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A Pilot Study of Metformin Therapy in Patients With Relapsed Chronic Lymphocytic Leukemia (CLL) and Untreated CLL

UMCC 2012.025: A Phase II Pilot Study of Metformin Therapy in Patients with Relapsed Chronic Lymphocytic Leukemia and untreated CLL patients with genomic deletion 11q

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TREATMENT SCHEMA

Chronic lymphocytic leukemia is the most common leukemia in the Western world. CLL patients relapse at variable time intervals after therapy, and the disease remains incurable. In our recent preliminary studies, we have demonstrated that the insulin receptor (INSR) is aberrantly expressed at high levels in subsets of CLL. We also found the majority of CLL patients with high risk genomic lesion 11q express significantly high INSR levels. Ex vivo insulin treatment abrogates spontaneous apoptosis in CLL cells expressing the insulin receptor through activation of pro-survival pathways. We have also demonstrated that higher expression of INSR was associated with shorter time to first treatment and overall survival, thus indicating that INSR signaling influences CLL outcome. These findings suggest that CLL may belong to a class of cancers that may be insulin responsive, therefore allowing the development of therapies directed at the INSR/insulin axis. Previous studies have also demonstrated the involvement of the Akt-mTOR pathway in CLL pathogenesis suggesting that an inhibition of this pathway could retard disease progression.

Metformin is an antidiabetic drug which is an inexpensive and generally well tolerated medication. More recently metformin has been shown to act against carcinomas by two mechanisms: 1) an indirect, insulin-dependent mechanism which sensitizes tissues to insulin, inhibits hepatic gluconeogenesis, and stimulates uptake of glucose in muscle, thereby **reducing** fasting blood glucose and circulating levels of insulin, lowering the pro survival activity of the insulin/INSR axis, and 2) a direct, insulin-independent mechanism which activates the AMP-activated protein kinase (AMPK) pathway and leads to inhibition of the mTOR pathway. Given our preliminary published data on insulin and mTOR inhibition[1] metformin is an attractive candidate for a pilot clinical trial in CLL patients.

Our study subjects will consist of patients with confirmed CLL who are asymptomatic, and 1) in disease relapse (as indicated by an ALC >5000 on 2 consecutive occasions and increasing in trend or any clinically appreciated lymphadenopathy increased above best overall response persisting for more than 3 months) and <u>not in need of urgent</u> therapy or 2) with del11q genomic status previously treated or untreated and <u>not in need of urgent</u> therapy (as defined in section 12.1).

Metformin will be administered to 40 patients using the following treatment schema (increasing dose as tolerated): 500 mg po daily for week 1, 500 mg po BID for week 2, followed by the final target dose of 1000 mg po BID.

Treatment will be continued until treatment failure (defined in section 12.1), or until disease progression to active disease requiring chemotherapy as judged by the treating clinician.

Primary Trial Endpoint: Time to treatment failure as defined in section 12.1

Secondary endpoints: Time to first therapy (TTFT) in previously untreated 11q CLL subsets only.

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To evaluate time to treatment failure in untreated CLL patients with del11q treated with metformin (as defined in section 12.1).

2.2 Secondary Endpoints

To evaluate time to first treatment (TTFT) in untreated del11q CLL patients

To evaluate changes in the rate of increase of absolute lymphocyte count while on metformin therapy

To evaluate change in size and number of clinically appreciated lymphadenopathy and splenomegaly while on metformin therapy

To evaluate insulin receptor expression (INSR) and other biochemical markers in cells from CLL patients pre and post metformin therapy.

To evaluate changes in unstimulated baseline AKT phosphorylation and ex vivo insulin stimulated AKT phosphorylation

To evaluate changes in the fasting and postprandial insulin levels, fasting and postprandial IGF-1 and IGF-2 levels, and insulin resistance using the homeostasis model assessment (HOMA)-IR index.

3. BACKGROUND

3.1 Metformin

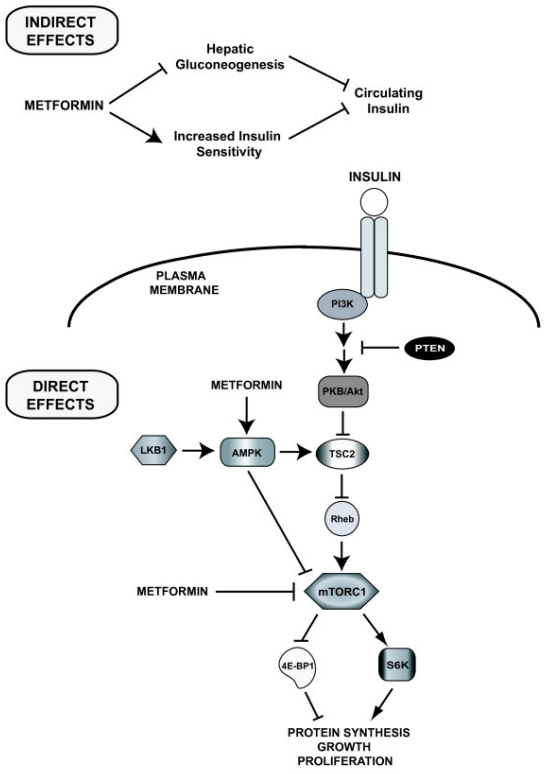
Metformin is a biguanide first introduced in the 1950s which is currently used as first line therapy for type 2 diabetes[2, 3]. It has been used for multicenter clinical trials in non-diabetics for diabetes prevention[4], as well as in patients with polycystic ovarian syndrome [5, 6]. Recently there has been more interest in metformin as an anti-cancer therapy[7-10]. Anti-proliferative effects of metformin on cancer cells are mediated through both an indirect, insulin-dependent mechanism and a direct, insulin-independent mechanism[7]. The indirect, insulin-dependent mechanism sensitizes tissues to insulin, inhibits hepatic gluconeogenesis, and stimulates uptake of glucose in muscle. Metformin reduces fasting blood glucose and thereby

circulating insulin levels, making it a first line treatment for diabetes. In non-diabetic subjects, pharmacokinetic studies have demonstrated that insulin levels immediately post-prandial (0-2 hours after a meal) are significantly lowered with metformin therapy[11]. Prior studies demonstrated that high insulin levels and obesity are poor prognostic factors in breast, prostate and colon cancer[12-15]. Several studies have shown that insulin has pro survival effects on tumor cells that have high expression of insulin receptor[12, 16, 17].

Through its direct, insulin-independent mechanism, metformin activates the AMP-activated protein kinase (AMPK) pathway which regulates cellular metabolism by increasing levels of AMP[18]. Activation of AMPK through tumor suppressor kinase LKB-1, phosphorylates tuberous sclerosis complex-2 (TSC-2), which leads to suppression of mammalian target of the rapamycin (mTOR) signaling pathway[18-23]. Metformin also directly inhibits the mTOR pathway independent of AMPK [24].Inhibition of the mTOR pathway abrogates downstream protein synthesis, cell growth and proliferation.

Metformin is generally well tolerated and its most common adverse effect is gastrointestinal distress. It may also cause vitamin B12 deficiency in about 7% of all patients[9, 25]. Hypoglycemia from metformin is rare, and is associated with fewer episodes than sulfonyureas and insulin, but more than diet alone [26]. Although it can increase lactate oxidation, it does not change the release of lactate from muscle or plasma, making lactic acidosis very rare [27, 28].

Figure 1: **Mechanism of Metformin as an Anti-Cancer Therapy**[7]



3.2 Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world[29]. Its clinical course is highly variable, and although it is treatable it remains incurable. In an attempt to identify progressive disease, there have been extensive studies into different factors related to disease progression: Increased expression of zeta-associated protein of 70kDa (ZAP-70), mutation status of immunoglobulin heavy-chain variable region (IgVH) genes, elevated genomic complexity as measured through SNP arrays, presence of del17p/p53 aberrations, and presence of del11q have all been associated with a more aggressive disease course and overall shorter survival[30-51]. Most CLL patients are not treated at time of diagnosis, and asymptomatic CLL patients are typically managed with an observation approach. Symptomatic CLL patients are first treated with anti-neoplastic and immunotherapy combinations including fludarabine, cyclophosphamide and rituximab (FCR), pentostatin, cyclophosphamide and rituximab (PCR), bendamustine and rituximab (BR), and alemtuzumab, alone or in combination. Because the disease remains incurable, all patients will relapse at variable times after treatment is stopped.

Interstitial deletions on the long arm of chromosome 11 (del11q) occur in approximately 15% to 20% of all patients with CLL, and have been associated with more progressive and aggressive CLL. More recently, using integrated genomic profiling approaches focusing on CLL patients with and without del11q, we have identified high aberrant INSR expression in the majority of patients with CLL and 11q as well as sporadic patients without 11q deletions. We have furthermore demonstrated that elevated expression of the INSR correlates to a shorter time to first treatment (TTFT) and shorter overall survival (OS)[1].

3.3 Preclinical Data

We demonstrated that insulin treatment activates canonical insulin signal transduction pathways including the AKT-mTOR pathway. Given this observation, we proceeded to CLL ex vivo short term cultures with CLL cells with or without INSR expression performed in the presence or absence of insulin. With insulin treatment, spontaneous apoptosis was inhibited in CLL cells expressing INSR but no effects were seen in CLL without INSR expression [1]. The implication of these studies are that CLL cases with INSR expression may belong to a class of cancers which are insulin responsive, and may respond to therapies that decrease insulin levels.

Several mouse and cancer cell models have shown inhibition on cell proliferation with metformin treatment in prostate, colon, breast, endometrial, and ovarian cancers[52-57]. Metformin has demonstrated inhibition of insulin-induced malignant cell growth in pancreatic cancer through the AMPK/mTOR pathway[58]. Metformin also induced apoptosis in endometrial cancer, glioma and triple negative breast cancers[56, 57, 59].

3.4 Clinical Studies on Metformin and Cancer

There has been ongoing interest over the past decade in regards to hyperinsulinemic states, such as diabetes, and increased risk of cancer. Several epidemiologic studies have demonstrated increased cancer risk in type 2 diabetic patients, including breast, colon, pancreatic and endometrial cancer[60-64].The most current clinical studies on metformin therapy and cancer risk have been retrospective studies, and most of these have been on diabetic patients. Evans et al. first described a decreased incidence of cancer in patients taking metformin therapy, with a protective effect with greater length of exposure[65]. The ZODIAC-16 retrospective study involved 1353 diabetic patients in a 9.6 year follow up, and demonstrated that cancer related mortality was decreased in diabetic patients taking metformin, with an adjusted hazard ratio of 0.43 (95% CI 0.23-0.80)[66].

Metformin use was also demonstrated to be associated with a better response to neoadjuvant chemotherapy. One recent epidemiologic study of 2,529 breast cancer patients reported higher pathologic complete response (pCR) rates to neoadjuvant chemotherapy in patients receiving metformin (pCR 24%) compared to diabetics not taking metformin (pCR 8%) and non-diabetics (pCR 16%) [67]. However, use of metformin did not significantly improve survival rate over 3 years. Chemotherapy with metformin therapy also improved chemotherapy outcomes and overall survival in diabetic patients with non-small cell lung cancer[68].

There have been some studies performed on non-diabetic cancer patients. A Phase II study on early breast cancer patients demonstrated that metformin significantly decreased levels of fasting insulin and HOMA index (measuring insulin sensitivity) in non-diabetic patients over 6 months of therapy[15]. A small randomized study on non-diabetic patients treated with low doses of metformin therapy showed a significant decrease in rectal aberrant crypt foci (ACF), suggesting metformin therapy as a potential prevention therapy for colorectal cancer[69].

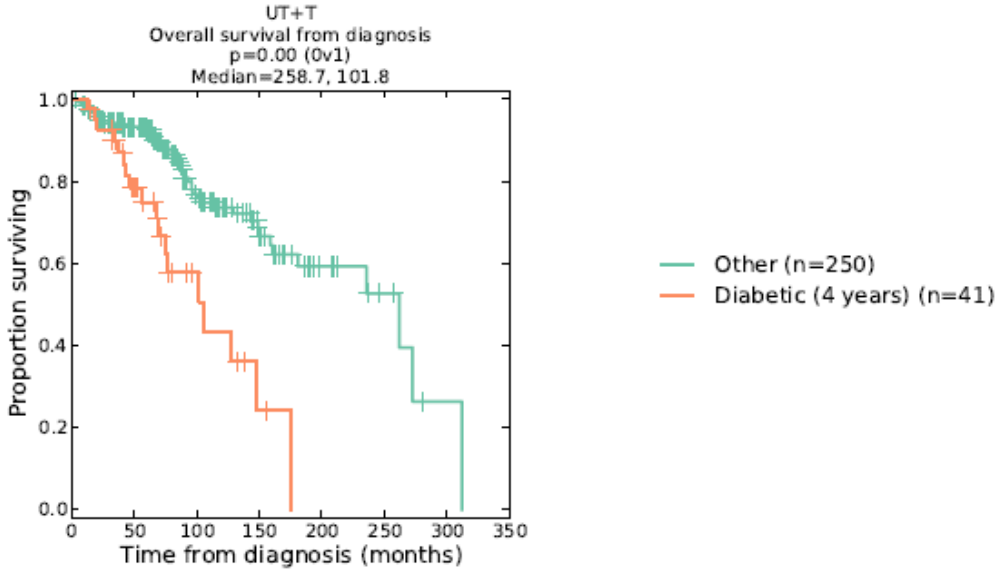
Given that most clinical data to date is retrospective and on diabetics, the evidence is confounded and limited. There are several larger randomized clinical trials on breast, prostate, endometrial, and pancreatic cancer that are currently ongoing (clinicaltrials.gov). A recent consensus report from the Amercian Diabetes Association and American Cancer Society concluded that although still limited, early evidence suggests that metformin is associated with lower risk of cancer[70]. Metformin is a relatively well-tolerated and inexpensive medication, making it an attractive candidate for primary prevention and adjuvant therapy clinical trials. Metformin has yet to be described as a use of therapy in adult hematologic malignancies.

3.5 Rationale for the current clinical trial in CLL

We have shown in our preclinical studies that CLL apoptosis ex vivo is abrogated with insulin treatment, and that higher level of insulin receptor expression on CLL cells correlates to shorter TTFT and shorter OS. Therefore, INSR is a growth and survival factor for CLL cells. Given

this observation, CLL may belong to the class of insulin responsive cancers that could respond to non-insulin anti-diabetic therapy.

Within our database of 291 CLL patients, 41 patients had diagnosed type 1 or 2 diabetes requiring treatment (documented diet modification and/or use of anti-diabetic medication) prior to or within 4 years of enrollment, accounting for 14% of our population. (Nine patients with steroid-induced diabetes, who were on steroids and diabetic therapy for a temporary amount of time, were excluded in our subset of diabetics). In a retrospective study using univariate analysis of this database, overall survival (OS) of all patients from time of diagnosis was significantly shorter in diabetic patients, from a median OS of 258.7 months in non-diabetics compared to 101.8 months in diabetics ($p < 0.001$). The same trend was found when comparing all previously untreated CLL patients prior to enrollment into our database, with a median OS of 288.8 months in non-diabetics compared to 103.3 months in diabetics ($p < 0.001$). Upon review of causes of deaths among these patients (17 total), 35% of these cases were secondary to infection, 23% were due to CLL progression, and 42% remaining deaths to unknown or other non-CLL related causes. Although the power of this study is limited, it suggests that CLL patients who are diabetics may have a higher mortality and more disease related deaths compared to non-diabetics.



Our goal is to investigate whether anti-diabetic therapy and targeted inhibitors of mTOR pathway serve as a potential treatment for CLL with success defined as retardation of disease progression. Metformin is a well-tolerated medication that both decreases overall insulin levels, inhibits the mTOR pathway and has direct cytotoxic effects on CLL cells in ex vivo cultures, making it an attractive candidate for therapy in CLL with the goal of retarding CLL progression.

Given the often high expression of the INSR in CLL with 11q deletions, the progressive nature of CLL in almost all 11q patients and the need for agents that slow disease progression we will target this subgroup of patients independent of prior treatment status.

4. DRUG INFORMATION [25, 71]

4.1 Other US Brand names: Fortamet, Glucophage, Glucophage XR, Glutmetza, Riomet

4.2 Pharmacologic Category: antidiabetic agent, biguanide

4.3 Description: Metformin hydrochloride is an oral anti-hyperglycemic agent used in the management of type 2 diabetes. Compound name: N, N-dimethylimidodicarbonimidic diamide hydrochloride. It is a white to off-white crystalline compound with a molecular formula of C4H11N5 HCl and a molecular weight of 165.63. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin is 6.68.

4.4 Mechanism: Metformin sensitizes tissues to insulin, inhibits hepatic gluconeogenesis, and stimulates uptake of glucose in muscle. Further information regarding mechanism as an anti-cancer therapy are described in section 3.1.

4.5 How supplied: Supplied as tablets for oral administration containing 500 mg, 850 mg, or 1000 mg of Metformin hydrochloride.

4.6 Source of drug: Metformin will be purchased by the Investigational Drug Service pharmacy using study funds.

4.7 Drug Accountability: Accountability of metformin tablets at the study site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. The investigator may assign the drug accountability responsibilities to a pharmacist. Drug availability records will indicate the inventory at the site and the use by each patient. At a minimum, accountability records will include dates, quantities, lot numbers, expiration, patient initials, study numbers, and doses. The appropriate number of tablets will be counted into light resistant dispensing bottle. Drug that is returned by patients will be counted and recorded on the drug accountability records. All used, unused or expired metformin tablets will be disposed of at the study site according to the institution's Standard Operating Procedure and documented.

4.8 Storage and Stability: Metformin tablets will be stored at the investigational drug services in a locked secured area separated from the storage of commercial metformin. Medication that is returned from patients will be stored separately from the medication that needs be dispensed. Metformin is store at controlled room temperature at 20° to 25°C (68° to 77°F) with excursion permitted to 15° to 30°C (59°to 86°F).

4.9 Route of Administration: Oral

4.10 Adverse Side Effects:

>10%:

Gastrointestinal: Diarrhea (10 to 53%), nausea/vomiting (7% to 26%), flatulence (12%)

Neuromuscular & skeletal: Weakness (9%)

1% to 10%:

Cardiovascular: Chest discomfort, flushing, palpitation

Central nervous system: Headache (6%), chills, dizziness, lightheadedness

Dermatologic: Rash

Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Indigestion (7%), abdominal discomfort (6%), abdominal distention, abnormal stools, constipation, dyspepsia/heartburn, taste disorder

Neuromuscular & skeletal: Myalgia

Respiratory: Dyspnea, upper respiratory tract infection

Miscellaneous: Decreased vitamin B12 levels (7%), increased diaphoresis, flu-like syndrome, nail disorder

<1% (Limited to important to life threatening): Lactic acidosis, leukocytoclastic vasculitis, megaloblastic anemia, pneumonitis

4.11 Contraindications

1. Hypersensitivity to metformin or any component of the formulation

2. Renal disease or renal dysfunction (serum creatinine greater than or equal to 1.5 mg/dl in males or greater than or equal to 1.4 mg/dl in females)

3. Significant decrease of creatinine clearance from any cause, including shock, acute myocardial infarction, or septicemia

4. Acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis)

4.12 Concerns related to adverse effects:

Cardiovascular mortality: Administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality, metformin does not appear to share this risk

Lactic acidosis: [U.S. Boxed Warning]: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mM/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an

increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 mcg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.[71]

4.13 Disease-related concerns:

Heart failure: Use caution in patients with congestive heart failure requiring pharmacologic management, particularly in patients with unstable or acute heart failure; risk of lactic acidosis may be increased secondary to hypoperfusion.

Hepatic impairment: Avoid use in patients with impaired liver function due to potential for lactic acidosis.

Renal impairment: Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy. Use of concomitant medications that may affect renal function (i.e., affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.

Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

4.14 Special populations:

Elderly: Metformin should not be initiated in patients ≥80 years of age unless normal renal function is confirmed.

4.15 Other warnings/precautions:

Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism.

Iodinated contrast: Therapy should be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Metformin should be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal.

Surgical procedures: Therapy should be suspended for any surgical procedures (resume only after normal oral intake resumed and normal renal function is verified).

4.16 Drug and Food Interactions

Cephalexin: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Cimetidine: May increase the serum concentration of MetFORMIN. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Dofetilide: MetFORMIN may increase the serum concentration of Dofetilide. *Risk C: Monitor therapy*

Glycopyrrolate: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Iodinated Contrast Agents: May enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. Management: Withhold metformin from all patients receiving intravascular iodinated contrast agents prior to or at the time of the procedure and for at least 48 hrs. thereafter. *Risk D: Consider therapy modification*

Thiazide Diuretics: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Ethanol: Avoid or limit ethanol (incidence of lactic acidosis may be increased; may cause hypoglycemia).

Food: Food decreases the extent and slightly delays the absorption. May decrease absorption of vitamin B_{12} and/or folic acid.

Herb/Nutraceutical: Caution with chromium, garlic, gymnema (may cause hypoglycemia).

5. STUDY DESIGN

5.1 General Design

Patients diagnosed with chronic lymphocytic leukemia (CLL), who have already completed at least one frontline chemotherapy (see 5.2.2), will be identified as relapsed CLL if there is increase of their absolute lymphocyte count (ALC >5000 on 2 consecutive occasions and increasing), or increase in clinically appreciable lymphadenopathy persisting more than 3 months, in the absence of symptoms. CLL patients with del11q deletion who are untreated will also be included in this study. We anticipate enrollment of a total of 20 relapsed patients and 20 CLL patients with del11q. Patients will remain on metformin until objective criteria for treatment failure are met (see section 12.1).

5.2 Eligibility Criteria

5.2.1 Patients should have a confirmed diagnosis of chronic lymphocytic leukemia defined as all of the following:

1. ALC > 5000

2. Positive for either CD19 or CD 20 together with CD23 and CD5.

3. Less than 55% atypical cells

5.2.2 Patients who relapse after receiving a one or more courses of fludarabine, bendamustine, cytoxan, rituxan, chlorambucil, or campath based therapy.

5.2.3 Patients should have findings of relapse by one or both of the following:

1. ALC > 5000 on 2 consecutive occasions and increasing

2. Any increase in lymphadenopathy over best response that has persisted for more than 3 months

5.2.4 Patient with confirmed del11q mutation may be included if untreated.

5.2.5 Age > or equal to 18 years old and < 80 years of age during the course of therapy

5.2.6 ECOG performance 0-2 (see Appendix A)

5.2.7 Life expectancy > 12 months

5.2.8 Patients must have normal organ function as defined as below:

- AST and ALT < 2 times the upper limit of normal

- alkaline phosphatase < 2 ULN

-serum conjugated bilirubin < 1.5 ULN (exception of Gilbert disease)

-serum creatinine less than or equal to 1.5 in males, or 1.4 in female

-GFR > 59

5.2.9 Ability to understand and the willingness to sign a written informed consent document

5.2.10 Patient must be able to drink and eat more than 75% of their usual daily meals.

5.3 Exclusion Criteria

5.3.1 Patients with active CLL disease requiring urgent chemotherapy as defined in section 12.1

5.3.2 Patients may not be receiving any other investigational agents.

5.3.3 Patients less than 30 days from last treatment for CLL.

5.3.4 History of allergic reactions attributed to metformin or other biguinides.

5.3.5 Known diabetes (type 1 or 2), fasting glucose > or equal to 7.0 mmol/L (126 mg/dL), or HgbA1C > 6.5

5.3.6 Currently taking metformin, sulfonyureas, thiazolidenediones or insulin for any reason

5.3.7 Current or planned pregnancy or lactation in women of child bearing age (confirmed by negative pregnancy test prior to start of therapy).

5.3.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection and sepsis, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

5.3.9 Conditions which would increase risk of lactic acidosis including:

1. Known alcoholism or ingestion of more than 3 alcoholic beverages per day

2. History of congestive heart failure defined as NYHA class III or IV (see Appendix B)

3. History of metabolic acidosis

4. Ongoing or active infection concerning for sepsis or SIRS

5.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

6. STAGING CRITERIA: Rai Staging System

Stage 0: absolute lymphocytosis (>15,000/mm^3) without adenopathy, hepatosplenomegaly, anemia, or thrombocytopenia.

Stage I: absolute lymphocytosis with lymphadenopathy without hepatosplenomegaly, anemia, or thrombocytopenia.

Stage II: absolute lymphocytosis with either hepatomegaly or splenomegaly with or without lymphadenopathy.

Stage III: absolute lymphocytosis and anemia (hemoglobin <11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly.

7. REGISTRATION PROCESS

7.1 **General Guidelines**

Eligible patients will be entered on study centrally at the University of Michigan Rogel Cancer Center by the Study Coordinator

Following registration, patients should begin protocol treatment within 72 hours.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

7.2 **Registration Process**

To register a patient, the following documents should be completed by the research nurse or data manager (to be assigned) and faxed to 734-647-9654 or e-mailed to *smalek@med.umich.edu* to the Study Coordinator (to be assigned):

- Copy of required laboratory tests
- Signed patient consent form

- HIPAA authorization form
- *Eligibility Questionnaire Form (see forms)*

The research nurse or data manager at the participating site will then call 734-763-2194 or e-mail *smalek@med.umich.edu* the Study Coordinator (to be assigned) to verify eligibility. To complete the registration process, the Coordinator will

- assign a patient study number
- assign the patient a dose
- register the patient on the study
- the data manager at the O-CTSU will assign the study number and confirm registration with the study team.

8. TREATMENT PLAN

8.1 Metformin Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 4.10. Appropriate dose modifications for metformin are described in Section 8. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

The starting dose of metformin will be 500 mg po daily for one week. The dose can be escalated to 500 mg twice a day after one week, and further escalated to the final dose of 1000 mg twice a day in week 3 if the medication is tolerated without adverse side effects (refer to holding parameters described in section 9.3.3). All doses should be administered with food to decrease gastrointestinal upset.

Dose-Escalation Schedule	
Dose Level	Dose of *Metformin**
0	500 mg daily
1	500 mg BID
2	1000 mg BID

8.2 Dose Justification: The dose of metformin chosen is the typical dose used in the treatment of type 2 diabetes and polycystic ovarian syndrome. This is also the same maximum dose used in on-going clinical trials of metformin in other cancers.

8.3 Frequency of Monitoring: Patients labs (CBC with differential, comprehensive metabolic panel) will be monitored prior to therapy and at, 3 months, and every 3 months thereafter (range 2-4 months allowed) while on therapy. Correlative studies (see section 10) will be drawn prior to therapy, and at 3 months and 6 months during therapy. Patients will be evaluated every 3 months with a clinic visit when therapy is initiated until evidence of treatment failure, or progression to active disease requiring chemotherapy (see section 12.1).

In the first month of treatment, we will monitor side effects by phone call to the patient at the end of one week of therapy (at the end of week 1, week 2, and week 3) prior to escalation of their metformin dose to the next level.

8.4 Laboratory Monitoring:

All pretreatment evaluations should be performed within 2 weeks of enrollment. Serum samples will be performed prior to starting metformin therapy and will be sent for the following tests (for specific tubes needed for correlative studies, refer to section 9):

1. CBC with differential

2. Comprehensive metabolic panel (including creatinine, AST, ALT, Alk Phos, Total bilirubin, should be a **fasting sample of at least 10 hours** to include glucose)

3. Fasting glucose (included with comprehensive metabolic panel)

4. Fasting insulin levels

5. HgbA1C (drawn in lavender top tube)

6. Other serum correlative studies to be drawn and sent to Malek lab:

   a. Insulin receptor expression (will be analyzed by FACS)

   b. Baseline and insulin stimulated AKT phosphorylation

7. Postprandial insulin, (see section 10.2.4, 10.2.5)

8. Pregnancy test (serum beta HCG) for women of childbearing age (less than or equal to 50 years)

8.5 Monitoring Compliance: Patients will be asked to bring pill bottles to doctors' appointments. In addition patients will be asked to maintain a medication diary to share with their doctor at each visit (see Forms). Patients that will miss scheduled appointments will be contacted to reschedule a visit with 1-2 weeks. One missed visit will be allowed; more than one missed visit will lead to the patient's removal from study.

8.6 Supportive Care Guidelines: Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician.

8.7 **Study Discontinuation**

In the absence of treatment delays due to adverse events, treatment may continue until patients demonstrate treatment failure (as defined in Section 11.1). Patients will remain on study until one of the following criteria applies:

1. Disease progression to active disease requiring chemotherapy (defined in section 11.1)
2. Intercurrent illness that prevents further administration of treatment,
3. Unacceptable adverse event(s),
4. Patient decides to withdraw from the study, or
5. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

8.8 Duration of Follow Up

Patients will be followed for 1 year after removal from study or until death, whichever occurs first. Follow up visits will occur at 3 months and every 3 months thereafter. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

9. TOXICITIES/DOSE MODIFICATIONS

9.1 Toxicities: Monitoring for adverse events will occur at every clinic visit every 3 months. Physicians may monitor interim labs at their discretion.

9.2 Adverse events associated with Metformin: Refer to Section 3.10.

9.3 Dose Modifications for Metformin

9.3.1 If toxicities are attributed to Metformin the treating physician will reduce the dose to the next lower level and monitor the patients (see table 9.3.3). Patient will stay on the Metformin dose level that allows as acceptable side effect profile (see below).

Dose Level	**Metformin Dose**
0	*500 mg daily*
1	*500 mg BID*
2	*1000 mg BID*

9.3.2 Hematologic toxicities: There are no hematologic toxicities associated with metformin other than vitamin B12 deficiency (7%), therefore there will be no dose modifications due to hematologic toxicities.

9.3.3 Non-Hematologic toxicities and dose modifications:

Toxicity	Grade	Modification
Diarrhea	Grade 1	Patient should be encouraged to remain on full dose. Diarrhea is expected to resolve within 2 weeks of starting metformin. If patient is unwilling to remain on full dose, follow instructions for Grade 2 toxicity.
Diarrhea	Grade 2	Treat diarrhea with loperamide and fluid hydration as needed at the discretion of the patient's physician. If diarrhea persists for more than 2 weeks despite optimal medical management, follow instructions for Grade 3 diarrhea
Diarrhea	Grade 3	Hold metformin until recovery to Grade 1, when resuming metformin reduce the dose by one level.
Diarrhea	Grade 4	Patients with persistent diarrhea despite medical management and dose reduction to level -1 will be removed from the study.
Nausea/vomiting/ Constipation	Grade 1-2	No dose modification needed, supportive measures at the discretion of the patient's physician.
Nausea/vomiting/ Constipation	Grade 3	Reduce the dose of metformin by one level.
Headache	Grade 1	Receive appropriate supportive medical management by patient's physician without dose adjustment.
Hepatic dysfunction Bilirubin > 1.5 x ULN except Gilbert's disease	Grade 1	Hold metformin for 4 weeks. If bilirubin returns to normal in that time frame, begin 500 mg daily for one week, then 500 mg BID for one week, then 1000 mg BID.

Hepatic dysfunction AST or ALT = 1.8 – 3.0 X ULN	Consult CTC AE for grade	Hold metformin. Repeat AST & ALT every 2 weeks. Resume metformin once AST & ALT < 1.8 x ULN, starting at 500 mg daily until next annual reassessment of LFTs, then increase to 500 mg BID if AST & ALT remains < 1.8X ULN. If liver enzymes do not recover, remove from study.
Hepatic dysfunction AST or ALT > 3.0 X ULN	Consult CTC AE for grade	Hold metformin. Repeat AST & ALT every 2 weeks. Once repeat AST & ALT < 1.8 x ULN, resume metformin starting at 500 mg daily until next annual reassessment of LFTs, then increase to 500 mg BID if AST & ALT remains < 1.8X ULN. If repeat AST & ALT > 3.0 x ULN, continue to hold metformin and initiate work up for liver disease. If liver enzymes do not recover, remove from study.
Renal dysfunction Creatinine increase above 1.4 mg/dl	Consult CTC AE for grade	Hold metformin. Repeat basic metabolic panel in 2 weeks. If creatinine recovers, resume metformin at level -1. Recheck basic metabolic panel in 2 weeks to assure creatinine remains < 1.4, and increase to level 1 and stay at this dose. If creatinine does not recover or there is a second episode, patient will be removed from the study.
Clinical diagnosis of congestive heart failure	Grade 3	Hold metformin for 4 weeks. Resume metformin if underlying condition (ex. Acute MI) has resolved. Resume metformin starting at 500 mg daily for one week, then 500 mg BID for one week, then 1000 mg BID, and stay at this dose. Do not restart metformin if persistent or ongoing treatment for CHF is required.
Acidosis Lactate > 5.0 mM pH < 7.3	Grade 3	Stop metformin and do not restart. Report as a serious adverse event. Please consult protocol section 13.
Macrocytic Anemia	Grade 1	Perform CBC and check B12 level. Treat B12 deficiency if evident.

MCV > 105		Continue metformin at current dose.
Skin Reactions Major – generalized urticaria, bullous rashes, exfoliative dermatitis	Generalized	Stop study drug and remove from study.
Stevens Johnson Syndrome	Localized	If rash is definitely related to metformin use, stop metformin and remove from study.
Hospitalization for any reason	Grade dependent on reason for hospitalization	Hold metformin up to 4 weeks. The investigator is to determine when it is safe to re-start. May need to hold for ongoing sepsis, CHF, renal failure, liver failure, etc. If metformin is held for 2 weeks or longer, the drug will be restarted on a ramp up schedule of 500 mg daily for one week, followed by 500 mg BID for one week, followed by 1000 mg BID. If metformin is held for less than 2 weeks, then continue metformin at the current dose.

9.3.4 Other Situations:

Radiologic studies: Metformin should be suspended the day prior to any iodinated contrast studies (example, intravenous urogram, intravenous cholangiography, angiography, and computer tomography (CT) scans with intravascular contrast materials) and held for 48 hours after the study. If renal compromise is a concern, metformin should only be reinitiated after confirming normal renal function by the patient's treating physician.

Surgical Procedures: Metformin should be suspended the day prior to any surgical procedures (except minor procedures not associated with restricted intake of food and fluid), should be held for 48 hours after surgery, and resumed only after normal oral intake has resumed. If renal compromise is a concern, metformin should only be reinitated after confirming normal renal function by the patient's treating physician.

Hypoxic states: Cardiovascular shock from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and lead to hypoperfusion and pre-renal azotemia. When such events occur on metformin therapy, the drug should be discontinued.

10. Correlative Studies

10.1 Laboratory Correlative Studies

Study	Collection of Specimen	Handling of Specimen (if collected at UMHS)	Timing of Collections (for specific timepoints refer to study calendar section 11)
Fasting glucose	SST (serum-separating tube, yellow top) tube with 0.5 mL – 1.0mL serum	Collect blood specimen in SST tube and send to UMHS laboratory.	Pre-therapy, during metformin therapy,
Fasting insulin	Green top tube (sodium or lithium heparin) with 0.5mL – 1.0mL plasma	Collect specimen in a green top tube from a fasting patient (at least 10 hours fast) and send to UMHS laboratory.	Pre-therapy and during metformin therapy.
Postprandial insulin	Green top tube (sodium or lithium heparin) with 0.5mL – 1.0mL plasma	Collect specimen in a green top tube from patient at 60 mins and 120 mins after 75g glucose load, and send to UMHS laboratory	*Fasting sample to be drawn prior to 75g glucose load, then at 60 mins and 120 mins after glucose. Will be drawn pre-therapy, and during therapy
CLL cell insulin receptor expression	10 cc of blood in preservative-free heparinized tubes (1)	Call Malek lab for pick up 763-1222	Pre-therapy and during metformin therapy,
Unstimulated baseline AKT phosphorylation	Use specimens (1)	Call Malek lab for pick up 763-1222	Pre-therapy and during metformin therapy,
Ex vivo insulin stimulated AKT phosphorylation	Use specimens (1)	Call Malek lab for pick up 763-1222	Pre-therapy and during metformin therapy,

10.2 Descriptions of correlative studies

10.2.1 Fasting insulin/fasting glucose: We plan to examine fasting insulin levels and observe whether metformin will lower fasting insulin levels during therapy. We hypothesize that lowering insulin levels may retard disease progression. Along with fasting glucose, we will also use the Homeostasis Model Assessment (HOMA) to estimate insulin sensitivity which correlates well with the glucose intolerance test [72], to establish whether insulin resistance is also reduced in CLL patients during metformin therapy. (For calculation of HOMA refer to Appendix C.)

10.2.2 CLL cell insulin receptor expression: We have shown that higher levels of insulin receptor (INSR) in CLL patients correlates to early progression of disease. We will

measure INSR on CLL cells to observe changes in expression pre-therapy and during metformin therapy.

10.2.3 Unstimulated baseline AKT phosphorylation and ex vivo insulin stimulated AKT phosphorylation: we will measure baseline and insulin stimulated AKT phosphorylation on isolated CLL cells from patients prior and during therapy on metformin.

10.2.4 *Postprandial serum insulin: Patients will fast for at least 10 hours and then receive a 75g oral glucose load in the morning. Patients will then have postprandial levels drawn prior to glucose load, and at 60 mins and 120 mins after glucose is consumed.

11. STUDY CALENDAR Pre-Study Evaluation: All pretreatment evaluations should be performed within 2 weeks of study enrollement

Investigation	Timing
Informed Consent	Prior to treatment
History and Physical including: Weight, Height, and Physical Exam including assessment of lymph nodes and hepatosplenomegaly Performance Status Completion of Eligibility Questionnaire (see Forms)	Prior to treatment
Hematology: CBC with differential	Prior to treatment
Biochemistries: Comprehensive Metabolic Panel (including creatinine, AST, ALT, Alk Phos, total bilirubin, **drawn as a fasting sample to obtain fasting glucose**)	Prior to treatment
Other studies: fasting insulin, post-prandial insulin	Prior to treatment
Other studies: CLL INSR expression by FACS, baseline and insulin stimulated AKT phosphorylation	Prior to treatment
Pregnancy test (serum beta HCG)	Prior to treatment
HgbA1C	Prior to treatment

Evaluation during metformin therapy: To be completed during active metformin treatment

Investigation	Timing
History and Physical including: Weight, Height, and Physical Exam including assessment of lymph nodes and hepatosplenomegaly Performance Status Compliance: Patients will bring in their bottles and medication diaries (see Forms)	Every 3 months with clinic visit
Hematology: CBC with differential	At 3 months, and every 3 months thereafter
Biochemistries: Comprehensive Metabolic Panel (including creatinine, AST, ALT, Alk Phos, total bilirubin, **drawn as a fasting sample to obtain fasting glucose**)	At 3 months, and every 3 months thereafter
Other studies: fasting insulin	At 3 months and 6 months
Other studies: postprandial insulin	At 3 months and 6 months
Other studies: CLL INSR expression by FACS, baseline and insulin stimulated AKT phosphorylation	At 3 months and 6 months
Adverse events: Adverse events (related to study treatment only) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events	Throughout treatment course and assessed every clinic visit every 3 months

Evaluation after completion of metformin therapy: To be completed one- three months after metformin therapy is discontinued as part of routine clinic visits

Investigation	Timing
History and Physical including: Weight, Height, and Physical Exam including assessment of lymph nodes and hepatosplenomegaly Performance Status	1-3 month post therapy
Hematology: CBC with differential	1-3 month post therapy
Biochemistries: Comprehensive Metabolic Panel (including creatinine, AST, ALT, Alk Phos, total bilirubin, **drawn as a fasting sample to obtain fasting glucose**)	1-3 month post therapy
Adverse events: Adverse events (related to study treatment only) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events	1-3 month post therapy

12. EVAULATION CRITERIA

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every *3 months*.

12.1 Definitions

Relapsed disease: Will be defined as asymptomatic CLL patients with one or both of the following:

1. ALC > 5000 on 2 consecutive occasions and increasing in trend
2. Any clinically appreciated lymphadenopathy increased above best overall response and persisting over 3 months.

Time to treatment failure: While patients are on metformin therapy, time to treatment failure will be defined as one or all of the following criteria:

1. ALC > 5000 on 3 occasions after start of metformin treatment and increasing by 25% or more on each occasion, which will be measured every 3 months.
2. An increase of Rai Stage (0-3) by one stage.
3. An increase in any lymph node by >50% as assessed by either physical exam (all patients) or CT scanning (only if ordered as part of routine clinical management).
4. Worsening cytopenias (Hemoglobin <11 g/dl) associated with a bone marrow biopsy result indicating advanced stage CLL (packed CLL marrow).

Time to first treatment (TTFT): This will be defined as the time interval (in months) from time of diagnosis to time of first treatment with anti-neoplastic chemotherapy.

Active disease requiring chemotherapy: will be defined as at least one of the following (according to IWCLL updates to NCI-Working Group Guidelines)[73]

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
2. Massive (at least 6 cm below left costal margin) or symptomatic splenomegaly
3. Massive nodes (at least 10 cm in longest diameter) or symptomatic lymphadenopathy
4. Progressive lymphocytosis with an increase of more than 50% over a two month period or lymphocyte doubling time (LDT) of less than 6 months.
5. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
6. Constitutional symptoms, defined as anyone or more of the following disease-related symptoms or signs:
    a. Unintentional weight loss of 10% or more within the previous 6 months
    b. Significant fatigue (i.e. ECOG 3 or worse; inability to work or perform usual activities)
    c. Fevers higher than 100.5 F or 38.0 C for 2 or more weeks without other evidence of infection
    d. Night sweats for more than 1 months without evidence of infection

12.2 **Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g. palpable lymph nodes).

12.3 **Response Criteria**

Our primary endpoints will be defined by time to treatment failure as discussed in Section 12.1. Disease response criteria are based on the National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia[74].

Complete Remission (CR):
• Absence of constitutional symptoms attributable to CLL (i.e., ≥ 10% wt. loss, significant fatigue, fevers >100.5ºF for ≥2 weeks, or night sweats for >1 month)
• No LN >1.5 cm on exam
• No hepatosplenomegaly on exam
• ANC >1500
• Plt >100,000
• Untransfused Hgb >11

• No clonal lymphocytes in the peripheral blood by immunophenotyping

Partial Response (PR): (at least one from Group 1 and one from Group 2, one of which has been > 2 months)

Group 1:
• A decrease in ALC by ≥50%
• A reduction in previously enlarged LN by ≥50% percent (i.e., defined by the sum of the products of up to 6 lymph nodes) with no increase in the size of any single lymph node (i.e., an increase of <25 percent in a lymph node <2cm is not considered significant) and no new enlarged lymph nodes.
• If enlarged prior to therapy, the liver and spleen should be reduced in size by ≥50% by exam or US/CT

Group 2:
• ANC ≥1500 or >50% over baseline without G-CSF
• Plt ≥100,000 or >50% over baseline.
• Hgb ≥11 or >50% over baseline w/o PRBC or EPO

13. ADVERSE EVENTS

13.1. Adverse events (AE's) will use the descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Toxicity Criteria (CTC).

A copy of the CTC version 4.0 can be downloaded from the CTEP home page:
http://ctep.info.nih.gov/reporting/ctc.html

13.2. Definition of Adverse Events (AE)

13.2.1 Serious Adverse Event: Any adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

At the University of Michigan Rogel Cancer Center CTC grades III-V are categorized as serious adverse events.

13.2.2 Unexpected Adverse Event: Any Grade 3 or 4 adverse experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. (In addition to this definition, the

IRBMED (Medical Institutional Review Board) will interpret any adverse event not included in the informed consent document as a risk as "unexpected".)

13.2.3 Expected (Known) Adverse Event: An adverse event, which has been reported in the Investigator's Brochure. (In addition to this definition, the IRBMED will consider an adverse event as "expected," only if it is included in the informed consent document as a risk.)

13.2.4 Adverse event definitely associated with an investigational drug: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, for which no alternative cause is present.

13.2.5 Adverse event probably associated with an investigational drug: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, but for which a potential alternative cause may be present.

13.2.6 Adverse event possibly associated with an investigational drug: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, but a potential alternative cause does not exist.

13.2.7 Adverse event unrelated to an investigational drug: An adverse event, for which there is evidence that it is definitely related to a cause other than the investigational drug/agent. In general, there is no timely relationship to the administration of the investigational drug/agent, or if there is a timely relationship, the event does not follow a known pattern of response, and there is an alternative cause.

13.3 Reporting Procedures

13.3.1. Serious adverse Events (SAE's) that are unexpected and/or definitely, probably or possibly related to protocol therapy will have a written report sent to the Oncology Clinical Trials Support Unit:

The Oncology Clinical Trials Support Unit (O-CTSU) staff will coordinate the reporting process between the Investigator and the IRBMED as well as other applicable reporting using the Medwatch form. Copies of all related correspondence and reporting documents will be maintained in the regulatory file.

13.3.2 Deaths or life-threatening adverse events (regardless of relatedness) will be reported to the University of Michigan Medical Institutional Review Board (IRBMED) immediately, phone # (734) 763-4768, and fax # (734) 763-9603 with formal written notification within 7 days of the event. IRBMED reporting form templates can be downloaded from the IRBMED website located at: http://www.med.umich.edu/irbmed/Appguide.

13.3.3 Reporting requirements for AEs are dependent on the Phase of the trial, grade, and attribution and whether the event is expected or unexpected as determined by the

NCI Specific Expected Adverse Event List, IRB approved protocol and/or Investigator's Brochure.

13.3.4 Adverse events which are serious (but not life threatening or not resulting in death) have a causal relation to the research (possibly, probably, or definitely related), and are unexpected must be reported to the IRBMED immediately by phone or email; followed by a written report within 7 days of the event.

13.3.5 If the adverse event requires modification of the study protocol and informed consent they should be provided to the IRBMED with the report of the adverse event.

13.3.6 All adverse events 30 days post-dose will be noted in the case report forms**.**

Adverse Event Reporting Guidelines
University of Michigan IRBMED

Event	**Expected**	**Unexpected**
Fatal Event/Grade V Toxicity Occurring within 30 days of last study intervention	**Immediately** by phone or email; followed by an AE Form within 7 days regardless of relatedness	**Immediately** by phone or email; followed by an AE Form within 7 days regardless of relatedness
Fatal Event/Grade V Toxicity Occurring after 30 days of last study intervention	**Within 7 days** if possibly, probably or definitely related.	**Within 7 days** if possibly, probably or definitely related.
Life Threatening Event/Grade III Toxicity, Grade IV Toxicity, Serious Adverse Event	**Within 7 days** regardless of relatedness	**Within 7 days** regardless of relatedness
Serious Adverse Event/Grade III Toxicity	Do not report	**Immediately** by phone or email; followed by an AE Form **within 7 days** if possibly, probably, or definitely related
Grade II Toxicity	Do not report	**Within 15 days** if possibly, probably, or definitely related
Grade I Toxicity	Do not report	**Prior to or concurrent with submission of Scheduled Continuation Application** when frequency is different than expected in consent or protocol

This guidance table is not to be used in place of IRBMED procedures. It is intended as a guide to the investigator when writing a protocol. If discrepancies occur, all IRBMED procedures in the reporting of adverse events SUPERCEED this guidance table.

14. DATA AND SAFETY MONITORING

14.1 Scheduled meetings will occur every quarter or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and data managers involved with the conduct of the protocol.

14.2 During these regular meetings, the study team will discuss matters related to:

1. Safety of study participants (SAE/UaP reporting)
2. Validity and integrity of the data
3. Enrollment rate relative to expectations, characteristics of participants
4. Retention of participants, adherence to protocol (potential or real protocol deviations)
5. Data completeness

14.3 Study team meetings will be documented by the Protocol Specific Data and Safety Monitoring Report (DSMR). The data manager or designee assigned to the trial will be responsible for completing the report. DSMRs will be signed by the Principal Investigator or by one of the co-investigators and will be kept on file in the Oncology Clinical Trials Support Unit.

14.4 The University of Michigan Rogel Cancer Center Data and Safety Monitoring Committee (DSMC) will provide independent oversight of the safety and data integrity for this trial. DSMRs and any other pertinent documents will be submitted to the DSMC for review on a quarterly basis unless specified more frequently by a DSMC ruling.

14.5 The Principal Investigator or designee will forward all correspondence and recommendations generated by the DSMC to the Institutional Review Board per institutional guidelines.

15. STATISTICAL CONSIDERATIONS

15.1 **Study Design/Endpoints** (refer to section 2)

15.2 **Stratification/Sample Size/Accrual Rate**

This trial will accrue two separate patient populations, those with relapsed CLL with or without del11q and untreated patients who are known to have del11q, subject to the additional eligibility criteria set forth in Sections 4.2 and 4.3 of this protocol. The sample size for these two groups has been based upon the consideration of the primary hypothesis, to increase the proportion of patients progression-free after 6 months of study treatment with metformin. Historically 90% of patients meeting this study's eligibility criteria would be expected to have progressive disease as defined in this protocol in the absence of therapy prior to or after 6 months of observation. In relapse patients, we hypothesize that metformin treatment will reduce that proportion to 70%. In untreated patient with the del11q the effect of anti-insulin therapy with metformin is thought to be more pronounced as many of these patients express very high INSR levels. We hypothesize the treatment will reduce the proportion of patient with progression to 60%. For each hypothesis the study is

adequately powered, >80%, to detect the hypothesized difference significantly, using one-sided tests, with at most 2.5% type I error. Statistical comparisons will be made for evaluable patients. For patients to be evaluable they must have progressed prior to 6 months of therapy, received all six months of metformin therapy, or discontinued therapy due to toxicity. Patients discontinuing therapy due to toxicity will be considered treatment failures. Patients that discontinue therapy due to reasons unrelated to disease status or metformin toxicity will be replaced.

We have enrolled 32 patients and upon interim data analysis have observed long-term responses in patients carrying 11q deletions but also in occasional patients with relapsed CLL. Going forward, we will therefore preferentially enroll patients with 11q deletions and close the trial after N=40 patients are enrolled. This amendment brings enrollment more in line with real life enrollment numbers at the University of Michigan and will still allow for meaningful conclusions to be reported.

15.3 **Analysis of Endpoints**

Primary endpoint: The distribution for time to treatment failure will be estimated using the product-limit method of Kaplan and Meier. Elapsed time will be calculated from that first date of metformin therapy until treatment failure. Treatment failure is defined as discontinuation of metformin due to toxicity and disease progression. Patients discontinuing therapy for reasons unrelated to toxicity and/or progression will be replaced; however for estimates of the TTF distribution their experience will be used, with their TTF censored on their last date of metformin therapy. The study's primary endpoint, estimated proportion of patients without treatment failure after 6 months of therapy will be estimated by both the crude proportion and exact 95% binomial confidence interval and by the product-limit estimate and the complementary log-log-transformation for 95% confidence intervals. The estimates for the primary endpoint will be reported separately for the two study groups. Secondary endpoints: For this trial all secondary endpoints are considered exploratory and hypothesis generating. First - to evaluate the increase in absolute lymphocyte count in relapsed patients during metformin treatment, longitudinal lymphocyte counts will be modeled using mixed models methodology, whereby both fixed effects (dose of metformin) and random effects (intercept – starting lymphocyte count) can be modeled. Second – to evaluate clinically appreciated improvement in lymphadenopathy and splenomegaly/hepatomegaly, the proportion of patients that begin metformin therapy with these conditions will be summarized, along with the proportions at study defined clinical assessment points during therapy. No statistical models will be employed, but proportions and 95% exact binomial confidence intervals will be reported for descriptive purposes. Third – to evaluate TTFT in untreated patients, the product-limit method of Kaplan and Meier will be used similarly to the primary endpoint. The main difference between this endpoint and the primary endpoint is that TTFT will be defined from the date of CLL diagnosis for untreated delq11 patients. Fourth – to evaluate the insulin level, IGF-1 levels, and insulin resistance by the HOMA –IR model, serial measurements per subject may be modeled using mixed models methodology as described above to characterize the change over time, or simple descriptive estimates and confidence intervals may be reported at serial study measurement time points.

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B

New York Heart Association Classification System

NYHA Classes

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Appendix C

Homeostasis Model Assessment (HOMA)

The Homeostasis Model Assessment (HOMA) estimates steady state beta cell function (%B) and insulin sensitivity (%S), as percentages of a normal reference population. These measures correspond well, but are not necessarily equivalent, to non-steady state estimates of beta cell function and insulin sensitivity derived from stimulatory models such as the hyperinsulinaemic clamp, the hyperglycaemic clamp, the intravenous glucose tolerance test (acute insulin response, minimal model), and the oral glucose tolerance test (0-30 delta I/G). [72] [75] A downloadable HOMA calculator is available at http://www.dtu.ox.ac.uk/homacalculator/index.php

A Phase II Pilot Study of Metformin Therapy in Patients with Relapsed Chronic Lymphocytic Leukemia or CLL at any treatment status with 11q deletion.

Eligibility Questionnaire

Date (dd/mm/yyyy): _____ UMHS MRN: _____

Patient Initials: _____ Date of Birth (dd/mm/yyyy) : _____

Registering Physician: _____

Phone:_____ Fax: _____

Answers to questions 1, 2, and 4 through 13 OR 1, 3, and 4 through 13 must be YES in order to be eligible for this study.

1. Does the patient carry a diagnosis of chronic lymphocytic leukemia?	Yes	
2. Does the patient have confirmed del11q status and previously treated or untreated with anti-neoplastic chemotherapy?	Yes	
3. If the patient does not have del11q status, do they have a prior history of being treated with fludarabine or bendamustine based chemotherapy?	Yes	
4. Is the patient currently asymptomatic of any symptoms related to their CLL?	Yes	
5. Does the patient have evidence of one or both of the following: a. ALC >5000 on two consecutive occasions and increasing in count b. Any lymphadenopathy increase over best response that has persisted over more than 3 months	Yes	
6. Is the ECOG performance status 0-2?	Yes	
7. Is the patient > 18 years old and < 80 years old?	Yes	
8. Does the patient have normal organ function as defined as the limits described below, within 14 days prior to registration? (ULN = upper limit of normal) Date of labs: _____ Creatinine < 1.5 (if male), < 1.4 (if female) _____(male/female) GFR > 59 _____ Conjugated Bilirubin < ULN _____ ULN: _____ ALT < 1.8 X ULN _____ ULN: _____ AST < 1.8 X ULN _____ ULN: _____ Alkaline phosphatase < 2X ULN _____ ULN: _____	Yes	
9. Is the patient willing to provide blood samples for correlative studies?	Yes	
10. Is the patient competent and willing to provide written documentation of informed consent?	Yes	
11. Is the patient mentally, physically and geographically able to undergo treatment and follow up?	Yes	

12. Does the patient have a life expectancy > 12 months?	Yes	
13. Is the patient able to eat more than 75% of their usual daily meals?	Yes	

Answers to questions 14 through 25 must be NO in order to be eligible for this study.

14. Does the patient have a history of diabetes mellitus (type 1 or type 2)?	No	
15. Does the patient have a fasting glucose > 7.0 mMol/L (126 mg/dL) and/or Hgb A1C > 6.5?	No	
16. Does the patient have an allergy to metformin or other biguanides?	No	
17. Has the patient received metformin therapy in the last 6 months?	No	
18. Is the patient currently taking metformin, 38ulfonylureas, thiazolidenediones or insulin for any reason?	No	
19. Is the patient pregnant or breast feeding?	No	
20. Does the patient currently have uncontrolled intercurrent illness? (Including, but not limited to, ongoing or active infection and sepsis, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements)	No	
21. Does the patient have known alcoholism or drinks more than 3 alcoholic beverages a day?	No	
22. Does the patient have a history of lactic or metabolic acidosis?	No	
23. Does the patient have a history of congestive heart failure defined as NYHA stage III or IV?	No	
24. Is the patient receiving any other investigational drugs?	No	
25. Has it been less than 30 days since the patient's last CLL treatment?	No	

Pretreatment Evaluation: The following studies should be performed within 2 weeks of study enrollment

Study	Date Performed (dd/mm/yyyy)
History and Physical Exam	
CBC with differential	
Comprehensive Metabolic Panel (obtain fasting sample to get fasting glucose)	
Hgb A1C	
Height and Weight	
Pregnancy Test (in women of childbearing age)	

Is the patient eligible for this study? ____ Yes ____ No

Registrar Signature: _____ Date: _____

Investigator Signature: _____Date: _____

A Pilot Study on Metformin in Relapsed Chronic Lymphocytic Leukemia

Medication Diary

Patient Initials:_____

Please be sure to fill out this form every day and bring this with you along with your Metformin bottles (empty or not) to you next clinic visit.

You should give this form and the metformin bottles to the research nurse or assistant in clinic.

If you have any side effects that may be related to taking metformin, call the clinic at

_____

Day	Date	Dose of one tablet	Number of tablets taken	Side effects (if any)
Day 1: Start taking metformin 500 mg once a day with meals.				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8: Start taking metformin 500 mg twice a day with meals.				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15: Start taking metformin 1000 mg twice a day with meals.				
Day 16				

Day	Date	Dose of one tablet	Number of tablets taken	Side effects (if any)
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22				
Day 23				
Day 24				
Day 25				
Day 26				
Day 27				
Day 28				
Day 29				
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Day 53				
Day 54				
Day 55				
Day 56				

Day	Date	Dose of one tablet	Number of tablets taken	Side effects (if any)
Day 57				
Day 58				
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Day 89				
Day 90				

PROTOCOL SPECIFIC DATA AND SAFETY MONITORING REPORT

UMCC PROTOCOL #: _____ **DSMC DATE:** _____

STUDY STATUS: _____ **DATE OF LAST REPORT:** _____

PROTOCOL TITLE			
ATTENDANCE			
PROTOCOL ACTIVITY			
Planned Accrual Duration:		Global Accrual to Date / Goal:	0 / 0
Date First UM Patient Enrolled:		UM Accrual to Date / Goal: List multi-stages individually	0 / 0
Consented Since Last Report:		Accrual Since Last Report:	
Eligible Since Last Report:		Ineligible Since Last Report:	
Eligibility Exceptions to Date:			

Specifically for Phase I and/or Dose Escalating Trials:	
Dose Level	Accrual
1	
2	
3	
4	

SAE/UaP REPORTING SINCE LAST REPORT♦ List event, patient study ID number, date of occurrence, and date IRB notified. Attach SAE reports. Attach the updated SAE/UaP spreadsheet summarizing ALL events that have occurred since trial initiation.
1]
2]
3]

PATIENTS COMPLETED/OFF PROTOCOL SINCE LAST REPORT ♦ Provide reason [progression, death, toxicity, completed therapy, etc]. Provide detailed supplemental information for patients off study treatment due to toxicity or death.

PROTOCOL DEVIATIONS SINCE LAST REPORT ♦ Include both *purposeful and accidental* variances in the approved procedures outlined for a study in its IRB approved protocol; provide date reported to Regulatory Affairs or IRB. Attach any protocol deviation forms.

PROTOCOL AMENDMENTS SINCE LAST REPORT♦ Include amendment summary, date submitted to regulatory bodies, and date approved.

OTHER COMMENTS

Investigator Signature:		**Data Manager Signature:**	
Date:		**Date:**	

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