Mayo Clinic Cancer Center

A Phase II study of Daratumumab and Ibrutinib for Relapsed / Refractory Chronic Lymphocytic Leukemia Treatment (DIRECT)

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FDA IND#: EXEMPT

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Drug Availability
Commercial Agents: Ibrutinib (capsules)
Drug Company Supplied: Daratumumab and hyaluronidase (daratumumab SC)

√Study contributor(s) not responsible for patient care

Document History

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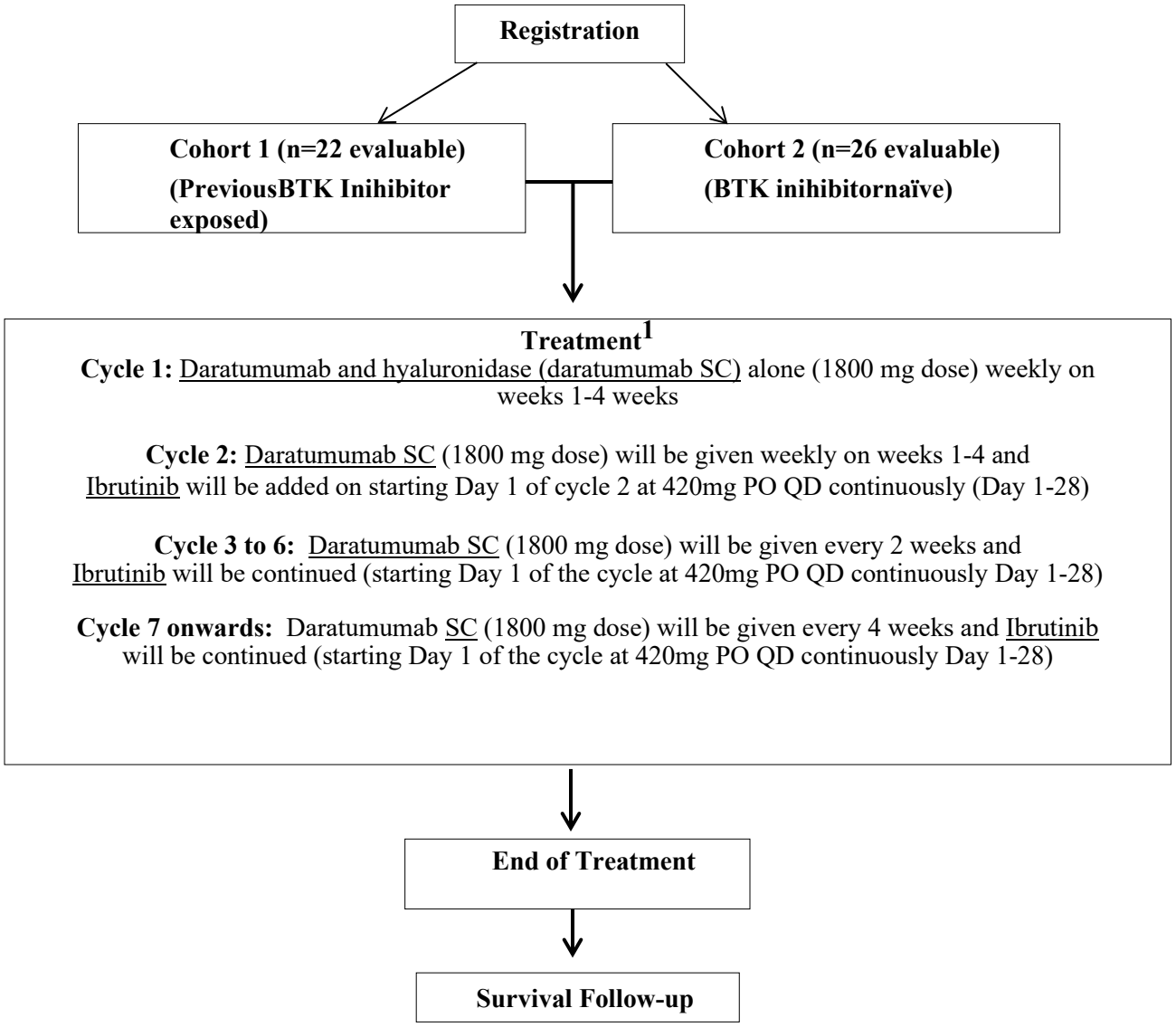
Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Serious Adverse Event Reporting	FDA Coordination Team [redacted]

*No waivers of eligibility allowed

Schema



1. Cycle length = 28 days (±4 days); Last cycle may be up to 56 days to accommodate the End of Treatment visit

Study Drug Generic name: Daratumumab and hyaluronidase Brand name(s): Darzalex Faspro Mayo Abbreviation: Dara Availability: Provided by Janssen	Generic name: Ibrutinib Brand name(s): Imbruvica Mayo Abbreviation: Ibr Availability: Commercial

1.0 Background

1.1 **Overview on CLL:** CLL is a lymphoproliferative malignant disorder that remains incurable in the majority of the patients when using standard therapeutic approaches. It is manifested by the progressive accumulation of functionally-incompetent, mature-looking lymphocytes in the blood, bone marrow and lymphoid tissues. It is a heterogeneous disease with a variable clinical spectrum ranging from an indolent variety (Rai Stage 0), where the patients enjoy a long-term survival of over 12 years, vs. advance-stage disease (Stage III/IV), where the median survival is about 2.5 years.[1] Treatment options have included alkylating agents (Chlorambucil, Cyclophosphamide) or purine analogues (fludarabine, pentostatin) and/or monoclonal antibodies (rituximab, alemtuzumab, ofatumumab, and obinutuzumab). These agents are often used in combination regimens with variable responses. As CLL is incurable, current treatment strategy remains anchored in disease control at time of symptom development with the clinical course being punctuated with frequent relapses and the eventual death of the patient from progressive disease[2]. New agents and novel therapeutic strategies are thus needed for the treatment of CLL[3]to cure the disease, induce a prolonged remission, or maintain remission. In reviewing the natural history of this disease, it is clear that these aims are unlikely until complete remission can be achieved in higher proportions of this patient population. Most recently, it has been further reported that eradication of minimal residual disease or MRD, which can be detected by flow cytometry or by polymerase chain reaction (PCR) is associated with more prolonged disease control and is an important end point that determines longer disease free interval.[4-6]

With the availability of novel non-chemotherapeutic agents, increase in overall response rates are noted, however ability of these agents to induce CR or MRD by themselves remains limited prompting consideration for development of novel combination regimens. Section 1.2 visits the overall therapeutic landscape for CLL recognizing that new agents are rapidly questioning the status quo on CLL treatment.

1.2 **Treatment:** Due to the incurable nature of the disease and limited therapeutic options, treatment of CLL is often only instituted when patients develop symptomatic or persistently progressive disease. The criteria for treatment interventions are outlined in the IWCLL/Hallek, December 2008 formulation (see Appendix IV).[7]

Chemotherapy in CLL

Traditionally, the initial treatment for CLL patients that require therapy[8] included either (a) a single agent alkylating agent (chlorambucil) or a (b) purine analogue (fludarabine or pentostatin). Compared to chlorambucil, higher overall response rate (ORR) and complete remission (CR) rate were observed with fludarabine, but there was no superiority in overall survival (OS) or progression-free survival (PFS) noted in randomized studies.[9,10] Kanti Rai reported on the CALGB randomized Chlorambucil vs. Fludarabine vs. the combination of Fludarabine and Chlorambucil.[9] Among the 170 patients treated with fludarabine, 20% achieved a CR, while 43% achieved a partial remission (PR). The median duration of remission and the median PFS in this group were 25 and 20 months, respectively. Despite improvement in the ORR, no survival benefit was reported. Thus, up until very recently, the standard of care for this disease remained the use of single agent oral chlorambucil or fludarabine with a CR rate of 4% and 20%, respectively.

Combining these agents with steroids and/or other chemotherapy agents (such as vincristine or an anthracycline) also did not result in improvement in survival.[11-13] Importantly, even early disease stage patients treated with these agents did not alter the overall clinical outcome. Despite evaluation of various combination regimens, purine analogues remained the most active agents in patients with CLL, yielding higher overall and complete response rates.[9,14,15] Eventually all patients with CLL will relapse. Although retreatment with fludarabine can result again in response, especially in those with an initial clinical response lasting for more than 1 year, continued treatment with fludarabine is difficult due to cumulative marrow toxicity resulting in prolong cytopenia and inability to further treat the patient. Patients who do not achieve durable remission after first fludarabine therapy have only a modest response with a second round of fludarabine.[16] For these patients, the combination of this drug with alkylating agents (cyclophosphamide) has been used with improved outcome.[14,17] Various investigators reported combination of fludarabine with cyclophosphamide as salvage regimen in patients with CLL.[17,18]

Monoclonal antibodies and chemoimmunotherapy

The development of monoclonal antibodies heralded a new era and modified the therapeutic approach to treatment of CLL.

Rituximab is a chimeric humanized monoclonal antibody that showed an ORR of approximately 50-60% in patients with relapsed and refractory low-grade non-Hodgkin's lymphoma.[19-21] Because CLL is a B-cell lymphoproliferative disease with expression of CD20, rituximab was investigated for the treatment of CLL. Interestingly, despite expression of CD20 on the CLL cells, single agent rituximab (on standard dosing schedule) failed to demonstrate any meaningful clinical response. However, more frequent dosing e.g., three times weekly for 4 weeks (at 375 mg/m^2 per dose) showed a better response rate 45% (3% CR, 42% PR) with a median duration of response of 10 months .[22] Higher doses may have more anti-tumor efficacy but are cost prohibitive, and the true long-term benefit remains undetermined.[23]

While results of single agent rituximab in CLL were disappointing, the results of the combination with fludarabine (chemoimmunotherapy) were impressive.[24,25] Clinical experience of combination of rituximab with fludarabine or fludarabine and cyclophosphamide demonstrated higher CR rates.[17,22,23,26-29] ORR of fludarabine + rituximab combination are in the range of 90% with 47% CR. In another clinical investigation the FC (Fludarabine/Cyclophosphamide) regimen was also combined with rituximab. Phase III randomized clinical trial of FC vs. FCR confirmed superiority of the chemoimmunotherapy approach in survival outcomes for patients.[30] This strategy of chemoimmunotherapy, although yielding higher response rates, is often associated with significant toxicity and morbidity to the patients. Thus these regimens are often preferred for younger patients with good performance statuses. Despite the higher response rates and increase rates of reported CR, all patients eventually relapse and die of progressive disease or its complications. Nevertheless, the chemoimmunotherapy approach is now the most commonly used front-line treatment approach in CLL.

Obinutuzumab: is a novel CD20 targeting monoclonal antibody that recently received approval for the treatment of elderly patients with CLL. Prior studies of rituximab in combination with chlorambucil showed higher ORR and CR rates, and this led to the clinical trial comparing Obinutuzumab/chlorambucil vs. rituximab/chlorambucil vs. chlorambucil alone. This study demonstrated a higher ORR in favor of

chemoimmunotherapy; 77% vs. 65% vs. 31%, respectively. PFS was also significantly improved with Obinutuzumab/chlorambucil combination vs. the other arms.[31]

Despite these high ORR and CR rates noted with the chemoimmunotherapy approach, all patients eventually relapse and develop resistance to therapy. Up until very recently, the only approved treatments for these patients were alemtuzumab (monoclonal antibody targeting CD52) and ofatumumab (monoclonal antibody targeting CD20).

Alemtuzumab: is a humanized monoclonal antibody that targets CD52 and has demonstrated a clinical response in over 30% of CLL patients with relapsed or refractory disease. Notably, the CR rate remains low (<5%). An important and limiting adverse event of alemtuzumab has been severe immunodeficiency resulting from depletion of both T and NK cells along with B cells. This often results in infectious complications and has limited its use in the community.[32,33]

Ofatumumab: Ofatumumab is another monoclonal antibody that targets CD20, and it is one of the three currently available. It has demonstrated efficacy and is approved in patients with relapsed or refractory CLL; however, similar to the experience with other CD20 monoclonal antibodies, by itself the drug has very low CR rates.[34] Currently ofatumumab is approved for the treatment of CLL patients who are refractory to fludarabine and alemtuzumab.[35]

Bruton tyrosine kinase inhibitors

Ibrutinib (also referred to as PCI-32765 or JNJ54179060) is a first-in-class, potent, orally administered covalent inhibitor of Bruton's tyrosine kinase (BTK). BTK is a mediator of critical B-cell signaling pathways implicated in the pathogenesis of B-cell cancers. *In vitro* studies have shown that ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent inhibition of BTK enzymatic activity. In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited auto-phosphorylation of BTK, phosphorylation of BTK's physiological substrate, phospholipase-Cγ (PLCγ). It also inhibited the phosphorylation of a further downstream kinase, extracellular-regulated kinase (ERK). Ibrutinib inhibited the proliferation of cell lines derived from diffuse large B-cell lymphoma (DLBCL) patients with a median effective concentration, EC50, of 1 or 2 nM. In primary chronic lymphocytic leukemia (CLL) cells, ibrutinib reduced proliferation at concentrations of 500 and 1000 nM. Preclinical studies have also shown that ibrutinib inhibits numerous processes, e.g., NFκB deoxyribonucleic acid (DNA) binding, CpG-mediated CLL cell proliferation, and tumor cell migration and adhesions. At concentrations relevant to exposure levels in patients, ibrutinib has remarkable selectivity for inhibition of B-cell receptor (BCR) signaling over T-cell receptor (TCR) signaling.[36-39]

Clinical efficacy: The clinical benefit of ibrutinib was first shown in the initial clinical study PCYC-04753, which was a Phase 1, multicenter, open-label, dose-escalation study of ibrutinib in subjects with recurrent B-cell lymphoma, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), DLBCL, and follicular lymphoma (FL), or Waldenströms macroglobulinemia (WM). It was initiated in February 2009. Thirty-three of the 66 subjects enrolled responded to treatment with ibrutinib monotherapy, including 10 CR. Responses were observed at each dose level and across all included histologic types, with highest response rate observed in subjects with MCL and CLL/SLL (85.7% each). The maximum tolerated dose (MTD) of ibrutinib was not reached using intermittent dosing cohorts up to 12.5 mg/kg/day and

continuous dosing cohorts at 560 mg. However, it was noticed that subjects treated on the lowest dosing cohort of 1.25 mg/kg/day, which did not reach full BTK occupancy, reported the lowest overall response rate (25.0%) compared with all other tested dose levels.[40]

The favorable overall safety profile of ibrutinib and the high incidence of objective responses observed in these subjects with advanced and heavily pretreated B-cell lymphomas and CLL support the role of BTK as a crucial mediator of growth and survival in B-cell malignancies and was further demonstrated in subsequent Phase 2 studies in relapsed or refractory MCL and relapsed or refractory CLL/SLL.

In Study PCYC-1104-CA, 111 subjects with relapsed and/or refractory MCL were treated with 560 mg daily continuously until disease progression or until the subject could no longer tolerate the treatment. The overall response rate was 68%, and complete response (CR) rate was 21%. The median duration of response (DOR) was 17.5 months, and the median progression-free survival (PFS) was 13.9 months. Based on these data, 560 mg daily dosing was chosen for further development in MCL, FL, and DLBCL.[41]
In Study PCYC-1102-CA, subjects with relapsed or refractory or treatment-naïve CLL/SLL were treated with 420 mg or 840 mg daily continuously until disease progression or until the subject could no longer tolerate the treatment. A total of 85 patients (mostly with high risk CLL) were included in this study (51 received 420mg and 34 received 840mg dose). Ibrutinib produced an overall response rate of 71 % in both the groups. Objective responses appeared independent of poor-risk factors, including adverse cytogenetic characteristics. The median overall survival was 83% and at 26 month the progression-free survival was recorded as 75%. The 840 mg dose level did not appear to improve efficacy. Therefore, 420 mg daily dose was chosen as the recommended dose for further development in CLL/SLL.[42] The subsequent section will provide more detail on some of the important safety aspects of ibrutinib.

Safety: Over 736 subjects have been treated with either single agent use of ibrutinib (506 subjects plus 100 healthy volunteers) or in combination with immunotherapy and/or chemotherapy (130 subjects) in nonrandomized studies. In addition, approximately 537 subjects have been treated with either ibrutinib or placebo in five randomized (controlled and open-label) studies. In the absence of an established MTD, responses have been observed in all histologic subtypes treated to date. Ibrutinib has been well tolerated across various dose levels. The most commonly reported treatment-emergent adverse events (AEs) in studies where ibrutinib was administered as monotherapy (n=506) were diarrhea (42.1%), fatigue (33.8%), and nausea (26.1%). The majority of the adverse events were of Grade 1 or 2 in severity. The most commonly reported adverse events considered related to ibrutinib were diarrhea (30.2%), fatigue (17.8%), nausea (15.0%), and thrombocytopenia (9.9%). The majority of these adverse events were of Grade 1 or 2 in severity. Adverse events of Grade 3 or higher in severity were not common and were primarily hematologic in nature including neutropenia (9.7%), thrombocytopenia (6.5%), and anemia (4.9%). Grade 3 or higher pneumonia occurred in 7.7% of subjects. Serious adverse events (SAEs) in the monotherapy studies were commensurate with patient population, the disease state or its complications, the most common being pneumonia (7.9%) and atrial fibrillation (3.2%).
Treatment related Lymphocytosis: Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood (Stevenson 2011).

A reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (approximately 69% to 75%) with CLL/SLL treated with single agent ibrutinib. This effect has also been observed in some subjects (33%) with MCL treated with single agent ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy (ie, 27% of subjects receiving ibrutinib + BR in Study 1108) or immunotherapy (ie, 55% of subjects receiving ibrutinib + ofatumumab in Group 2 of Study 1109). A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/μL) has been observed in a subset of subjects. There have been isolated cases of leukostasis reported in subjects treated with ibrutinib.

Bleeding-related events: There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and some major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage and hematuria.

Rash: Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS), with a fatal outcome, was reported in a subject with CLL. The subject received ibrutinib (420 mg/day) and was also receiving various antibiotics and antigout medication (allopurinol) known to be associated with SJS.

Cardiac arrhythmias and cardiac failure: Fatal and serious cardiac arrhythmias or cardiac failure have occurred in patients treated with ibrutinib. Patients with significant cardiac comorbidities may be at greater risk of events, including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia, and cardiac failure have been reported, particularly in patients with acute infections, or cardiac risk factors, including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns. For signs and symptoms that persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines.
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Other Malignancies: Other malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Across the MCL (PCYC-1104-CA) and CLL/SLL studies (PCYC-1112-CA and PCYC-1102-CA)), skin cancers and non-skin cancers were

reported in 5.0% (18/357) and 2.5% (9/357) of subjects who received ibrutinib, respectively.

Infection: Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection, and sepsis. Isolated cases of JC virus reactivation resulting in progressive multifocal leukoencephalopathy (PML) have been observed and resulted in death. Two cases in relapsed CLL subjects have been reported. One case occurred after multiple prior rituximab regimens and less than one year after the last dose of rituximab and high dose steroid administration. The second case occurred during concomitant administration of rituximab, bendamustine and ibrutinib.

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

Diarrhea: Approximately one-third of subjects treated with ibrutinib monotherapy and two-thirds treated with combination therapy reported diarrhea. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe, with only a small number of Grade 3 events, and no Grade 4 events reported to date.

Summary:
Pooled safety data for subjects treated with ibrutinib monotherapy in 11 nonrandomized studies (PCYC-1102-CA, PCYC-1117-CA, PCYC-1112-CA [crossover only], PCYC-1104-CA, PCI-32765MCL2001, PCI-32765MCL4001, PCYC-1106-CA, PCYC-1111-CA, PCI-32765FLR2002, PCYC-04753, and PCI-32765-JPN-101) has been evaluated ibrutinib Investigator's Brochure [IB], version 15.0, dated 10 December 2021).
The most frequently reported treatment-emergent adverse events in more than 10% of subjects receiving ibrutinib as monotherapy in nonrandomized studies (N=1061) were diarrhea (35.9%), fatigue (28.6%), nausea (20.2%), cough (17.5%), and anemia (15.2%). The most commonly reported Grade 3 or 4 adverse events that were hematologic in nature were neutropenia (10.7%), thrombocytopenia (6.2%), and anemia (5.5%). Pneumonia (5.7%), fatigue (2.9%), hypertension (2.7%), and atrial fibrillation (2.6%) were the most frequently reported nonhematologic Grade 3 or 4 adverse events.
The incidence of treatment-emergent SAEs reported was 41.3% (N=1061); pneumonia (7.0%), atrial fibrillation (2.8%), and febrile neutropenia (2.3%) were the most commonly reported treatment-emergent SAEs .

In a randomized Phase 3 study in subjects with CLL/SLL (PCYC-1112-CA), the most frequently reported treatment-emergent adverse events in the ibrutinib arm were diarrhea (47.7%), fatigue (27.7%), nausea (26.2%), pyrexia (23.6%), anemia (22.6%), and neutropenia (21.5%). Adverse events reported at a higher incidence (> 10% difference) in the ibrutinib arm than in the ofatumumab arm included diarrhea (ibrutinib: 47.7%, ofatumumab: 17.8%), arthralgia (17.4%, 6.8%), and petechiae (13.8%, 1.0%).

The most commonly reported Grade 3 or 4 adverse events in more than 2% of ibrutinib treated subjects that were hematologic in nature were neutropenia (16.4%), thrombocytopenia (5.6%), and anemia (4.6%). Pneumonia (6.7%) was the most frequently reported nonhematologic Grade 3 or 4 adverse event. The most frequently reported SAEs in ibrutinib subjects were pneumonia (8.7%), atrial fibrillation (3.1%),

pyrexia (3.1%), lung infection (2.6%), lower respiratory tract infection (2.1%) and urinary tract infection (2.1%).
For more detailed information refer to the current version of the IB.

Long-term use and safety: Analysis of adverse events over a 3-year follow-up period is now available (*see Investigator Brochure for details, Item 5.3.1.4; v15_10DEC2021_*) and shows that most AEs of clinical interest, including hematological and non-hematological AEs, either decreased or stayed the same overtime.

1.3 **Rationale for the study**

Although several new treatments have recently been approved for patients with the disease, complete remissions (CR) are rare, particularly in those with high-risk features and as such CLL remains incurable.[2,43] Biologically, the oncogenic drive of the malignant CLL clone is propelled by overactive B-cell receptor (BCR) signaling as well as through several elements in the microenvironment, which transmit their pro-survival effects through a variety of receptors on the CLL cell surface.[44-46] Some of these transmembrane antigens include the BCR itself, CD19, CD20 and CD38. Therapeutic agents targeting BCR signaling (ibrutinib) and CD20 (rituximab) have already demonstrated a significant clinical benefit and experimental strategies targeting CD19 are being investigated.[46-48] CD38 targeting has not been tested to date. With the availability of Daratumumab (an IgG monoclonal antibody targeting CD38)[49] this strategy is now possible.

Biological rationale: CD38 is a high value target in CLL engaged in CLL cell proliferation.[50,51] Clinically, CD38 positivity is associated with enhanced clonal aggressiveness and an overall worse clinical outcome as compared to CD38 (negative) CLL.[52] Furthermore, CD38 expression positively correlates with all of the other negative prognostic markers, including cytogenetic abnormalities, soluble CD23, soluble B2M and p53 function.[52-54] For prognostic purposes the expression density of CD38 has an arbitrary cutoff at 30% and this demonstrates that those patients who have a higher CD38 expression (>30%) are associated with compromised progression free and overall survival outcome[52,53]. However, for therapeutic purpose this **may not** be applicable. Thus, CD38 is not merely a marker but carries important operative significance, which CLL cells utilize for survival. Functionally, CD38 acts as a molecular hub, which integrates signals from the BCR, CD19 and the microenvironment, driving disease progression.[55] Indeed, the downstream signaling cascade activated upon ligation of CD38 by an agonistic mAb is almost identical to CD19-mediated signaling.[56] Ligation of CD38 induces tyrosine phosphorylation and kinase activity of SYK as well as PLCy2 and of the PI3K p85 subunit-leading to increased cell proliferation.[57] CD38 also function in a co-receptorial fashion synergizing with ZAP-70 signaling and CD38 engagement has been shown to result in a transient but significant tyrosine phosphorylation of ZAP-70 in CD38 /ZAP-70+ CLL cells.[58] CLL clones are known to manipulate other cells in the microenvironment for their own benefit. It has been shown that CD31 that is expressed on nurse-cells interacts with CD38+ CLL cells to maintain tumor proliferative capacity.[50,59,60] Additionally, CLL cells attract Th1-like T-cells by secretion of type 1 chemokines; which establishes a collaborative relationship between the cells and involves IFN-g and increased T-bet levels, resulting in increased CD38 expression on the CLL cells.[61]

Undoubtedly, CD38 is an important target whose functional activity can be mitigated with anti-CD38 mAbs such as daratumumab and whose anti-tumor effect may be enhanced when used in combination with ibrutinib. Biologically this combination is highly attractive and anticipated to enhance anti-CLL effects. Notably, we have observed that ibrutinib treatment of malignant lymphoid cells does not downregulate CD38 surface receptor levels and thus unlikely to

compromise the binding and therapeutic impact of daratumumab (Manna et al ASH 2017). No clinical study has been done to date to evaluate the role of daratumumab in the management of CLL. Given the target (CD38) is equally expressed in CLL patients, it is highly relevant to explore daratumumab's therapeutic potential in these patients and its combination with ibrutinib. We hypothesize that daratumumab engages CD38 signaling, induces death in malignant B CLL and thus can be developed as an effective CLL therapeutic. This proposal focuses on this novel strategy to treat CLL patients using daratumumab to enhance the efficacy of currently established and approved therapeutic *ibrutinib*. To address this the clinical trial is designed to enroll patients with relapsed or refractory CLL, in these adult patients ibrutinib is an effective and approved treatment, however most patients with this agent only achieve partial remission as is noted in section 1.2. Clearly to make a larger impact on the clinical course of the disease to enhance the depth of clinical response (such as achieving MRD) new combination will be required to boost the effect of existing therapy and the design of this study addresses this critical aspect.

Preclinical Data to Support the Biological Rationale of Targeting CD38 in CLL: CD38 has emerged as a high-impact therapeutic target in multiple myeloma, with the approval of daratumumab (anti-CD38 mAb). The clinical importance of CD38 in patients with CLL as a therapeutic target remains understudied. The biological effects and antitumor mechanisms engaged by daratumumab in primary CLL cells have been reported. Besides its known immune-effector mechanisms (antibody-dependent cell-mediated cytotoxicity, complement-dependent death, and antibody-dependent cellular phagocytosis), direct apoptotic effects of daratumumab alone or in combination with ibrutinib were measured. *In vivo* antileukemic activity was assessed in a partially humanized xenograft model. The influence of CD38 on B-cell receptor (BCR) signaling was measured via immunoblotting of Lyn, Syk, BTK, PLCγ2, ERK1/2, and AKT. In addition to immune-effector mechanisms; daratumumab also induced direct apoptosis of primary CLL cells, which was partially dependent on FcγR cross-linking. For the first time, we demonstrated the influence of CD38 on BCR signaling where interference of CD38 downregulated Syk, BTK, PLCγ2, ERK1/2, and AKT; effects that were further enhanced by addition of ibrutinib. In comparison to single-agent treatment, the combination of ibrutinib and daratumumab resulted in significantly enhanced anti-CLL activity *in vitro* and significantly decreased tumor growth and prolonged survival in the *in vivo* CLL xenograft model. Overall, the data demonstrate the antitumor mechanisms of daratumumab in CLL; furthermore, we show how co-targeting BTK and CD38 lead to a robust anti-CLL effect, which has clinical implications.[59]

Overall design: This is a phase II clinical trial of two novel drugs (daratumumab and hyaluronidase given SC and ibrutinib given orally) for treatment of patients with relapsed or refractory CLL. During the first cycle of the treatment, patients are given daratumumab as a single agent (for conduct of correlative studies – please see section 7.0), and starting cycle 2 patients will have both ibrutinib and daratumumab given together. Patients will be grouped in independent cohorts based upon whether they previously received a BTK inhibitor (Cohort 1) vs. BTK inhibitor naïve (Cohort 2). A total of 52 eligible patients will be enrolled in two separate cohorts (i.e. Cohort 1 and 2). A total of 25 cycles (including the first cycle with single agent daratumumab) will be given. The primary goal is to determine ORR of this regimen in each arm.

2.0 Goals

Given the patient population investigated in each cohort is different, the endpoint for each cohort is specific and noted below:

2.1 Primary Goals

For Cohort 1

2.11 Determine the overall response rate after 6 cycles of treatment with daratumumab in combination with ibrutinib in patients who are on /or are previously treated with ibrutinib.

For Cohort 2

2.12 Determine the overall response rate after 6 cycles of treatment with daratumumab in combination with ibrutinib in patients who are naive to ibrutinib treatment.

2.2 Secondary Goals

For Cohort 1

2.21 Determine the best overall response rate to treatment with daratumumab plus ibrutinib at any time during the course of the therapy.

2.22 The overall incidence of MRD (minimal residual disease) negative state and the time to achieving MRD negativity at any time during this therapy.

2.23 Progression free survival (as determined by the IWCLL criteria) among all patients.

2.24 The overall toxicity profile of daratumumab/ibrutinib treatment in this group of patients.

For Cohort 2

2.25 Determine the best overall response rate to treatment with daratumumab plus ibrutinib at any time during the course of the therapy.

2.26 The overall incidence of MRD (minimal residual disease) negative state and the time to achieving MRD negativity at any time during this therapy.

2.27 Progression free survival (as determined by the IWCLL criteria) among all patients.

2.28 The overall toxicity profile of daratumumab/ibrutinib treatment in this group of patients.

3.0 Registration Patient Eligibility

3.1 Registration - Inclusion Criteria

3.11 Age ≥ 18 years.

3.12 Diagnosis of B-CLL, confirmed by flow cytometry and as per the criteria outlined by the IWCLL/Hallek December 2008 (Refer to Appendix III).

3.13 Patients must have relapse or refractory CLL/SLL who have received at least 1 prior anti-CLL/SLL therapy. (**Note**: There is no upper limit of how many lines of therapy the patient may have received previously)

Note: For the purpose of a particular therapy/regimen to be counted towards the number of prior treatments a patient must have received at least 2 cycles of the regimen e.g., a patient who change their treatment regimen after only 1 cycle (due to toxicity or any other reason) will not be considered to have "2" prior therapies.

3.13a Patients on low dose prednisone (≤ 10 mg) for treatment of conditions other than CLL are eligible.

3.14 Cohort 1 only: Exposed to previous BTK inhibitor. Patients must meet one of the following criteria:

- They have been previously treated with a previous BTK inhibitor and were taken off for any reason (except grade 4 toxicity definitely attributed to BTK inhibitor) as long as deemed safe by the treatment physician to receive ibrutinib
- Currently on a BTK inhibitor and now have progressive disease (BTK inhibitor refractory)
- Currently on BTK inhibitor and have failed to achieve either a complete remission after at least 12 cycles of treatment with BTK inhibitor or have suboptimal response (< PR) after being on BTK inhibitor treatment for 6 cycles.

3.15 Patients must have a measurable disease as defined in Section 11.0

3.16 ECOG performance status of 0, 1 or 2 at registration (see Appendix I).

3.17 The following laboratory values obtained ≤ 14 days prior to registration:

- Absolute neutrophil count ≥ 1000/mm^3
- Hemoglobin ≥ 7 g/dl
- Platelets ≥50,000/mm^3.
- Serum creatinine <= 1.5 x ULN or creatinine clearance >25ml/min (major emphasis on the or part).
- Total bilirubin ≤ 1.5 mg/dL or direct bilirubin ≤ 1.0 mg/dL for patients with Gilbert's syndrome
- SGOT (AST) and SGPT (ALT) ≤ 3 x ULN

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

3.19a Negative pregnancy test done ≤14 days prior to registration, for persons of childbearing potential only.

NOTE: If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.19b Provide written informed consent.

3.19c Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study)

3.2 Registration - Exclusion Criteria

3.21 Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

3.22 Patient is known to have **chronic obstructive pulmonary disease** with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal (Note: FEV1 testing is required for subjects suspected of having chronic obstructive pulmonary disease and subjects must be excluded if FEV1 <50% of predicted normal.)

3.23 Patient is known to have **moderate or severe persistent asthma** within the past 2 years, or currently has uncontrolled asthma of any classification (Note: subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study.)

3.24 Since this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown, any of the following will deem the subject ineligible for the study:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.25 Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

3.26 Patients who have received **no prior therapy** for CLL.

3.27 Patients with history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix, unless in complete remission and off therapy for that disease for >3 years).

3.28 Patients who have **previously received daratumumab or any other anti-CD38 therapy** on a clinical trial or for any other malignancy.

3.29 Prior or current exposure to any of the following:

- Exposure to an investigational drug (including investigational vaccine) or invasive investigational medical device for any indication within 4 weeks or 5 pharmacokinetic half-lives, whichever is longer.
- Focal radiation therapy within 14 days prior to randomization with the exception of palliative radiotherapy for symptomatic management but not on measurable extramedullary plasmacytoma

3.30 Concomitant use of warfarin or other Vitamin K antagonists (see section 9.5)

3.31 Requires treatment with a strong cytochrome P450 modulators (CYP3A inhibitor and/or CYP3A inducers) [see Section 9.5]. NOTE: A comprehensive list of inhibitors, inducers, and substrates may be found at [redacted] This website is continually revised and should be checked frequently for updates.

3.32 Major surgery ≤ 4 weeks prior to registration.

3.33 Patients who are:

- Seropositive for human immunodeficiency virus (HIV)
- Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. **EXCEPTION:** Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
- Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

3.34 Clinically significant cardiac disease, including:

- Myocardial infarction within 6 months before randomization, or unstable or uncontrolled disease/condition related to or affection cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV)
- Uncontrolled cardiac arrhythmia

- Screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec.

3.35. Known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, Dara SC or its excipients (refer to the IB) or known sensitivity to mammalian-derived products

3.36. Have received vaccination with live attenuated vaccines within 4 weeks of first study agent administration

3.37. Patients with inability to swallow capsules or tablets, or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption (malabsorption syndrome, resection of the small bowel, poorly controlled inflammatory bowel disease, etc.)

4.0 Test Schedule

4.1 Test schedule for Relapsed / Refractory Chronic Lymphocytic Leukemia

Tests & Procedures	Active Monitoring Phase					
	Prior to Registration		Cycle 1 Day 1	Cycle 1 Day 15	Prior to subsequent Treatment (Cycles 2 – and 24 , Day 1)[14]	End of Treatment
	≤ 28 days	≤ 14 days				3-4 weeks from the last dose of treatment
Window			±4 days	±4 days	±4 days	±4 days
Complete medical history (including prior treatment regimen)	X					
Adverse event assessment	X		X		X	X
Physical exam, including weight and vital signs, and PS		X	X		X	X
Clinical Response assessment (Tumor measurement by physical exam)[1,2]		X			X	X
CT scans (Chest, Abdomen, Pelvis)[3]	X					X
EKG/ECHO[4]	X					
CBC with differential[5]		X	X	X	X	X
Chemistry group (SGOT [AST], SGPT [ALT], serum creatinine, direct bilirubin[13] and total bilirubin, LDH, uric acid, phosphorus, alkaline phosphate, sodium potassium,)[5]		X	X	X	X	X
Quantitative Immunoglobulins[6]	X				X	X
Minimal residual disease assessment[7]	X				X	X[15]

Flow Cytometry-CLL Panel[8]	X					
Bone marrow biopsy and/or aspirate[9]	X				X	X
CLL FISH Panel[10]	X					
B2M, Zap 70, CD38, IgHV[11]	X					
Urine/blood Pregnancy test [13]		X				
Hepatitis B (HBV) serology[16]	X					
HBV DNA testing[17]	X		X[17]		X[17]	X[17]
Dara and Ibrutinib[18]			X	X	X	

1. The physical exam should measure the spleen and liver, noting the maximal distance below the respective costal margins and should record the bi- dimensional diameter of the largest palpable node in each area of involvement including the following sites: left neck (sub-mandibular, cervical, supra-clavicular), right neck (sub-mandibular, cervical, supra-clavicular), left axillary, right axillary, left groin (inguinal, femoral) and right groin (inguinal, femoral).
2. Clinical response assessment: will be done per IWCLL criteria starting with evaluation of disease state at baseline and then at the end of Cycle 1 and every 3 cycles during combination treatment and at the end of treatment.
3. CT scans should be done as clinically indicated for the management of the patient and in accordance with the IWCLL guidelines. CT scans may be done with patient's primary physician (if outside Mayo Clinic), results of these will be entered in the source document.
4. EKG or ECHO only if clinically indicated.
5. Hematology (CBC) / Serum Chemistry: During cycle 1 (Day 15) will be done at the treating physician discretion based on patient's clinical needs and/or can be done based on risk for TLS or for conduct of correlative studies. Monitoring for TLS is considered standard of care. In subsequent cycles CBC/chemistry will be done prior to beginning of each cycle as standard of care and additional testing will only be done as clinically indicated to be determined by treating physician. Laboratory workup may be done with patient's primary physician (if outside Mayo Clinic), results of these will be entered in the source document.
6. Quantitative immunoglobulin will be done at baseline and thereafter can be done every 3 cycles, and at the end of treatment at the discretion of the treating physician and as per standard clinical practice.
7. Minimal residual disease: MRD assessment will be done at baseline, during the treatment phase and then during end of treatment. The MRD will be done on peripheral blood and / or bone marrow aspirate using flow cytometry standardized Mayo Clinic panel. In general bone marrow aspirate evaluation will only be required when the peripheral blood is recorded at least twice (at two separate evaluations 3 months apart) to be negative. If blood is positive for MRD assessment then bone marrow aspirate evaluation for the MRD will not be needed and can be deferred. **MRD assessment in the Blood: (a) Baseline:** all patients will have MRD assessed in the peripheral blood prior to initiating the study. **(b) During treatment phase:** all patients will have MRD assessed in the peripheral blood every 3 cycles, with the first assessment occurring at the end of Cycle 4. **(c) During end of treatment:** all patients will have MRD assessed ≤ 3-4 weeks of completion of the last treatment cycles **MRD assessment in the Bone marrow aspirate:** The schedule of assessment of the bone marrow aspirate for MRD will be different and dependent upon the results of the MRD status in the blood. **(a) Baseline:** If the peripheral blood MRD results are positive then a BM aspirate assessment for MRD will not be needed. If the peripheral blood MRD results are negative then a BM aspirate assessment for MRD will be needed. (b) **During the treatment phase:** The MRD assessment of the Bone marrow aspirate will only be required once the peripheral blood MRD is recorded to be negative for at least 2 evaluations that are separated at least 3 months apart. If the blood evaluation demonstrates positivity for MRD then Bone marrow aspirate evaluation will not be required and can be deferred until the peripheral blood is noted to be negative x 2. **(c) During the end of treatment:** The MRD assessment of the Bone marrow aspirate will only be required if the post treatment peripheral blood assessment (i.e., that done ≤ 4 weeks of the last treatment dose) was noted to be negative. If the post treatment blood evaluation was noted to be positive then no bone marrow aspirate evaluation is required. It is possible though unlikely that during end of treatment, the peripheral blood may convert to negative. If this is observed that a bone marrow aspirate for MRD will be done only is 2 consecutive blood MRD assessments are recorded to be negative. **Note:** Bone marrow aspirate done solely for MRD will be considered research, however if the procedure is done to assess response to therapy (such as to document complete remission as part of clinical care as required by the IWCLL guidelines) then it will be

considered standard of care. See detailed section on the MRD (see Section 11.3).

8. Flow cytometry-CLL Panel: The objective of this is to confirm diagnosis as per standard of care (pretreatment). Patients who have a flow cytometry done at any time prior to starting the clinical trial which validates the diagnosis of B-CLL will not be required to have it repeated.
9. **Bone marrow biopsy/aspirate:** At baseline documentation of bone marrow assessment (aspirate and biopsy) will be required to determine the extent of marrow involvement. This is standard of care as per the IWCLL guidelines to accurately assess response to treatment. During study treatment and at the end of treatment, a repeat bone marrow biopsy will only be required to establish the response of complete remission as recommended by the IWCLL guidelines and this will be at the discretion of the treating physician who will determine the appropriate timing based on clinical response assessment (this is consistent with the IWCLL guidelines and is standard of care to). Bone marrow aspirate will be done for assessment of MRD and the timing of this will be followed as noted in detail in foot note 8.
10. FISH (*florescent in situ hybridization*) in blood or bone marrow (if no CLL cells in the blood): May be performed any time prior to initiation of therapy. If already done previously, the results will be obtained and recorded, repeat testing will not be needed unless clinically indicated and at the discretion of the treating physician. The FISH panel will include the standard CLL related genomic aberrations including del 17p, del 11q, del 13q, +12.
11. These tests may be performed any time prior to initiation of therapy. If already done previously (prior to initial induction therapy), the results will be obtained and recorded, repeat testing will not be needed unless clinically indicated and at the discretion of the treating physician.
12. Only for patients with Gilbert's syndrome and the total bilirubin >1.5 mg/dL.
13. For women of childbearing potential only. Must be done ≤ 14 days prior to registration. NOTE: If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
14. After Cycle 7, patients may return every 3 cycles at PI's discretion. Daratumumab subjects will need to return every cycle to get their dara injections.
15. Not required for patients ending treatment due to progressive disease.
16. All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at screening.
17. Every 12 weeks during study treatment, at the end of treatment visit, every 12 weeks up to 6 months after the last dose of study treatment. (NOTE: **ONLY** for subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at screening by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. Where required by local law, the results of HBV testing may be reported to the local health authorities.
18. Please refer to dosing table in section 7.2

R Research funded.

4.2 Survival Follow-up

	Survival Follow-up				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	Second Primary Malignancy
Survival Follow-up	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.

5.0 Grouping Factor:

5.1 Prior ibrutinib Use

- Previously received BTK inhibitor (Cohort 1) vs.
- BTK inhibitor naïve (Cohort 2)

6.0 Registration Procedures

6.1 Registration (Step 1):

6.11 Registering a patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office ([redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic Florida, under the supervision of a medical oncologist.

6.5 Treatment start

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.6 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.7 Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.8 Study drug

Study drug is available on site.

6.9a Blood draw kits

Blood draw kit is available on site.

6.9b Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

Overall Treatment Schedule: Overall treatment schedule (for both Cohorts) include patient receiving Daratumumab SC alone in C1 followed by addition of ibrutinib to daratumumab starting C2 (and onwards). For patients already on BTK inhibitor who are entering Cohort 1, BTK inhibitor will be stopped (see also note below for more detailed clarification) for at least 1 week prior (washout period) to initiating C1 (daratumumab alone). Once these patients have completed the C1, ibrutinib will be started as part of the combination regimen starting C2.

Note: Treatment can be initiated/continued independent of disease activity during the washout period i.e. if the disease is progressing while on Daratumumab alone. Also, given the clinical course of patients resistant to BTK inhibitor can be rapid, if in treating physician opinion stopping the BTK inhibitor can impact adversely patient's disease course than patient may continue the BTK inhibitor up until starting study treatment and then Ibrutinib plus daratumumab will be started in lieu of BTK inhibitor. In such a case, Cycle 1 will have both ibrutinib + Daratumumab. The schedule and dosing of Daratumumab will follow the same design as noted in 7.2. This, however must be approved by the Principal Investigator [redacted] of the study protocol.

Duration of treatment: Patient will be treated as indicated in section 7.0, unless they have progressive disease or unacceptable toxicity. Patients who complete treatment per protocol will continue to the end of treatment visit and then, survival follow-up.

DARATUMUMAB

7.1 Daratumumab Subcutaneous schedule (Cycle length = 28 days, ±4 days):

- **Cycle 1 & 2:** Daratumumab SC alone (1800 mg dose) weekly (Days 1, 8, 15, 22 of each cycle).
- **Cycle 3-6:** Daratumumab SC (1800 mg dose) will be given every 2 weeks (Days 1, 15 of each cycle).
- **Cycle 7 onwards:** Daratumumab SC (1800 mg dose) will be given every 4 weeks (Day 1 of each cycle).

7.2 Daratumumab Preparation

Daratumumab-SC will be provided as a fixed-dose (1800 mg) which is a combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.. Detailed instructions for preparation and administration of daratumumab will be supplied in the package insert.

Agent	Dose	Route	Days
CYCLE 1			
Daratumumab	1800 mg dose	SC	weekly (Days 1, 8, 15, 22)
CYCLE 2			
Daratumumab	1800 mg dose	SC	weekly (Days 1, 8, 15, 22)
Ibrutinib	420 mg QD	Oral	1-28
CYCLE 3-6			
Daratumumab	1800 mg dose	SC	every 2 weeks (Days 1, 15)
Ibrutinib	420 mg QD	Oral	1-28

CYCLE 7-and 24			
Daratumumab	1800 mg dose	SC	every 4 weeks (Day 1)
Ibrutinib	420 mg QD	Oral	1-28
Cycle length = 28 days (±4 days) # For patients in Cohort 1, ibrutinib will be stopped for at least 1 week prior (washout period) prior to initiating C1 (daratumumab alone). Subjects treatment until PD			

7.3 Dosing schedule and duration:

Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3 – 5 minutes in the abdominal subcutaneous tissues in the left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. Reasons for continued observation on subsequent daratumumab injection may include but are not limited to the following: subjects with a higher risk of respiratory complications (e.g., subjects with mild asthma or subjects with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history), subjects with IRR with the first injection of study drug, subject with decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study..

Dara-SC Dosing:

Dara-SC dosing schedule (whether in combination or monotherapy)

Weeks	**Schedule**
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9 to 24[a]	Every two weeks (total of 8 doses)
Week 25 and onward until PD[b]	Every four weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9

[b] First dose of the every-4-week dosing schedule is given at Week 25

All daratumumab administrations will be in an outpatient setting. Subjects will receive pre injection medications and post-injection medication as outlined in Section 7.5.

Vital signs should be monitored extensively on Cycle 1 Day 1 before, and after the first administration of daratumumab. For all other administrations, vital signs should be measured before the start of injection and at the end of the injection. If the subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE.

If an IRR develops, then the injection should be temporarily interrupted or slowed down. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, dara-SC should be discontinued, and no additional dara-SC should be administered to the participant. See Section 7.6 for instructions on the management of IRR and local ISRs.

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7.5 Guidelines for Prevention of Infusion Reactions

All participants will receive the following medications 1 to 3 hours prior to each study drug administration:

Pre-Dose Medication:

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine: diphenhydramine 25-50 mg IV or PO or equivalent. Avoid IV use of promethazine.
    - After Cycle 6, if a participant has not developed an infusion-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.
- Corticosteroids (Long-acting or intermediate-acting):
    - *Monotherapy:* Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg or equivalent).
    - If the subject does not experience a major systemic administration-related reaction after the first 3 doses, consider discontinuing the administration of corticosteroids (excluding any background regimen-specific corticosteroid).

Pre-dose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional in Cycle 1 Day 1 and can be administered up to 24 hours before infusion as per investigator discretion.

If necessary, all PO pre-infusion medications may be administered out of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

Post-infusion Medication -

Administer post-infusion medication to reduce the risk of delayed infusion related reactions as follows:

- *Monotherapy studies:*
    - In an effort to prevent delayed infusion-related reactions, all participants will receive long- or intermediate-acting corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following all daratumumab infusions (beginning the day after the infusion).
    - In the absence of infusion related AEs after the first 3 infusions, post-infusion corticosteroids should be administered per investigator discretion.
- *Combination therapy:*
    - Consider administering low-dose methylprednisolone (≤ 20 mg) or equivalent, the day after the infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone) is administered the day after the infusion, additional post-infusion steroids are not required, but may be considered by the investigator.
- For participants with a higher risk of respiratory complications (e.g. participants with mild asthma or participants with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history) the following post-infusion medication should be considered:
    - Antihistamine (diphenhydramine or equivalent)
    - Leukotriene inhibitor (montelukast or equivalent)
    - Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
    - Control medications for lung disease (e.g. inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists with asthma; long-acting

bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for participants with COPD)

- In addition, these at-risk participants may be hospitalized for monitoring for up to 2 nights after daratumumab administration. If participants are hospitalized, then an improvement in FEV1 should be performed and documented prior to discharge. If these participants are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If the participant has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after participants are released from the hospital/clinic. If an at-risk participant experiences no major infusion-related reactions, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.
- Any post-infusion medication will be administered after the infusion has completed.

7.6 Management of Infusion-related Reactions and Local Injection-site Reactions of Daratumumab-SC

Infusion-related Reactions (IRRs):

Infusion-related reactions (IRRs) are systemic reactions related to daratumumab administration. Participants should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, and a defibrillator) must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time. If an infusion-related reaction develops during Dara SC administration, then the administration should be temporarily interrupted. Subjects who experience adverse events during daratumumab SC administration must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply: (**a**) Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. (**b**) In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject.

7.7 Administration-Related Events of Grade 1 or Grade 2:

If the investigator assesses a Grade 1-2 IRR to be related to the daratumumab administration, then the Dara-SC administration should be interrupted. When the subject's condition is stable, Dara-SC administration may be restarted at the investigator's discretion. Refer to the USPI for further details regarding continuation of Dara-SC administration.. If the subject experiences a Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve ≤ 6 hours from the onset, then the subject must be permanently discontinued from Dara-SC treatment..

7.8a Administration-Related Reactions of Grade 3 or Higher:

For infusion-related adverse events that are Grade 4, the Dara-SC administration must be stopped and treatment with daratumumab will be permanently discontinued for that subject. For infusion-

related adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the Dara-SC administration must be stopped, and the subject must be observed carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the Dara-SC administration may be restarted at the investigator's discretion. Refer to the USPI for further details regarding continuation of Dara-SC administration.. If the intensity of the adverse event returns to Grade 3 after restart of the Dara-SC administration, then the participant must be permanently discontinued from Dara-SC treatment.. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject.

7.8b Recurrent Administration-related Reactions:

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent Dara-SC administration, the participant must be permanently discontinued from Dara-SC treatment.

7.8c Injection Site Reactions:
In clinical studies, SC administration of daratumumab was associated with local injection site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection-site reactions should be managed per institutional standards.

7.9a Ibrutinib oral treatment

- Treatment schedule: Ibrutinib will be started on **Day 1 of Cycle 2**.
- Dose: 420mg PO QD.
- Four weeks will constitute 1 treatment cycle

Treatment will be discontinued if (**a**) patients develop unacceptable side effects, (**b**) if patients develop disease progression while on treatment (recommended to be confirmed on two independent occasions at least 2 week apart and consistent with the IWCLL guidelines, see Section 11.23), (**c**) if the patient is removed from the study by the treating physician due to concern of overall wellbeing and in the best interest of the patient, (**d**) patients who have stable disease (a response <PR) at the end of cycle 7and are tolerating treatment well may be continued on ibrutinib/daratumumab at the discretion of the treating physician if deemed beneficial for the patient.

7.9b Response Assessment

- Patients will be evaluated for response after first 4 weeks (or later if completion of cycle 1 is delayed) of single agent daratumumab (completed Cycle 1) and thereafter every 2 treatment cycles of combination therapy.
- MRD status will be recorded every 3 cycles (as discussed previously in Section 4.0, see detailed MRD section 11.3).

7.9c Treatment by Local Medical Doctor (LMD)**:**

Patient will need to return to Mayo Clinic for every treatment cycle for daratumumab therapy. If patient stop treatment and is on follow-up this can be done in conjunction with patients' primary medical doctor.

7.9d Return to treating institution

For this protocol, the patient must return to the consenting institution for evaluation and drug

administration at least every 28 days during treatment for the first 6 cycles. After the first 7 cycles, patients may elect to return every 3 cycles per treating MD's discretion as long as there are no active ongoing toxicities that have not returned to baseline. Clinical evaluation and blood tests can be obtained per test schedule and mailed/faxed to the consenting institution and patient can return at least every 3 cycles for follow up to the consenting institution. The cycle length will remain at 28 days and data collection forms will be due at the end of each cycle. Adverse events and adherence to study treatment will be collected at the end of each cycle by telephone call for cycles where the patient does not return to the clinic. The patient should retain the pill diaries and medication bottles (even if unopened or empty) along with any unused pills for each cycle and bring them to their next visit so that dosing can be recorded on the evaluation/treatment forms for each cycle.

8.0 Dosage Modification Based on Adverse Events

An evaluation of potential treatment-induced toxicity in patients with CLL can be difficult. Moreover, some conventional criteria are not applicable to studies involving patients with hematologic malignancies in general and CLL in particular. An example is hematologic toxicity: patients with advanced CLL may exhibit deterioration in blood counts which may represent either treatment-related toxicity or progressive bone marrow failure from disease itself.
Toxicity grades below are described using the NCI Common Terminology Criteria for Averse Events (CTCAE) version 5.0.

8.1 Dose Levels (Based on Adverse Events in Tables 8.*2* and 8.3)

Dose Level	**Ibrutinib**
1*	420 mg daily
-1	280 mg daily
-2	140 mg daily

*Dose level 1 refers to the starting dose.

NOTE: If either of Daratumumab or Ibrutinib is discontinued, the patient can continue on the other drugs, unless specified otherwise in the dose modification tables. If both are discontinued, the patient will go to survival follow-up (Section 4.2). No dose modifications are allowed for daratumumab

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 5.0* unless otherwise specified*** ← ←
*Located at [redacted]

8.2 Dose Modifications

Any dose/dosage adjustment must be overseen by medically qualified study site personnel (principal or subinvestigatorsub-investigator) unless an immediate safety risk appears to be present.

Daratumumab Subcutaneous
Individual dose modification of Dara SC is not permitted. For managing Dara SC-related toxicities, either a dose interruption or a dose delay is recommended. ONLY if any of the

following criteria are met and the event cannot be ascribed to lenalidomide, bortezomib, dexamethasone, carfilzomib (if applicable) or underlying MM, the Dara SC administration must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 hematologic toxicity (except for Grade 4 lymphopenia)
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Grade 4 Neutropenia with any grade infection
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of Dara SC
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of Dara SC

Administration of Dara SC may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.
If Dara SC administration does not commence within the prespecified window (Table 8.3) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 8.3 Dara SC-related Toxicity Management (28-day Cycles)

Cycles	Frequency	Missed Dose	Dosing Resumption
1-2	Weekly	>3 days	Next planned weekly dosing date
3-6	Every 2 weeks	>7 days	Next planned every 2-week dosing date
7-24	Every 4 weeks	> 14 days	Next planned every 4-week dosing date

Abbreviation: SC=subcutaneous; TE=transplant eligible.

If a dose is delayed, then the dates of all subsequent doses must be adjusted. Any AE deemed to be related to Dara SC that requires a dose hold of more than 28 days will be evaluated by the investigator to determine if further dosing will be safe and efficacious.

Subjects who miss ≥3 consecutive planned doses of daratumumab for reasons other than toxicity will be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

Ibrutinib

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Blood and lymphatic system disorders	≥ Grade 3 Febrile neutropenia	Ibrutinib	Hold (day 1) or omit (days 2-28) Ibrutinib until fever resolves and ANC ≥ 1000/μL, then resume Ibrutinib at the previous dose.
Gastrointestinal disorders	≥ Grade 3 Nausea (if persistent despite optimal antiemetic therapy) ≥ Grade 3 Vomiting (if persistent despite optimal antiemetic therapy) ≥ Grade 3 Diarrhea (if persistent despite optimal anti-diarrheal therapy)	Ibrutinib	Hold (day 1) or omit (days 2-28) Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose for first occurrence. Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤ 1 or baseline. If AE occurs at lowest dose discontinue treatment.
Investigations	Neutrophil count decreased Grade 4 lasting > 7 days	Ibrutinib	Hold (day 1) or omit (days 2-28) Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose for first occurrence. Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤ 1 or baseline. If AE occurs at lowest dose discontinue treatment. NOTE: Baseline cytopenia: In patients whose baseline (i.e., prior to starting protocol therapy) ANC is 1000/μL, the above Ibrutinib dose modifications, if required, would not be applied until Cycle 3.
Other non-hematologic	Any other Grade 4 AE or any unmanageable Grade 3 AE	Ibrutinib	Hold (day 1) or omit (days 2-28) Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose for first occurrence. Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤ 1 or baseline. If AE occurs at lowest dose discontinue treatment.

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
  Discontinue = The specified drug(s) are totally stopped.

Dose delay: Ibrutinib may be held for toxicity considerations for a maximum of 28 consecutive days. Study medication should be discontinued permanently in the event of a toxicity lasting more than 28 days. If Ibrutinib is interrupted for a reason other than toxicity (e.g. unrelated illness) it must be restarted ≤ 60 days. If interrupted for more than 60 days, study medication should be discontinued permanently and go to survival follow-up.

- Dose re-escalation: Patients who require a dose reduction during a given cycle will remain at that dose for at least 2 additional cycles. **At the investigator discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to this reduction**. This is particularly reasonable based upon the long-term safety data now available in ibrutinib treated patients that show that most of the hematological or non-hematological AEs either decreased or remained stable (see investigator brochure section 5.3).
- If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.
- Dose modifications are for adverse events attributed to study treatment only. Dose modifications are not required for adverse events if they are deemed unrelated to study treatment.
- Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO) should be considered. Consider Pneumocystis pneumonia or viral pneumonitis

8.3 Dose Modification for Hematological Toxicities (Platelet and Hemoglobin only)

Note: hematological toxicity is not based on CTCAE 5.0 except neutrophil, but based on CLL specific hematological toxicity (this table and Appendix V).

Dose modification guidelines for drug-related hematological (hemoglobin and platelets) adverse events						
Toxicity	**Grade [1, 2]**	**Decrease from pretreatment**	**Hold Treatment (Y/N)**	**Timing for restarting treatment**	**Dose/Schedule for restarting treatment**	**Discontinue Subject (after consultation with PI)**
CLL/NHL specific Hematological Toxicity (Appendix V)	1 2	11-24% decrease in HGB or PLT 25-49% decrease in HGB or PLT	No	N/A	N/A	N/A
	3	50-74% decrease in HGB or PLT	Yes	Toxicity resolves to Grade 0-1 or baseline	**Hold** (day 1) or **omit** (days 2-28) Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose for first occurrence. Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤ 1 or baseline. If AE occurs at lowest dose, discontinue treatment.	Toxicity does not resolve within 8 weeks of last treatment ***Permanent discontinuation*** *should be considered for any severe or life-threatening event.* Go to event monitoring if ≥ 1 cycles of therapy was given.
	4	≥75% decrease in HGB or PLT	Yes	Toxicity resolves to Grade 0-1 or baseline		

[1] If, at any level of decrease the platelet count is < 20,000/μL, this will be considered grade 4, unless the initial platelet count was ≤ 20,000 μL in which case the patient is inevaluable for toxicity referable to platelet counts.

[2] If, at any level of decrease from the baseline value the platelet and/or hemoglobin counts are within normal limits, this will be considered a grade 0.

9.0 Ancillary Treatment/Supportive Care

9.1 Growth factors

Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines. They should be utilized as clinically warranted and following institutional policies and recommendations. Growth factors can be used during the treatment cycle as clinically indicated. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology. Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence- Based, Clinical Practice Guidelines.

9.2 Supportive care:

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate. (A) Any blood transfusions administered must be irradiated blood products to reduce risk of transfusion- mediated graft versus host disease in CLL patients receiving T-cell suppressive therapy. Leukocyte reduction of all blood products for patients on protocol is also required. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records. (B) Antiemetics may be used at the discretion of the attending physician. (C) Prophylactic antibiotics and antifungals may be prescribed at the treating physicians' discretion and as clinically indicated, or as per the institutional guidelines. (D) Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent. (E) Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. (F) Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

9.3 Tumor Lysis Syndrome (TLS) prophylaxis and treatment:

Patients who are at risk of TLS as determined by the treating physician, may receive Allopurinol 300 mg/day (or an equivalent standard agent for prevention of hyperuricemia) orally for the first two weeks of the first cycle of protocol therapy. Allopurinol may be continued after the first two weeks at the investigator's discretion and as clinically indicated. Subjects should be observed closely for signs and symptoms of TLS during the initial cycle of therapy. Subjects should be encouraged to drink an abundant amount of fluid prior to treatment. Subjects should maintain adequate hydration and urine output.

9.4 Treatment related lymphocytosis:

Lymphocytosis has been reported with ibrutinib, however since in this clinical trial patient will have received daratumumab prior to initiating the ibrutinib it is not known if this lymphocytosis will still happen upon treatment with ibrutinib. Patients who develop this reaction will be monitored as per standard clinical protocol without specific intervention unless other specific symptoms / signs of disease progression is noted (such as increase in lymph node size that is progressive and persist beyond 3 months of therapy, worsening of cytopenia from the time of initiation of therapy that is considered to be due to progressive disease and is consistent with the IWCLL guidelines requiring therapeutic intervention, development of B symptoms persisting for more than 2 months while on therapy or other factors such as organomegaly demonstrating disease progression).

9.5 Medications to be used with caution: (a) CYP3A/CYP3A4 - Inhibitors//Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate

CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and $AUC_{0\text{-last}}$, of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing ibrutinib dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A. Co-administration of ibrutinib with strong CYP3A inducers, rifampin, in healthy subjects decreases ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction. A comprehensive list of inhibitors, inducers, and substrates may be found at [redacted]. This website is continually revised and should be checked frequently for updates. (b) Drugs that may have their plasma concentrations altered by ibrutinib: *In vitro* studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 μg/mL). Ibrutinib is not expected to have systemic drug- drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, co-administration of narrow therapeutic index P-gp substrates (e.g., digoxin) with ibrutinib may increase their blood concentration and should be used with caution and monitored closely for toxicity. (c) QT prolonging agents: Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered. (d) Antiplatelet agents and anticoagulants: Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

9.6 Prohibited concomitant medications:

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment. Corticosteroids for the treatment of the underlying disease (CLL) is prohibited. However, corticosteroids as pre-medication (and management of daratumumab related side effect) are allowed.

9.7a Management of Hepatitis B Virus Reactivation

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

For subjects who develop HBV reactivation while on study treatment, study treatment should be suspended and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of study treatment in patients whose HBV reactivation is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

9.7b Prophylaxis for Herpes Zoster Reactivation:

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase, as per institutional guidelines. Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting study treatment and continue for 3 months following study treatment. Acceptable antiviral therapy includes acyclovir (eg 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famcyclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug.

9.8 Guidelines for ibrutinib management with surgeries or procedure:

Ibrutinib may increase the risk of bleeding with invasive procedures or surgery. Consider the benefit- risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding. The following guidance may be applied to the use of ibrutinib in the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib: (a) Minor surgical procedures - For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for 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. (b) Major surgical procedures - For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes. (c) Emergency Procedures - For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting [redacted]	Mayo Sites – attach to MCCC Electronic SAE Reporting Form [redacted] Will automatically be sent to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted] AND attach MedWatch 3500A: [redacted]	Will automatically be sent to [redacted]

Definitions
Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting

Events reported to sponsor within 24 hours, 3 days or 7 days of study team becoming aware of the event.

Routine Reporting

Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0 A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: [redacted]

a. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE is clearly NOT related to the agent(s)/procedure.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the <u>SAME</u> (Combination) Arm**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

[redacted]

10.32 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported in an expedited manner[1]
Investigations	Neutrophil count decreased	≤Grade 3
	Platelet count decreased	≤Grade 3
	White blood count decreased	≤Grade 3
	Lymphocyte count decreased	≤Grade 3
Blood and lymphatic system disorders	Anemia	≤Grade 3

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND Agents

10.41 **Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention**[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour
3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] investigational agents or commercial/investigational agents on the same arm.

All SAE notifications must be sent to Janssen via fax.

Janssen Drug Safety Contact Information: US Fax: [redacted]

For commercial agents (for commercial agent(s) on its own arm):
Attach the MedWatch 3500A form to the Mayo Expedited Event Report form [redacted]

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, 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
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form [redacted] o submit to

[redacted] The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to disease progression should be reported as **Grade 5 "Disease Progression"** under the system organ class (SOC) of the **General disorders and administration site conditions**. Evidence that the death was a manifestation of underlying disease (e.g.), radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form:

[redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy loss"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.
A neonatal death should be reported expeditiously as **Grade 4 "Neonatal loss"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 **Baseline and Adverse Events Evaluations**

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Platelet count decreased*	X	X
Blood and lymphatic system disorders	Anemia*	X	X
Cardiac disorders	Atrial Fibrillation	X	X
General disorders and administrative site conditions	Fatigue	X	X
	General disorders and administrative site conditions – other, hemorrhage[1]	X	X
Injury, poisoning and procedural complications	Infusion related reaction	X	
	Bruising	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X
Musculoskeletal and connective tissue disorders	Arthralgia	X	X
Vascular disorders	Hypertension	X	X

* Grading will be performed by the study statisticians at the time of analysis based on the CLL toxicity grading scale for blood counts in Appendix V. CTCAE grades for platelet count decreased and anemia will also be recorded for reporting purposes.

[1]Includes hemorrhages of all systems.

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Janssen Scientific Affairs, LLC Additional Event Reporting Instructions

10.81 Overview

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

10.82 Management of Safety Data

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

For the purposes of this study, the J&J medicinal product is: DARZALEX®™ (daratumumab)

FASPRO™ (daratumumab-SC)

For the purposes of this study, the J&J medicinal product is:

IMBRUVICA® (Ibrutinib)

10.83 Definitions

- Adverse Events (AE). See section 10.0 for definition.
- Adverse Events of Special Interest. See section 10.0 for definition. These Daratumumab adverse events are actively monitored by J&J:
    - Infusion reactions ≥ grade 3
    - Infections ≥ grade 4
    - Cytopenias ≥ grade 4
    - HBV Reaction
    - Other malignancies
    - ocular toxicity
- These Ibrutinib adverse events are actively monitored by J&J:

    Major Hemorrhage

    Major hemorrhage is defined as:

    - Any treatment-emergent hemorrhagic AE of Grade 3 or higher.*
    - Any treatment-emergent SAE of bleeding of any grade
    - Any treatment-emergent CNS hemorrhage/hematoma of any grade

    **All hemorrhagic AEs requiring a transfusion of red blood cells should be reported as a Grade 3*

        - *or higher AEs per NCI-CTCAE.*

Specific AEs or groups of AEs will be followed as part of standard safety monitoring activities by the sponsor. These events should be reported to the sponsor within 3 business days of awareness irrespective of seriousness (ie, serious and nonserious AEs)

following the procedure described above for SAEs and will require enhanced data collection.

These adverse events are:

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

- Individual Case Safety Report (ICSR). A valid ICSR must contain the 4 minimum criteria required to meet regulatory reporting requirements:
  - An identifiable subject (but not disclosing person information such as the subject's name, initials or address)
  - An identifiable reporter (investigational site)
  - A J&J medicinal product
  - An adverse event, outcome, or certain special situations

10.84 Minimum information required is:

- Suspected J&J 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)
- J&J protocol ID
-

10.85 Product Quality Complaint (PQC)

A PQC may have an impact on the safety and efficacy of a Company product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the Company, and are mandated by regulatory agencies worldwide. The Company has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. The Institution agrees that Lot and/or Batch #s shall be collected, when available, for all PQC reports, including reports of failure of expected pharmacological action (i.e., lack of effect) of a Janssen Medicinal Product. A sample of the suspected product shall be maintained for further investigation if requested by the Company.

Any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or delivery system is considered a PQC. Not all PQCs involve a patient.

Examples of PQC include but are not limited to:

- Mislabelling or misbranding
- Information concerning microbial contamination, including a suspected transmission of any infectious agent by a product
- Any significant chemical, physical, or other changes that indicate deterioration in the distributed product

- Any foreign matter reported to be in the product
- Mixed product, e.g., two drugs are mixed-up in the packaging process
- Incorrect tablet sequence (e.g., oral contraceptive tablets)
- Insecure closure with serious medical consequences, e.g., cytotoxics, child-resistant containers, potent drugs
- Suspected counterfeit or tampered product

- Adverse Device Effects including any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation, installation, operation, or any malfunction of a medical device or combination product. This also includes any event that is a result of a use error or intentional misuse and dosing device malfunctions (e.g., auto-injector button not working, needle detaching from syringe, etc.)
- Physical defect (e.g., abnormal product odour, broken or crushed tablets, etc.)

10.86 Unlisted (Unexpected) Adverse event/Reference Safety Information

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

[redacted]

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

For Imbruvica (Ibrutinib):
[redacted]

Special Reporting Situations

The following special situations must be reported expeditiously (reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report) to Janssen with or without an associated serious adverse event (SAE):

- Drug exposure during pregnancy (maternal or paternal)
- Suspected of any infectious agent via administration of a Janssen Product(s) under study.

The following special situations must be reported to Janssen expeditiously (reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report) (when associated with a serious adverse event (SAE):

- Overdose of a J&J medicinal product
- Exposure to a J&J medicinal product from breastfeeding
- Suspected abuse/misuse of a J&J medicinal product
- Inadvertent or accidental exposure to Janssen Product(s) under study
- Any failure of expected pharmacological action (i.e., lack of effect) of Janssen Product(s) under study

- Medication error (includes potential, intercepted or actual) involving a Janssen product (with or without patient exposure to the Janssen Product(s) under study, e.g., name confusion)
- Unexpected therapeutic or clinical benefit from use of Janssen Product(s) under study

If no SAE is associated with these Special Situations, the special situation should be reported in the annual non-serious adverse event listing provided to Janssen.

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

1. 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 J&J ≤ 24 hours of becoming aware of the event.

2. Pregnancy: All initial reports of pregnancy must be reported to J&J by the PRINCIPAL INVESTIGATOR ≤ 24 hours of becoming aware of the event using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment. Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR ≤ 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner. **Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.**

10.87 Maintenance of Safety information

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

10.88 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinial Products to J&J

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a J&J medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a J&J medicinal product.
All (serious and non-serious) adverse events reported for a J&J medicinal product should be followed up in accordance with clinical practice.

10.89a SAEs, AEs of Special Interest and Special Reporting Situations

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

1. The event resolves
2. The event stabilizes
3. The event returns to baseline, if a baseline value/status is available
4. The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
5. 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)
6. The PRINCIPAL INVESTIGATOR will transmit all SAEs, AESIs and special situations following exposure to a Janssen product under study in a form provided by J&J in accordance with Section 16, Transmission Methods, in English within 3 business days of becoming aware of the event(s).
7. All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, within 3 business daysbecoming aware, to J&J using the J&J Serious Adverse Event Report
8. All available clinical information relevant to the evaluation of a related SAE, AESI, serious ADR or special situation is required.
9. The PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.
10. Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the J&J Product under study, are to be provided to J&J using a transmission method in Section 10.0 within 24 hours of such report or correspondence being sent to applicable health authorities.

10.89b Non-Serious AEs

All non-serious adverse events should be reported to J&J according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

10.89c PQC Reporting

- A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and J&J, and are mandated by regulatory agencies worldwide. J&J has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.
- All initial PQCs involving a J&J medicinal product under study must be reported to J&J by the PRINCIPAL INVESTIGATOR within 3 business days after being made aware of the event. The Janssen contact will provide additional information/form to be completed.
- If the defect for a J&J medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to J&J according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by J&J.

10.89d <u>Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products</u>

For SAEs, special reporting situations and PQCs following exposure to a non-J&J medicinal product under study, the PRINCIPAL INVESTIGATOR 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.

10.89e Transmission Methods

The following methods are acceptable for transmission of safety information to J&J:

- Electronically via Janssen SECURE Email service to [redacted] (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report to [redacted]
  - Telephone (if fax is non-functional). Please contact the J&J Trial Manager, [redacted] at [redacted]

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or in vitro testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

11.0 Treatment Evaluation/Measurement of Effect

Formal response evaluation should occur every 3 treatment cycles as per standard clinical practice. However, first response evaluation will occur at the end of 4 treatments of daratumumab (completion of cycle 1).This will allow correlation of the clinical activity of the single agent daratumumab with the correlative studies planned. Thereafter the clinical response will be evaluated after completion of every 3 cycles during combination therapy. Objective status should be classified as PD vs. Not PD on cycles when a formal response evaluation does not occur.

Patients will also be assessed as MRD^{+} vs MRD^{-} (See section 11.4). Prior to the response evaluation (after 3 cycles of the combination), baseline on study measurements will be used to determine disease progression (e.g. not cycle by cycle comparisons). Once patients undergo formal response evaluation, the nadir value at either baseline or time of response evaluation will be used for evaluating future disease progression. In addition to a baseline scan, confirmatory scans should also be obtained as needed to document objective response at sites of non-palpable lymphadenopathy or organomegaly as indicated in Section 4 or as needed clinically.

NOTE: Information from CT scans is not considered in the standard classification of response.

Note: Treatment-related lymphocytosis is a known phenomenon with ibrutinib and is not representative of PD. As noted in the Leukemia Research Foundation Workshop report[62]: "Patients with lymphocytosis and no other evidence of PD should continue therapy until they develop other definitive signs of PD (i.e., at least one feature suggesting worsening of the CLL other than lymphocytosis (e.g., anemia, thrombocytopenia, lymphadenopathy, or hepatosplenomegaly) or the occurrence of another reason to discontinue therapy."

PD: "If PD is suspected, clinical examination, computed tomography, and peripheral blood counts should be obtained, and a bone marrow biopsy considered, to provide objective assessment of CLL status. Similarly, persistent lymphocytosis should not interfere with the time of designation of a PR, which should be based more on the other measurable aspects of the disease than on lymphocytosis."

11.1 Schedule of Evaluations:

(a) **Clinical Response:** Will be evaluated and documented at baseline. Clinical response will be recorded after 4 week of single agent therapy on daratumumab (completion of cycle 1). Thereafter clinical response will be evaluated and documented every 3 cycles of combination treatment. Best response will be documented at completion of 6 cycles of combination treatment. Clinical response will thereafter be determined every 3 treatment cycle until PD is determined or treatment is stopped. Patients will be classified as PD vs. Not PD on cycles when a formal response evaluation does not occur.

(b) **MRD status: We anticipate patient having a higher probability of achieving MRD.** Therefore information on MRD will be collected throughout the course of this clinical trial.

Note: Bone marrow aspirate done solely for MRD will be considered research. As outlined by the IWCLL guidelines a bone marrow biopsy / aspirate is required to document complete remission. Thus a bone marrow biopsy / aspirate relapse that is done as part of the clinical response to therapy (such as to document complete remission as part of clinical care as required by the IWCLL guidelines) will be considered standard of care. Additionally, if the bone marrow biopsy or aspirate is done as part of the clinical care of the patient (as determined by the treating physician) that procedure will be considered standard of care.

11.2 Definitions

The International Working Group criteria (IWCLL)[7] will be used to assess response to therapy.

11.21 **COMPLETE RESPONSE (CR)** requires all of the following for a period of at least 2 months:

11.211 Absence of lymphadenopathy (e.g. lymph nodes >1.5 cm) by physical examination.

11.212 No hepatomegaly or splenomegaly by physical examination.

11.213 Absence of constitutional symptoms.

11.214 CBC demonstrating:

- Neutrophils >1500/ul.
- Platelets >100,000/ul (untransfused).
- Hemoglobin >11.0 gm/dl (untransfused).
- Peripheral blood lymphocytes <4000/uL.

Note: Patients who fulfill all criteria for a CR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL will be classified as **CR with incomplete marrow recovery (CRi)** according to the international criteria (Hallek, 2008).

11.215 Bone marrow aspirate and biopsy should be performed **within two months** after documentation of clinical and laboratory evidence of a complete response to document that a **complete response (CR)** has been achieved as per standard practice based upon IWCLL. The marrow sample should ideally be at least normocellular with <30% of nucleated cells being lymphocytes. Samples are to be analyzed by a pathologist and the presence or absence of nodules noted. Repeat bone marrow aspirate and biopsy are not necessary to document sustained CR.

NOTE: Patients who fulfill all criteria for a CR but who have hypocellular marrow will be classified as a **CR with incomplete marrow recovery (CRi)**.

In a subset of patients who are otherwise in a complete response, bone marrow nodules can be identified histologically. In such cases, special stains will be performed to determine whether such nodules represent "regenerative nodules" or residual "clonal nodules". The presence of regenerative nodules is consistent with CR while the presence of residual clonal nodules will be classified as an **nPR (nodular PR)** which is a sub-classification of PR. Per the PR criteria, patients must fulfill one or more of the blood count parameters (Section 11.224, 11.225, 11.226) but are not required to meet all 3 of these conditions.

NOTE: In a patient who achieves clinical and laboratory evidence of a complete response, the objective status should be recorded as a CCR on the cycle where the formal response evaluation occurred until a bone marrow biopsy and aspirate have been performed. At that time, the objective status should be amended to classify the patient as a CR, CRi, or nPR **on the cycle where the formal response evaluation occurred**.

11.216 Patients who have clinical and laboratory evidence of CR but who have not yet had a bone marrow biopsy to distinguish between CR and nPR will be classified as having a **Complete Clinical Response (CCR)** until the marrow biopsy is obtained. Patients must meet all of the blood count parameters listed in section 11.214.

11.217 In some settings MRD assays may be considered as a surrogate of response as discussed in section 11.3. No other laboratory assays (e.g., quantitative immunoglobulins) will be used currently as an index for response but will be recorded for clinical correlations.

11.218 For patients whose only measurable disease at the time of enrollment is on CT scan (i.e. SLL with no palpable nodes), a CT scan showing absence of lymphadenopathy (e.g. lymph nodes >1.5 cm) is required before classifying patients a CR.

11.22 **PARTIAL RESPONSE (PR)** requires the patient exhibits at least two of the features in Sections 11.221, 11.222, and 11.223 below (if abnormal prior to therapy) as well as one or more of the remaining features (Sections 11.224, 11.225, 11.226) for at least 2 months. In addition to the parameters listed below, the presence or absence of constitutional symptoms will be recorded.

11.221 ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value. Note: This criteria will not be applicable if patients are experiencing ibrutinib associated lymphocytosis as noted above in section 11.0. (LRF workshop)[62]

11.222 ≥ 50% reduction in the sum of the products of the maximal perpendicular diameters of the largest measured node or nodal masses in the right and left cervical, axillary, and inguinal lymph node regions on physical examination.

11.223 ≥ 50% reduction in size of liver and/or spleen as measured by physical exam noting the maximal distance below the respective costal margins of palpable hepatosplenomegaly during rest.

11.224 Neutrophils >1500/ul or 50% improvement over baseline.

11.225 Platelets >100,000/ul or 50% increase over baseline.

11.226 Hemoglobin >11.0 gm/dl or 50% increase over baseline without transfusions.

11.227 For patients whose only measurable disease at the time of enrollment is on CT scan, a CT scan demonstrating > 50% reduction of target nodes enlarged at baseline is required before classifying patients a PR.

11.23 **PROGRESSION (PD):** Patients will continue to receive protocol therapy unless they have evidence of disease progression according to the IWCLL criteria[6] as evidenced by:

11.231 ≥ 50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive determinations 2 weeks apart (at least one node must be ≥2 cm) or the appearance of new palpable lymph nodes >1.5 cm not due to a tumor flare. Enlargements or the appearance of new nodes due to a tumor flare do NOT qualify as progression.

11.232 ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin on 2 consecutive determinations 2 weeks apart and with a minimum of a ≥ 2 cm increase in size from baseline; or appearance of hepatomegaly or splenomegaly which was not previously present at baseline and not due to a tumor flare.

11.233 Transformation to a more aggressive histology (e.g. Richter's transformation).

Note: If a patient develops DLBCL at any time, it will be considered disease progression. If the patient develops any other hematologic malignancy while on study, it will not be considered progressive disease.

11.234 ≥ 50% increase in the absolute number of circulating lymphocytes NOT due to infection or tumor flare (taking as reference for progressive disease the smallest absolute lymphocyte count recorded since the treatment started). The absolute lymphocyte count must be at least 5000/mm3 to qualify as disease progression.

11.235 In the absence of progression as defined by 1, 2, 3, or 4 above, the presence of a ≥ 2 g/dl decrease in HGB, or ≥ 50% decrease in platelet count, or absolute neutrophil count will NOT exclude a patient from continuing the study. Work-up of such decreases to exclude auto-immune hemolytic anemia, pure red cell aplasia, or idiopathic thrombocytopenic purpura (ITP) should be considered.

11.236 For patients who achieve a CR or nodular PR, progression will be defined as recurrence of circulating leukemia cell clone and an ALC >5000 or recurrence of adenopathy >1.5 cm not due to a tumor flare.

11.24 **STABLE DISEASE (SD):** Patients who do not meet criteria for CR, CRi, nPR, CCR, PR, or PD will be classified as having "stable disease".

11.25 **Not PD**: The patient was evaluated for progression only this cycle and a formal response evaluation did not occur. The patient did not meet the criteria for progression per section 11.23.
Note: Formal response evaluation should occur every 2 cycles during treatment, with the first response evaluation occurring at the end of cycle 1. Formal response evaluation should occur at the end of treatment . Objective status should be classified as PD vs. Not PD on cycles when a formal response evaluation does not occur.

11.3 **EVALUATION OF MINIMAL RESIDUAL DISEASE (MRD):**
MRD will be assessed by flow cytometry in the bone marrow.

MRD definition
Patients will be considered MRD-negative when they have **bone marrow less** than one CLL cell per 10,000 leukocytes (or bone marrow consistent with <0.01% involvement).

Patients will be recorded to have either MRD+vs. MRD^- disease.

A. **Baseline:** All patients will have MRD will be assessed on patients if their absolute lymphocyte count (ALS) in blood is <5,000 assessed by flow cytometry at baseline prior to initiation of therapy. This can be done either in the peripheral blood (PB) and/or the bone marrow aspirate (BM). (Note: If blood is **positive** for MRD then bone marrow aspirate analysis is not required for the clinical protocol, however if peripheral blood is **negative** then a bone marrow aspirate can be done to document MRD+ status of the patient as long as the bone marrow procedure is being considered as part of the standard of care for patient's disease management).

B. **On treatment:** All patients will have the MRD evaluated by flow cytometry on the peripheral blood **every 3 treatment cycles** while on maintenance therapy, with the first assessment occurring at the end of Cycle 4. MRD will first be done on the PB (to avoid excessive / unwarranted bone marrow biopsy procedure). If this is **positive, then** NO BM analysis will be required, but if the PB is **negative (on two consecutive evaluations at least 3 months apart), then** a BM aspirate analysis for MRD will be done. If the ibrutinib/Daratumumab treatment is held ≥ 21 days for toxicity or for any other reason(s) then the MRD testing will be delayed to accommodate 3 treatment cycles prior to testing.

Methodology
We will employ Mayo Clinic Standard of care MRD assay.
Flow cytometry: we will conduct 8 color flow cytometry to assess MRD.

Flow cytometry panel for MRD
(i) CD19/CD5/CD20/CD23/CD38/CD45/kappa/lambda. (8-color panel)

11.4 Summary Definition of objective response for patients with B–CLL

	CCR[1]	CR[2]	CRi[3]	nPR[4]	PR[5]	PD[6]
PHYSICAL EXAMINATION						
Nodes[7]	None	None	None	None	<50%	>50% increase, new nodes
Liver/spleen[8]	Not palpable	Not palpable	Not palpable	Not palpable	<50%	>50% increase, newly palpable
Symptoms	None	None	None	None	N/A	N/A
PERIPHERAL BLOOD						
ANC	>1500/µL	>1500/µL	See footnote 3	>1500/µL or >50% improvement from baseline	>1500/µL or >50% improvement from baseline	See footnote 6
Platelets	>100,000/µL	>100,000/µL	See footnote 3	>100,000/µL or >50% improvement from baseline	>100,00/µL or >50% improvement from baseline	See footnote 6
Hemoglobin	>11.0 g/dL without transfusion	>11.0 g/dL without transfusion	See footnote 3	>11.0 g/dL or >50% improvement from baseline without transfusion	>11.0 g/dL or >50% improvement from baseline without transfusion	See footnote 6
Lymphocytes	<4000/µL	<4000/µL	<4000/µL	<4000/µL	≥50% decrease	>50% increase to at least 5,000/µL
BONE MARROW	N/A	Normocellular[3]; <30% lymphocytes; no nodules	<30% lymphocytes; no nodules	<30% lymphocytes; bone marrow nodules[4]	N/A	N/A

1. Clinical complete response (CCR) requires fulfillment of all physical exam and peripheral blood criteria as noted in the table above. No bone marrow biopsy is required to call a patient a CCR; however, patients should have a bone marrow analysis performed within two month of the formal response evaluation where clinical and laboratory evidence of complete response was first seen as instructed in the test schedule to confirm CR as per standard guidelines by the IWCLL.
2. Complete response (CR) requires fulfillment of all physical exam and peripheral blood criteria for a duration of ≥2 months. A bone marrow aspirate and biopsy are required to document the response as a complete within two month of the formal response

evaluation where clinical and laboratory evidence of complete response was first seen (see Section 11.21).

3. Patients who fulfill all criteria for a CR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL or have hypocellular marrow will be classified as CR with incomplete marrow recovery(CRi).
4. Nodular partial response (nPR) is essentially a patient who appeared to have a CR but nodules were present in the bone marrow. It requires fulfillment of all physical exam and lymphocyte criteria for CR; however, when the bone marrow is done to confirm CR, nodules of malignant lymphocytes are found. Patients must fulfill one or more of the blood count parameters (ANC, Platelets, Hemoglobin) but are not required to meet all 3 of these conditions. See Section 11.215 regarding the distinction between clonal and regenerative nodules.
5. Partial response (PR) requires fulfillment of at least two of the above-noted decrease in circulating lymphocytes, regression in adenopathy and regression in hepatosplenomegaly, and at least one other parameter listed above for a duration of ≥ 2 months. See Section 11.22.
6. Progression: Fulfilling the criteria as noted in section 11.23. Prior to the formal response evaluation, baseline on study measurements will be used to determine disease progression (e.g. not cycle by cycle comparisons). Once patients undergo formal response evaluation, the nadir value at either baseline or time of response will be used for evaluating future disease progression. In the absence of other indices of clinical progression, the presence of a ≥ 2 g/dL decrease in hemoglobin or a ≥ 50% decrease in platelet count and/or absolute neutrophil count will not exclude a patient from continuing on the study. Although not mandatory, bone marrow aspirate and biopsy are strongly encouraged to better define the cause of the suppressed counts (e.g., treatment versus disease-related).
7. Measurement of lymphadenopathy will be determined on physical exam by adding the sum of the products of the maximal perpendicular diameters of measured lesion(s). No simultaneous increase in the size of any lesions or the appearance of any new lesions may occur for 2 consecutive evaluations at least 1 month apart Minor fluctuations are acceptable as long as they don't exceed 50% of previous measurement. However, if they do exceed 50% of the previous measurement, treatment should be held for 2 consecutive cycles to rule out the possibility of nodes that wax and wane. For purposes of determining CCR and nPR, all nodes on physical exam need to be ≤ 1.5 cm in maximal dimension or documented to be free of CLL by biopsy. NOTE: Information from CT scans regarding lymphadenopathy is not considered in the standard classification of response with the exception of the patients fitting criteria of section 11.218 and 11.227.
8. Measurement of hepatosplenomegaly will be determined by noting the maximal distance below the respective costal margins of palpable hepatosplenomegaly during rest (e.g., not during deep inspiration). NOTE: Information from CT scans regarding hepatosplenomegaly is not considered in the standard classification of response with the exception of the patients fitting criteria of section 11.218 and 11.227.

12.0 Descriptive Factors

12.1 Rai Stage: 0 vs. 1 vs. 2 vs. 3 vs. 4. (Appendix II)

12.2 $CD38^{+}$ expression: Positive (≥30%) vs. negative (<30%).

12.3 Chromosomal anomalies as detected by FISH: 13q- vs. 12+ vs. 11q- vs. 17p- vs. other abnormality vs. negative FISH.

12.4 IgVH mutation status: Mutated (≥2%) vs. unmutated (<2%) vs. indeterminate.

12.5 ZAP-70 expression: Positive (≥20%) vs. negative (<20%).

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CCR, CR, CRi, nPR, PR, or SD will continue treatment per protocol.

13.2 Progressive disease (PD)

If the patient develops PD at any time during active treatment they will complete an end of treatment visit 3-4 weeks from the last dose of treatment. The patient will then go to survival follow-up. Patients will then be followed in survival follow-up per Section 4.2.

13.3 If the patient develops unacceptable adverse events, if the treating physician feels it is in the patient's best interest, or if the patient refuses treatment, study treatment will be discontinued and the patient will complete an end of treatment visit 3-4 weeks from the last dose of treatment. The patient will then go directly to survival follow-up. Patients will then be followed in survival follow-up per Section 4.2.

13.4 Duration of therapy

Patient will be treated as indicated in section 7.0, unless they have progressive disease or unacceptable toxicity or withdrawal. Patients who discontinue treatment will complete an end of treatment visit and continue to survival follow-up.

13.5 Ineligible

A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Survival follow-up will be required per Section 4.2.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.6 Cancel

A patient is deemed *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.7 Major Violation

A patient is deemed a major violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

13.8 DLBCL

If a patient develops DLBCL at any time (except prior to end of cycle 1 of the combination treatment), it will be considered progressive disease. The patient will continue to survival follow-up per section 4.2. If the patient develops any other hematological malignancy while on study, it will not be considered progressive disease.

Note: Due to the nature of the disease, if the patient is diagnosed with DLBCL during the first cycle of treatment, it will be assumed that the DLBCL was present at registration. The patient will be deemed ineligible per Sec 3.27. Such a patient may continue treatment online protocol but will not be considered for statistical analysis for reporting.

14.0 Body Fluid Biospecimen

None.

15.0 Drug Information

15.1 Daratumumab (Darzalex®, Darzalex Faspro™, JNJ-54767414)

Please consult the most current Investigator's Brochure and package insert for complete drug information.

15.11 **Background**: Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.
CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other cell types and tissues and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). Myeloid derived suppressor cells (MDSCs) and a subset of regulatory T cells (CD38+Tregs) expresses CD38 and is susceptible to daratumumab mediated cell lysis.

15.12 **Formulation**:

- SC formulation: Daratumumab and hyaluronidase-fihj injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution supplied in a single-dose vial for subcutaneous administration. Each 15 mL single-dose vial contains 1800 mg daratumumab and 30,000 units hyaluronidase, histidine, sorbitol, methionine, polysorbate 20, and sterile water for injection with a pH of 5.6.

15.13 **Preparation and storage**:

- Study drug labels will contain information to meet the applicable regulatory requirements.

  All Daratumumab SC study drug vials must be stored in the original carton in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab SC does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

  Daratumumab and hyaluronidase-fihj SC injection is directly drawn from the vial into a syringe and is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles. Vials should be removed from the refrigerator and allowed to equilibrate to ambient temperature (15℃ to 30℃). Store the unpunctured vial at ambient temperature for a maximum of 24 hours. Withdrawn 15mL from the vial into a syringe. After the solution is withdrawn into the syringe, replace the transfer needle with a syringe cap. To avoid needle clogging, attach the

hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection. If not used immediately, store the withdrawn solution for up to 4 hours at ambient temperature and light.

15.14 **Administration**:

- Administer pre-infusion and post-infusion medications. Refer to section 7 of the protocol.
- SC administration: Utilizing a hypodermic injection needle or subcutaneous infusion set, inject 15 mL of the daratumumab and hyaluronidase-fihj solution into the subcutaneous tissue of the abdomen approximately 3 inches to the right or left of the navel over approximately 3-5 minutes. Rotate injection sites for successive injections. Never inject DARZALEX FASPRO into areas where the skin is red, bruised, tender, hard or areas where there are scars. Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by pausing or slowing down delivery rate, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose. During treatment with DARZALEX FASPRO, do not administer other medications for subcutaneous use at the same site as DARZALEX FASPRO. No data are available on performing the injection at other sites of the body

15.15 **Pharmacokinetic information for administration**:

SC daratumumab and hyaluronidase-fihj Administration:

Following the administration of the recommended dose of 1,800 mg daratumumab and 30,000 units hyaluronidase subcutaneously once weekly for 8 weeks, the mean ± standard deviation (SD) maximum trough concentrations (Ctrough following the 8th dose) were 593±306 µg/mL compared to 522±226 µg/mL for daratumumab 16 mg/kg administered intravenously, with a geometric mean ratio of 108% (90% CI: 96, 122). The estimated median daratumumab area under the concentration-time curves (AUC0-7 days) and daratumumab peak concentration (Cmax) following the 8th dose were comparable between subcutaneous and intravenous daratumumab (4017 µg/mL•day vs. 4,019 µg/mL•day for AUC0-7 days and 592 µg/mL vs. 688 µg/mL for Cmax).
The absolute bioavailability of daratumumab-hyaluronidase is 69%, with peak concentrations occurring around 3 days (Tmax). The estimated mean (coefficient of variation, CV) volume of distribution for the central compartment is 5.2 L (37%) and peripheral compartment was 3.8 L with the daratumumab-hyaluronidase formulation. Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. The estimated mean (CV%) linear clearance of daratumumab is 119 mL/day. The estimated mean (CV%) elimination half-life associated with linear clearance is 20 days (22%).

As expected with subcutaneous administration, concentration-time curves following administration in all cohorts indicate a later T_{max} of approximately 72h post-dose, compared with IV administration when T_{max} occurs at or near the end of infusion. The range of C3D1 C_{trough} observations for the SC cohort is within the range observed following 16 mg/kg IV dosing, and the variability appeared to be similar for the daratumumab SC and 16 mg/kg IV cohorts. The observed C_{max} values from the daratumumab SC cohort is within the range observed for daratumumab 16 mg/kg IV.

Special Populations
Pediatric Use: The safety assessment in pediatric participants is based on the limited safety data from analysis of the PK, safety and efficacy of combination daratumumab at 16 mg/kg IV in pediatric and young adult participants (1 to <30 years of age) with relapsed/refractory B-cell ALL and T-cell ALL/LL. Based on PK analysis, exposure in this population was within the exposure range for adult participants with MM and was similar across all age subgroups.

Hepatic Impairment: Population PK analysis demonstrated no clinically important differences in the exposure to daratumumab were observed between patients with normal hepatic function and mild hepatic impairment in studies of both daratumumab IV and SC. There were few patients with moderate-severe hepatic impairment to make meaningful conclusions for these populations..

15.16 **Potential Drug Interactions**: Clinical PK assessments with SC formulations and lenalidomide, bortezomib, thalidomide, pomalidomide, melphalan ,prednisone, cyclophosphamide, dexamethasone, and carfilzomib indicated no clinically relevant drug-drug interactions.

Effects on laboratory tests:
Interference with Indirect Antiglobulin Tests: Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching and may persist for up to 6 months after the last daratumumab administration. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, non-cross matched ABO/RhD compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests: Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

15.17 **Known potential toxicities:**
Very common known potential toxicities, ≥ 10%:
Injury, poisoning, and procedural complications: infusion related reaction
Infections and infestations: upper respiratory tract infection, bronchitis pneumonia,
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, anemia, lymphopenia, leukopenia

Nervous system disorders: headache peripheral sensory neuropathy, headache, paresthesia
Metabolism and nutrition disorders: decreased appetite
Respiratory, thoracic, and mediastinal disorders: cough, dyspnea,
Musculoskeletal and connective tissue disorders: back pain, arthralgia
General disorders and administration site conditions: fatigue, pyrexia, peripheral edema, asthenia

Common known potential toxicities, 1% - <10%:
Cardiac disorders: atrial fibrillation
Gastrointestinal disorders: pancreatitis
General disorders and administration site conditions: injection site reaction, chills
Immune system disorders: hypogammaglobulinemia
Infections and infestations: urinary tract infection, influenza, sepsis
Metabolism and nutrition disorders: hypokalemia, hyperglycemia, dehydration
Musculoskeletal and connective tissue disorders: musculoskeletal chest pain
Respiratory, thoracic, and mediastinal disorders
hypoxia, pulmonary edema
Vascular disorders: hypertension
Skin and subcutaneous tissue disorders: pruritis

Uncommon and rare known potential toxicities, <1%:
Infections and infestations: cytomegaloviral infection, hepatitis B reactivation,
Respiratory, thoracic, and mediastinal disorders: laryngeal edema

Daratumumab SC studies demonstrated that the incidence of anti-daratumumab antibodies was low [<1%] following daratumumab administration in multiple myeloma (SC) and amyloidosis (SC) participants. Treatment emergent anti-rHuPH20 antibodies developed in 7.1% (60/840) of participants who received daratumumab SC in monotherapy and combination clinical studies.

Hepatitis B virus (HBV) reactivation, in some cases fatal, have been reported in patients treated with daratumumab. HBV screening should be performed in all patients before initiation of treatment with daratumumab and as clinically indicated. Treatment interruption may be warranted in the event of HBV reactivation while on daratumumab.

Please refer to the Investigator Brochure and package insert for a more comprehensive list of treatment-emergent adverse events.

15.18 **Drug procurement**: Daratumumab (Darzalex®, Darzalex Faspro®) commercially available

15.19 **Nursing Guidelines**:

1. Daratumumab can cause severe infusion reactions, usually during the first infusion. Patients who have experienced a reaction may experience further reactions with subsequent infusions. Most reactions occur during or within 4 hours of infusion, however may occur up to 48 hours after an infusion. Warn patient of this possibility. Monitor patient throughout infusion for bronchospasm, hypoxia, SOB, and hypertension. Patients may also

experience symptoms of anaphylaxis. Administer emergency medication as ordered.

2. Patients may experience infections, including URI and pneumonia. Patients who have an ongoing infection should not receive agent.
3. Patients may experience gastrointestinal side effects including diarrhea and nausea. Treat symptomatically and monitor for effectiveness.
4. Warn patients about the possibility of peripheral neuropathy, dizziness, and insomnia.
5. Fatigue is common. Instruct patient in energy conserving lifestyle.
6. Rarely patients may experience cardiac issues including, atrial-fibrillation, peripheral edema, and hypertension. Instruct patient to report any chest pain, heart palpitations, and swelling to the study team.
7. Monitor CBC w/diff as cytopenias (thrombocytopenia, neutropenia, anemia, and lymphopenia) have been seen. Instruct patient to report any unusual, bruising, bleeding and/or infections/fever to the study team.
8. If using SC, injection should be in the abdomen over 3-5 minutes. There is no data on SC injections on other parts of the body.

15.2 Ibrutinib for Oral Administration (Ibruvica™, PCI-32765)

15.21 **Background**: Ibrutinib is a potent and irreversible inhibitor of Bruton's tyrosine kinase (BTK), an integral component of the B-cell receptor (BCR) and cytokine receptor pathways. Constitutive activation of B-cell receptor signaling is important for survival of malignant B-cells; BTK inhibition results in decreased malignant B-cell proliferation and survival.

15.22 **Formulation:** Commercially available for oral administration as a capsule: 70 mg, 140mg (limited availability). Capsules are packaged in aclar blister pack with aluminum lidding foil, or high-density polyethylene bottles with an induction seal and a child resistant screw-top cap. The number of capsules in each aclar blister pack or per bottle is indicated on the label. Commercially available for oral administration as a tablet: 140 mg, 280 mg, 420 mg, and 560 mg.

15.23 **Preparation and storage:** Refer to package insert for complete dispensing instructions. Store capsules and tablets at room temperature between 20°C and 25°C (68°F and 77°F). Excursions are permitted between 15° and 30°C (59°F to 86°F. Keep tablets in original packaging.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. The manufacturer recommends ibrutinib should be taken with water at the same time every day. Ibrutinib can be taken with or without food. The capsules or tablets should be swallowed whole with water followed by a drink of water after swallowing; the capsules should not be opened, broken, or chewed; the tablets should not be broken or chewed.. Ibrutinib should be held at least 3-7 days pre- and post- surgery depending upon the type of surgery and the risk of bleeding. . Hazardous agent; use appropriate precautions for handling and disposal.

15.25 **Pharmacokinetic information:**
Distribution: ~10,000 L
Bioavailability: Administration with food increased the maximum concentration by ~2 to 4-fold and the AUC 2-fold (compared with overnight fasting). Administration under fasting conditions resulted in exposure of ~60% compared

to when administered either 30 minutes before or after a meal, or 2 hours after a high-fat meal.
Protein binding: ~97%
Metabolism: Hepatic via CYP3A (major) and CYP2D6 (minor) to active metabolite PCI-45227
Ibrutinib is metabolized in the liver
Time to peak: 1 to 2 hours
Elimination –The excretion of ibrutinib is predominantly via the feces with approximately 80% recovered mostly within 2 days, whereas ~8% is excreted in urine. Approximately 1% of the ibrutinib is recovered as unchanged drug, all in feces. The half-life elimination is 4-6 hours. Overall, these PK characteristics resulted in minimal accumulation of both parent compound and metabolite PCI-45227 on repeated daily dosing of ibrutinib.
Special populations: a small increase in bioavailability was estimated with increasing age. Population PK indicated that in older subjects (67 to 81 years), a 14% higher ibrutinib exposure is predicted. Dose adjustment by age is not warranted. No statistically significant effects were observed for the other covariates tested, i.e., sex, race, mild and moderate renal impairment, mild hepatic impairment and B-cell histology. No dose adjustment is needed for subjects with mild or moderate renal impairment (with creatinine clearance greater than 30 mL/min). Hydration should be maintained, and serum creatinine levels monitored periodically. There are no data in patients with severe renal impairment or patients on dialysis. Monitor patients with liver impairment for signs of ibrutinib toxicity and follow dose modification guidance as needed. For subjects with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily. For subjects with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily. It is not recommended to administer ibrutinib to subjects with severe hepatic impairment (Child-Pugh Class C).
Patients with cGVHD: The recommended dosage is 140 mg daily for patients 12 years of age and older with total bilirubin level >1.5 to 3 × upper limit of normal (ULN) (unless of non-hepatic origin or due to Gilbert's syndrome). The recommended dosage is 80 mg/m2 daily for patients 1 to <12 years of age with total bilirubin level >1.5 to 3 × ULN (unless of non-hepatic origin or due to Gilbert's syndrome). Avoid the use of ibrutinib in these patients with total bilirubin level >3 × ULN (unless of non-hepatic origin or due to Gilbert's syndrome). Based on pooled population pharmacokinetic analysis in pediatric patients with cGVHD treated with ibrutinib at 240 mg/m2 once daily (patients aged ≥1 to <12 years) or 420 mg once daily (patients aged ≥12 years), exposure in this population was within the exposure range for adult patients with cGVHD. The safety and efficacy of ibrutinib have been evaluated in children aged 1 year and older with previously treated moderate or severe cGVHD. Ibrutinib is not recommended for use in children and adolescents younger than 18 years of age for other indications

15.26 **Potential Drug Interactions:**
Metabolism Effects: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4/5. Avoid concomitant use of ibrutinib with any of the following: CYP3A4 inducers (strong), CYP3A4 inhibitors (strong or moderate) and herbs that are CYP3A4 inducers or inhibitors. The levels of ibrutinib may be increased by CYP3A4 inhibitors and decreased by CYP3A4 inducers (the active metabolite has inhibitory activity towards Bruton's tyrosine kinase that is approximately 15 times lower than that of ibrutinib).

Transport Effects: Ibrutinib is a P-glycoprotein/ABCB1 inhibitor and may increase the serum concentrations of: afatinib, bosutinib, brentuximab, colchicine, active metabolites of dabigatran etexilate, doxorubicin, edoxaban, everolimus, ledipasvir, naloxegol, pazopanib, prucalopride, rifaximin, rivaroxaban, silodosin, topotecan and vincristine.

Ibrutinib may enhance the adverse/toxic effect of clozapine, leflunomide, natalizumab, pimecrolimus, tofacitinib, tacrolimus, and live vaccines. It may also enhance the adverse/toxic effect of anticoagulants and agents with antiplatelet properties. Dipyrone may enhance the adverse/toxic effect of ibrutinib.

Grapefruit juice and Seville oranges moderately inhibit CYP3A and may increase ibrutinib exposure.

15.27 **Known potential toxicities**: Consult the package insert for the most current and complete information.
Common known potential toxicities, >10%:
Atrial fibrillation
Pyrexia

Dermatologic: Skin rash, skin infection, pruritis

Gastrointestinal: Diarrhea

Hematologic & oncologic: Febrile neutropenia,
Respiratory: pneumonia
Miscellaneous: Fever

Less common/Rare known potential toxicities, 1% - 10%:
leukocytosis, neutropenia, thrombocytopenia, cardiac failure, congestive cardiac failure, ventricular tachycardia, eye hemorrhage, nausea, stomatitis, vomiting, mouth ulceration, peripheral edema, sepsis, cellulitis, urinary tract infection, septic shock, pneumocystis jirovecii pneumonia, bacterial pneumonia, upper respiratory tract infection, bronchopulmonary aspergillosis, neutropenic sepsis, fungal pneumonia, bacteremia, erysipelas, viral pneumonia, skin infection, bacterial sepsis, haemophilus pneumonia, klebsiella pneumonia, sinusitis, staphylococcal bacteremia, staphylococcal sepsis, urosepsis, atypical pneumonia, cellulitis orbital, enterococcal sepsis, Escherichia sepsis, folliculitis, lung abscess, paronychia, pneumonia cytomegaloviral, pneumonia legionella, pneumonia pseudomonal, pulmonary tuberculosis, pseudomonal sepsis, streptococcal bacteremia, staphylococcal skin infection, subdural hematoma, neutrophil count decreased, platelet count decreased, tumor lysis syndrome, myalgia, arthralgia, musculoskeletal pain, basal cell carcinoma, cerebrovascular accident, ischemic stroke, transient ischemic stroke, dizziness, interstitial lung disease, pneumonitis, epistaxis, rash, rash maculopapular, dermatitis bullous, drug eruption, purpura, urticaria, hypertension, hematoma
Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias or cardiac failure have occurred in patients treated with ibrutinib. Patients with significant cardiac comorbidities may be at greater risk of events, including sudden fatal cardiac

events. Atrial fibrillation, atrial flutter ventricular tachyarrhythmia and cardiac failure, have been reported, particularly in subjects with acute infections or cardiac risk factors, including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed.

Cerebrovascular accidents: Cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

Limited to important or life threatening: Dermatologic disorder (neutrophilic dermatosis), abnormal platelet aggregation, hepatic cirrhosis, acute hepatic failure, hypersensitivity (includes anaphylactic shock, angioedema), hyponatremia, interstitial pulmonary disease, onychoclasis, peripheral neuropathy, pneumonia due to *Pneumocystis carinii*, pneumonitis, progressive multifocal leukoencephalopathy, reactivation of HBV, renal failure syndrome, Stevens-Johnson syndrome, tumor lysis syndrome, urticaria

15.28 **Drug procurement**: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing Guidelines:**

1. There are numerous drug to drug interactions. Record all of patient's medications including OTC, and herbal use. Avoid concomitant use with agents as listed in section 15.26.
2. Ibrutinib should be taken with water at approximately the same time each day and can be taken with or without food. Capsules should be swallowed whole.
3. Patients should be instructed to avoid eating grapefruit (including juice) and Seville oranges while on ibrutinib.
4. Peripheral edema is common. Instruct patients to report this to the study team.
5. Gastrointestinal side effects are common (diarrhea, nausea, constipation, abdominal pain, vomiting, etc). Treat symptomatically and monitor for effectiveness of intervention.
6. Monitor CBC w/diff. Instruct patients in energy conserving lifestyle (anemia) and to report any unusual bruising or bleeding and/or signs or symptoms of infection to study team.
7. Arthralgias, myalgias, and muscle spasm can be seen. Treat symptomatically and monitor for effectiveness.
8. Monitor renal function/uric acid levels, especially in patients who may be experiencing dehydration.
9. Respiratory symptoms may include, cough, SOB, and URI. Instruct patients to report these symptoms to the study team.
10. Rarely patients can experience secondary skin cancers. Instruct patients to report any new skin lesions to the study team.
11. Rash can be seen. Instruct patient to report to study team.

12. Cardiac arrhythmias have been seen with this agent including a-fib, atrial flutter and ventricular tachyarrhythmia's, some of which have led to death. Instruct patients who experience any palpitations, lightheadedness, syncope, or SOB to see medical care immediately. This is especially important in patients who have pre-existing cardiac issues.
13. Warn patients of the risk of bleeding. Patients should not take warfarin or other vitamin K antagonists while on ibruitinib, unless the protocol allows for it. Additionally, patients should be cautioned to avoid fish oil and Vitamin E supplements.
14. Patients who are concurrently on iburitinib and venetoclax should be monitored closely for excess toxicity.
15. Ibrutinib should be held at least 3-7 days pre and post-surgery, depending on type of surgery.
16. There have been reports of CVA and TIA in patients on ibrutinib. Instruct patients to report any headaches and/or neurologic changes immediately or seek out emergency care.
17. Patients may experience dry eyes, blurred vision or decreases in vision. Instruct patients to report this to the study team.

16.0 Statistical Considerations and Methodology

16.1 Overview:

This is a Phase II study designed to assess the overall response rate of daratumumab and ibrutinib for relapsed/refractory CLL in two groups independently: Previously received Ibrutinib (Cohort 1) and Ibrutinib naïve (Cohort 2).

16.11 Primary Endpoint:

The primary endpoint in each cohort is the overall response rate after 6 cycles of treatment with daratumumab in combination with ibrutinib (end of Cycle 7). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for overall response, with the exception of patients who are determined to be a major treatment schedule violation.

16.12 Sample Size:

The phase II study design to be used in each group is fully described in section 16.2. A maximum of 22 evaluable Cohort 1 and 26 evaluable Cohort 2 patients will be accrued unless undue toxicity is encountered. We anticipate accruing an additional 4 patients (2 Cohort 1, 2 Cohort 2) to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is 52 patients overall.

16.13 Accrual Rate and Study Duration:

The anticipated accrual rate is approximately 2-3 patients per month. Therefore, the accrual period for this phase II study is expected to be about 2 years. The maximum total study duration is expected to be approximately 7 years, or until the last patient accrued has been observed for at least 5 years. The earliest date anticipated for presentation of results is at approximately 2.5 years, or when the last patient accrued has completed the cycle 7 response assessment.

16.2 Statistical Design:

16.21 Decision Rule for previously received Ibrutinib group (Cohort 1)

Since patients in this group have been previously treated with Ibrutinib, the patients may have a plateaued response to ibrutinib. A response rate of at least 20% with the addition of daratumumab to ibrutinib would be of interest. The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 5%, representing a response by chance alone. The smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 20%. The following one-stage binomial design uses 22 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 5%.

16.211 <u>Final Decision Rule</u>

Enter 22 evaluable patients into the study. If 2 or fewer successes are observed in the first 22 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 3, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.212 Power and Significance Level

Assuming that the number of responses is binomially distributed, with a significance level of 9%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.05	0.10	0.15	0.20
Then the probability of declaring that the regimen is promising and warrants further study is…	0.09	0.38	0.66	0.85

16.22 Decision Rule for Ibrutinib naïve group (Cohort 2):

In a previous study including 85 patients with relapsed/refractory CLL treated with single agent ibrutinib, the overall response rate at 8 months was 54%. The overall response rate was the same regardless of dose level received (51 patients received 420 mg and 34 received 840 mg). An increase in overall response rate after 8 months of treatment with the combination of daratumumab and 420 mg of ibrutinib would be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 50%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 75%. The following one-stage binomial design uses 26 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 50%.

16.221 Final Decision Rule: Enter 26 evaluable patients into the study. If 16 or fewer successes are observed in the first 26 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 17, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.222 Power and Significance Level: Assuming that the number of responses is binomially distributed, with a significance level of 8%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.50	0.55	0.60	0.65	0.70	0.75
Then the probability of declaring that the regimen is promising and warrants further study is…	0.08	0.19	0.36	0.57	0.77	0.91

16.23 Other Considerations: Toxicity, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.24 Over Accrual: If more than the target number of patients are accrued, then the

additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.34.

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair in accordance with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when the last patient has been followed for at least 6 cycles of combination treatment (7 cycles total).

16.31 **Primary Endpoint (to be evaluated in each cohort independently)**

16.311 Definition: The primary endpoint in each cohort is the overall response rate after 6 cycles of treatment with daratumumab in combination with ibrutinib. A response is defined as an objective status of CR, CRi, CCR, nPR, or PR after 6 cycles of combination treatment (end of cycle 6). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients who are determined to be a major treatment schedule violation.

16.312 Estimation: In each cohort, the proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety- five percent exact binomial confidence intervals for the true success proportion will be calculated.

16.32 Secondary Endpoints (to be evaluated in each cohort independently)

16.321 The best overall response rate at any time during the course of treatment with daratumumab plus ibrutinib will be estimated by the number of patients who achieve a CR, CRi, CCR, nPR, or PR at any time during combination treatment divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success rate will be calculated.

16.322 The MRD response rate at any time during the course of treatment with daratumumab plus ibrutinib will be estimated by the number of patients who achieve MRD negative response in both blood and bone marrow at any time during combination treatment divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success rate will be calculated. In patients who achieve MRD negative response, time to achieve MRD negative response will be summarized descriptively (median, range). Time to achieve MRD negative response is defined as time from registration to the earliest date of documentation of MRD negative response in both blood and bone marrow.

16.323 Progression-free survival is defined as the time from registration to the earliest date of documentation of disease progression or death due to any cause. Patients who receive subsequent treatment for CLL before disease progression will be censored on the date of their last disease assessment prior to initiation of the subsequent treatment. The distribution of progression-free survival will be

estimated using the method of Kaplan-Meier.

16.324 Adverse Events: Platelets and hemoglobin will be graded according to the Grading Scale for Hematologic Adverse Events in CLL Studies in Appendix V. The maximum grade for each type of adverse event, regardless of causality, will be recorded and reported for each patient, and frequency tables will be reviewed to determine adverse event patterns. Adverse events will continue to be recorded and reported up to 30 days after the last day of study drug treatment.

16.34 Over Accrual: If more than the target number of patients are accrued, then the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.35 Data & Safety Monitoring

16.351 The principal investigator(s) and the study statistician will review the study at least every quarter to identify accrual, adverse events, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.352 Adverse Event Stopping Rule (to be evaluated in each cohort independently): The stopping rule specified below is based on the knowledge available at study development. We note that the rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatments under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to the cohort if at any time we observe events considered at least possibly related to study treatment (e.g., an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy either of the following:

- If 3 or more of the first 12 treated patients experience a grade 4 or higher non-hematologic adverse event (except infusion related reactions) at least probably related to treatment except infusion related reactions.

- If after the first 12 patients have been treated, 25% of all patients experience a grade 4 or higher non-hematologic adverse event (except infusion related reactions) at least probably related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related," to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.4 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the [redacted] website. The Primary and Secondary Endpoints along with other required information for this study will be reported on [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time all patients registered have completed the cycle 7 response assessment (or discontinued treatment before completion of 7 cycles of treatment.)..

16.5 Subset Analyses for Minorities

16.51 Study Availability

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.52 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.53 Regional population

The geographical region served by Mayo Clinic has a population that includes approximately 3% minorities. Based on prior Mayo Clinic studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race, and about 30% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	2	3
Not Hispanic or Latino	15	34	49
Ethnic Category: Total of all subjects*	**16**	**36**	**52**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	2	3
Native Hawaiian or other Pacific Islander	0	0	0
White	15	34	49
Racial Category: Total of all subjects*	**16**	**36**	**52**

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." **Not Hispanic or Latino**
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

None.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy. These documents include lab reports and/ or imaging reports and should be submitted within 14 days of registration (for prior to study entry materials) or within 14 days after the visit at which response or progression is determined.

18.6 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient: All routine clinical care.

19.2 Tests to be research funded: None.

19.3 Other budget concerns: Janssen will provide Mayo Clinic with funding to support the costs of running this study.

Janssen will provide the study drug, Daratumumab, for use in this study.

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Appendix I ECOG Performance Status Scale

ECOG Performance Status Scale

Grade	*Descriptions*
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix II Rai Staging System for CLL

Modified 3-stage System	Rai Stage	Clinical Features
Low Risk	0	Lymphocytes (L) in blood > 5000/mm^3 and marrow > 30% only
Intermediate Risk	I	L+ enlarged lymph nodes (LN)
	II	L + spleen and/or liver (LN + or -)
High Risk	III	L + anemia (Hb < 11 g/dl)
	IV	L + Thrombocytopenia < 100,000/µl.

Subjects in the intermediate risk group must have evidence of active disease as demonstrated by at least one of the following criteria:

Massive or progressive splenomegaly and/or lymphadenopathy; (Massive splenomegaly is here defined by spleen tip > 6 cm below costal margin.)

Presence of weight loss > 10% over the preceding 6 month period;

Grade 2 or 3 fatigue;

Fevers > 100.5°F or night sweats for longer than 2 weeks without evidence of infection;

Progressive lymphocytosis with an increase of > 50% over a 2-month period or an anticipated doubling time of less than 6 months;

Worsening anemia or thrombocytopenia.

Appendix III Criteria for Diagnosis of Disease

Specific diagnosis of B-Cell CLL meeting the following criteria at any time during the course of disease (e.g., at initial diagnosis, at relapse, etc.):

- An absolute lymphocytosis of > 5,000/mm^3.
- Morphologically, the lymphocytes must appear mature with < 55% prolymphocytes by manual differential.
- The aspirate smear must show > 30% of nucleated cells to be lymphoid or the bone marrow core biopsy must show lymphoid infiltrates compatible with marrow involvement by CLL. The overall cellularity must be normocellular or hypercellular.
- Local institution lymphocyte immunophenotype must reveal a predominant B-cell monoclonal population sharing a B-cell marker (CD19, CD20, CD23, CD24) with the CD5 antigen in the absence of other pan-T-cell markers. While the absence of CD23 expression will not exclude subjects, it should prompt close re-examination of the lymphocyte morphology to exclude the diagnosis of mantle cell lymphoma in the leukemic phase.

Appendix IV Definition of Symptomatic B-Cell

Active disease should be clearly documented for protocol therapy. At least one of the following criteria should be met:

Evidence of progressive marrow failure as manifested by the development of or worsening of anemia (Hb < 11.0 g/dL) and/or thrombocytopenia (Platelets < 100 x 10^9)

Massive (e.g., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly

Massive nodes (e.g., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy

Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than 30 x 10^9/L (30 000/µL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.

Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.

Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:

Unintentional weight loss of 10% or more within the previous 6 months; significant fatigue (e.g., inability to work or perform usual activities);

fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or

night sweats for more than 1 month without evidence of infection.

Appendix V Grading Scale for Hematologic Toxicity in CLL Studies

Non Hematologic Toxicity will be scored using NCI CTCAE (version 5.0) for toxicity and adverse event reporting.

Hematologic toxicity will be assessed using IWCLL/Hallek December 2008[6] Grading scale for hematologic toxicity in CLL studies

Grade*	Decrease in platelets or Hb (nadir) from pretreatment value, %	Absolute neutrophil count/µL (nadir)
0	No change to 10%	≥2000
1	11%-24%	≥1500 and < 2000
2	25%-49%	≥1000 and < 1500
3	50%-74%	≥500 and < 1000
4	≥75%	< 500

* Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

† Platelet counts must be below normal levels for grades 1 to 4. If, the platelet count is < 20 x 10^9/L (20 000/µL) at any level of decrease, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (eg, 20 x 10^9/L [20 000/µL]) was present pretreatment. In this case, the patient will not be evaluable for toxicity referable to platelet counts.

‡ Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§ If the absolute neutrophil count (ANC) reaches < 1 x 10^9/L (1000/µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating neutrophils are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L (1000/µL) before therapy, then the patient will not be evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity but should be documented.

Appendix VI Patient Medication Diary

Name _____ **Study ID Number** _____

Please complete this diary on a daily basis. Write in the amount of the dose of ibrutinib (420 mg) that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

Ibrutinib should be taken with water at approximately the same time each day and can be taken with or without food. Swallow the capsules whole; do not open, break, or chew the capsules.

Please avoid grapefruit and Seville oranges during your ibrutinib treatment. Supplements such as fish oil and vitamin E preparations should also be avoided.

Drug	**Dose**
Ibrutinib	420 mg

Week of: _____

	Day 1	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***
Date							
Ibrutinib							

Week of: _____

	Day 8	***Day 9***	***Day 10***	***Day 11***	***Day 12***	***Day 13***	***Day 14***
Date							
Ibrutinib							

Week of: _____

	Day 15	***Day 16***	***Day 17***	***Day 18***	***Day 19***	***Day 20***	***Day 21***
Date							
Ibrutinib							

Week of: _____

	Day 22	***Day 23***	***Day 24***	***Day 25***	***Day 26***	***Day 27***	***Day 28***
Date							
Ibrutinib							

Patient signature: _____

Health or medical complaints during this time:

Other medications or supplements taken during this time:

Name of medication or supplement	How much did you take? (example: Two 500mg pills)	When did you take it (examples: Every day Or Day 19 and Day 20)

Use a separate sheet of paper if more space is needed.

My next scheduled visit is: _____

If you have any questions, please call: _____

Study Coordinator Use Only

Number of pills returned _____ Number of vials returned: _____

Discrepancy Yes____/No____ Verified by _____ Date_____