 (Shipping Instructions); 9.3 (Assay Methodology)	Referenced Sequenta Laboratories for analysis of correlative peripheral blood	Removes Sequenta and instead refers to lab manual.	Sequenta is no longer providing services for correlative analysis. Referencing the lab manual allows for flexibility as a new lab is identified and avoids unnecessary future protocol amendments
Throughout	n/a	Updates minor formatting and grammatical changes	Administrative update
Amendment 8 – January 15, 2020			
Section(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
Title Page and Throughout	Protocol version dated March 19, 2019 (Amendment 7)	Updates to a new protocol version dated January 15, 2020 (Amendment 8)	Administrative update.
Title Page	The Biostatistician was Denise Scholtens, PhD.	The Biostatistician has been changed to Masha Kocherginsky, PhD.	Administrative update due to staffing change.
Table of Contents	N/A	Updates page numbers	Administrative update.
1.2.3 (Toxicity Data)	N/A	Adds the below text: Refer to the investigator's brochure for additional toxicity information.	Administrative update. Adds text for clarity.
4.3.2 (Dose Modifications)	Stated: The actions described below should be taken for the following drug-related toxicities:… • Any other Grade 4 or unmanageable Grade 2 or 3 drug-related toxicities. The PI should be contacted in these	Now states: The actions described below should be taken for the following drug-related toxicities:… • Any Grade 4 drug-related toxicity • Any unmanageable Grade 2 or 3 drug-related toxicities. The PI	Revises language for clarity; separates Grade 4 events and Grade 2/3 events into two bullet points.

	cases.	should be contacted in these cases.	
7.2.4 (UPIRSO); 7.3.3 (Expedited Reporting of SAEs & Other Events); 7.3.3.2 (Reporting to the NU IRB; 11.2 (Amendmentsl); 11.6.2 (Other Protocol Deviations); 11.8 (Publication Policy)	N/A	Updates standard language to align with new Northwestern University protocol template and updates contact information for the Janssen assigned Trial Manager	Administrative update
8.1.10 (Side Effects of Ibrutinib)	N/A	Updates risk language for ibrutinib	Updates risk language to align with the release of a new ibrutinib investigator brochure, Edition 13.
Throughout	N/A	Minor corrections to typographical errors, style, and formatting.	Administrative update.
Amendment 9 – November 18, 2021			
Section(s) Affected	Revision		Rationale
Cover page & throughout	Updates the principal investigator from Dr. Barbara Pro to Dr. Reem Karmali and provides contact information		Administrative revision
Throughout	Editorial revisions: Updates the protocol version/date and Appendix IV (Protocol History of Changes)		Administrative revision

Amendment 10 – February 22, 2022		
Section(s) Affected	**Revision**	**Rationale**
Section 8.1.10 (Side Effects)	Deletes informed consent template risk language from the trial protocol. Instructs end	Deletes informed consent template risk language from

	users to refer to the current investigator's brochure for toxicity information.	the trial protocol. This information is located in the patient-facing informed consent document. Additional toxicity information is located in the current investigator's brochure.
Section 8.1.10 (Side Effects) & Exclusion criterion 3.2.17	The following breastfeeding language is moved from Section 8.1.10 to Section 3.2.17: "It is not known whether ibrutinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibrutinib, breastfeeding should be discontinued during ibrutinib treatment."	Administrative revision for ease of use by end users
Section 8.1.10 (Side Effects), Inclusion criterion 3.1.8, & Section 7.2.6 (Pregnancy)	The following contraception language is moved from Section 8.1.10 to Section 3.1.8: Adequate contraception "is defined as a method that has a low failure rate (i.e. less than 1% per year) when used consistently and correctly and includes implants, injectables, birth control pills with two hormones, some intrauterine devices (IUDs), sexual abstinence (which is defined as refraining from all aspects of sexual activity) or a sterilized partner. If using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (e.g., condoms) must be used. The following pregnancy language is moved from Section 8.1.10 to Sections 3.1.8 and 7.2.6: "Men must notify the study staff if their partner becomes pregnant while on study treatment or within 3 months of last dose. Women must notify the study staff if they become pregnant while on study treatment or within 1 month of last dose of ibrutinib, and must immediately stop taking the study treatment."	Administrative revision for ease of use by end users
Throughout	Editorial revisions: Updates formatting, the protocol version/date, the Table of Contents, and Appendix IV (Protocol History of Changes)	Administrative revision

Amendment 11 – August 08, 2022		
Section(s) Affected	**Revision**	**Rationale**
Section 4.3.2 Dose Modifications, Table 4-1 Dose Modification	The actions described below should be followed for the indicated drug- related toxicities per Table 4-1:	Updated Section 4.3.2 and Table 4-1 due to release of updated prescribing

Actions	• Grade 3 (ANC <1000/mm3) or Grade 4 neutropenia (ANC <500/mm3) • Grade 3 thrombocytopenia (platelets <50,000/mm^3) in the presence of significant bleeding • Grade 4 thrombocytopenia (platelets <25,000/mm^3) • Grade 3 or 4 neutropenia with infection or fever • All other Grade 4 hematological toxicities • Grade 3 or Grade 4 non-hematological toxicities including nausea, vomiting or diarrhea (if persistent despite optimal antiemetic or antidiarrheal therapy), exceptions noted below for cardiac related toxicities (see Sections 4.3.2.1 & Section 4.3.2.1.1) • Grade 2 cardiac failure • Any unmanageable Grade 2 or Grade 3 drug-related toxicities. The PI should be contacted in these cases. Table 4-1 revised.	information for ibrutinib dated 05/2022 and dear investigator letter from Janssen Scientific Affairs, LLC dated June 21, 2022.
4.3.2.1 Dose Modifications for Grade 3 Cardiac Arrhythmias & 4.3.2.1.1 Dose Modifications for Grade 3 and higher Cardiac Failure & Grade 4 Cardiac Arrhythmias, Table 4-2 Dose Modification Actions for Grade 3 Cardiac Arrhythmias	4.3.2.1 Dose modifications for Grade 3 Cardiac Arrhythmias The actions described below should be followed for the indicated following drug-related toxicities: • Grade 3 cardiac arrhythmias See new Table 4-2 4.3.2.1.1 Dose Modifications for Grade 3 and higher Cardiac Failure & Grade 4 Cardiac Arrhythmias Ibrutinib is to be discontinued if the following drug related toxicities occur: • Grade 3 or 4 cardiac failure • Grade 4 cardiac arrhythmias Table 4-2 revised, see Table 4-2.	New sections and new Table (Table 4-2) added due to updated prescribing information for ibrutinib dated 05/2022 and dear investigator letter from Janssen Scientific Affairs dated June 21, 2022.
Table 4-3: Dose Modifications for Use with CYP3A Inhibitors	Table revised, see Table 4-3.	Table updated to appropriate sections in the protocol per revised prescribing information for ibrutinib dated 05/2022 and dear investigator letter from Janssen Scientific Affairs dated June 21, 2022.
Cover page and throughout document	Editorial , updated document to clarify Amendment 11 and version date with this revision to the protocol; update to statistician on Cover page, Xinlei Mi, PhD, replacing former statistician.	Administrative changes

Throughout document	Editorial changes for typos/spacing.	Administrative changes
Section 11.6.2	All protocol deviations will be documented by the study team on eCRFs in NOTIS, as they occur. At NU, deviations will be reviewed during research meetings by the PI, with PI review and responses being documented and entered into the appropriate eCRF. Other participating sites will follow local procedures or SOPs for PI review of deviations. For all sites deviations should be entered into the eCRF in real time with regular PI review, and immediate routing to QA after PI review. Deviation reports (with appropriate documentation of PI review) will be made available to the assigned QAM on request, during monitoring visits and at time of audit.	Revised protocol deviation language per RHLCCC updated template language for protocol deviation reporting.