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CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II STUDY OF BUPARLISIB IN PATIENTS WITH RELAPSED AND REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

CCTG Protocol Number: **IND.216**

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SUPPORTED BY:	Novartis

(For contact information of study personnel see Final Page.)

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Novartis.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG and Novartis to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Novartis and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Novartis and CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG or Novartis with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Novartis and CCTG and must be kept in confidence in the same manner as the contents of this protocol. Publication will proceed per policy and as per protocol. Novartis require a review period of fifteen (15) working days for presentation materials and abstracts and forty-five (45) working days for manuscripts.

Please note: Novartis has not provided a contractual indemnification to investigators or study sites for any claims arising out of or in connection with the administration or use of the drugs being studied through the study ("study drugs") during the course of this study.

_____ _____

Qualified Investigator
(printed name and signature) Date

_____ _____

Institutional Representative
(printed name and signature) Date

Protocol Number: CCTG IND.216

CENTRE: _____

TREATMENT SCHEMA

A phase II study of buparlisib in patients with relapsed and refractory chronic lymphocytic leukemia.

Eligibility Criteria

- Previously documented CLL as defined by the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines that is recurrent or relapsed after previous therapy and that requires treatment (see Appendix VI);
- Measurable disease with at least one of lymphocyte count $\geq$ 10 x 10^9/L *OR* at least one pathologically enlarged lymph node ($\geq$ 2 x 2 cm) by CT scan;
- ECOG performance status of 0, 1 or 2;
- At least one prior systemic treatment regimen (single agent or combination therapy, may include autologous or allogeneic stem cell transplantation) and have recovered from all reversible toxicity related to prior systemic therapy and have adequate washout period (See Section 5.1.6);
- Age $\geq$ 18 years;
- Life expectancy of at least 12 weeks;
- Neutrophils $\geq$ 1.0 x 10^9/L;
- Platelets $\geq$ 50 x 10^9/L and more than 5 days since last transfusion;
- Creatinine clearance $\geq$ 50 mL/min;
- Bilirubin $\leq$ 1.5 x upper normal limit (UNL) (direct if known Gilbert's);
- AST and ALT $\leq$ 1.5 x UNL ($\leq$ 3 x UNL if hepatic involvement with CLL);
- Potassium and calcium (within normal limits for laboratory (supplementation permitted));
- Fasting glucose < 7.8 mm/L (AND HbA1c $\leq$ 8% if diabetic).

Ineligibility Criteria

- Prior treatment with buparlisib (BKM120);
- Progression to high grade lymphoma or myelodysplasia;
- History of other malignancies, except those which have been curatively treated and require no ongoing therapy;
- Known hypersensitivity to study drug or its components;
- Serious illness or medical condition;
- Uncontrolled or significant cardiovascular disease including left ventricular ejection fraction < 50%;
- Mood disorders (see Section 5.2.6);
- Impairment of gastrointestinal function or GI disease that may significantly alter the absorption of buparlisib;
- Patients unable to swallow capsules;
- Patients on strong CYP3A inhibitors/inducers or therapeutic doses of warfarin-like anticoagulants;
- Patients on drugs with a known risk to induce Torsades de Pointes (see Appendix VIII)
- Patients receiving high dose steroid therapy or another immunosuppressive agent;
- Patients with known HIV positivity;
- Patients with known CLL involvement of the central nervous system.

Pre-Treatment Evaluations

- History, physical exam, vital signs, ECOG performance status, toxicity/baseline symptoms, 12-lead ECG (within 7 days prior to registration);
- Hematology, biochemistry and coagulation (within 7 days prior to registration);
- Mood Questionnaires (within 7 days prior to registration);
- MUGA/LVEF (only if clinically indicated) (within 28 days prior to registration);
- Pregnancy test (within 7 days prior to registration) (if applicable);
- Direct anti-globulin test (DAGT) (within 7 days prior to registration);
- CT scan of neck, chest, abdomen and pelvis (within 21 days prior to registration);
- Bone marrow aspirate and biopsy for routine local pathology to assess CLL (within 28 days prior to registration);
- Hepatitis B surface antigen (HBsAg) (within 28 days prior to registration);
- Hepatitis C serology (within 28 days prior to registration);
- Fluorescence in situ hybridization (FISH) for 17p and 11q deletion (within 28 days prior to registration);
- Immunoglobulin variable region (IgV_H) mutation status (any time prior to registration);
- Peripheral blood for correlatives (within 28 days prior to registration).

Treatment

- Buparlisib will be given orally daily starting day 1 cycle 1. A cycle is defined as 28 days of treatment.

On Treatment Evaluations

- Physical exam, ECOG, vital signs (Day 1 each cycle);
- Hematology and Biochemistry (Days 1 and 14 cycle 1 and 2, then Day 1 each cycle thereafter; more frequently if clinically indicated);
- CT scan of neck, chest, abdomen and pelvis. (To be repeated 8, 16, and 24 weeks from registration and thereafter every 12 weeks. Patients who have no evidence of disease on CT at baseline can omit follow up scans unless palpable disease arises or there is clinical suspicion of disease progression.);
- Bone marrow aspirate and biopsy (at time other criteria for CR first met and 8 weeks later to confirm sustained CR; or if cytopenia of uncertain cause) (see Section 9);
- Assessment for minimal residual disease (MRD) (Optional – if CR criteria otherwise met) (see Section 9);
- Mood Questionnaires (Day 1 and 14 in cycles 1 and 2, then Day 1 each cycle and End of Treatment visit);
- Correlative blood work (At time of disease progression-if applicable) (See Section 17 and Laboratory Manual);
- Adverse events -patients to be evaluated continuously for adverse events.

Correlative Blood Work

- See Section 17 and Laboratory Manual.

Duration of Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgment of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 8.0;
- Tumour progression or disease recurrence as defined in Section 10.0;
- Request by the patient;
- Completion of therapy as outlined in Section 8.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

1.0 OBJECTIVES

1.1 Primary Objective

To determine the overall response rate (complete + partial response) to oral buparlisib in patients with relapsed and refractory chronic lymphocytic leukemia.

1.2 Secondary Objectives

1.2.1 To evaluate the safety and tolerability of buparlisib administered at 100 mg per day on a 28 day cycle, in patients with previously treated chronic lymphocytic leukemia.

1.2.2 To evaluate additional measures of efficacy including:

- duration of response rate
- progression free survival

1.2.3 To explore potential molecular factors which may be prognostic or predictive of response or of relapse including:

- correlation between clinical response to buparlisib and MTT assay (cell viability assay) in B-CLL exposed ex-vivo to buparlisib
- correlation between response to buparlisib and western blot and flow cytometry analysis of key proteins involved in the PI3K pathway
- identification of mechanisms of resistance among patients who relapse after therapy with buparlisib

1.2.4 To prospectively validate a survival prediction scale.

2.0 BACKGROUND INFORMATION AND RATIONALE

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of malignant B lymphocytes expressing the surface antigens CD19, CD20, CD23 and CD5 *[Klein 2001]*. These B-CLL cells display altered apoptosis that is caused by both primary tumour features and co-dependent stromal elements *[Burger 2000]*. Current treatments for this disease include alkylating agents (chlorambucil, cyclophosphamide, bendamustine), purine analogs such as fludarabine, and immunotherapeutic agents (rituximab, alemtuzumab), either given as single agents or in combination. The current gold standard for CLL treatment is fludarabine, cyclophosphamide and rituximab (FCR). However, none of these standard treatments result in cure, supporting the need for investigation of new therapeutic targets and drug development in CLL as well as markers that can predict clinical response to therapy *[Gribben 2011]*.

The phosphatidylinositol 3-kinase (PI3K) cascade is a critical component of survival signaling including PI3K-activated Akt (phosphorylated Akt) which inhibits cell death pathways by inactivating pro-apoptotic proteins such as Bad, procaspase-9 and members of the Forkhead transcription factor family. Overexpression of PI3K appears to play a critical role in B-CLL cell survival. Recently, the PI3Kδ inhibitor idelalisib showed preclinical activity in CLL lymphocytes and is now in clinical trials in combination with chemotherapeutic and immunotherapeutic agents in patients with relapsed B-cell malignancy including CLL *[Herman 2010, Lannutti 2011, Furman 2014]*. The pan class I PI3K inhibitor buparlisib (BKM120, Novartis Pharma AG, Basel, Switzerland) is currently under investigation in phase I, II and III clinical trials in patients with advanced solid tumours *[Bendell 2012]*, *clinicaltrials.gov*).

In view of the critical role of PI3K in CLL homeostasis *[Liu 2009]*, *in vitro* cytotoxic effect of buparlisib was assessed in 3 B-CLL cell lines and in primary B-lymphocytes isolated from 65 B-CLL patient samples utilizing the MTT assay. The IC_{50} (drug concentration resulting in 50% cell death) obtained in the B-CLL cell lines JVM2, EHEB and MEC2 were 0.9±0.1, 0.7±0.1 and 0.7±0.1 μM respectively. Buparlisib was cytotoxic (IC_{50} below the maximum concentration (20μM) of buparlisib used in the MTT assay) in 78% of the primary B-CLL lymphocyte samples tested. It is known that patients whose CLL bears a 17p (del17) or 11q (del11) deletion have a poorer response to standard therapy and a shortened overall survival *[Grever 2007]*. Buparlisib was demonstrated to be cytotoxic in all patient samples harboring these deletions *[Amrein 2013].*

In the phase I clinical study, the maximum plasma concentration (Cmax) of buparlisib obtained after administration of the maximum tolerated dose of the drug was 5μM *[Grever 2007]*. Interestingly, 60% of the B-CLL samples tested by Amrein *[Amrein 2013]* have an IC_{50} below this Cmax. Furthermore, 5 out of the 6 patient samples with del11 or del17 have a clinically achievable IC_{50}. These results indicate that buparlisib may be useful as a single agent in CLL. MTT assay demonstrated buparlisib to be 3.6 times more toxic than idelalisib in malignant B-CLL lymphocytes *in vitro* in 20 patient samples. Furthermore buparlisib was cytotoxic (IC_{50}< 20μM) in 80% of these 20 samples tested while idelalisib was only cytotoxic (IC_{50}< 50μM) in 45% of these samples. CLL has a widely variable response to therapy. Positive correlations were observed between buparlisib cytotoxicity and the basal expression of Akt (r = 0.592, p = 2.468E-06, n =54), rictor (r = 0.418; p = 1.65E-03; n = 54), raptor (r = 0.463; p = 4.5E-03; n = 54), p70S6K (r = 0.584, p = 3.561E-06, n = 54) and 4E-BP1 (r = 0.371, p = 5.75E-03, n = 54) but not with PTEN, mTOR, IgVH or CD38 expression. Only patients very sensitive to buparlisib ($IC_{50} \leq 3$ μM) expressed low basal levels (below the cut off) of mTOR, raptor and p70S6K simultaneously. Thus, simultaneous expression of low basal levels of these three proteins may be useful to predict response to buparlisib.

In vitro studies have identified that stromal cells promote cell survival and drug resistance of B-CLL lymphocytes by cell-cell interaction and secretion of chemokines *[Hayden 2012]*. Buparlisib induced apoptosis in primary B-CLL lymphocytes both in the presence, and in the absence of BMS2 stromal cell support, indicating that malignant lymphocytes are not protected against the cytotoxic effect of buparlisib by the stromal microenvironment *[Amrein 2013]*. There is increasing evidence that the major cause of resistance to therapy in CLL patients is a consequence of a small number of leukemic cells that remain after treatment. This phenomenon, called minimal residual disease (MRD), is in part a consequence of protection conferred by the stromal microenvironment to the malignant lymphocytes; eradication of MRD by alemtuzumab and other agents improved overall and treatment-free survival in CLL patients *[Hayden 2012, Moreton 2005]*.

Although many patients are asymptomatic at diagnosis, CLL is a progressive disease and most patients eventually require treatment. Standard chemo-immunotherapy regimens are not curative and most patients require retreatment for their disease. Preclinical results demonstrate that the class I PI3K inhibitor buparlisib may be useful as a single agent in CLL patients independently of their IgVh mutational status, CD38expression or genomic deletions (del11 and del17). Furthermore, combination of different biomarkers (expression of mTOR, raptor and p70S6K) may predict the response to buparlisib treatment. Also, buparlisib abolishes the protection against apoptosis and drug resistance conferred by the microenvironment to the primary B-CLL lymphocytes *in vitro*. For these reasons, this clinical trial will test buparlisib in patients with relapsed and refractory CLL. The efficacy of buparlisib will be determined and predictors of response to therapy will be validated. Ultimately, the identification of predictive biomarkers can help personalize the use of PI3K inhibitors in patients with CLL.

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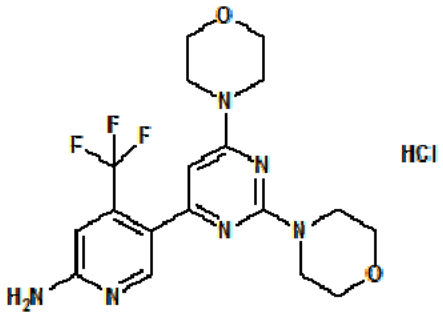

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4.0 TRIAL DESIGN

This is an open-label, single-arm phase II study of buparlisib, 100 mg orally daily for patients with relapsed or refractory chronic lymphocytic leukemia. This trial is being conducted by the Canadian Cancer Trials Group, with support in the form of partial funding and study drug provision from Novartis.

5.0 STUDY POPULATION

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of registration. Questions about eligibility criteria should be addressed prior to registration.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Previously documented CLL as defined by the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines *[Hallek 2008]* that is recurrent or relapsed after previous therapy and that requires treatment (see Appendix VI).

5.1.2 Age $\geq$ 18 years.

5.1.3 ECOG Performance Status score of 0, 1 or 2 (See Appendix II).

5.1.4 Patients must have a life expectancy of at least 12 weeks. Those who have previously completed curative treatment of a malignancy other than CLL will be eligible.

5.1.5 Patients must have at least ONE of:

Lymphocyte count $\geq$ 10 x 10^9/L

OR

At least one pathologically enlarged lymph node ($\geq$ 2 x 2 cm) by CT scan

5.1.6 *Previous Therapy*

Patients must have received at least 1 prior systemic treatment regimen (single agent or combination therapy). There is no upper limit on number of prior regimens. Patients who have received prior autologous or allogeneic stem cell transplantation are eligible.

Patients must have recovered (to $\leq$ grade 2) from all reversible toxicity related to prior systemic therapy, and have adequate washout from prior chemotherapy and investigational agents defined as the longest of:

- two weeks
- standard cycle length of prior regimen (e.g. 28 days for FCR)
- 5 half-lives for investigational drugs

Not permitted:

- prior treatment with buparlisib (BKM120)

Radiation:
Patients may have had radiation, provided a minimum of 21 days has elapsed prior to enrollment. (Exceptions may be made for low dose palliative radiotherapy. Please call CCTG at 613-533-6430 PRIOR to registration if questions arise about the interpretation of this criterion). Patients must have recovered from any acute toxic effects from radiation prior to registration.

Surgery:
Previous surgery is permitted provided that wound healing has occurred and at least 14 days have elapsed if surgery was major.

5.1.7 *Laboratory Requirements*
(must be done within 7 days prior to registration)

Hematology	Absolute neutrophil counts (ANC)	$\geq 1.0 \times 10^9$/L
	Platelets	$\geq 50 \times 10^9$/L and more than 5 days since last transfusion
Chemistry	Creatinine clearance*	≥ 50 mL/min
	Bilirubin**	≤ 1.5 x upper normal limit (UNL)
	Alanine aminotransferase (AST) and aspartate aminotransferase (ALT)	≤ 1.5 x UNL ≤ 3 x UNL if hepatic involvement with CLL
	Potassium and calcium	Within normal limits for laboratory (supplementation permitted)
	Glucose (fasting)	< 7.8 mmol/L (AND HbA1c ≤ 8% if diabetic)

* Creatinine clearance as calculated by Cockcroft-Gault formula or by 24 hour urine measurement:

Females: $GFR = \frac{1.04 \times (140\text{-age}) \times \text{weight in kg}}{\text{serum creatinine in } \mu\text{mol/L}}$

Males: $GFR = \frac{1.23 \times (140\text{-age}) \times \text{weight in kg}}{\text{serum creatinine in } \mu\text{mol/L}}$

** Direct if patient known to have Gilbert's syndrome

5.1.8 Patient consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the CCTG Study Coordinator that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, a standard consent form for the trial will not be provided but a sample form is provided on the IND.216 webpage. A copy of the initial REB approval and approved consent form must be sent to the central office. The patient must sign the consent form prior to registration and prior to tests which are considered to be study specific (see Section 6). Please note that the consent form for this study must contain a statement which gives permission for the CCTG and monitoring agencies to review patient records.

5.1.9 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. (Please call CCTG at 613-533-6430 if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves that patients registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.10 In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient registration.

5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

5.2.1 Progression to high grade lymphoma (Richter's transformation) or myelodysplasia.

5.2.2 Patients with a history of other malignancies, except those which have been curatively treated and require no ongoing therapy.

5.2.3 Patients with known hypersensitivity to the study drug or its excipients.

5.2.4 The following are exclusions for enrolment on the study:

- Pregnant or lactating women. (N.B. All women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to registration).
- Men and women of childbearing potential who do not agree to use adequate contraception (barrier method of birth control or abstinence, see Section 11.3.1)
  - prior to study entry
  - while taking buparlisib
  - and after completion of study therapy for 12 weeks in men and 4 weeks in women.

  (Should a woman become pregnant or suspect she is pregnant, or should a man father a child, while participating in this study, she/he should inform the treating physician immediately).

5.2.5 Serious illness or medical condition which would not permit the patient to be managed according to the protocol, including, but not limited to:

a) active uncontrolled or serious infection (viral, bacterial or fungal);
b) pulmonary disease requiring oxygen;
c) known HIV infection or other immune deficiency disorders (except for CLL);

d) uncontrolled auto-immune hemolytic anemia (AIHA) or auto-immune thrombocytopenia (ITP)
e) acute or chronic pancreatitis

5.2.6 Uncontrolled or significant cardiovascular disease including:

- Myocardial infarction within 12 months
- Uncontrolled angina within 6 months
- Clinically significant congestive heart failure (eligible if controlled and LVEF $\geq$ 50%)
- Stroke, TIA or other ischemic event within 12 months
- Severe cardiac valve dysfunction
- Left ventricular ejection fraction < 50% (only required if symptoms suggestive or history of cardiovascular disease)
- Uncontrolled hypertension

5.2.7 Patient has any of the following mood disorders:

- Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g. risk of doing harm to self or others)
- Score of $\geq$ 12 on the PHQ-9 questionnaire (posted on IND 216 website)
- Score of $\geq$ 15 on the GAD-7 mood scale (posted on IND 216 website)
- $\geq$ CTCAE Version 4.0 grade 3 anxiety
- Patient selects a positive response of '1,2,3' to question 9 (suicidal ideation) in the PHQ-9 questionnaire

5.2.8 Patients who have received prior buparlisib (BKM120.

5.2.9 Patients with impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of buparlisib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

5.2.10 Patients who are unable to swallow capsules.

5.2.11 Patients on strong CYP3A inhibitors/inducers or therapeutic doses of warfarin-like anticoagulants (must have discontinued $\geq$ 7 days prior to day 1). Patients may receive low molecular weight heparin if indicated. See Appendix VII for a list of prohibited medications.

5.2.12 Patients on drugs with a known risk to induce Torsades de Pointes (see Appendix VIII).

5.2.13 Patients receiving high dose steroid therapy or another immunosuppressive agent. Note: Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed. Patients who are on stable moderate dose corticosteroid treatment for treatment of conditions other than CLL ($\leq$ dexamethasone 4 mg/day, prednisone 25 mg/day) for at least 14 days before start of study treatment are eligible.

5.2.14 Patients with known HIV positivity.

5.2.15 Patients with known CLL involvement of the central nervous system.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	• history • height/weight • ECOG performance status • vital signs: blood pressure & pulse • clinical tumour / organomegaly measurements (if applicable)	Within 7 days prior to registration
Hematology	CBC, differential (including lymphocytes)	
Coagulation	PT, PTT	
Biochemistry	• creatinine • potassium • bilirubin (fractionated if known Gilbert's) • AST, ALT • alkaline phosphatase • calcium • albumin • glucose (fasting) • LDH • B2 microglobulin • HbA1c (if diabetic)	
Radiology[1]	• CT scan of neck, chest, abdomen and pelvis	Within 21 days[2] prior to registration
Mood Questionnaires[3]	• Patient self-rating mood scales for depression (PHQ-9) and anxiety (GAD-7)*	Within 7 days prior to registration
Cardiac Investigations	• 12-lead ECG	Within 7 days prior to registration
	• MUGA/LVEF (only if symptoms suggestive or history of cardiovascular disease)	Within 28 days prior to registration
Bone Marrow Studies	• Bone marrow aspirate and biopsy for routine local pathology to assess CLL	Within 28 days prior to registration
Other Investigations	• Direct anti-globulin test (DAGT)	Within 7 days prior to registration
	• Serum or Urine Pregnancy test* (for women of childbearing potential)	
	• Fluorescence in situ hybridization (FISH) for 17p and 11q deletion. Can be tested in bone marrow aspirate sample OR peripheral blood. Patient can be enrolled on trial before results are known.	Within 28 days prior to registration
	• Hepatitis B surface antigen (HBsAg) • Hepatitis C serology	
	• Immunoglobulin variable region (IgV_H) mutation status. Can be tested on blood or bone marrow. Patient can be enrolled on trial before results are known.	Any time prior to registration
Correlative blood work	• Peripheral blood processed as per Section 17 and Laboratory Manual*	Within 28 days prior to registration
Adverse Event[4]	• Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	Within 7 days prior to registration

[1] To ensure comparability, baseline and subsequent CT scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

[2] Twenty-eight days if negative.

[3] Patient self-rating mood questionnaires (PHQ-9 and GAD-7) are posted on the IND 216 website.

[4] Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V) with the exception of hematological and psychiatric toxicity which should be graded according to IW CLL guidelines (see Section 8.3).

* These tests are considered study-specific and must be performed AFTER the informed consent form has been signed.

7.0 ENTRY/REGISTRATION PROCEDURES

7.1 Entry Procedures

All registrations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the IND. 216 trial specific web-site. If sites experience difficulties accessing the system and/or registering patients, please contact the help desk (link in EDC) or the IND.216 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG IND.216)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- height and weight

7.2 Registration

Registration will be provided electronically.

Note: All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration.

8.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient registration.

8.1 Chemotherapy Treatment Plan

8.1.1 *Drug Administration*

Agent	Route	Starting Dose	Frequency	Schedule
Buparlisib (BKM120)	oral	100 mg	Daily	Every 28 days
Safety will be reviewed after the first 3 patients are enrolled. If excess toxicity observed, starting dose will be reduced to 80 mg daily for subsequent patients. CCTG will advise.				

A complete treatment cycle of buparlisib is defined as 28 days of once daily continuous treatment with a flat-fixed dose, i.e. not based on body weight or body surface area. There will be no breaks between dosing cycles.

The following general guidelines should be followed for buparlisib administration:

- Patients should be instructed to take the dose of buparlisib once daily in the morning, at approximately the same time each day.
- Buparlisib can be taken with or without food.
- Buparlisib should be taken with a glass of water. Patients should swallow the capsules whole and not chew them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- If the patient forgets and does not take their dose before 6:00 pm, then the dose should be withheld that day and buparlisib should be restarted the following day.
- Patients must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, starfruits and cranberry juice from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A interaction. Regular orange (Citrus X sinensis) juice is allowed.

8.1.2 *Premedication*

Routine anti-emetic premedication is not required but may be administered at the physician's discretion. Nausea and vomiting should be managed symptomatically if they arise. Non-steroid therapies are preferred since steroids may confuse the interpretation of response. Strong CYP3A inhibitors / inducers are prohibited and other CYP450 substrates should be used with caution (see Appendix VII).

Tumour lysis syndrome is uncommon in patients treated with buparlisib or idelalisib, an alternative PI3 kinase inhibitor. Investigators should follow standard local procedures for prophylaxis (e.g. hydration and allopurinol for those with high disease burden).

Buparlisib may cause lymphopenia thus prophylaxis with appropriate anti-microbial agents could be considered for patients at particular risk for serious viral infection or pneumocystis at the discretion of the investigator according to local protocols. Strong CYP3A inhibitors / inducers are prohibited and other CYP450 substrates should be used with caution (see Appendix VII).

Details of any premedication given must be properly recorded on the electronic CRFs.

8.2 Patient Self Rating Mood Questionnaires

The patient must complete two different mood questionnaires (PHQ-9 and GAD-7) on day 1 and day 14 in cycles 1 and 2, then day 1 each cycle, as well as the End of Treatment visit (Questionnaires are posted on the IND.216 website).

Instructions on how to instruct the patient to complete the questionnaires, as well as how to determine the scores will be provided together with each instrument.

8.3 Toxicity Grading

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V) with the exception of hematological and mood questionnaires toxicity which should be graded according to IW CLL guidelines below. Guidance is also provided for interpretation of mood questionnaire scores.

Toxicity grading based on mood questionnaire scores:

PHQ-9 (Depression Score)			**GAD-7** (Anxiety Score)		
Score	Severity	CTCAE grading	Score	Severity	CTCAE grading
0-4	None	Normal	0-4	None	Normal
5-9	Mild	Grade 1	5-9	Mild	Grade 1
10-19	Moderate	Grade 2	10-14	Moderate	Grade 2
20-27	Severe	Grade 3	$\geq$ 15	Severe	Grade 3
Investigator assessment for suicidal ideation is required for any patient who does not answer Question #9 or the whole PHQ-9 questionnaire. The grading guidance above may be overruled at the discretion of the provider performing a psychiatric consult.					

Hematology toxicity grading based on IW CLL guidelines:

Grade*	Decrease in platelets** (nadir) from pre-treatment value	Decrease in Hb*** (nadir) from pre-treatment value	Absolute neutrophil**** count/µL (nadir)
0	No change to 10%	No change to 10%	≥ 2000
1	11 – 24%	11 – 24%	≥ 1500 and < 2000
2	25 – 49%	25 – 49%	≥ 1000 and < 1500
3	50 – 74%	50 – 74%	≥ 500 and < 1000
4	≥ 75% OR platelets < 20 at any time	≥ 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 pre-treatment will be recorded as grade 5.

** Platelet counts must be below normal levels for grades 1 to 4. If at any level of decrease, the platelet count is < 20 x 10^9/L, this will be considered grade 4 toxicity.

*** Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. In the event of red cell transfusion within 14 days prior to the baseline value, patient will be inevaluable for Hb toxicity. 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, 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. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

Grading scale for hematologic toxicity in CLL studies [Hallek 2008]

8.4 Dose Adjustments

Dose Level	Daily dosing of buparlisib in 28 day cycle
-1	Reduce by 20 mg daily
-2	Reduce by 20 mg daily
-3	If required patients must discontinue protocol therapy

Doses will be reduced for hematologic and other adverse events considered related to buparlisib. Dose adjustments are to be made according to the system showing the greatest degree of toxicity.

The most frequently observed toxicities with buparlisib include transaminitis, skin toxicity, hyperglycemia, GI effects (diarrhea, anorexia, constipation, nausea, vomiting, mucositis), fatigue, abdominal pain and mood alterations.

The guidelines which follow outline buparlisib dose adjustments for several of these toxic effects. If a patient experiences several toxicities and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

Doses of buparlisib reduced for toxicity may not be re-escalated. For each patient, a maximum of 2 dose reductions will be allowed. Patients requiring an additional dose reduction will stop buparlisib and come off study.

Patients requiring a buparlisib dose delay of > 28 days must permanently discontinue buparlisib and come off study.

8.4.1 *Hematologic Toxicity*

Worst Hematologic Toxicity*	Management
Grade 1 or 2	Maintain dose level
Grade 3 or 4 neutropenia Grade 3 thrombocytopenia	Omit dose until resolved to ≤ grade 1 (or baseline) then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then decrease one dose level ***
Grade 4 thrombocytopenia	Omit dose until resolved to ≤ grade 1 (or baseline) then decrease one dose level ***
Febrile neutropenia**	Omit dose until resolved to ≤ grade 1 then decrease one dose level

* As defined according to IW CLL guidance in Section 8.3.

** ANC < 1 x 10^9/L with a single temperature of ≥ 38.3°C or a sustained temperature of ≥ 38°C for more than one hour.

*** After treatment is resumed at a lower dose, if the same toxicity recurs with the same severity, then the next treatment should be resumed at a lower dose regardless of duration. If the same toxicity occurs with a worse severity, then the patient must discontinue treatment with buparlisib.

If a third dose reduction is required, patients must discontinue protocol therapy.

If therapy is delayed by > 28 days, patients must discontinue protocol therapy.

8.4.2 *Renal Toxicity*

Worst Toxicity Serum creatinine	Management
Grade 1	Maintain dose level
Grade 2 (> 1.5-3 x baseline or ULN)	Omit dose until resolved to ≤ grade 1 (or baseline) then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then decrease one dose level*
Grade 3 or 4 (> 3 x baseline or ULN)	Permanently discontinue buparlisib

* After treatment is resumed at a lower dose, if the same toxicity recurs with the same severity, then the next treatment should be resumed at a lower dose regardless of duration. If the same toxicity occurs with a worse severity, then the patient must discontinue treatment with buparlisib.

If a third dose reduction is required, patients must discontinue protocol therapy.

If therapy is delayed by > 28 days, patients must discontinue protocol therapy.

8.4.3 *Hepatic Toxicity*

In event of hepatotoxicity, consider alternate causes (cholestasis, viral, malignant, concomitant medication, etc.) and refer to hepatologist as clinically indicated.

Bilirubin*	**Dose of buparlisib******	**Follow-up**
Grade 1	No change	See Section 9
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ grade 1 then: If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, decrease one dose level**	LFTs weekly or more frequently if clinically indicated until resolved to ≤ grade 1.
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ grade 1 then: If resolved in ≤ 7 days, decrease one dose level** If resolved in > 7 days, discontinue buparlisib	LFTs weekly or more frequently if clinically indicated until resolved to ≤ grade 1, then every other week until off treatment and recovered to ≤ grade 1
Grade 4 (>10 x ULN)	Discontinue buparlisib	LFTs weekly or more frequently if clinically indicated until resolved to ≤ grade 1 (or stable)
AST or ALT		
Same grade as baseline:	No change	See Section 9
Increase from baseline: • < 1.5 ULN at baseline, increases to 1.5 to < 3 x ULN • Grade 1 to grade 2	Continue with a one dose level reduction	LFTs weekly or more frequently if clinically indicated until resolved to ≤ grade 1
Increase of two grades from baseline: • Grade 0 to Grade 2*** • Grade 1 to Grade 3***	Omit dose until resolved to ≤ grade 1 then reduce 1 dose level**. If no recovery ≤ 28 days, permanently discontinue buparlisib.	LFTs weekly or more frequently if clinically indicated until resolved to ≤ grade 1, then every other week until off treatment and recovered to ≤ grade 1
Grade 4 (> 20.0 x ULN)	Discontinue buparlisib	LFTs weekly or more frequently if clinically indicated until resolved to ≤ grade 1 (or stable)
AST/ALT and bilirubin*		
AST or ALT > 3 x ULN (grade 2) and total bilirubin > 2 x ULN	Discontinue buparlisib	LFTs weekly or more frequently if clinically indicated until resolved to ≤ grade 1 (or stable)

* If known Gilbert's, use direct bilirubin to grade

** After treatment is resumed at a lower dose, if the same toxicity recurs with the same severity, then the next treatment should be resumed at a lower dose regardless of duration. If the same toxicity occurs with a worse severity, then the patient must discontinue treatment with buparlisib.

*** If grade 2 or 3 and bilirubin > 2 x ULN, meets criteria below to discontinue buparlisib. In case of recurring Grade 3 or higher toxicity after re-challenge, buparlisib should be permanently discontinued.

**** If a third dose reduction is required or therapy is delayed by > 28 days, patients must discontinue protocol therapy.

8.4.4 *Mood Disorders (e.g. Anxiety, Depression, Agitation)*

Worst Toxicity*	Management
Grade 1 or grade 2 without increase in GAD7/PHQ9 scores from baseline	Maintain dose level. Consider psychiatric consultation at the investigator's discretion and introduce optimal management.
Grade 2 with increase in GAD7/PHQ9 scores from baseline	Omit dose until resolved to ≤ Grade 1 or baseline status. Consider psychiatric consultation at the investigator's discretion and introduce optimal management**. First event: if the condition resolves to Grade ≤ 1 or to baseline status, continue to co-medicate and then maintain the dose level. Second and further events: if the condition resolves to Grade ≤ 1 or to baseline status, continue to co-medicate and then decrease 1 dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1 or baseline status, then decrease one dose level***. Co-medicate** Psychiatric referral recommended.
Grade 4	Discontinue buparlisib Urgent psychiatric referral
Suicidal ideation regardless of grade	Interrupt buparlisib. Refer for psychiatric consultation for optimal management and to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient's PHQ-9 self-assessment.

* See Section 8.3.

** Under the guidance of the psychiatrist if needed. Possible first line management for anxiety might include lorazepam (e.g. 0.5 mg po tid), clonazepam (e.g. 1 mg po bid) or haloperidol (0.5-1 mg po bid). Options for first line treatment of depression might include citalopram (e.g. starting doses 10-20mg, usual treatment dose 20-60 mg/d). In the event of agitation interrupting sleep, consider trazodone (e.g. 25 to 50 mg at night).

*** After treatment is resumed at a lower dose, if the same toxicity recurs with the same severity, then the next treatment should be resumed at a lower dose regardless of duration. If the same toxicity occurs with a worse severity, then the patient must discontinue treatment with buparlisib.

If a third dose reduction is required, patients must discontinue protocol therapy.

If therapy is delayed by > 28 days, patients must discontinue protocol therapy.

8.4.5 *Hyperglycemia*

Fasting plasma glucose (FPG)	Management *
Grade 1	Maintain dose level Check FPG at least weekly for 8 weeks, then at least every 2 weeks
Grade 2	If signs or symptoms of hyperglycemia (e.g. mental status changes, excessive thirst, polyuria) manage as per grade 3 below If asymptomatic, maintain dose and recheck FPG in 24 hours. If grade worsens or improves follow specific grade recommendations. If remains at grade 2: • Maintain dose level and monitor FPG at least weekly until resolves to ≤ grade 1 • Initiate or intensify appropriate anti-diabetic treatment** such as metformin; consider adding a second oral agent if no improvement after several days • If FPG does not resolve to ≤ grade 1 within 14 days after institution of anti-diabetic treatment, reduce buparlisib by one dose level*** Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
Grade 3	Omit buparlisib, initiate or intensify medication with anti-diabetic therapy, recheck FPG within 24 hours. If grade worsens or improves follow specific grade recommendations. If remains at grade 3: • Continue to omit buparlisib • Monitor FPG at least twice weekly until resolves to ≤ grade 1 • If FPG resolves to ≤ grade 1 in 7 days or less then restart buparlisib and decrease one dose level *** • If FPG remains greater than grade 1 severity for more than 7 days, then discontinue buparlisib • Continue oral anti-hyperglycemic therapy** such as metformin as appropriate • Check FPG weekly for 8 weeks, then every 2 weeks
Grade 4	Omit buparlisib, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. If grade improves then follow specific grade recommendations. If FPG is confirmed at Grade 4: • discontinue buparlisib • check FPG at least weekly for 8 weeks, then at least every 2 weeks until resolved

* At any grade give appropriate dietary advice

** Some oral anti-diabetic drugs are CYP2C9 substrates (glipizide, glimepiride, gliclazide, glibenclamide, nateglinide, rosiglitazone) and should be used with caution. See Appendix VII.

*** If a third dose reduction is required, patients must discontinue protocol therapy.
If therapy is delayed by > 28 days, patients must discontinue protocol therapy.

8.4.6 *Interstitial Pneumonitis*

Symptoms suggestive of pneumonitis require evaluation and investigation with CT imaging and bronchoscopy as clinically appropriate.

Worst Toxicity	Management*
Grade 1	Maintain dose level
Grade 2	Reduce by one dose level** and continue therapy OR Omit buparlisib if symptoms are troublesome. If resolved to ≤ grade 1 within 28 days, may restart at a reduced dose level.
Grade 3	Omit dose until resolved to ≤ grade 1. May restart buparlisib within 28 days at a reduced dose level**, if evidence of clinical benefit.
Grade 4	Discontinue buparlisib

* Consider corticosteroids if symptoms troublesome and infective origin excluded (patients requiring high dose steroids may become inevaluable for response assessment)

** After treatment is resumed at a lower dose, if the same toxicity recurs with the same severity, then the next treatment should be resumed at a lower dose regardless of duration. If the same toxicity occurs with a worse severity, then the patient must discontinue treatment with buparlisib.

If a third dose reduction is required, patients must discontinue protocol therapy.

If therapy is delayed by > 28 days, patients must discontinue protocol therapy.

8.4.7 *Skin Reactions*

Worst Toxicity	Management*
Grade 1	Maintain dose level
Grade 2	Tolerable maculopapular rash: • Initiate/intensify appropriate skin toxicity therapy, e.g. with topical steroids BID and oral antihistamines. • Maintain dose level. Intolerable maculopapular rash: • Omit dose and initiate/intensify appropriate skin toxicity therapy, e.g. with topical steroids BID, oral antihistamines and oral steroids if required*. First occurrence: • If resolved to grade ≤ 1 in < 2 weeks, maintain dose level. • If resolved grade ≤ 1 in more than 2 weeks, reduce 1 dose level. • Consider continuing skin toxicity therapy up to 2 weeks after re-introduction of buparlisib. In case of flare after cessation of skin toxicity therapy, consider prompt reimplementation. Second occurrence: omit dose and follow treatment guidance above. • Once resolved to grade ≤ 1, reduce 1 dose level**.
Grade 3	Omit dose until resolved to ≤ grade 1 then decrease one dose level**
Grade 4	Discontinue buparlisib

* Co-medicate as appropriate with antihistamines, topical or oral steroids (patients requiring high dose steroids may become inevaluable for response assessment), moisturizers, sunscreen. In addition for acneiform rash consider topical or oral antibiotics and bacterial swab if infection suspected.

** After treatment is resumed at a lower dose, if the same toxicity recurs with the same severity, then the next treatment should be resumed at a lower dose regardless of duration. If the same toxicity occurs with a worse severity, then the patient must discontinue treatment with buparlisib.

If a third dose reduction is required, patients must discontinue protocol therapy.

If therapy is delayed by > 28 days, patients must discontinue protocol therapy.

8.4.8 *Other Non-Hematological Adverse Events, Including Diarrhea*

Worst Toxicity	Management
Grade 1	Maintain dose level
Grade 2	Symptomatic management*; continue dosing with no change. For persistent grade 2 effects, investigator may decrease by one dose level
Grade 3 **	Omit dose*** until resolved to ≤ grade 1 then decrease one dose level****
Grade 4	Permanently discontinue buparlisib

* For buparlisib induced diarrhea, standard treatment including prompt commencement of loperamide is recommended alongside rehydration (can refer to Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea, *[Benson 2004]*).

** Omit for grade 3 nausea or vomiting only if it cannot be controlled with optimal anti-emetics.
Omit for fatigue only if significant worsening from baseline (investigator discretion).

*** Patients requiring treatment hold for >28 days will discontinue protocol therapy.

**** After treatment is resumed at a lower dose, if the same toxicity recurs with the same severity, then the next treatment should be resumed at a lower dose regardless of duration. If the same toxicity occurs with a worse severity, then the patient must discontinue treatment with buparlisib.

8.5 Duration of Therapy

Treatment will continue until the criteria for removal from protocol treatment have been met (see section 12.0).

8.6 Concomitant Therapy

Permitted:

- Other supportive and palliative care (e.g. pain control) as required throughout the study.
- Anti-emetics or anti-diarrheal agents as required.
- Growth factors may be used according to centre policy.
- Low molecular weight heparin if indicated.

Permitted with caution:

- CYP450 substrates other than strong CYP3A4 inhibitors and inducers (see Appendix VII).
- Drugs with possible or conditional risk of inducing Torsades de Pointes (see Appendix VIII).

Not permitted:

- Strong CYP3A4 inhibitors and inducers (see Appendix VII).
- Drugs with known risk to induce Torsades de Pointes (see Appendix VIII).
- Warfarin.
- Other anti-cancer therapy or investigational therapy.

Details of any concomitant medications given should be recorded on the appropriate Electronic Case Report Form.

Infections including Pneumocystis Jiroveci pneumonia (PJP) and cytomegalovirus (CMV) reactivation have been observed in patients with CLL treated with alternate PI3 kinase inhibitors. Opportunistic infections have not been associated with buparlisib therapy to date. Physicians should remain vigilant and investigate as clinically appropriate in event of fever or respiratory symptoms. Prophylaxis can be considered in those at high risk at investigator discretion.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

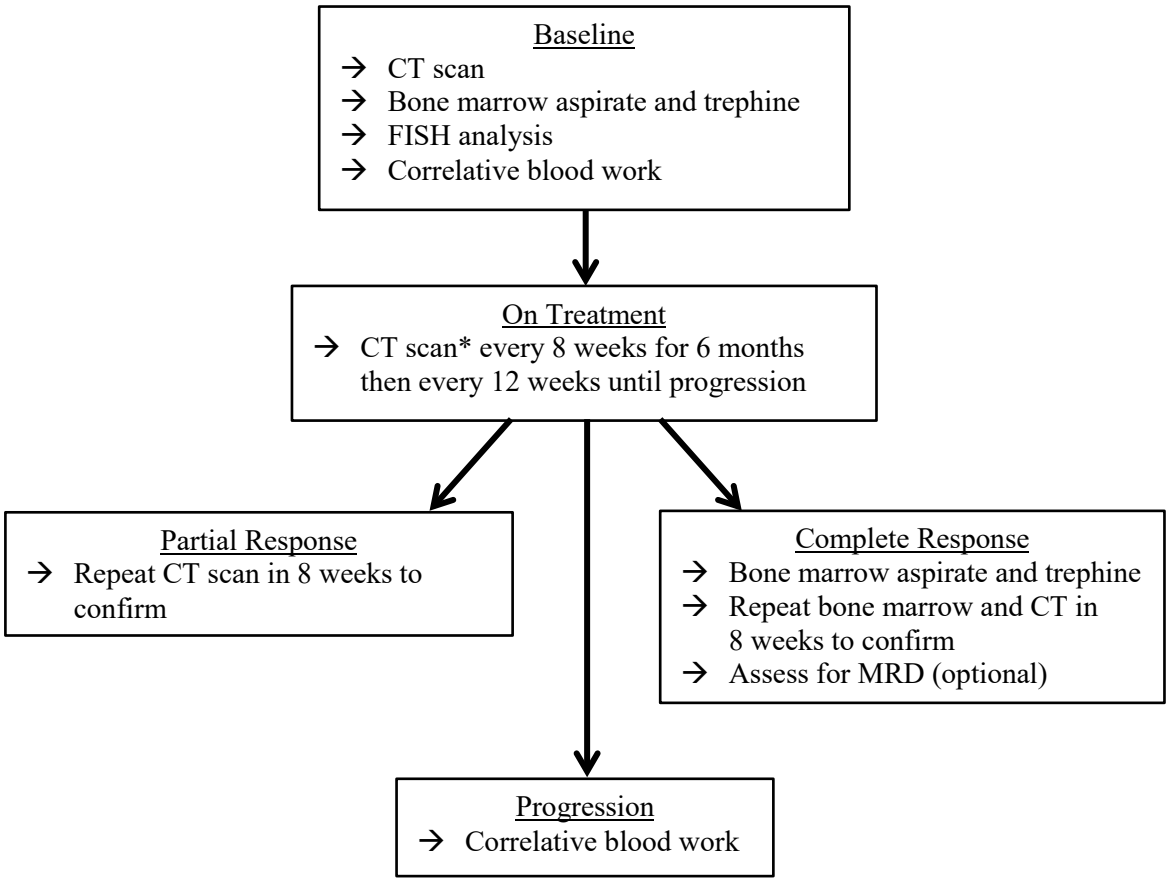
9.1 Evaluation During Protocol Treatment

Investigations			Timing
History and Physical Exam including:	• History • Weight • ECOG Performance status • Blood pressure and pulse • Clinical tumour / organomegaly measurements (if applicable)		Day 1 each cycle
Hematology[1]	CBC, differential (including lymphocytes)		Days 1 and 14 cycle 1 and 2[2] Day 1 each cycle thereafter[2] Tumour lysis monitoring on days 1, 2, and 3 of cycle 1 required only in first 4 patients treated, see below[6]
Biochemistry[1]	• creatinine • potassium • bilirubin (fractionated if known Gilberts) • LDH • AST, ALT	• calcium • albumin • glucose (fasting)[5] • phosphate[6] • uric acid[6] • lipase	
Radiology[3]	• CT scan of neck, chest, abdomen and pelvis		• To be repeated 8, 16, and 24 weeks from registration and thereafter every 12 weeks[7]. • At time PR or CR criteria are otherwise met and 8 weeks after PR or CR to confirm.
Assessment for Minimal Residual Disease (MRD) (Optional)	MRD assessment either by: • 4-color Flow Cytometry (MRD Flow) or • Allele Specific Oligonucleotide PCR on peripheral blood or • Flow cytometry or immunohistochemistry on bone marrow		Desirable if CR criteria otherwise met, but optional.
Bone Marrow	• Bone marrow aspirate and biopsy		At time other criteria for CR first met and 8 weeks later to confirm sustained CR or if cytopenia of uncertain cause.
Correlative blood work	• Whole blood processed as per Section 17 and Laboratory Manual		At time of disease progression (if applicable)
Mood Questionnaire	• Patient self-rating mood scales for depression (PHQ-9) and anxiety (GAD-7)		Days 1 and 14 cycle 1 and 2, Day 1 of each cycle thereafter and end of treatment visit
Adverse Events[4]	Patients must be evaluated each cycle for adverse events		

footnotes on next page …

1	Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
2	See Section 8 for additional monitoring of AST/ALT and bilirubin with hepatic toxicity.
3	To ensure comparability, the baseline CT scans and subsequent CT scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Patients with an unconfirmed PR or CR should have scans repeated after 8 weeks to confirm response.
4	Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V) with the exception of mood questionnaires and hematological toxicity which should be graded according to IW CLL guidelines (see Section 8.3). Patients whose treatment is interrupted due to an adverse event or clinically significant laboratory value must be followed up at least once a week for 4 weeks and subsequently at approximately 4 week intervals until resolved to ≤ grade 2.
5	More frequently in event of hyperglycemia, see Section 8.4.5.
6	The first 4 patients treated on study will require monitoring for tumour lysis on days 1, 2 and 3 of cycle 1 only: calcium, creatinine, potassium, phosphate, uric acid. CCTG will notify centres if this applies at the time of registration.
7	Patients who have no evidence of disease on CT at baseline can omit follow up scans unless palpable disease arises or there is clinical suspicion of disease progression.

9.2 Overview of Efficacy Evaluations



* Patients who have no evidence of disease on CT at baseline can omit follow-up scans unless palpable disease arises or there is clinical suspicion of disease progression.

Always consult Tables in Section 6 and 9 for details of all investigations required.

9.3 Evaluation After Protocol Treatment

All patients will be seen 4 weeks after the end of the last cycle (4 Week Post Treatment Report).

Patients whose treatment is permanently discontinued due to an adverse event or non-hepatic clinically significant laboratory value, should be followed as clinically indicated until resolved to ≤ grade 2. See Section 8.4.3 for more detailed guidance on patients who discontinue study treatment due to hepatic toxicity.

Follow-up beyond the 4 week treatment report is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ grade 2), late toxicities (including second malignancies) and death if within 30 days of last dose.

For patients who go off protocol treatment with objective CR, PR or SD ongoing, follow up including response assessment will be required every three months until relapse/progression (Follow-Up Report). If the patient starts new anticancer therapy, contact the study coordinator to discuss whether further follow-up is required.

For patients who go off protocol therapy with suspected PR or CR, an 8 week confirmatory response assessment including CT scanning will be required as per Sections 9.1 and 10.4, if not already performed.

A Death Report is only required if death occurs within 30 days of last dose or if patient dies before progression/relapse; due within 2 weeks of knowledge of death (see Appendix IV –Documentation for Study).

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 *Evaluable for Response*

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below, as recommended by Revised International Workshop on Chronic Lymphocytic Leukemia 2008 *[Hallek 2008]* and incorporating updated recommendations for refinement of clinical trial endpoints when using novel targeted agents *[Cheson 2012]*.

10.2 Documenting Enlarged Lymph Nodes

A maximum of the 6 largest nodes or nodal masses (minimum size > 1.5 x 1.5 cm) will be followed for response if enlarged at baseline. Wherever possible, enlarged nodes should be documented in the nodal disease case report form and followed by CT scan.

Notes:
If a patient does not have baseline lymphocytosis of at least 10 x 10^9/L, he or she must have at least one node $\geq$ 2 x 2 cm on CT scan to be eligible.

For additional enlarged lymph nodes/nodal masses beyond the maximum of 6 recorded, record them as "multiple enlarged nodes" as a single entry on the nodal disease case report form. Do not list each individual non-target node or node group as separate lesions.

10.3 Documenting Organomegaly

If hepatomegaly is documented on the baseline CT scan, record as extra nodal lesion ("Liver") on the baseline extra nodal case report form. Splenomegaly or splenic lesions on the baseline CT scan are considered nodal disease and should be recorded on the nodal case report form. At the time of follow-up CT examination, record "present" (if still enlarged or continuing enlargement seen) or "absent" (if normal size). Record "increased" ONLY if unequivocal progression of *substantial magnitude is seen (estimated 50% increase) and is believed sufficient to consider overall that the patient has progressed*.

10.4 Response

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below. In patients with limited disease at study entry, response will be assessed using only parameters that were abnormal at baseline.

Complete Response (CR): CR requires all of the following criteria, maintained for a period of at least 8 weeks.

- Peripheral blood lymphocytes (evaluated by blood and differential count) < 4 x 10^9/L;
- Absence of significant lymphadenopathy > 1.5cm in diameter on physical examination and CT scan

- No hepatomegaly or splenomegaly by CT scan
- Absence of constitutional symptoms attributable to disease
- Normal blood counts above the following values:
  - Neutrophils more than 1.5 x 10^9/L without need for exogenous growth factors
  - Platelets more than 100 x 10^9/L without need for exogenous growth factors
  - Hemoglobin more than 110 g/L without red blood cell transfusion or need for exogenous erythropoietin.
- A marrow aspirate and biopsy should be performed to demonstrate that a CR has been achieved at the time other criteria for CR are met.
  - To define a CR, the marrow sample must be at least normocellular for age, with < 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If lymphoid nodules are found, they will often reflect residual disease. These nodules should be recorded as "nodular PR". Immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells.
  - If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or when peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow.
  - Optional: The quality of the CR may be assessed for minimal residual disease by flow cytometry or by immunohistochemistry (IHC).
- Patients who fulfill all the criteria for a CR (including the marrow examinations described above) but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity will be considered as CR with incomplete marrow recovery (CRi). A repeat bone marrow should ideally be done in these patients when counts recover fully. If the bone marrow at this time reveals no CLL, these patients will be considered as having CR at that time.

Partial Response (PR): To define a PR, at least 1 of the criteria of Group A plus 1 of the criteria of Group B must be met and persist for ≥ 8 weeks, in the absence of any criteria definitive of progressive disease.

Group A:

- A 50% or more decrease in peripheral blood lymphocytes from the value before therapy.
- A 50% or more reduction in lymphadenopathy (by CT scan) either in the sum products of up to 6 measurable lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.
- A 50% or more reduction in the noted pretreatment enlargement of the spleen or liver, as estimated by CT scan.

Group B:

- The blood count should show one of the following results:
  - Neutrophils more than 1.5 x 10^9/L without need for exogenous growth factors or 50% improvement over baseline without need for exogenous growth factors.
  - Platelet counts greater than 100 x 10^9/L or 50% improvement over baseline without need for exogenous growth factors.

- Hemoglobin greater than 110 g/L or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

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

- Progression of lymphadenopathy
  - Appearance of any new lesion, such as new enlarged lymph nodes (> 1.5 x 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.
  - An increase by 50% or more in greatest determined diameter (= greater than 65% increase in bidimensional product) of any previously recorded measurable node.
- An unequivocal increase in the previously noted enlargement of the liver or spleen by an estimated 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- Transformation to a more aggressive histology (e.g. Richter syndrome).
  - Whenever possible, this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL.
  - During therapy:
    - During therapy, cytopenias cannot be used to define disease progression.
  - After treatment:
    - The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L, or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Note:
B cell receptor targeted drugs can mobilize CLL cells from tissues into the peripheral blood, interfering with their homing. This characteristic pharmacologic action can be prominent early in therapy, but can also persist over time. This occurrence should not be confused with PD unless the treated patient develops other CLL-related signs or symptoms of PD. In the absence of other objective evidence of PD, **lymphocytosis alone should not be considered an indicator of PD** *[Cheson 2012].*

Stable Disease (SD): Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a nonresponse).

10.5 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

10.6 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

10.7 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from study entry until disease progression or death.

10.8 Methods of Measurement for CT-Scan Evaluation

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up as indicated in Section 9. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

10.8.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred. Lymph nodes should be measured by CT scan as described in section 10.2 if followed.

10.8.2 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

11.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix V). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events, regardless of whether they are unexpected or related to protocol treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported in an expedited manner. Any late serious adverse event occurring after this 30-day period which is unexpected and related to protocol treatment must also be reported in an expedited manner (see Section 11.2 for reporting instructions).
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

Note: Adverse events which are unequivocally only related to the underlying malignancy or disease progression are NOT reportable Serious Adverse Events. These include such adverse events as admission for pain control, palliative care or paracentesis of malignant effusions.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the IND. 216 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.

Within 7 days: Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

Linda Hagerman, Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2411

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the IND 216 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

11.3 Other Protocol Reportable Events – Pregnancy/Exposure Reporting

In accordance with CCTG's inclusivity in research policy, women of childbearing potential (WOCBP) may be enrolled in this clinical trial. WOCBP are defined as women who have had a menstrual period during the last year and have not had a hysterectomy. Precautions are required to be taken to prevent pregnancy during the clinical trial when the research population includes WOCBP. This includes pregnancy testing, use of effective methods of birth control, and pregnancy as an exclusion factor. The trial sample informed consent form includes the potential for unidentified risks to the embryo/fetus. It also includes general information on pregnancy prevention and the required minimum period during which birth control must be utilized.

11.3.1 *Pregnancy Prevention*

WOCBP and males who are enrolled in the trial must be informed of the requirement to use appropriate contraception. Investigators are advised to inform the female partners of male participants when appropriate and compliant with local policy.

Sexually active males should use a condom during intercourse while taking drug and for 12 weeks after the final dose of study treatment. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

WOCBP must use highly effective contraception while taking drug and for at least 4 weeks after the final dose of study treatment. Highly effective contraception is defined as

i. total abstinence
ii. male partner sterilization
iii. use of a combination of both:
    a. placement of an intrauterine device (IUD) or intrauterine system (IUS) AND
    b. barrier methods of contraception: condom or occlusive cap (diaphragm or cervical /vault camps) with spermicidal foam/gel/film/cream/vaginal suppository

Note hormonal contraception methods (oral, injected and implanted) are not allowed as buparlisib decreases the effectiveness of hormonal contraceptives.

11.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 6 months after the completion of study treatment must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812 / safety-desk@ctg.queensu.ca).

If the pregnancy results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

11.3.3 *Exposure Reporting (Non-study Participants)*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non- study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure in a timely manner, within 24 hours of learning of the exposure, using the CCTG Exposure Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812 / safety-desk@ctg.queensu.ca).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

11.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

The CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

11.5 CCTG Responsibility for Reporting Serious Adverse Events to Novartis

Novartis will be notified of all reportable serious adverse events (SAE) and pregnancies reported as SAEs, within 15 calendar days of receipt.

11.6 Novartis Reporting Responsibilities

Novartis will send all regulatory reportable serious unexpected suspected adverse reactions (SUSARs) from non-CCTG trials (Safety Updates) for buparlisib to CCTG. Novartis will report these events to Health Canada.

11.7 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial IND 216 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial IND 216 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 8.0.
- Progression or disease recurrence as defined in Section 10.0.
- Request by the patient.
- Completion of therapy as outlined in Section 8.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Duration of Protocol Treatment

(see Section 10.0 for response definition)

- For patients who achieve a complete or partial response, therapy will continue until objective disease progression or unacceptable toxicity, whichever occurs first.
- For stable patients, therapy will continue for a maximum of 6 cycles (24 weeks). Patients who have no evidence of tumour shrinkage at this point should go off therapy and receive other treatment at the investigator's discretion.
- Patients who progress (treatment failure) will go off study at the time progression is documented clinically and/or radiographically.

12.3 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

12.4 Follow-up Off Protocol Treatment

See Section 9.3.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

There will be no central radiology review for this study.

13.2 Central Pathology Review

There will be no central pathology review for this study.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This is a single arm, open label, phase II study designed to assess the efficacy and toxicity of buparlisib in patients with relapsed and refractory chronic lymphocytic leukemia. The primary endpoint is objective response rate. Secondary end points include duration of response and progression-free survival.

14.2 Sample Size and Duration of Study

PI3K Inhibitor Naïve Cohort

The null hypothesis at which buparlisib will be considered of no value in this disease is an overall response rate of $\leq$ 5%. The alternative hypothesis at which the drug will be considered worthy of further study is $\geq$ 30%. Enrolment of 12 evaluable patients is required to test this hypothesis with a one-sided α of 0.1 and 80% power.

According to the Simon 2 stage design, 5 patients will be enrolled in the first stage. If at least one PR or CR is observed, then a total of 12 patients will be enrolled. When 2 or more patients among 12 evaluable patients achieve CR or PR, the null hypothesis will be rejected.

Exploratory Cohort

Outcomes of individuals previously treated with alternative PI3 kinase inhibitors will be presented descriptively. It is anticipated these numbers will be small, in which case any observed CR or PR will be of interest and considered worthy of further study. If for example 8 patients are enrolled, this would enable detection of a 5% versus 20% overall response rate with 53% power at a one sided α of 0.1. A maximum of 17 individuals will be enrolled on this exploratory cohort.

Overall

Accrual of up to 29 patients overall is anticipated to take place over 24 months. Follow-up of 6 months will be required after the last patient is enrolled. Thus, total duration of study is expected to be 30 months.

14.3 Safety

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings. Adverse events will be categorized using the NCI Common Terminology Criteria for Adverse Events (CTCAE) or other protocol specified criteria for hematological and psychiatric toxicity (see Appendix V). The worst event for each patient in each category or subcategory will be described. Both events related and unrelated to treatment will be captured.

Clinical and laboratory data will be tabulated and compared to normal ranges for the institution.

14.4 Correlative Studies

Secondary objectives related to correlative studies are exploratory in nature. Peripheral blood will be assayed to investigate the correlation, if any, between response and potential biomarkers. Chi-square (categorical results) or regression models (continuous results) will be used to explore the relationship between laboratory findings and response or early progression.

14.5 Prospective Validation of Survival Scale

We have previously designed and validated a scale which can predict 90 day mortality among patients with hematological malignancies enrolled in Phase I and II clinical trials *[Jamal 2012]*. This scale uses 5 easy to measure, objective clinical variables, including albumin, LDH, diagnosis (AML vs non AML), platelet count and alkaline phosphatase. Each is attributed one point. A patient having 3 or more points has up to a 40% chance of mortality within 3 months of treatment on a clinical trial. The initial validation did not include patients with CLL. We therefore intend to validate this scale in CLL in the context of this trial.

The scale will be applied to each individual patient and mortality risk calculated. A Kaplan Meier survival curve will be generated and hazard ratio for death estimated comparing low and high risk patients within this study, in order to determine the ability of the scale to distinguish mortality risk between these two groups.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and Novartis, may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results
CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by Novartis, the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

16.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

16.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner, exposed individual) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them.

Trial-specific consent forms for "Pregnancy Follow-up" and "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy/exposure. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/legal guardian.

For reporting an exposure, the parent/guardian is required to sign an "exposure follow-up" consent form (even if they are a participant in the main study) prior to collecting information about the child.

16.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

16.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

16.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

16.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

Novartis has reserved the right to audit participating centres. Audits may only be conducted after consultation with CCTG.

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, are to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration and Data Management Guidebook" posted on the IND. 216 area of the CCTG web-site (www.ctg.queensu.ca).

17.0 CORRELATIVE BLOOD WORK

Collection of Lymphocytes From the Peripheral Blood (Mandatory)

The collection of malignant lymphocytes is an important part of this trial. This is mandatory for participation in the study.

See Lab Manual posted on the IND 216 webpage for complete details.

17.1 Objectives

Samples will be used to determine:

1) In vitro sensitivity to buparlisib using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, correlated with clinical response.

2) Level of biomarkers predictive of sensitivity to buparlisib by protein isolation and flow cytometry. The candidate proteins include raptor and p70S6K which are involved in the PI3K signaling pathway.

3) In relapsing patients after treatment with buparlisib, protein, RNA and DNA will be isolated in order to identify mechanisms of resistance to buparlisib and potentially to other PI3K inhibitors.

17.1.1 *Rationale for Correlative Blood Work*

PI3K inhibitors are effective therapies for CLL. However not all patients respond and many relapse as evidenced by the recent publication of data on idelalisib *[Furman 2014]*. The correlative blood work proposed here aims to identify by MTT assay and by the identification and validation of biomarkers, those patients likely to respond to therapy. Recent translational studies demonstrated that simultaneous low raptor and p70S6K protein expression may be predictive of sensitivity to buparlisib *in-vitro [Amrein 2013]*.This clinical trial aims to confirm if these two proteins involved in the PI3K signaling pathway, can be used as biomarkers to predict clinical response of patients with CLL to buparlisib therapy. This will allow for better selection of patients for PI3K inhibitor therapy in the future. In addition, mechanisms of resistance to PI3K inhibitors is unknown; the research to be conducted using patient samples will allow exploration of resistance mechanisms.

17.2 PIK3CA Gene Amplification Analysis

PI3K mutations are well described in solid tumours (particularly in PIK3CA-the gene which encodes p110α), however activating PI3K mutations are noticeably absent in B cell malignancies such as CLL *[Marincevic 2009; Ortiz-Maldonado 2015; Thorpe 2015]*. A recent study of 188 patients with CLL showed no point mutations in p110α, -δ or -β isoforms, despite PI3K pathway constitutive activation *[Brown 2012]*; however, the same study demonstrated that amplifications of the PIK3CA locus were present in 6% of CLL patients (with 80% of the CLL cohort investigated being treatment naïve). Thus, gene amplification will be studied as a mechanism for PI3K pathway activation in this relapsed/refractory CLL population, by investigation of the copy number status of the genes PIK3CD and PIK3CA, which encode the p110δ and p110α isoforms respectively. Gene amplification will be measured using digital PCR, a highly sensitive and accurate methodology, in all patients treated on the IND 216 trial, both prior to therapy and after disease progression correlating with development of drug resistance.

Univariate analysis will be attempted to investigate for any association of copy number variation with known clinical characteristics and prognostic factors (age, gender, number of prior lines of therapy, cytogenetics, unmutated IgHV status and response and duration of response to buparlisib).

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Prestudy *(within 7 days prior to registration unless otherwise indicated)*	Days 1 & 14 cycle 1 and 2; thereafter day 1 each cycle *(and as clinically indicated)*	Day 1 each cycle	At 8, 16 and 24 weeks from registration, and thereafter every 12 weeks	4 weeks after Off Protocol Therapy
History and Physical					
Physical Exam (including height, weight)	X		X		X
ECOG Performance Status					
Pulse, blood pressure					
Clinical tumour / organomegaly measurements (if applicable)			X	To confirm PR or CR and as clinically indicated[1]	
Hematology					
CBC, differential (including lymphocytes)	X	X			X (and at 8 weeks if required to confirm PR or CR)
PT, PTT	X	As clinically indicated			
Biochemistry[1]					
creatinine, potassium, bilirubin, AST, ALT, alkaline phosphatase, LDH, albumin, calcium, glucose (fasting), phosphate[2], uric acid[2]	X	X			X
lipase		X			
HbA1c (if diabetic), Beta 2 microglobulin	X				
Radiology					
Neck/chest/abdominal/pelvic CT	X[3]			X[4]	X[4]
Assessment for MRD (optional)				X *(at CR only)*	X *(at CR only)*
Cardiac Investigations					
12-lead ECG	X	As clinically indicated			
MUGA/LVEF	X[5]	As clinically indicated			
Other Investigations					
Pregnancy test *(serum or urine for women of childbearing potential only)*	X				
Fluorescence in situ hybridization	X[5]				
Direct antiglobulin test (DAGT)	X				
Bone Marrow Aspirate and Biopsy	X[6]			X[7]	X[7]
Immunoglobulin variable region (IgV_H) mutation status	X[8]				
Mood Questionnaires[9]	X	X			X[10]
Hepatitis B surface antigen (HBsAg)	X[11]				
Hepatitis C serology	X[11]				
Correlative Blood Work					
Peripheral Blood (See Section 17 and Laboratory Manual for details)	X[11]			X *(at progression) (if applicable)*	
Adverse Events					
CTCAE v 4.0	X	continuously			

footnotes on next page …

1. See section 8 for additional monitoring of AST/ALT and bilirubin with hepatic toxicity.
2. The first 4 patients treated on study will require monitoring for tumour lysis on days 1, 2 and 3 of cycle 1 only: calcium, creatinine, potassium, phosphate and uric acid. CCTG will notify centres if this applies at the time of registration.
3. Within 21 days prior to registration (within 28 days if negative).
4. Patients with an unconfirmed PR or CR should have scans repeated after 8 weeks to confirm response. Scans should also be repeated at 8, 16 and 24 weeks from study registration and thereafter every 12 weeks.
5. Within 28 days prior to registration (only if symptoms suggestive or history of cardiovascular disease).
6. Within 28 days prior to registration for routine local pathology to assess CLL
7. At time CR criteria first met, 8 weeks later to confirm sustained CR, or if cytopenia of uncertain cause.
8. Can be done any time prior to registration on peripheral blood or bone marrow.
9. Patient self-rating mood questionnaires (PHQ-9 and GAD-7) are posted on the I216 website.
10. Mood questionnaires also required to be completed by patient at the End of Treatment visit.
11. Within 28 days prior to registration.

APPENDIX II - PERFORMANCE STATUS SCORES

ECOG (Zubrod)	
Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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	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	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Drug Distribution
Buparlisib will be sent by Novartis to participating centres.

Drug Labelling
Drug supplies for this study will be labelled in accordance with Health Canada regulations. The labels contain all information required under the drug labelling regulations.

Initial Drug Supply
Once a centre is locally activated (following receipt and review of all required documentation), the CCTG will authorize a start-up supply of buparlisib to be shipped directly to the centre. The drug will be shipped to the centre within 5 working days of local activation. Drug accountability and drug re-order forms will be included with the drug shipment and are also available on the trial website: (www.ctg.queensu.ca/trials/ind/216/216.html).

Drug Ordering (Re-supply)
Fax a copy of the buparlisib drug re-order form (available at www.ctg.queensu.ca/trials/ind/216/216.html) to Novartis.

Please allow sufficient time for shipment of drug.

Drug Accountability
The investigational products are to be prescribed only by the investigator and co-investigators on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained accounting for the receipt of the investigational product and for the disposition of the product (Drug Accountability Log).

Drug Destruction or Return:
Details to be supplied at the time of study closure.

**PLEASE NOTE **

DRUG FROM THIS SUPPLY IS TO BE USED ONLY

FOR PATIENTS REGISTERED ON THIS STUDY

Study drug shipped to participating centres may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy. Investigational agent may NOT however, be transferred to pharmacies or physicians outside the participating centre.

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of registration and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting (see section 11.0 for details regarding SAE reporting). For details about accessing the EDC system and completing the on-line Case Report Forms, please refer to the Data Management Guidebook posted on the IND 216 area of the CCTG website (www.ctg.queensu.ca).

Form	To be Completed/Submitted Electronically:	Supporting Documentation to be sent using Supporting Document Upload Tool
PATIENT ENROLLMENT FOLDER	Must be completed at time of registration to confirm eligibility.	
BASELINE REPORT	Due within 2 weeks of patient registration.	Copies of the signed signature page(s) of the consent form; relevant pathology and radiology reports; mood questionnaires; ECG reports; MUGA/LVEF report (if applicable)
TREATMENT REPORT	To be completed every 28 days (i.e. after each cycle). Due within 2 weeks of end of cycle. This form documents treatment, adverse events, investigations and response assessment for each cycle.	Relevant radiology reports. Patient diary. Mood questionnaires.
CORRELATIVE BLOOD WORK	See Section 17 and Laboratory Manual for details.	
END OF TREATMENT REPORT	To be completed when patient permanently discontinues protocol treatment. Due within 2 weeks of end of protocol treatment.	Mood questionnaires.
4 WEEK POST TREATMENT REPORT	To be completed once on all patients, 4 weeks after the end of the last cycle. Due within 2 weeks after contact with patient.	Relevant radiology reports.
FOLLOW-UP REPORT	Continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to $\leq$ grade 2) and late toxicities (including second malignancies). For patients who go off protocol therapy with suspected PR or CR, an 8 week confirmatory response assessment including CT scanning will be required as per sections 9.1 and 10.4, if not already performed. For patients who go off protocol treatment with objective CR, PR or SD ongoing, a follow-up report will be required every 3 months until relapse/progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
RELAPSE/ PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.

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Form	To be Completed/Submitted Electronically:	Supporting Documentation to be sent using Supporting Document Upload Tool
DEATH REPORT	Required only on patients who die during protocol therapy, within 30 days after last dose, or within the protocol defined follow-up period for patients with response or stable disease ongoing.* Due within 2 weeks of knowledge of death.	Autopsy report, if done.
SERIOUS ADVERSE EVENT REPORT FORM	All reportable serious adverse events must be reported as described in Section 11.0. All reportable serious adverse events must be reported as described in Section 11.0. Preliminary CCTG Serious Adverse Event Report due within 24 hours. Updated CCTG Serious Adverse Event Report due within 7 days.	
* NB It is the investigator's responsibility to investigate and report the date/cause of death of any patient who dies during this period. Any death that occurs during this period and that is *thought to be treatment related* must also be reported as a Serious Adverse Event as described in Section 11.		

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Please note:
HEMATOLOGICAL AND PSYCHIATRIC TOXICITY SHOULD BE GRADED ACCORDING TO CRITERIA DESCRIBED IN SECTION 8.3.

APPENDIX VI - CLL DIAGNOSTIC CRITERIA AND INDICATIONS FOR TREATMENT

(Abbreviated from the 2008 International Workshop on Chronic Lymphocytic Leukemia Guidelines)

Diagnosis

a. Presence of at least 5 x 10^9 B lymphocytes /L (5000/µL) in the peripheral blood, of which prolymphocytes comprise no more than 55%.

b. Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing at least one B-cell marker (CD19, CD20, or CD23) and CD5.

Indications for treatment

a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia or thrombocytopenia.

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

c. Massive nodes (i.e. At least 10 cm in longest diameter), progressive, or symptomatic lymphadenopathy.

d. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months (which may be extrapolated). Lymphocyte doubling time 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 indication for treatment.

e. Constitutional symptoms, defined as 1 or more of the following disease-related symptoms or signs:
   - Unintentional weight loss of 10% or more within the previous 6 months prior to screening
   - Significant fatigue (inability to work or perform usual activities)
   - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without evidence of infection or
   - Night sweats for more than 1 month without evidence of infection.

APPENDIX VII - CYP3A INHIBITORS/INDUCERS AND CYP450 SUBSTRATES

Table 1. List of prohibited CYP3A inhibitors and inducers

Strong CYP3A inhibitors	Strong CYP3A inducers
boceprevir	avasimibe
clarithromycin*	carbamazepine *
conivaptan	fosphenytoin *
elvitegravir	phenobarbital *
indinavir	phenytoin *
itraconazole	primidone *
ketoconazole	rifabutin
lopinavir*	rifampin
mibefradil	St. John's Wort
nefazodone	
nelfinavir	
posaconazole	
ritonavir*	
saquinavir*	
telaprevir	
telithromycin	
tipranavir	
troleandomycin	
voriconazole	

* These drugs are Enzyme Inducing Anti-Epileptic drugs

This database of CYP inhibitors and inducers was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, from the University of Washington's Drug Interaction Database based on in vitro studies and from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table.

Table 2. List of CYP450 substrates to be used with caution

CYP2C8	CYP2C9	CYP2C19	CYP3A*	
amodiaquine	celecoxib	amitriptyline	adinazolam	felodipine[1]
cerivastatin	diclofenac	citalopram	alfentanil[1,2]	fentanyl[2]
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine[1]	flunitrazepam
repaglinide	fluvastatin	clomipramine	alprazolam	fluticasone[1]
rosiglitazone	glibenclamide (glyburide)	clopidogrel	amlodipine	lovastatin[1]
torasemide	gliclazide	diazepam	aripiprazole	maraviroc[1]
troglitazone	glimepiride	fluoxetine	atorvastatin	midazolam[1]
	glipizide	imipramine	brecanavir	nifedipine
	indomethacin	lansoprazole	brotizolam[1]	nisoldipine
	irbesartan	mephobarbital	budesonide[1]	nitrendipine
	ketobemidone	moclobemide	buspirone[1]	perospirone[1]
	lornoxicam	omeprazole	capravirine	quinine
	losartan	pantoprazole	cerivastatin	sildenafil[1]
	meloxicam	progesterone	chlorpheniramine	simvastatin[1]
	naproxen	quazepam	cyclosporine[2]	sirolimus[1,2]
	nateglinide	rabeprazole	darifenacin[1]	tolvaptan
	piroxicam	sertraline	diazepam	trazodone
	rosiglitazone	S-mephenytoin	diergotamine[2]	triazolam[1]
	S-ibuprofen		ebastine[1]	
	sulfamethoxazole		eletriptan[1]	
	tenoxicam		eplerenone[1]	
	tolbutamide		ergotamine[2]	
	torasemide		estazolam	
	valdecoxib		everolimus[1]	

* CYP3A substrates were compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; and supplemented by the FDA's "Guidance for Industry, Drug Interaction Studies" and the University of Washington's Drug Interaction Database.

1 Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a strong inhibitor of the respective enzyme.

2 Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of strong inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

APPENDIX VIII - QT PROLONGING DRUGS

Updates to this list will be published on the trial website.

List of prohibited QT prolonging drugs with known risk of Torsades de Pointes

Drug	**QT risk(*)**	**Comment**
Amiodarone	Known risk for TdP	Females>Males, TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate

(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT
Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

Note: drugs with a known risk for TdP that are also strong inhibitors of CYP3A are not repeated here and only mentioned in Table 1.

List of QT prolonging drugs to be used with caution

Updates to this list will be published on the trial website.

Drug	**QT risk (*)**
Alfuzosin	Possible risk for TdP
Amantadine	Possible risk for TdP
Amitriptyline	Conditional risk for TdP
Azithromycin	Possible risk for TdP
Chloral hydrate	Possible risk for TdP
Citalopram	Conditional risk for TdP
Clomipramine	Conditional risk for TdP
Clozapine	Possible risk for TdP
Desipramine	Conditional risk for TdP
Diphenhydramine	Conditional risk for TdP
Dolasetron	Possible risk for TdP
Doxepin	Conditional risk for TdP
Dronedarone	Possible risk for TdP
Escitalopram	Possible risk for TdP
Flecainide	Possible risk for TdP
Fluoxetine	Conditional risk for TdP
Foscarnet	Possible risk for TdP
Galantamine	Conditional risk for TdP
Gatifloxacin	Possible risk for TdP
Gemifloxacin	Possible risk for TdP
Granisetron	Possible risk for TdP
Imipramine	Conditional risk for TdP
Indapamide	Possible risk for TdP
Isradipine	Possible risk for TdP
Levofloxacin	Possible risk for TdP
Lithium	Possible risk for TdP
Mexiletine	Conditional risk for TdP
Moexipril/HCTZ	Possible risk for TdP
Moxifloxacin	Possible risk for TdP
Nicardipine	Possible risk for TdP
Nortriptyline	Conditional risk for TdP
Octreotide	Possible risk for TdP
Ofloxacin	Possible risk for TdP
Ondansetron	Possible risk for TdP
Oxytocin	Possible risk for TdP
Paliperidone	Possible risk for TdP
Paroxetine	Conditional risk for TdP
(*) Classification according to the QTdrugs.org Advisory Board of the Arizona CERT	

table continued on next page …

Drug	**QT risk (*)**
Perflutren lipid microspheres	Possible risk for TdP
Protriptyline	Conditional risk for TdP
Ranolazine	Possible risk for TdP
Risperidone	Possible risk for TdP
Roxithromycin*	Possible risk for TdP
Sertindole	Possible risk for TdP
Sertraline	Conditional risk for TdP
Solifenacin	Conditional risk for TdP
Tizanidine	Possible risk for TdP
Trazodone	Conditional risk for TdP
Trimethoprim-Sulfa	Conditional risk for TdP
Trimipramine	Conditional risk for TdP
Venlafaxine	Possible risk for TdP
Ziprasidone	Possible risk for TdP
(*) Classification according to the QTdrugs.org Advisory Board of the Arizona CERT	

LIST OF CONTACTS

PATIENT REGISTRATION

All patients must be registered via the web-based, password-operated electronic data system at the CCTG web page before any treatment is given.

	Contact	Tel. #	Fax #
STUDY SUPPLIES Data Management Guidebook, Protocol, Safety Information, Electronic Case Report Forms. Available on CCTG Website:	http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Linda Hagerman Study Coordinator CCTG Email: lhagerman@ctg.queensu.ca or: Dr. Annette Hay Senior Investigator, CCTG Investigational New Drug Program Email: ahay@ctg.queensu.ca	613-533-6430	613-533-2411
STUDY CHAIR	Dr. Sarit Assouline Study Chair Email: sarit.assouline@mcgill.ca	514-340-8207	514-340-8281
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Annette Hay Senior Investigator CCTG or Linda Hagerman Study Coordinator CCTG	613-533-6430	613-533-2411
DRUG ORDERING	See Appendix III and trial website: (www.ctg.queensu.ca/trials/ind/216/216.html) for details		