Ibrutinib monotherapy in early stage CLL/SLL without IWCLL treatment indications but with high-risk features for disease progression

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Contents

1.0 OBJECTIVES

1.1 Primary endpoint: Complete remission (CR) or complete remission with incomplete count recovery (CRi) rate at 24 months.

1.2 Secondary endpoints:

1. Progression-free survival (PFS) at 2 years.
2. Overall response rate (ORR) at 6, 12 and 24 months, CR/CRi rate at 6 and 12 months.
3. Time to best response.
4. Time to alternative treatment.
5. Overall survival at 5 years.

1.3 Exploratory endpoints:

1. Effect of ibrutinib treatment on immune function.
2. Effect of ibrutinib on frequency of subclonal driver mutations.
3. Incidence of emergence of subclonal resistance mutations (e.g. C481S mutation in *BTK* and mutations in *PLCG2*).

2.0 HYPOTHESES

1. We will see a high overall response rate, of approximately 90%, similar to that seen in first line treatment of CLL.
2. We anticipate seeing a higher rate of complete remission than in treatment of first-line CLL, given patients will have a lower disease burden. In the early report of a large, phase III study of ibrutinib in the first line setting, the CR/CRi rate was 4%, but this increased to approximately 16% after 2 years of follow-up (Pharmacyclics, internal data). We would expect the CR/CRi rate to potentially double when we treat patients early in their disease course; thus, we anticipate a complete remission rate at 2 years of approximately 30%.
3. We anticipate approximately 10-15% of patients will stop therapy due to toxicity. In the phase III study mentioned above, the treatment discontinuation rate was 9% at a median follow-up of 18 months. We expect that in an early treatment population, the rates of discontinuation may be somewhat higher, as there may be less willingness from patients and physicians to tolerate troublesome side effects.
4. We anticipate that ibrutinib will have beneficial effects on immune function, including improvement in immunoglobulin levers, including IgA(1) and T-cell function.
5. We anticipate a low rate of development of resistance mutations.

3.0 BACKGROUND AND RATIONALE

3.1 Clinical course of CLL.

CLL is the most common leukemia in the United States and Western hemisphere.(2) There is remarkable clinical diversity in patients with CLL. Following diagnosis, some patients have smoldering, asymptomatic disease that may not progress for many years, others are diagnosed with advanced stage and still others are diagnosed with early stage disease that rapidly progresses, causing symptoms and/or bone marrow failure and require treatment. Wierda et al. developed a nomogram designed to predict the time to first treatment for previously untreated CLL patients who did not have an indication for treatment at their initial assessment.(3) Patients with increased cervical lymph node size, unmutated *IGHV* gene, elevated LDH, ≥3 involved lymph node sites, del(11q) or del(17p) demonstrated more rapid disease progression, with shorter time-to-first-treatment.(3)

3.2 Studies of early versus deferred treatment in CLL.

No study has demonstrated a survival benefit for early versus deferred treatment in CLL, although the initial studies were done with alkylating agent-based treatment, which would be considered ineffective given current standards of care. Also, historic trials included all patients and did not have reliable tools to screen out low-risk patients who may never need treatment. Two large French studies definitively demonstrated a lack of survival benefit for early versus deferred treatment with chlorambucil monotherapy,(4) while a large meta-analysis also showed no survival benefit for early treatment with either chlorambucil or anthracycline-based chemotherapy.(5) More recently, a German-French co-operative study showed event-free survival, but not overall survival benefit for early treatment with FCR, although follow-up was short.(6) Given the lack of demonstrable survival benefit with early therapy, early-stage CLL is managed with “watchful waiting”. Patients are considered for treatment only if significant disease-related symptoms or marrow failure develop.(7) The lack of survival benefit seen in early therapy studies, despite prolonged PFS, also relates to a combination of toxicity from chemotherapy, as well as inability to eradicate the CLL clone with the result that the disease is less treatment-sensitive at relapse. Therefore, these older trials lacked our current understanding of high-risk features, including low-risk patients, and utilized ineffective therapies, which probably contributed to the negative findings.

3.3 Early-stage CLL is associated with increased infection risk and a higher incidence of other cancers.

Even untreated, early stage CLL or its precursor condition, monoclonal B-cell lymphocytosis (MBL), are associated with significant infection risk(8, 9) and infection remains a leading cause of morbidity and mortality in CLL. In addition, there is an increased incidence of other hematologic(10, 11) and non-hematologic cancers(12, 13) in patients with even early-stage CLL or high-count MBL. Treatment with a non-immunosuppressive, non-genotoxic agent, may potentially reduce these risks.

3.4 Adverse effects of chemotherapy-based treatment in CLL.

Patients with CLL have a higher risk of second cancers, particularly skin, AML/MDS and Richter transformation.(14) While the impact of specific therapy is controversial, it was suggested that fludarabine-based treatment may increase the risk of Richter transformation(15) (and M. Keating, unpublished data). Fludarabine-based chemotherapy is also associated with myelosuppression, lymphocyte depletion, and infection risk.(16) Therefore, delay of initiation of chemoimmunotherapy is a desirable goal. Early studies were conducted prior to the availability of highly-effective, non-myelosuppressive and non-mutagenic agents, such as ibrutinib. Although data is currently lacking, early treatment with ibrutinib could reasonably be expected to result in a lower incidence of both treatment-related infectious complications and second cancers relative to chemoimmunotherapy.

3.5 Ibrutinib as first-line therapy in CLL.

Ibrutinib demonstrated remarkable efficacy in first-line treatment of CLL in elderly patients.(17) Treatment was well tolerated, with few serious adverse events. Mild diarrhea was the most common adverse event,(17) but generally self-limited. Grade 3 toxicity requiring temporary treatment interruption was seen in 29% of patients, but no patient permanently ceased treatment due to toxicity. Of 31 patients, with a median follow-up of 22 months, only 1 patient progressed; this patient, who had del(17p), developed Richter transformation after approximately 6 months on treatment. In this study 96% remained progression-free at 24 months. More recently, the RESONATE-2 study demonstrated a survival benefit relative to chlorambucil and an impressive 90% PFS at 18 months, leading to first line approval of ibrutinib by the U.S. Food and Drug Administration. Rare, but serious adverse events include atrial fibrillation, which occurred in approximately 6% of patients in the ibrutinib arm; minor bleeding is more common in ibrutinib-treated patients, but major bleeding is rare.(18) An update of this study at ASH 2016 demonstrated increasing rate of CR/CRi over time and 89%

PFS at 24 months, with 79% of patients remaining on therapy at a median follow-up of 28.5 months.(19)

3.6 Resistance to ibrutinib therapy.

Resistance mutations developed during ibrutinib therapy in relapsed/refractory patients, particularly those with del(17p) and complex karyotype. It could be postulated that early treatment, when patients have a lower total disease burden, may result in lower incidence of resistance mutations and superior responses.

3.7. Potential advantages of early therapy with ibrutinib.

Ibrutinib therapy may have beneficial effects on immune function, by inhibiting ITK and skewing T cell responses to T_H1-type;(20) Ibrutinib also reduces PD1/PDL1 expression on CLL cells and PD1 expression on T cells(21) and enhances *in vitro* response to viral peptides (K Kondo, P Thompson and K Rezvani, manuscript submitted). Notably, during continued long-term therapy, infections are noted more frequently within the first year of treatment than subsequently.(22) Improvement in IgA levels(1) has also been seen in patients treated with ibrutinib.

At the time of treatment patients with CLL have significant intra-tumor clonal heterogeneity, with multiple sub-clones, notable for different driver mutations. Treatment with cytoreductive therapy, particularly cytotoxic chemotherapy, results in selection of aggressive subclones, such as those with *TP53* mutation;(23) clones containing *TP53* mutation invariably predominate at relapse, even if their initial frequency is low.(24) CLL cells containing chromosomal abnormalities or mutations which confer resistance to conventional cytotoxic chemotherapy (e.g. del(17p)) show similar sensitivity to novel therapies such as ibrutinib, compared to CLL cells lacking these deleterious mutations.(25, 26) However, during long-term therapy, such patients are more likely to develop novel mutations such as the C481S mutation in *BTK* and activating mutations in *PLCG2*, conferring ibrutinib resistance.(26) To the limits of sensitivity of available testing, these mutations do not pre-date ibrutinib therapy and are thus thought to develop during therapy.(25) Early treatment, at a time when the total burden of CLL cells containing deleterious mutations is likely low, presumably will reduce the mathematical likelihood that a subclone containing an ibrutinib resistance mutation will develop.

3.8 Toxicity of the proposed regimen.

Toxicities associated with ibrutinib are discussed in detail in section 6.4.5. Ibrutinib is generally well-tolerated and over 90% of patients remained on therapy at 18 months of follow-up. The most commonly reported AEs are diarrhea, fatigue, cough and nausea, which are generally mild and not treatment-limiting. In the first line setting, 2.5% of patients had grade 3-4 hemorrhage and 6% developed atrial fibrillation.(18)

4.0 STUDY POPULATION

4.1 Inclusion criteria.

1. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria.(7)
2. Patients must be aged over 18 years at the time of informed consent, understand and voluntarily sign an informed consent, and be able to comply with study procedures and follow-up examinations.
3. No treatment indication according to IWCLL criteria.(7)
4. Estimated time to first treatment of 3 years or less according to MDACC nomogram.(3)
5. ECOG performance status of 0-2.(27)
6. Male and female subjects who agree to use both a highly effective method of birth control (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) and a barrier method (e.g., condoms, vaginal ring, sponge, etc.) during the period of therapy and for 30 days after the last dose of study drug for females and 90 days for males. OR Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy).
7. Adequate hepatic and renal function as indicated by all of the following: Total bilirubin </=1.5 x institutional Upper Limit of Normal (ULN) except for patients with bilirubin elevation due to Gilbert's disease or of non-hepatic origin who will be allowed to participate; an ALT </=2.5 x ULN; and estimated creatinine clearance

[1] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

(CrCl) of > 30 mL/min, as calculated by the Cockroft- Gault equation unless disease related.

8. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder).
9. Free of prior malignancies for 3 years with exception of patients diagnosed with basal cell or non-metastatic squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix or breast, who are eligible even if they are currently treated or were treated and/or diagnosed in the past 3 years prior to study enrolment.
10. A negative urine pregnancy test (within 7 days of enrollment date) is required for women with childbearing potential. Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (≥1 year of no menses, by history).

4.2 Exclusion criteria.

1. Receipt of any prior therapy for CLL. Patients who have received “early intervention” with INVAC-1 vaccine against hTERT will be eligible provided all the following exist:
   i) They had no response to the vaccine treatment (persistent CLL >1% in bone marrow).
   ii) ≥3 months have elapsed since the last dose of vaccine.
   iii) No residual toxicities attributable to the vaccine exist at the time of study enrollment.
   iv) The patient does not meet IWCLL criteria for requiring treatment.
2. Richter transformation.
3. Active malignancy requiring systemic therapy, other than CLL, with the exception of: adequately treated *in situ* carcinoma of the cervix uteri; adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin; previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
4. Systemic anticoagulation with warfarin or other Vitamin K antagonists.
5. Active and uncontrolled autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (ITP) requiring daily prednisone dose of >20 mg.
6. Current and concurrent use of strong CYP3A4 inhibitors or activators.
7. Pregnant or breast-feeding females.

8. Uncontrolled and active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
9. Any other severe concurrent disease, or history of serious organ dysfunction or disease involving the heart, kidney, liver or other organ system that, in the investigator's opinion, may place the patient at undue risk to undergo therapy with ibrutinib.
10. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
11. History of ischemic stroke within 6 months prior to enrollment.
12. Evidence of bleeding diathesis or coagulopathy within 3 months (e.g., von Willebrand's disease or hemophilia).
13. Any history of symptomatic intracranial hemorrhage.
14. Major surgical procedure with 4 weeks of first dose of study drug; open biopsy, or significant traumatic injury within 7 days prior to enrollment date; anticipation of need for major surgical procedure during the course of the study.
15. Minor surgical procedures, fine needle aspirations or core biopsies within 3 days prior to enrollment date. Bone marrow aspiration and/or biopsy are allowed.
16. Serious, non-healing wound, ulcer, or bone fracture.
17. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
18. Active, uncontrolled infection.
19. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
20. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix L)

5.0 TREATMENT PLAN

5.1 Recommended prophylactic medications:

The following are recommended prophylactic medications. For individuals who are allergic, an equivalent replacement may be identified:

- Allopurinol 300 mg PO daily for the first 7 days of course 1 is recommended for tumor lysis prophylaxis.
- Valacyclovir 500 mg PO daily for all treatment courses and for at least 3 months after completion of treatment is recommended, for herpes virus prophylaxis.

5.2 Treatment regimen.

Ibrutinib monotherapy will be administered at 420mg once daily until either:

1. Disease progression or
2. Achievement of complete remission with negative MRD, on two separate assessments, at least 6 months apart. For the purposes of determining treatment cessation, MRD analysis must be performed on bone marrow, using standardized 4-color flow cytometry and demonstrate sensitivity of at least 0.01%.(28) We anticipate a low rate of MRD-negative CR/CRi, which may require prolonged treatment to achieve. Patients who discontinue ibrutinib due to achievement of MRD-negative CR/CRi, will continue to have routine clinical follow-up every 3 months, which will include MRD analysis in peripheral blood, performed at least once per year.
3. Completion of 2 years of therapy.

5.3 Long term follow-up.

Patients who remain on therapy at 2 years (the timing of the primary endpoint) may continue ibrutinib, at the discretion of their physician. This would, however, require transition to commercial supply of ibrutinib and should be discussed with the PI. If patients choose to have follow-up at M.D. Anderson, they will be seen every 3-6 months, at the discretion of their physician. If they are receiving follow-up at an outside center, they will be telephoned by study staff every 6 months (until disease progression, death or receipt of a new therapy) to determine:

- Whether they are still receiving study drug.
- Whether any significant toxicity has occurred.
- Whether their disease remains in remission.
- Whether they have had any other cancer therapy.

6.0 BACKGROUND DRUG INFORMATION

Ibrutinib

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. Ibrutinib 420 mg will be administered orally once daily. Ibrutinib should be administered at the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose.

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be redispensed to anyone.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g. ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is prohibited. Concomitant use of strong CYP3A inducers (e.g. rifampin, rifabutin, phenytoin, carbamazepine, and St. John's Wort) is prohibited. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

6.1 How Supplied

Supplied as 140mg capsules. Ibrutinib will be supplied by Pharmacyclics LLC for a total of 2 years of therapy.

6.2 Stability

Store bottles at room temperature 20°C to 25°C.

6.3 Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk.(29) *In vitro*, ibrutinib is a potent inhibitor of Btk activity (IC50 = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity

and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC50 = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression.(30)

6.4 Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 6 hours, with a median time to maximum plasma concentration (T_{max}) of 1 to 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by CYP 3A4-mediated metabolic pathways. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. About 8% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

6.5 Summary of Clinical Safety

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

6.6 Precautions and warnings.

Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. In an *in vitro* platelet

function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs and symptoms of bleeding.

Supplements such as fish oil and vitamin E preparations should be avoided.

See Section 8.2.2 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 8.4 for guidance on ibrutinib management with surgeries or procedures.

Subjects with congenital bleeding diathesis have not been studied.

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk. Consider temporarily withholding ibrutinib. Subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Infections

Infections (including sepsis, bacterial, viral or fungal infections) were observed in patients treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in patients treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Blood counts should be monitored monthly.

Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 7.1)

Cardiac arrhythmias

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 7.1).

Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

Non-Melanoma Skin Cancer

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

Hypertension

Hypertension has occurred in subjects treated with ibrutinib. Regularly monitor blood pressure and initiate or adjust anti-hypertensive medication throughout treatment as appropriate.

6.7 Other safety observations.

Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attach, 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.

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 7.1).

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in study 1112. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events erythema, urticarial and angioedema have been reported.

Lymphocytosis

Upon initiation of single agent treatment with ibrutinib, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib as single agent. This effect has also been observed in some subjects with MCL (35%) treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types,

lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL (range 0.1-104 weeks).

When ibrutinib was administered in combination with BR or with obinutuzumab in subjects with CLL/SLL, lymphocytosis was infrequent (7% with ibrutinib + BR versus 6% with placebo + BR and 7% with ibrutinib + obinutuzumab versus 1% with chlorambucil + obinutuzumab)

Lymphocytosis was not observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib.

Overdose

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

Refer to Section 11.4 for further information regarding AE reporting.

7.0 DOSE DELAYS AND MODIFICATIONS

Section 7.1-7.3 outline recommendations for management of ibrutinib-associated toxicity. However, dose adjustments outside these guidelines can be made by the investigator if considered to be in the patient's best interests.

7.1 Recommended dose modifications:

Recommended dose modifications of ibrutinib are described below. For adverse reactions listed in Table 1, interrupt ibrutinib. Once the adverse reaction has improved to Grade 1 or baseline (recovery), follow the recommended dosage modifications.

Adverse Reaction	Occurrence	Dose Modification After Recovery Starting Dose = 420 mg
Grade 2 cardiac failure	First	Restart at 280 mg daily[c]
	Second	Restart at 140 mg daily[c]
	Third	Discontinue IMBRUVICA
Grade 3 cardiac arrhythmias	First	Restart at 280 mg daily[c]
	Second	Discontinue IMBRUVICA
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue IMBRUVICA
Other Grade 3 or 4 non-hematological toxicities[d] Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	First	Restart at 280 mg daily
	Second	Restart at 140 mg daily
	Third	Discontinue IMBRUVICA

See *Warnings and Precautions.*

[b] Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria, or International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for hematologic toxicities in CLL/SLL.

[c] Evaluate the benefit-risk before resuming treatment.

[d] For Grade 4 non-hematologic toxicities, evaluate the benefit-risk before resuming treatment.

These updated dosage modification recommendations may reduce the occurrence of additional serious events and are intended to improve tolerability for continued Imbruvica treatment.

7.2 Hematologic toxicity:

Interrupt ibrutinib for any Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the toxicity has resolved to Grade ≤1 or baseline, reinitiate ibrutinib as per the table above.

7.3 Non-hematologic toxicity:

Interrupt treatment for any grade 3 or greater non-hematological toxicity. Once the toxicity has resolved to grade ≤1 or baseline, restart the study drugs as per the guidelines for the hematologic toxicity as above.

If the dose of ibrutinib is reduced, at the investigator's 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 the reduction. Dose changes will be recorded in the medical record.

7.4 Leukocytosis/Leukostasis:

A high number of circulating malignant cells (>400000/mcL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and investigator should be contacted.

7.5 Dose Modification for Hepatic Impaired Subjects

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in Section **Error! Reference source not found.**. Ibrutinib is metabolized in the liver. In the population PK analysis (1,202 subjects), 179 subjects (14.9%) had mild hepatic impairment according to National Cancer Institute criteria and 12 subjects (1.0%) had moderate hepatic impairment. These subjects did not show a significantly higher ibrutinib exposure compared with subjects with normal hepatic function. In a hepatic impairment study, data showed an increase in ibrutinib exposure. For subjects with mild liver impairment (Child-Pugh class A), the recommended dose is 280mg daily. For subjects with moderate liver impairment (Child-Pugh class B), the recommended dose is 140mg daily. Monitor subjects for signs of ibrutinib toxicity and follow dose modification guidance as needed. It is not recommended to administer ibrutinib to subjects with severe hepatic impairment Subjects with clinically significant chronic hepatic impairment at the time of Screening (Child- Pugh class C) are excluded from study participation. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer to Appendix D for Child-Pugh classification. Please refer to Table 3 for dose modifications due to hepatic impairment.

Table 1. Dose Modification Guidance for Hepatic Impaired Subjects

	Child Pugh class A (Mild hepatic impairment)*		**Child Pugh Class B (Moderate hepatic impairment)****		**Child Pugh class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Ongoing at time of enrollment	Develops during study	Develops during study

Ibrutinib Dose (daily)	280 mg	280mg	140 mg	140 mg	Hold until improves to moderate [Class B] or better)

* If further reduction is needed due to non-hepatic toxicity, dose may be reduced to 140 mg. In the event that additional reduction is needed, ibrutinib should be held for non-hepatic toxicity until resolution.

** If further reduction is needed due to non-hepatic toxicity, ibrutinib should be held until resolution.

8.0 CONCOMITANT THERAPY

8.1 Allowed concomitant therapy

All concomitant medications will be noted in the patient's medical record. Patients should receive full supportive care during study participation, including hematopoietic growth factors, transfusion of blood products, fluid and electrolyte replacement, anti-emetics, anti-diarrheals, medications to control tumor lysis syndrome and hypersensitivity reactions, and antibiotics when appropriate. Anti-infective prophylaxis for viral, fungal, bacterial or *Pneumocystis* infections is permitted.

Short courses (<=14days) 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.

8.2. Medications to be Used with Caution

8.2.1 CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure, and strong CYP3A inhibitors should be avoided.

Strong CYP3A inhibitors

Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased exposure (Cmax and AUClast) of ibrutinib by 29- and 24-fold, respectively. In a dedicated drug-drug interaction study in subjects with B-cell malignancies, co-administration of voriconazole increased Cmax and AUC by 6.7-fold and 5.7-fold,

respectively. In clinical studies, the maximal observed ibrutinib exposure (AUC) was ≤2-fold in 37 subjects treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 subjects not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 subjects treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Voriconazole and posaconazole can be used concomitantly with ibrutinib. All other strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided, and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, please discuss recommendations for dosing with the PI and document the discussion in the medical record.

Moderate and mild CYP3A inhibitors

In subjects with B-cell malignancies, co-administration of the CYP3A inhibitor erythromycin increased Cmax and AUC by 3.4-fold and 3.0-fold, respectively. If a moderate CYP3A inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) is indicated, reduce the ibrutinib dose to 280 mg once daily for the duration of the inhibitor use or as per recommended dose modifications described in the specific clinical study protocol.
In subjects with cGVHD, if a co-administration of voriconazole and posaconazole (at doses less than or equal to suspension 200 mg twice daily) is indicated, reduce the ibrutinib dose to 280 mg once daily. If a co-administration of higher doses of posaconazole (i.e., suspension 200 mg three times daily or 400 mg twice daily; IV injection 300 mg once daily; delayed-release tablets 300 mg once daily) is indicated, reduce the ibrutinib dose to 140 mg once daily. No ibrutinib dose modifications for moderate inhibitors are required for cGVHD subjects. Follow the specific instructions described in the clinical study protocol.
No dose adjustment is required in combination with mild inhibitors. Monitor subjects closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A.

Strong CYP3A inducers.

Administration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%.

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

8.2.2 Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 8.4).

Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation) should be monitored closely for signs and symptoms of bleeding and the risks and benefits of continuing ibrutinib treatment should be considered.

8.3 Excluded concomitant therapy

Use of the following therapies is prohibited during the study:

- Any therapies intended for the treatment of lymphoma/leukemia whether FDA-approved or experimental (outside of this study)
- Radiotherapy (Note: Localized radiotherapy to an area not compromising bone marrow function is allowed)
- Steroid therapy for anti-neoplastic intent. Short courses (<=14days) 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.
- Strong CYP3A inhibitors which would be taken chronically, with the exception of voriconazole and posaconazole, as outlined in section 8.2.1.
- Grapefruit, Seville oranges, Star fruit
- Strong CYP3A inducers (e.g. rifampin, rifabutin, phenytoin, carbamazepine, and St. John's Wort) are not recommended
- The use of warfarin is not allowed during this study

8.4 Guidelines for Ibrutinib Management with Surgeries or Procedure

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

8.4.1 Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

8.4.2 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 sero-sanguineous drainage or the need for drainage tubes.

8.4.3 Emergency Procedures

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, or for at least 7 days after the urgent surgical procedure, whichever is longer.

9.0 PRETREATMENT EVALUATIONS

1. Pretreatment evaluation will include a complete history and physical examination including vital signs, ECOG performance status, height and weight and recording of concurrent medications (within 30 days of the first dose)
2. Complete blood count (hemoglobin, white blood cell count, platelet count, white blood count differential) (within 30 days of the first dose)
3. Clinical laboratory evaluation will include serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, LDH, β-2 microglobulin, immunoglobulins (within 30 days of the first dose)

4. Coagulation profile (PT, aPTT)
5. Immunologic evaluation (within 30 days of the first dose).
6. CLL prognostic markers, including CLL FISH panel, *IGHV* mutation status, ZAP-70, CD38, and CLL next generation sequencing panel (within 30 days of the first dose). This testing can be done either in peripheral blood or bone marrow. Retesting for *IGHV* mutation status and ZAP70 is not required if previously done at MDACC. Additionally, if CLL next generation sequencing panel and FISH has been performed within the past year at MDACC, these do not need to be repeated.
7. HIV Ab, Hepatitis C Ab, HBsAg, anti-HBcAb (within 30 days of the first dose)
8. Women of childbearing potential must have a negative serum or urine β-hCG pregnancy test result (within 7 days of the first dose)
9. 12-lead EKG (within 30 days of the first dose)
10. MUGA or Echocardiogram (within 30 days of the first dose)
11. Bone marrow aspiration and biopsy (within 90 days of the first dose if no intervening treatment for CLL given)
12. CT scan of the neck, chest, abdomen, and pelvis with IV and oral contrast, within 90 days of the first dose with no intervening treatment for CLL given. Patients with palpable cervical lymphadenopathy noted at screening physical examinations should have imaging of the neck included in their screening imaging studies and at subsequent time points for response assessment. Note: PET scan or MRI may be used instead of the CT scan imaging.
13. Immunologic evaluation. Peripheral blood samples will be taken to evaluate immune function and the relationship between immune function and outcome, as a research test.
14. Circulating tumor DNA analysis and sequencing of peripheral blood mononuclear cells will be done in Sarah-Jane Dawson's lab at Peter MacCallum Cancer Center, Melbourne, Australia, as a research test.

10.0 EVALUATION DURING THERAPY

Cycle	**Screening/ baseline(1)**	**1**	**2**	**3**	**6**	**9**	**12**	**18**	**24**	**At progression**
Day within cycle(2)	**-30 to 1**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	
Informed consent(3)	**X**									

Medical history(4)	X	X	X	X	X	X	X	X	X	X
Physical examination including vital signs(5)	X				X		X	X	X	X
Concomitant medications(6)	X									
Complete blood count with differential(7)	X	X	X	X	X	X	X	X	X	X
Biochemistry(8)	X	X	X	X	X	X	X	X	X	X
CT scan(9)	X				X		X		X	X
Bone marrow examination and cytogenetics(10)	X				X		X		X	X
ECG(11)	X									
Echocardiogram(12)	X									
Pregnancy test(13)	X									
QOL evaluation(14)	X						X		X	X
Immunologic evaluation(15)	X			X	X		X			X
Circulating tumor DNA analysis(16)	X	X		X	X		X		X	X

(1) Screening period testing. All the above must be completed within 30 days of study enrolment, except where stated otherwise in section 9.0.

(2) Evaluations within the first 3 cycles of therapy must take place within +/- 7 days of scheduled time. Evaluations during cycle 6-12 must take place within +/- 2 weeks of scheduled date. Evaluation during cycles 18-24 must take place within +/- 4 weeks of scheduled time.

(3) Informed consent. All patients must take part in the informed consent process. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Adequate time must be allowed for questions and for the patient to make a voluntary decision. No protocol-specific procedures are to be performed until the patient has signed and dated an Institutional Review Board (IRB)/Ethics Committee (EC)-approved informed consent form. Each patient's participation in the trial begins with the signing and dating of the informed consent form.

(4) Medical history. Medical and surgical history and demographic information will be recorded. Medical and surgical history includes diagnoses, therapies, and medical and surgical treatments. A complete medical history will be obtained at screening/baseline, prior to first administration of study drug and at the end-of-treatment visit. At all other visits, the medical history taking can be focused to the needs of the patient but should pay particular attention to adverse events that are potentially related to ibrutinib, infections, and disease-related symptoms. During the CoVID19 epidemic, medical history may be obtained by the patient's M.D. Anderson Physician in a telephone or videoconference interview and documented in the chart.

(5) Physical examination, including vital signs. Vital signs are temperature, pulse, respiratory rate, and blood pressure (when the patient is seated). A complete physical examination, including measurement of weight, must be performed at screening/baseline, prior to the first administration of study drug, and at the end-of-treatment Visit. Height need only be recorded at the initial visit. Following the screening/baseline physical examination, with the exception of the end-of-treatment Visit, all subsequent physical examinations can be focused to the individual needs of the individual patient. Given that, during the CoVID19 epidemic, many patients will not be able to come to M.D. Anderson, some assessments may be conducted remotely. Wherever possible, patients should have a physical exam at least every 6 months and, if unable to come to M.D. Anderson, this should be done by a local physician and the records obtained. If even this is not possible, the reasons for this should be documented in the patient's chart.

(6) Concomitant medications. These will be recorded in the electronic medical record.

(7) Complete blood count with differential. CBC with differential is defined as peripheral blood total white blood cell (WBC) count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and WBC differential, reported individually for each cell type. Hematologic assessments must be obtained at screening and at every subsequent assessment, as specified in the Schedule of Events, or more frequently as clinically indicated (e.g. to confirm loss of hematologic response as defined in section 9.1).

(8) Biochemistry. Serum chemistry consists of a peripheral blood draw with the following assessments: include serum sodium, potassium, calcium, BUN, creatinine, glucose,

phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, LDH, β-2 microglobulin, immunoglobulins.

(9) CT of the neck, chest, abdomen and pelvis will be performed for response evaluation. If PET/CT or MRI was performed pre-treatment, this should be performed instead of CT scan, if available. If patients achieve complete remission by CT criteria (see section 11.0), subsequent CT scans can be omitted, per investigator discretion.

(10) Bone marrow examination with CLL FISH panel and flow cytometry will be performed pre-treatment and at 6, 12, and 24 months. Conventional stimulated metaphase karyotyping will be performed at baseline and at disease progression, using local protocols. Pre-treatment, CLL FISH panel need not be repeated if performed at MDACC within the past year.

(11) ECG. ECG will be done prior to treatment, in the routine diagnostic lab and then as clinically indicated.

(12) Echocardiogram. ECHO or MUGA will be performed at screening (within 2 weeks of starting treatment) and at end of treatment or at 2 years, whichever is soonest. If a patient has undergone ECHO or MUGA as standard of care prior to entering the study, the procedures will not have to be repeated if results are available and the procedures were performed within 28 days of study entry.

(13) Pregnancy test. The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test, using either urine or serum. Women who are not of childbearing potential (status post-hysterectomy, status post-bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]) do not need to have the test performed. If the test is deemed necessary, it must be performed within 7 days preceding the commencement of study therapy and known to be negative. Women of childbearing potential at study commencement must also complete the pregnancy test at the End-of-Treatment Visit.

(14) QOL evaluation. Quality of life will be evaluated using the FACIT-Fatigue and EQ-5D-5L questionnaires pre-treatment, at 12 months, 24 months and at disease progression.

(15) Immunologic evaluation. Peripheral blood samples will be taken at baseline, 3, 6, 12 months and at disease progression, to evaluate immune function and the relationship between immune function and outcome. This will be done as a research test. Please note that, as a result of the CoVID19 epidemic, it may be impossible to obtain research lab draws. Missed research lab draws will not be considered as deviations.

(16) Circulating tumor DNA analysis and sequencing of peripheral blood mononuclear cells will be done in Sarah-Jane Dawson's lab at Peter MacCallum Cancer Center, Melbourne, Australia pre-treatment and at 1, 3, 6, 12, 24 months and at disease progression. Please note that, as a result of the CoVID19 epidemic, it may be impossible to obtain research lab draws. Missed research lab draws will not be considered as deviations.

11.0 CRITERIA FOR RESPONSE

Response will be assessed according to the 2008 IWCLL criteria.(7) Overall response is defined as a CR or PR. Patients with missing or no response assessment will be classified as non-responders. The full criteria are re-produced below. Please note that PET/CT or MRI can be performed for response assessment in lieu of CT scan, if these were performed for disease staging pre-treatment.

Criteria for Complete Remission (CR):

Requires all the following criteria to be met:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4000/μL)
- Absence of significant lymphadenopathy (lymph nodes >1.5 cm in diameter) by CT (or PET) examination of neck, thorax, abdomen and pelvis
- No hepatomegaly or splenomegaly by physical examination (and CT/PET if assessment was abnormal before therapy or if physical exam is inconclusive)
- Absence of constitutional symptoms
- Blood counts above the following values:
  - Neutrophils more than 1.5 x 10^9/L (1500/μL) without need for exogenous growth factors
  - Platelets more than 100 x 10^9/L (100 000/μL) without need for exogenous growth factors

- Hemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin

- Bone marrow aspirate and biopsy, demonstrating at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. Minimal residual disease will be assessed by 4 color flow cytometry from the bone marrow.

Patients who fulfill all the criteria for a CR, but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity are classified as complete remission with incomplete blood count recovery (CRi).

Criteria for Partial Remission (PR).

To meet criteria for PR the patient must have achieved at least one of criteria 1-3, below (if abnormal before therapy), as well as one or more of the features listed in section 4, below.

1. A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.
2. Reduction in lymphadenopathy as measured by PET/CT) as defined by the following:
   - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.
   - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (</=2 cm), an increase of less than 25% is not considered to be significant.
3. A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan.
4. The blood count should show one or more of the following results:
   - Neutrophils more than 1, without need for exogenous growth factors.
   - Platelet counts greater than 100 x10^9/L (100 000/μL) or 50% improvement over baseline without need for exogenous growth factors.
   - Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

Criteria for Stable Disease:

Stable disease is defined as not meeting criteria for complete remission, partial remission or progressive disease.

Criteria for Progressive Disease:

Progressive disease during or after therapy is characterized by at least one of the following:

1. Lymphadenopathy. Appearance of any new lesion (>1.5cm) or increase by 50% or more in greatest determined diameter of any previous site.
2. An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
3. An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
4. Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL.
5. After treatment, the progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of HGB levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L (100 000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Minimal residual disease (MRD) analysis.

MRD will be assessed in bone marrow after 6, 12, and 24 months, using a standardized 4-color flow cytometry assay, with a sensitivity of 0.01%.(28) Patients will be categorized as MRD-negative or MRD-positive.

12.0 ADVERSE EVENT REPORTING

Toxicities will be graded according to the NCI Expanded Common Toxicity Criteria (v4.03 or higher).(31)

12.1 Leukemia-specific Adverse Event Recording and Reporting Guidelines

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events.

An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. An adverse drug reaction is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all patients enrolled on the trial.

12.1.1 Adverse events will be documented in the medical record and entered into PDMS/Core.

12.1.2 These guidelines will be followed for the recording and reporting of adverse and serious adverse events.

- Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event.
  - Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed
  - Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
- If exact start date is unknown, month and year or year may be used as the start date of the baseline event. The maximum grade of the adverse event will be captured per course or protocol defined visit date.
- These adverse events will be recorded:

- Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
- All serious adverse events regardless of attribution to the study drug(s).
- Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.

- Serious adverse events will be reported according to institutional policy.
- Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

12.1.3 For abnormal hematologic and chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form. Please note that hematologic AEs will be graded according to NCI-WG/IWCLL criteria, which take into account the potential for abnormal pre-treatment values (Appendix N).

12.1.4 All adverse events will be collected for the purpose of grading, and determining attribution to study drugs by the PI using the following scale:

- Unrelated: The AE is clearly NOT related to the intervention.
- Unlikely: The AE is doubtfully related to the intervention.
- Possible: The AE may be related to the intervention.
- Probable: The AE is likely related to the intervention.
- Definite: The AE is clearly related to the intervention.

12.1.5 All grade 3 and greater non-hematological events that are felt to be related to protocol treatment drugs will be documented on the toxicity log. The toxicity log data must reflect the relationship to the drug the event is felt to be related to.

12.1.6 The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if

during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures

12.1.7 Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject or female partner of a male subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a female subject or female partner of a male subject from the time of first dose up until to 90 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies

with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II and sent via email or fax to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

12.1.8 Other Malignancies

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

12.1.9 Serious Adverse Event Reporting (SAE)

12.1.9.1 Definition of an SAE:

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience; this is defined as any adverse experience that places the patient, in view of the initial reporter, at immediate risk of death from the adverse experience, as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

12.1.9.2 Important medical events:

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21

CFR 312.32). Pregnancy, drug overdose, and secondary malignancy will be handled as SAE. Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator

12.1.9.3 SAE reporting:

- All SAEs should be reported to the study nurse or the Principal Investigator [Jan Burger, M.D., Ph.D, Telephone (713) 563-1487 or jaburger@mdanderson.org] within 24 hours of observing or learning of the event.
- All AEs should be reported to the study nurse.
- Expected therapy-related events include those known toxicities or side effects of ibrutinib. These grade 4 or less events, including, but not limited to diarrhea, atrial fibrillation, infection, hemorrhage, hypertension and joint pain/arthralgia will not be reported as individual SAEs, but will be summarized in the annual report to the IRB. However, these will be reported to Pharmacyclics within 24 hours of knowledge of the event.
- Adverse Events Requiring Expedited Reporting: Serious unexpected adverse events (SUSARs) considered associated with therapy should be reported to the study nurse or the Principal Investigator [Jan Burger, M.D., Ph.D, Telephone (713) 563-1487 or jaburger@mdanderson.org] within 24 hours of observing or learning of the event. These events must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, SUSARs must be reported to the IRB, within 5 working days of knowledge of the event).
- All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakeCT@pcyc.com) or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee, within 24 hours of the event.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines and Institutional Review Board policy.

12.1.10 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*.
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.6 above.

Investigator Communication with Supporting Companies:

- Any individual expedited SAE reports will be reported to Pharmacyclics.
- **All Serious Adverse Events must be reported to Pharmacyclics.**
- All SAEs, whether related or unrelated to ibrutinib and all pregnancies must be reported to Pharmacyclics (by the investigator or designee) within 24 hours of knowledge of the events.
- All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakeCT@pcyc.com) or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee , within 24 hours of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator

13.0 CRITERIA FOR REMOVAL FROM STUDY

Criteria for removal from study include, but are not restricted to, the following:

- Clinically significant progressive disease.
- Recurrent non-compliance by the patient with protocol requirements.
- Patient's request to be removed from the study.
- Occurrence of a CTCAE grade 4 non-hematologic adverse event, at least possibly related to ibrutinib. For CTCAE grade 4 adverse events that are numerically defined laboratory parameters, independent investigator assessment should be used to determine the risk:benefit for continuation of therapy.
- Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol specified safety criteria or desirable in the investigator's and/or the subject´s opinion

14.0 CORRELATIVE STUDIES

14.1 Comprehensive analysis of changes in immune function during ibrutinib therapy will be performed. Ibrutinib was shown to inhibit ITK in mice, resulting in skewing of T cell immune responses to a T_H1 phenotype(20) and also enhancing the efficacy of checkpoint blockade with PD-L1 antibodies.(32) We propose a comprehensive immune profiling of CLL patients treated with ibrutinib to understand the possible immunomodulatory effects of this drug. Immune reconstitution studies will be performed on 10-20 ml peripheral blood samples collected from CLL patients prior to initiation of ibrutinib, 3, 6, and 12 months after initiation of ibrutinib therapy and on discontinuation of therapy. We propose to use multi-parameter flow cytometry and *in vitro* functional assays to study T-cell and NK cell numbers, phenotype and function. Testing may include, but not be limited to the following:

1. Analysis of CD4+ and CD8+ T cell phenotype and function including naïve/central memory and effector phenotype (CD45RO, CD62L, CCR7 expression), cytokine profile following T cell receptor engagement and co-stimulation with anti-CD3/CD28 beads including Th1/Th2/Th17 profiles and regulatory T cell frequencies (CD4+CD25+CD127lo,foxp3+).
2. Analysis of antigen-specific T cell responses following stimulation with a viral peptide library pool (Influenza, Cytomegalovirus and Epstein-Barr Virus).

3. Assessment of normal B cell reconstitution during ibrutinib therapy by assessing transitional, naïve, switched and IgM memory B cell frequencies (CD24, CD38, CD10, IgM, IgD, CD27). We will perform *in vitro* studies to look at preferential BTK inhibition in gated normal B cell subsets using Phosflow assays in combination with surface phenotyping.
4. NK reconstitution including ratios of CD56dim/CD16+ and CD56bright/CD16lo, expression of activating receptors (NKp30, NKp44, NKp46, NKG2D, NKG2C) and inhibitory receptors (NKG2A and killer immunoglobulin receptors) to assess if ibrutinib impacts NK function and phenotype.
5. Cytokine analysis: CCL3, CCL4, IL-4, IL-5, IL-6, IL-10, IL-13, TGF-β, IFN-γ, IL-2, TNF-α.

   * The assays to perform these studies are set up and routinely performed in the Rezvani-Shpall Laboratories and analysis will be performed by Dr. Katy Rezvani.

14.2 Ibrutinib has been shown to produce synergistic anti-tumor efficacy with PD-L1 antibodies in mouse lymphoma and other tumor models(32) and to down-regulate PD1/PDL1 on CLL cells and PD1 expression on T cells in peripheral blood. However, the effect of ibrutinib treatment on expression of these immune checkpoint molecules in the marrow, where persistent CLL is frequently seen during ibrutinib therapy, has not been systematically explored. We plan to perform serial assessment of PD-L1, PD-L2 and PD1 by flow cytometry on CLL cells and T cells obtained from both blood and marrow.

14.3 Serial analysis of cellular and molecular biomarkers in CLL cells that predict resistance as well as persistence of the disease. A significant proportion of patients with progressive disease were identified to have specific point mutations in *BTK* (C481S) or activating mutations in PLC-γ2 and these mutations appear more common in patients with genomic instability such as those with del(17p) and/or complex metaphase karyotype.(25) We will perform targeted serial deep sequencing using next generation sequencing multiplex panels for known CLL-associated mutations pre-treatment; we will serially monitor the allelic frequency of clonal and subclonal mutations identified at baseline, to identify whether treatment with ibrutinib induces changes in the subclonal architecture. These studies will be performed pre-treatment and at 1, 3, 6, 12 and 24 months from peripheral blood in collaboration with Dr. Constantine Tam and Dr. Sarah-Jane Dawson at Peter MacCallum Cancer Center, Melbourne, Australia. Samples will also be obtained at disease progression.

This sequencing will include serial deep sequencing for BTK and PLC-γ2 mutations, to identify small sub-clones emerging at early time points, whether these expand over time and whether their emergence predicts clinical resistance to therapy.

15.0 STATISTICAL CONSIDERATIONS

15.1 This is a phase II single arm study of ibrutinib monotherapy in early stage CLL with a predicted time-to-treatment interval of less than 3 years, according to the MDACC nomogram developed by Wierda et al.(4) The primary objective is to evaluate the CR/CRi rate at two years. A maximum of 50 patients will be enrolled in the study with an estimated accrual rate of 4 patients per month; the accrual duration will be approximately 1 year.

15.2 The historical CR/CRi rate for patients who are treated when they have symptomatic disease requiring therapy, in the first line setting is 16% at 2 years (Pharmacyclics, internal data). We expect that early therapy with ibrutinib may increase this CR/CRi rate at two years from 16% to 30%. A sample size of 50 patients achieves 78% power to detect a difference of 14% in the 2-yr complete remission rate (i.e. to double the remission rate) using a one-sided binomial test. The target significance level is 0.05. These results assume that the population proportion under the null hypothesis is 16%.

15.3 For the primary analysis, we will calculate the proportion of patients with CR/CRi at 24 months, along with 95% confidence intervals. We will test the observed 2-year rate versus the null hypothesis of a 16% rate using a one-sided exact binomial test.

15.4 For secondary analyses, proportions of patients with objective response at 6, 12 and 24 months and CR/CRi at 6 and 12 months will be estimated along with 95% confidence intervals. The Kaplan-Meier method will be applied to estimate the progression free survival (PFS), the time to best response, the time to CR/CRi and time-to-alternative treatment survival curves. We will calculate the median time as well as the 2-year and 5-year survival rate and the corresponding 95% confidence intervals. In addition, we will directly compare the observed PFS time to each patient's individual predicted PFS time.

Protocol Amendments

Any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

16.0 REFERENCES

1. Sun C, Tian X, Lee YS, Gunti S, Lipsky A, Herman SE, et al. Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib. Blood. 2015;126(19):2213-9.
2. Gribben JG, O'Brien S. Update on therapy of chronic lymphocytic leukemia. J Clin Oncol. 2011;29(5):544-50.
3. Wierda WG, O'Brien S, Wang X, Faderl S, Ferrajoli A, Do KA, et al. Multivariable model for time to first treatment in patients with chronic lymphocytic leukemia. J Clin Oncol. 2011;29(31):4088-95.
4. Dighiero G, Maloum K, Desablens B, Cazin B, Navarro M, Leblay R, et al. Chlorambucil in indolent chronic lymphocytic leukemia. French Cooperative Group on Chronic Lymphocytic Leukemia. N Engl J Med. 1998;338(21):1506-14.
5. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. CLL Trialists' Collaborative Group. J Natl Cancer Inst. 1999;91(10):861-8.
6. Cymbalista F, Müller C, Busch R, Porcher R, Langerbeins P, Cazin B, et al. Early Versus Deferred Treatment With Combined Fludarabine, Cyclophosphamide and Rituximab (FCR) Improves Event-Free Survival In Patients With High-Risk Binet Stage A Chronic Lymphocytic Leukemia – First Results Of a Randomized German-French Cooperative Phase III Trial. Blood. 2013;122(21):524.
7. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.
8. Strati P, Shanafelt TD. Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification. Blood. 2015;126(4):454-62.
9. Moreira J, Rabe KG, Cerhan JR, Kay NE, Wilson JW, Call TG, et al. Infectious complications among individuals with clinical monoclonal B-cell lymphocytosis (MBL): a cohort study of newly diagnosed cases compared to controls. Leukemia. 2013;27(1):136-41.
10. Sanchez ML, Almeida J, Gonzalez D, Gonzalez M, Garcia-Marcos MA, Balanzategui A, et al. Incidence and clinicobiologic characteristics of leukemic B-cell chronic lymphoproliferative disorders with more than one B-cell clone. Blood. 2003;102(8):2994-3002.

11. Rodriguez-Caballero A, Henriques A, Criado I, Langerak AW, Matarraz S, Lopez A, et al. Subjects with chronic lymphocytic leukaemia-like B-cell clones with stereotyped B-cell receptors frequently show MDS-associated phenotypes on myeloid cells. Br J Haematol. 2015;168(2):258-67.
12. Solomon BM, Rabe KG, Slager SL, Brewer JD, Cerhan JR, Shanafelt TD. Overall and cancer-specific survival of patients with breast, colon, kidney, and lung cancers with and without chronic lymphocytic leukemia: a SEER population-based study. J Clin Oncol. 2013;31(7):930-7.
13. Mansfield AS, Rabe KG, Slager SL, Schwager SM, Call TG, Brewer JD, et al. Skin cancer surveillance and malignancies of the skin in a community-dwelling cohort of patients with newly diagnosed chronic lymphocytic leukemia. J Oncol Pract. 2014;10(1):e1-4.
14. Tsimberidou AM, Wen S, McLaughlin P, O'Brien S, Wierda WG, Lerner S, et al. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol. 2009;27(6):904-10.
15. Hamblin TJ. Richter's syndrome--the downside of fludarabine? Leukemia research. 2005;29(10):1103-4.
16. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164-74.
17. O'Brien S, Furman RR, Coutre SE, Sharman JP, Burger JA, Blum KA, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet Oncol. 2014;15(1):48-58.
18. Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015;373(25):2425-37.
19. Barr P, Robak T, Owen CJ, Tedeschi A, Bairey O, Bartlett NL, et al. Updated Efficacy and Safety from the Phase 3 Resonate-2 Study: Ibrutinib As First-Line Treatment Option in Patients 65 Years and Older with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Blood. 2016;128(22):234.
20. Dubovsky JA, Beckwith KA, Natarajan G, Woyach JA, Jaglowski S, Zhong Y, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood. 2013;122(15):2539-49.
21. Long M, Beckwith KA, Do P, Bethany ML, Gordon G, Lehman AM, et al. Ibrutinib Represents a Novel Class of Immune Modulating Therapeutics That Enhances the Survival

of Activated T Cells in Vitro and In Vivo through a Non-BTK Mediated Mechanism. Blood. 2016;128(22):3238.

22. Byrd JC, Furman RR, Coutre SE, Burger JA, Blum KA, Coleman M, et al. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015;125(16):2497-506.

23. Landau DA, Carter SL, Stojanov P, McKenna A, Stevenson K, Lawrence MS, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. Cell. 2013;152(4):714-26.

24. Rossi D, Khiabanian H, Spina V, Ciardullo C, Bruscaggin A, Fama R, et al. Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukemia. Blood. 2014;123(14):2139-47.

25. Woyach JA, Furman RR, Liu TM, Ozer HG, Zapatka M, Ruppert AS, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. N Engl J Med. 2014;370(24):2286-94.

26. Maddocks KJ, Ruppert AS, Lozanski G, Heerema NA, Zhao W, Abruzzo L, et al. Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. JAMA Oncol. 2015;1(1):80-7.

27. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6):649-55.

28. Rawstron AC, Villamor N, Ritgen M, Bottcher S, Ghia P, Zehnder JL, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia. 2007;21(5):956-64.

29. Pan Z, Scheerens H, Li SJ, Schultz BE, Sprengeler PA, Burrill LC, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. ChemMedChem. 2007;2(1):58-61.

30. Herman SE, Gordon AL, Hertlein E, Ramanunni A, Zhang X, Jaglowski S, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood. 2011;117(23):6287-96.

31. Institute NC. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03: U.S. Department of Health and Human Services; 2010 [updated June 14, 2010. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

32. Sagiv-Barfi I, Kohrt HEK, Czerwinski DK, Ng PP, Chang BY, Levy R. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. Proceedings of the National Academy of Sciences. 2015.