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A phase I clinical trial to evaluate dimethylfumarate (DMF) in relapsed/refractory patients with chronic lymphocytic leukemia/small lymphocytic lymphoma.

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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STUDY SUMMARY

Title	A phase I clinical trial to evaluate dimethylfumarate (DMF) in relapsed/refractory patients with chronic lymphocytic leukemia/small lymphocytic lymphoma.
Short Title	Dimethylfumarate for CLL
Phase	1
Methodology	Open label, non-randomized, single-arm
Study Duration	2 year
Study Center(s)	Single-center
Objectives	**Primary Objective:** To determine the maximum tolerated dose or biologically optimal dose of dimethylfumarate for patients with chronic lymphocytic leukemia. **Secondary Objectives** 1. To determine the safety and tolerability of DMF by evaluation of adverse events 2. To assess the clinical activity of DMF based on international working group guidelines (iwCLL 2008). 3. To evaluate the pharmacodynamic activity of dimethylfumarate (DMF) in chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) by evaluation of the Wnt and STAT pathways. 4. To assess the durability of clinical activity of DMF.
Number of Subjects	15-21 (3 cohorts of 3+3; one expansion cohort with 3 additional patients)
Diagnosis and Main Inclusion / Exclusion Criteria	Main Eligibility Criteria: 1. Clinical and phenotypic verification of B cell CLL/ SLL and measurable disease. Immunophenotyping of the leukemic cells (blood, lymph node, or bone marrow) must demonstrate a monoclonal (kappa or lambda light chain restricted) B cell population with immunophenotype diagnostic for CLL (eg: co-expressing CD19 and CD5). 2. Disease Status/ Prior Therapy: Previously treated with at least 1 regimen for CLL/SLL 3. Not eligible or amenable to available standard therapies (see page 11 for specific criteria). 4. Has recovered from the toxic effects of prior therapy to their clinical baseline. 5. Requires treatment for CLL/SLL by working group guidelines (iwCLL 2008, Hallek et al.) 6. Adequate hematologic function: a. Platelet count ≥ 50,000/μL; AND b. Hemoglobin ≥ 8.0 g/dL (may be supported by erythropoietin); AND c. Absolute neutrophil count > 1000 /uL
Study Product(s), Dose, Route,	DMF will be evaluated in 2 dose cohorts.

Regimen	Cohort 1: DMF will be administered 120 mg twice daily for 2 x 28 day cycles. Cohort 2: DMF will be administered 120 mg twice daily for 7 days, then 240mg orally twice daily (the approved dosage in MS) for the remainder of 2 x 28 day cycles. Cohort 3: DMF will be administered 120 mg twice daily for 7 days, then 360mg orally twice daily (a dosage tested previously in psoriasis) for the remainder of 2 x 28 day cycles. DMF should be taken at approximately the same times each day. It should be swallowed whole and intact. It should not be crushed or chewed. It can be taken with or without food.
Duration of administration	2 x 28 day cycles
Reference therapy	None

Statistical Methodology	A standard 3+3 dose escalation design will be used. There are three test dose levels with a potential de-escalation dose. A minimum of three subjects will be treated at each dose level. All three subjects in a cohort will be evaluated for DLT in the defined DLT evaluation period (within 56 days of starting study treatment) before enrollment of subjects at the next dose level may begin. For all dose levels, if no DLTs are observed during the evaluation period among the three treated patients, escalation to the next dose level may begin. If a DLT is observed in one of the first three subjects in the cohort, the cohort will be expanded to six subjects. If zero or one of six subjects in the cohort experiences a DLT within the evaluation period, escalation to the next dose level will occur. If a DLT is seen in two or more subjects in a cohort, escalation will be stopped and the Maximum Tolerated Dose (MTD) will be considered to have been exceeded. The next lower dose will be considered as MTD if six patients have already been treated at that dose. Otherwise if only three patients have been treated at the next lower dose, then an additional three patients should be enrolled at the next lower dose level for a total of six patients. If zero or one has DLTs among the 6 patients, then this dose is declared as MTD. Otherwise, there is further de-escalation according to the same scheme. As a result, the MTD is the highest dose where at most one-sixth of the patients developed DLT. If MTD is not reached, the higher dose will be selected. As with MTD, another 3 subjects will be treated at this dose if only 3 subjects have been treated. 1 additional cohort with 3 patients will be recruited at the selected dose to further evaluate the safety. The sample size of 9 subjects is considered to be sufficient to support preliminary tolerability, safety, and DLTs based on the established safety profile of this compound.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background: Chronic Lymphocytic Leukemia

Chronic Lymphocytic Leukemia (CLL)/ small lymphocytic lymphoma (SLL) are a malignancies of B-cells that comprise approximately 7% of new diagnosed cases of non-Hodgkin's lymphoma. It remains the most common adult leukemia in western world, with an incidence of 3-5 per 100,000 (*Maurer and Hallek*, 2013). The National Cancer Institute estimates that 15,680 Americans were diagnosed and 4,580 died from the disease in 2013.

CLL and SLL are closely related, both manifestations of a clonal proliferation of small, mature, aberrant B-lymphocytes that are typically CD5 positive by flow cytometry or immunohistochemistry. CLL is characterized by accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues, whereas SLL is characterized by predominance of disease in the lymph nodes and less than 5000 clonal B-cell per microliter in the peripheral blood (*Hallek et al.*, 2008). CLL and SLL are managed in the same way, so CLL/SLL will be referred to simply as CLL for the remainder of this document (*Hallek et al.*, 2008).

Although treatments for CLL have improved with the development of chemoimmunotherapy regimens and tyrosine kinase inhibitors, CLL remains an incurable disease. Treatment regimens that combine chemotherapy and immunotherapy (eg: Fludarabine + Cyclophosphamide + Rituximab) have produced high response rates and have been associated with an improved overall survival (*Hallek et al.*, 2010). However, patients inevitably relapse and many patients cannot tolerate chemoimmunotherapy regimens in the relapsed/refractory setting due to age, comorbidities, or compromised bone marrow function (*Brown*, 2011). Obinutuzumab (GA-101) in combination with chlorambucil was approved by the FDA in November 2013 based on efficacy as front-line therapy for patients older than 65. However, responses were not durable with this treatment either (*Goede et al.*, 2014).

Ibrutinib, an oral agent that inhibits the B-cell receptor associated tyrosine kinase, Bruton's tyrosine kinase (BTK), has been approved by the FDA for the treatment of patients with relapsed CLL (*Byrd et al.*, 2013). According to the package insert, the overall response rate is 58.3%, consisting of partial responses with no complete responses and duration of response ranging from 5.6 to 24.2 months. Ibrutinib intolerance related to diarrhea in 62% of patients and thrombocytopenia in over 20% of patients with bleeding events in 63% of patients and subdural hematomas in 4% of patients, infections, fatigue, renal insufficiency and other side effects have limited the number of patients amenable to chronic therapy. In addition, disease progression associated with resistance to ibrutinib has been noted to develop over time. Emergence of mutations in leukemia initiating cells renders patients resistant to ibrutinib therapy (*Woyach et al.*, 2014). Thus, to maximize the therapeutic potential of tyrosine kinase and other inhibitors, to prevent therapeutic resistance, and to obviate relapse, development of combination therapies has become the mainstay of recent CLL eradication strategies. Thus, development and testing of novel therapeutic strategies are warranted.

1.2 Study Agent: Dimethyl fumarate (DMF)

Dimethyl fumarate (DMF) is the methyl ester of fumaric acid. It has been evaluated formulated with other fumaric acid esters (FAE) in the treatment of various conditions. Specifically, DMF combined with three other FAEs was licensed in Germany under the trade name Fumaderm as an oral therapy for psoriasis. A DMF formulation, BG-12 (trade name Tecfidera) was also approved for the treatment of patients with multiple sclerosis, based on a phase III clinical trial that showed that DMF successfully reduced relapse rate and increased time to progression of disability in multiple sclerosis. (*Gold et al.*, 2012) See section 10.1 for full details.

DMF was identified by the Carson laboratory as a potential agent with activity in CLL due to inhibition of the Wnt pathway. The Wnt pathway is an embryonic pathway that is important in fetal development or maintenance of stem cells, but typically not active in normal adult tissues. In 2004, our group first reported that the canonical Wnt pathway is also active in CLL.(*Lu et al.*, 2004) We described several-fold elevated levels of mRNAs encoding multiple Wnt ligands (including Wnt16, a pro-B cell marker), Frizzled (FZD) receptors, the Wnt-activated transcription factor LEF1, and Wnt induced genes involves in growth and survival (cyclin D1 and cMyc) in CLL cells compared to normal B-lymphocytes. Pharmacologic stimulation of the canonical Wnt pathway by activation of GSK3/beta-catenin or by addition of Wnt5a promotes CLL survival.(*Filipovich et al.*, 2010) Furthermore, the non-canonical Wnt pathway is also active in CLL cells, and likely involved in migration and cell survival.(*Kaucka et al.*, 2013) This includes selective expression of the orphan Wnt5a receptor ROR1 in CLL.(*Fukuda et al.*, 2008) As the Wnt pathway is important in early embryonic development and in the maintenance of stem cells throughout life,(*Lu and Carson*, 2011) we hypothesize that the aberrant activation of the Wnt pathway in CLL reflects disordered de-differentiation and/or malignant transformation of a

primitive B cell population. For those reasons, the Wnt pathway is an attractive target for further drug development in CLL.

DMF inhibits the canonical Wnt signaling pathway. We used a cell based screening assay to identify agents with specific Wnt inhibiting activity. CellSensor® LEF/TCF-*bla* SW480 cells were plated at 50,000 cells per well and incubated with increasing concentrations of DMF for 16 hours. Wnt pathway inhibition was detected using the LiveBLAzer FRET-B/G Loading kit (Life Technologies) according to the manufacture's instruction. Emission ratios were calculated from these values and normalized with vehicle control. EC50 was calculated using Graphpad Prism 6 to be less than 10 uM **(FIGURE 2).** We suspect that the alpha-beta unsaturated ketone on DMF is reacting with essential free cysteines in LEF1 to account for this activity.

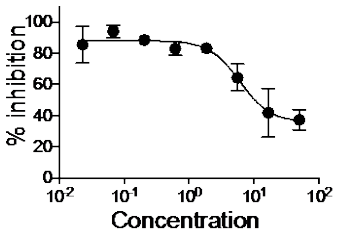

Figure 2: Plot of Wnt signaling activity and inhibition by DMF using cell based reporter gene assay. Concentration in μM.

DMF inhibits the viability of primary CLL cells *in vitro*. Leukemic cells from 10 CLL patients were cultured with increasing concentrations of single agent DMF (0.4 to 100 μM), Ibrutinib (10 μM), or a combination of both. Ibrutinib was selected for this assay as a potential clinically available agent for combination therapy. The cells were incubated for 48 hours and cell viability was measured using MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide). Data were transformed to percent of viable cells relative to vehicle control (**FIGURE 3**). The *in vitro* effect of DMF on relative viability was noted to be modest, although this assay did not assess the effect of microenvironment or stromal-derived Wnt factors.

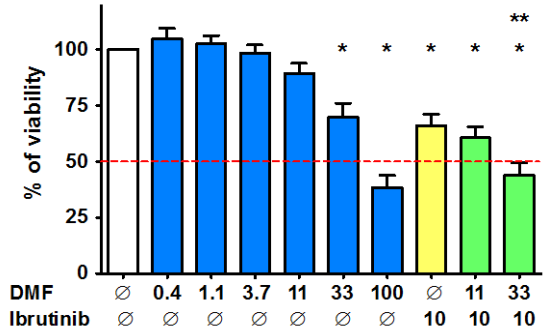

Figure 3. In vitro effect of DMF: Percent viability relative to vehicle control for each of three drug treatments, using leukemia cells from 10 CLL patients. Statistical analysis was performed using one way ANOVA with Tukey's multiple comparison test. * indicates significance in comparison to control (open bar); ** in comparison to ibrutinib (yellow bar). All concentrations are μM.

DMF induces clearance of CLL cells in a murine CLL xenograft model at the equivalent of human doses. To evaluate the *in vivo* activity of DMF in a supportive microenvironment, , we implanted primary leukemic cells from patients with CLL into the peritoneum of Rag2 deficient immunocompromised mice. Groups of mice (n=3) were then treated with DMF alone (doses ranging from 3 to 30 mg/kg oral gavage BID for 1 week). These doses are the same as those used in prior publications, and are equivalent to pharmacologically available doses in humans. DMF treatment dose dependently inhibited the survival of CLL cells in this model (**FIGURE 4**).

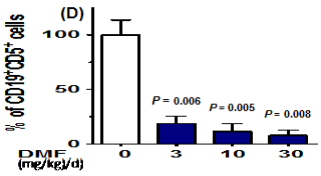

Figure 4. In vivo efficacy of DMF: Representative plot of percent viability relative to vehicle control for CLL cells recovered from the peritoneum of RAG2 deficient mice after 1 week of oral therapy. DMF treatment inhibits survival of CLL cells in this in vivo model.

DMF inhibits the Wnt and STAT pathways in CLL cells. To

identify candidate biomarkers of DMF activity for use in future clinical trials and to further explore the mechanism of action of DMF in CLL cells, we evaluated gene expression in CLL cells and normal peripheral blood mononuclear cells treated with DMF using the Nanostring PanCancer Pathway mRNA profiling assay. Following a 4-hour incubation of CLL cells with DMF or vehicle control, 20 genes from the Nanostring profile were significantly altered. Based on pathway analysis, not only was the WNT signaling pathway modulated, but the JAK/STAT pathway was also significantly affected by DMF.

1.3 Overview and justification for study and study population

This is a phase I clinical trial to evaluate the safety, tolerability, and maximum tolerated dose of DMF in patients with chronic lymphocytic leukemia. Patients with relapsed/refractory CLL not amenable to available therapies are eligible. This patient population is in need of novel therapies, particularly if progressing after, intolerant of, or unable to receive oral tyrosine kinase inhibitors (ie ibrutinib, idelalisib). The trial will initiate at the dose of DMF that is approved by the FDA for the treatment of patients with multiple sclerosis, with dose escalation to a dose previously tested in patients with psoriasis.

2.0 STUDY OBJECTIVES

Primary Objective:

To determine the maximum tolerated dose or biologically optimal dose of dimethylfumarate for patients with chronic lymphocytic leukemia.

Secondary Objectives

1. To determine the safety and tolerability of DMF by evaluation of adverse events

2. To assess the clinical activity of DMF in the treatment of patients with CLL by iwCLL

3. To evaluate the pharmacodynamic activity of dimethylfumarate (DMF) in chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (CLL) by evaluation of the Wnt and STAT pathways.

4. To assess the durability of clinical activity of DMF.

3.0 Endpoints

3.1 Primary Endpoint:

3.1.1 Rate of dose limiting toxicities (DLTs) and the maximum tolerated dose or biologically active dose.

3.2 Secondary Endpoints

3.2.1 Treatment-emergent adverse events, including infections (description, timing, grade [CTCAE v4.03], severity, seriousness, and relatedness)

3.2.2 Percent of patients who achieve an objective response (partial response, complete response, or nodular complete response) by international working group in CLL guidelines (iwCLL).

3.2.3 Pharmacodynamic activity including measurement of expression of LEF1, c-myc; Wnt and STAT pathway expression; and STAT1 phosphorylation.

3.2.4 Percent of patients able to complete 2 months of therapy without intolerance or disease progression.

3.2.5 Progression free survival, also based on the iwCLL definition of disease progression.

4.0 PHASE I PATIENT ELIGIBILITY

4.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Ability to understand and the willingness to sign a written informed consent.
2. Clinical and phenotypic verification of B cell CLL/ SLL/ or MBL and measurable disease. Immunophenotyping of the leukemic cells (blood, lymph node, or bone marrow) must demonstrate a monoclonal (kappa or lambda light chain restricted) B cell population with immunophenotype diagnostic for CLL (eg: co-expressing CD19 and CD5).
3. Relapsed or refractory disease, defined by failure to achieve a partial response within 6 months of initiation of therapy, or a 50% increase of baseline disease measurements after achieving a clinical response.
4. Previously treated with at least 1 regimen for CLL/SLL
5. Not appropriate or amenable to all approved therapies.
    a. All patients must have progressed on or after B-cell receptor targeted kinase inhibitor (eg: ibrutinib, idelalisib, ACP-196, CC-292), unless there is a relative contraindication (eg: history of recent bleeding, history of atrial fibrillation, unacceptable high out-of-pocket cost despite patient assistance programs).
    b. Patients with Del(17p) CLL must have progressed on or after BCL-2 inhibitor therapy (eg: venetoclax), unless there is a relative contraindication (eg: Creatinine clearance < 50ml/min, or unable to monitor for TLS due to living remotely from the medical center, unacceptably high out-of-pocket cost).
    c. Patients must have received a CD20-directed monoclonal antibody (eg: obinutuzumab, ofatumumab, rituximab), unless there is a relative contraindication (eg: history of hepatitis virus infection).
6. Has recovered from the toxic effects of prior therapy to their clinical baseline.
7. Subjects must be aged 18 years or older.
8. Both men and women of all races and ethnic groups are eligible for this trial.
9. Women of childbearing potential (not postmenopausal for at least one year or not surgically incapable of bearing children) must agree not to become pregnant for the duration of the study. Both men and women must agree to use a barrier method of contraception for the duration of the study and until 8 weeks after the final dose.
10. Subjects must have at least one of the following indications for treatment:
    - Symptomatic or progressive splenomegaly;
    - Symptomatic lymph nodes, nodal clusters, or progressive lymphadenopathy;
    - Progressive anemia (hemoglobin ≤ 11 g/dL);
    - Progressive thrombocytopenia (platelets ≤ 100 x 109/L);
    - Weight loss > 10% body weight over the preceding 6 month period;
    - Fatigue attributable to CLL;
    - Fever or night sweats for > 2 weeks without evidence of infection;

- Progressive lymphocytosis with an increase of > 50% over a 2-month period or an anticipated doubling time of less than 12 months.

11. Subjects must have an ECOG performance status of 0-2.
12. Adequate hematologic function:
    a. Platelet count ≥ 50,000/μL; AND
    b. Hemoglobin ≥ 8.0 g/dL (may be supported by erythropoietin); AND
    c. Absolute neutrophil count > 1000 /uL
13. Adequate renal function:
    a. Serum creatinine <1.5 times upper limit of normal; OR
    b. Calculated Creatinine clearance (CrCl) ≥ 50 mL/min (based upon the Cockcroft-Gault Equation [CrCl = (140-age) * actual wt (in kg) * (0.85 if female) / (72 * Cr)].
14. Adequate hepatic function:
    a. Total bilirubin ≤ 2.5 times upper limit of normal; AND
    b. ALT ≤ 2.5 times upper limit of normal.

4.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Pregnant or breast-feeding women will not be entered on this study. Women of childbearing potential must obtain a pregnancy test. Child-bearing potential is defined as having neither of the following:
    a. ≥ 12 months of non-therapy-induced amenorrhea)
    b. Surgically sterile (absence of ovaries and/or uterus
2. Patients who are currently receiving another investigational agent are excluded.
3. Patients who have had chemotherapy (e.g., purine analogues, alkylating agents), radiation therapy, or participation in any investigational drug treatment within 4 weeks of initiation of DMF or at any time during the study.
4. Patients who have had prior (within 8 weeks of initiation of DMF) or concurrent antibody therapy directed against CLL (i.e., Rituxan® and Campath®)
5. Patients who have had tyrosine kinase inhibitor therapy (eg: ibrutinib or idelalisib) within 7 half lives (or 28 days, which ever is shorter) of initiation of DMF.
6. Current infection requiring parenteral antibiotics.
7. Active malignancy within the previous 2 years (other than completely resected non-melanoma skin cancer or carcinoma in situ).
8. Insufficient recovery from surgical-related trauma or wound healing.
9. Impaired cardiac function including any of the following:
    a. Myocardial infarction within 6 months of starting study drug;
    b. Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
10. Patients who in the opinion of the investigator are unable to comply with the safety monitoring requirements of the study.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

For Dose Level 1, DMF (Tecfidera formulation) will be administered at a dose of 120 mg PO BID (approximately 12 hours apart) for 2 x 28 day cycles.

For Dose Level 2, DMF will be administered at the currently used dose for patients with multiple sclerosis: 120 mg PO BID for 1 week, then escalate to the dose of 240mg PO BID for the remainder of 2 x 28 day cycles. The 1 week lead-in at 120 mg is to assist in toleration and initial side effects and is as per the standard prescribing information.

For Dose Level 3, DMF will be administered at the currently used dose for patients with multiple sclerosis: 120 mg PO BID for 1 week, then escalate to the dose of 360mg PO BID for the remainder of 2 x 28 day cycles.

The medication can be taken with or without food. Capsules should not be crushed or chewed. Capsules will be self-administered on an outpatient basis. On days in which patients are scheduled for assessment, capsules will be taken in clinic. Missed or vomited doses will be skipped. Patients are assessed for safety and tolerability on Day 8, Day 1 of each subsequent cycle, and 28 days and 56 days following the last dose of DMF.

Dose Level	DMF dose (all cohorts start at 120 mg PO BID dose for 1 week, then increase to the assigned dose)
1	120 mg PO BID
2	240 mg PO BID
3	360 mg PO BID

5.2 Definition of Dose-Limiting Toxicity

Dose Limiting Toxicity (DLT) is defined as any of the following adverse events that are considered by the investigator to be possibly, probably or definitely related to DMF within the DLT evaluation timeframe.

- Non-hematologic adverse events: grade 3 (CTCAE 4) or higher, lasting more than 7 days despite appropriate medical management.
- Hematologic adverse events: grade 3 (iwCLL 2008) or higher, lasting more than 7 days despite appropriate medical management, with the exception of: any grade lymphopenia ; or any grade lymphocytosis.
- Grade 4 non-hematologic (CTCAE 4) of any duration
- Grade 4 hematologic (iwCLL 2008) of any duration.
- Any clinically significant toxicity that precludes administration of the next scheduled dose beyond 14 days

Replacement patients may be enrolled for patients who withdraw from investigational treatment for a reason that is definitely unrelated to toxicity of the study agent or disease progression (e.g. patient preference, loss to follow-up). Replacement patients will ensure enough patients are enrolled to evaluate the primary endpoint.

The DLT evaluation timeframe is from the first dose of DMF until day 56 of the trial.

5.3 Pre-Medications

None required. Anti-emetics may be administered per clinical discretion.

5.4 Permitted concomitant therapy

Medications required to treat adverse events, manage cancer symptoms or concurrent stable disease (e.g., controlled hypertension), or manage pain are permitted.

Supportive care agents, including erythropoietin, granulocyte growth factors, or blood transfusions are permitted only after patients have developed grade 3 or higher anemia or neutropenia.

Corticosteroids for the treatment of conditions other than CLL/SLL are permitted at maximum doses of prednisone 20mg daily (or steroid equivalent) are permitted, and at a stable does (ie. no higher than 20mg for at least 28 days prior to initiation of DMF).

The patient needs to notify the investigational site about any new medications he/she takes after the start of the study medication. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the CRF.

5.5 Prohibited concomitant therapy

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the treatment portion of the study.

5.6 Other Modalities or Procedures

Not applicable.

5.7 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03 for non-hematologic adverse events, and 2008 international working group criteria (iwCLL, Hallek et al, appendix B) for hematologic adverse events. Dose adjustments should be made according to the system showing the greatest degree of toxicity. Patients are assessed for safety and tolerability on Day 8, Day 28, and Day 42 after starting DMF.

Toxicity – NCI CTCAE Grade (Hematologic- iwCLL)	**Occurrence**	**Dose Modification**
Non-hematologic		
Grade ≥ 3	1st	Withhold study treatment until resolved to Grade ≤ 1.

		Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy.
Hematologic*		
Grade ≥ 3	1st	Withhold study treatment until resolved to ANC ≥1000/mm^3, hemoglobin is ≥ 8 gm/dL, and platelet count ≥50,000/mm^3. Resume study treatment at same dose.
	2nd	Withhold study treatment until resolved to ANC ≥1000/mm^3, hemoglobin is ≥ 8 gm/dL, and platelet count ≥50,000/mm^3. Resume study treatment at the next lower dose level.
	3rd	Permanently discontinue study treatment.
*Dose adjustments or dose holds for hematologic toxicity will apply even if the baseline values are lower than these thresholds due to heavily infiltrated marrow. In those cases, growth factors and/or blood product transfusion may be administered prior to continuing with DMF.		

Notes:

1. If any of the above are noted, the patient will be re-assessed within 7 days by the treating physician or investigator. Isolated laboratory abnormalities may be re-evaluated by laboratory draw only, or based on physician or investigator discretion.
2. DMF can be delayed for a maximum of 14 days; if not restarted in that time-span, study treatment will be permanently discontinued.
3. If dose is decreased for toxicity, dose re-escalation is not planned.
4. For invasive procedures, not including biopsies or venous catheter placement: withhold study treatment for 1 week prior to procedure, and at least 1 week following surgery until satisfactory wound healing has been achieved.

5.8 Duration of Therapy

In the absence of treatment delays due to adverse events, DMF will continue for 56 days as part of the clinical trial, or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients are not prohibited from continuing DMF through commercial source after the response assessment visit.

5.9 Duration of Follow Up

Patients will be followed for 1 year after removal from treatment or until disease progression, initiation of subsequent CLL therapy, or death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 STUDY PROCEDURES

6.1 Schedule of Events

	Screening	Cycle 1 Day 1 (C1D1)	C1 D8	C2, D1	Up to 28 days after last DMF dose	56 days after last DMF dose	Follow-up (q 56 days until 1 year)
Visit Number	1	2	3	4	5	6	7-
Window	+/- 3 days		+/- 2 d	+/-7 d	+/-7 d	+/-7 d	+/-14 d
Informed Consent	X						
Serum Pregnancy test	X						
History and PE	X	X	X	X	X	X	X
Performance Status	X	X		X	X	X	X
Toxicity (include DLT) Evaluations		X	X	X	X	X	
Tumor Measurements by physical examination	X	X	X	X	X	X	X
CBC with differential	X	X (x2 – pre and post dose)		X	X	X	X
Comprehensive Metabolic Panel *	X	X (x2 – pre and post dose)	X	X	X	X	X
LDH, uric acid, phos		X (x2 – pre and post dose)					
Correlative laboratory collection **	X	X (x2 – pre and post dose)	X	X	X	X	
CT or MRI scan with contrast of chest, abdomen, pelvis					X		
Bone marrow biopsy and aspirate ***					X (if clinical response and imaging is consistent with CR)		

* Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), BUN, creatinine, glucose.

** Up to 30 mL in anti-coagulated (ACD) tubes for screening visit; up to 20 mL in anticoagulated (ACD) tubes for subsequent visits. To be drawn prior to DMF dosing.

*** With flow cytometric and immunohistochemical evaluation of CLL cell infiltrate; and chromosome and FISH analysis (including 11q, 12p, 13q, and 17p).

6.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

6.2.1 Informed Consent

6.2.2 Medical history

Complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

6.2.3 Demographics

Demographic profile will include date of birth, gender, race, and ethnicity.

6.2.4 Review subject eligibility criteria

Review of eligibility criteria as described in Section 3 to ensure subject qualification for study entry.

6.2.5 Review previous and concomitant medications

All prior medication taken by the subject within 4 weeks before starting the study is to be recorded. Concomitant medications taken by the subject during the study are to be recorded up until 28-days after last study dose. If a reportable adverse event (see Section 7) occurs within 28-days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.

6.2.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight.
(height is only required at screening.)

Physical exam including bidimensional measurement of palpable lymph nodes, spleen size (below the costal margin), and liver size (craniocaudal size at the right midclavicular line).

6.2.7 Performance status

Performance status evaluated prior to study entry, using ECOG grading scale.

6.2.8 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 9 for Adverse Event monitoring and reporting.

6.2.9 Hematology

Hematology to include hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.2.10 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), BUN, creatinine, glucose, and LDH.

6.2.11 Blood draw for correlative studies

Up to 20 mL in anticoagulated tubes.

6.2.12 Pregnancy test (for females of child bearing potential)

Serum pregnancy test (in women of childbearing potential only, see definition in section 4.2); if serum pregnancy test has not been performed 14 days prior to dosing, a urine pregnancy test must be performed 7 days prior to dosing. If the test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.

6.2.13 Tumor assessment

CT scan or MRI scan with contrast of thorax, abdomen, and pelvis. This may be done within 90 days prior to D1. Physical exam including bidimensional measurement of palpable lymph nodes, spleen size (below the costal margin), and liver size (craniocaudal size at the right midclavicular line).

6.3 Procedures During Treatment

6.3.1 Visit 2: Day 1

6.3.1.1 Review concomitant medications

6.3.1.2 Physical exam including vital signs (temperature, pulse, respirations, blood pressure), weight; and including bidimensional measurement of palpable lymph nodes, spleen size (below the costal margin), and liver size (craniocaudal size at the right midclavicular line).

6.3.1.3 Performance status using ECOG grading scale.

6.3.1.4 Adverse event assessment: See Section 9 for adverse Event monitoring and reporting.

6.3.1.5 Hematology: hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.3.1.6 Serum chemistries: Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine,

electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Also: LDH, uric acid, phosphorous

6.3.1.7 Blood draw for correlative studies: Up to 20 mL in anti-coagulated (ACD) tubes.

6.3.1.8 Dispense DMF 120 mg PO BID x 7 day supply.

6.4.1.9 6-8 hours after DMF dosing: Repeat Hematology and serum chemistries, in addition to LDH, uric acid, and phosphorous. Blood draw for correlative studies: Up to 10 mL in anti-coagulated (ACD) tubes.

6.3.2 Visit 3: Day 8

6.3.2.1 Review concomitant medications

6.3.2.2 Physical exam including vital signs (temperature, pulse, respirations, blood pressure), weight; and including bidimensional measurement of palpable lymph nodes, spleen size (below the costal margin), and liver size (craniocaudal size at the right midclavicular line).

6.3.2.3 Performance status using ECOG grading scale.

6.3.2.4 Adverse event assessment: See Section 9 for adverse Event monitoring and reporting.

6.3.2.5 Hematology: hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.3.2.6 Serum chemistries: Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

6.3.2.7 Blood draw for correlative studies: Up to 20 mL in anticoagulated tubes.

6.3.2.8 Dispense DMF at assigned dose x 21 day supply

6.3.3 Visits 4: Day 1 of cycles 2

6.3.3.1 Review concomitant medications

6.3.3.2 Physical exam including vital signs (temperature, pulse, respirations, blood pressure), weight; and including bidimensional measurement of palpable lymph nodes, spleen size (below the costal margin), and liver size (craniocaudal size at the right midclavicular line).

6.3.3.3 Performance status using ECOG grading scale.

6.3.3.4 Adverse event assessment: See Section 9 for adverse Event monitoring and reporting.

6.3.3.5 Hematology: hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.3.3.6 Serum chemistries: Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

6.3.3.7 Blood draw for correlative studies: Up to 20 mL in anticoagulated tubes.

6.3.3.8 Dispense DMF at assigned dose x 28 day supply

6.3.4 Visit 5: Between 1 day and 28 days after cycle 2 day 28: Primary Endpoint Response Assessment

6.3.4.1 Review concomitant medications

6.3.4.2 Physical exam including vital signs (temperature, pulse, respirations, blood pressure), weight; and including bidimensional measurement of palpable lymph nodes, spleen size (below the costal margin), and liver size (craniocaudal size at the right mid-clavicular line).

6.3.4.3 Performance status using ECOG grading scale.

6.3.4.4 Adverse event assessment: See Section 9 for adverse Event monitoring and reporting.

6.3.4.5 Hematology: hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.3.4.6 Serum chemistries: Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

6.3.4.7 Blood draw for correlative studies: Up to 20 mL in anticoagulated tubes.

6.3.4.8 Tumor assessment: Only if there are no lymph nodes that are 1.5 cm or larger by physical exam: CT scan or MRI scan with contrast of thorax, abdomen, and pelvis. This may be done within 7 days prior to or after Visit 10.

6.3.4.9 Only if clinical response and imaging are consistent with a complete response, subjects will have bone marrow aspirate and biopsy with samples sent for differential, morphology, and >/= 4-color flow cytometry for MRD. This may be done within 7 days prior, or 28 days following visit 10.

6.3.5 Visit 6: 56 days after the last dose of DMF

6.3.5.1 Review concomitant medications

6.3.5.2 Physical exam including vital signs (temperature, pulse, respirations, blood pressure), weight; and including bidimensional measurement of palpable lymph nodes, spleen size (below the costal margin), and liver size (craniocaudal size at the right midclavicular line).

6.3.5.3 Performance status using ECOG grading scale.

6.3.5.4 Adverse event assessment: See Section 9 for adverse Event monitoring and reporting.

6.3.5.5 Hematology: hemoglobin (Hgb), platelets, total white blood cell count (WBC), and differential.

6.3.5.6 Serum chemistries: Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine,

electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

6.3.5.7 Blood draw for correlative studies: Up to 20 mL in anticoagulated tubes.

6.3.6 Visits 7-10: Every 56 days to one year (typically month 6, 8, 10, 12)

Patients will be followed every 56 days after completion of (or early withdrawal from) study treatment until subsequent CLL therapy, death, or discontinuation of trial participation. Follow-up will consist of survival contacts via medical record review, telephone call, or review of the Social Security Index.

6.4 Correlative Studies

Studies will be performed in the Kipps and/or Carson laboratories (though sample processing will occur in the Kipps laboratory using long-established SOPs for CLL cell isolation and storage). Biomarker assays will correlate with clinical responses. Samples will be taken at baseline/screening, during treatment and after treatment. However, not all assays will be performed for all time points for all patients, based on sample availability and leukemic cell number. Specimens will be banked in the Kipps laboratory (see below).

Assays from patient plasma may include:
- Measurement of cytokine levels (including IL2, IL12, and TNFα)

Isolation of leukemic cells by Ficoll-hypaque separation and assessment, which may include:
- Assessment of signaling modulation, including the canonical Wnt pathway by multiplex qPCR (eg: Nanostring PanCancer assay)
- Measurement of phosphorylation of STAT1 by intracellular flow cytometry.
- ZAP-70, CD38, and Immunoglobulin heavy chain variable region (IgVH) mutation in CLL cells

6.4.1 Sample Collection Guidelines

Sampling Schedule

Blood sample for correlative studies will be collected at the following time points:
- Screening
- Day 1 of each cycle, pre-treatment
- Day 8 of cycle 1.
- Between 1 day and 28 days after Cycle 2, day 28
- 56 days after last DMF dose visit.

Sample Collection and Handling Instructions

Blood samples (approximately 20-30 ml as specified in the protocol) will be collected in anticoagulated (ACD) tubes. The exact time that the sample is drawn along with the exact time that the drug is administered should be recorded.

Sample Processing

Samples will be processed in the translational lab of Dr. Thomas Kipps, with separation of plasma, followed by isolation of mononuclear cells by Ficoll differential centrifugation.

Sample Labeling
Each tube must be labeled with the patient's study number and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form, which must accompany the sample(s).

6.4.2 Specimen Banking

Patient samples collected for this study will be retained at the UCSD School of Medicine (Kipps Laboratory). Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens. Samples will be labeled with the subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

Dr. Kipps, Carson, and Choi will be responsible for reviewing and approving requests for research specimens from potential research collaborators outside of UCSD. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimens will be the property of UCSD for publication and any licensing agreement will be strictly adhered to.

The study research coordinator will review the subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. Samples and data extracted from the subject's medical record will be coded with a de-identified study number, and the subject's name and identifying information will be removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered

The specimens and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

6.5 Removal of Subjects from Study Treatment and Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.5.1 Patient completed study treatment;

6.5.2 Patient voluntarily withdraws from treatment (follow-up permitted);

6.5.3 Patient withdraws consent (termination of treatment and follow-up);

6.5.4 Patient is unable to comply with protocol requirements;

6.5.5 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

6.5.6 Patient experiences toxicity that makes continuation in the protocol unsafe;

6.5.7 Treating physician judges continuation on the study would not be in the patient's best interest;

6.5.8 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

6.5.9 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

6.5.10 Lost to follow-up.

If a research subject cannot be located to document survival after a period of 2 years the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented.

7.0 Measurement of Effect

7.1 Response Criteria for Patients with Chronic Lymphocytic Leukemia

Criteria for response will utilize the IWCLL Guidelines for response, which includes clinical, hematological, and bone marrow features as outlined below (*Hallek et al.*, 2008).

Minimal Residual Disease negative: less than 0.01% CLL cell involvement by 4-color flow cytometry of bone marrow aspirate (less than 1 in 10,000 events) and meeting all other criteria for complete response.

Complete response: Requires all of the following for a period of at least two months from completion of therapy:

- Absence of significant lymphadenopathy (e.g. >1.5cm in diameter) on physical exam;
- No hepatomegaly or splenomegaly on physical exam;
- Absence of constitutional symptoms;
- Blood counts corresponding to the following values: Lymphocytes < 4,000/uL, polymorphonuclear leukocytes >1500/μL, platelets >100,000/μL, hemoglobin >11.0 g/dL (untransfused)
- Bone marrow aspirate and biopsy must be normocellular for age with <30% of nucleated cells being lymphocytes. Lymphoid nodules must be absent. If the marrow is hypocellular, a repeat determination should be performed in one month.
- The marrow should be analyzed by flow cytometry and/or immunohistochemistry to demonstrate that the marrow is free of clonal B- CLL cells.
- A CT scan or MRI documenting absence of significant lymphadenopathy should be performed if previously abnormal.
- Patients who fulfill the criteria for CR with the exception of a persistent cytopenia that is believed to be treatment related will be considered CR with incomplete bone marrow recovery (CRi). Additionally, patients who fulfill the criteria of CR with exception of having bone marrow lymphoid nodules will be considered a nodular PR.

Partial response: Requires at least 2 of the following criteria from group A, and at least one of the criteria from group B, and for a period of at least 2 months:

Group A:

- ≥50% decrease in peripheral absolute lymphocyte count from pretreatment value, or less than 4,000/uL.
- ≥50% reduction in lymphadenopathy by examination or scan, or less than 1.5cm in size.
- ≥50% reduction in splenomegaly (cm below costal margin) by examination or scan
- ≥50% reduction hepatomegaly (total liver span) by examination or scan
- ≥50% reduction in marrow infiltrate or B-lymphoid nodules

Group B:

- Polymorphonuclear leukocytes ≥1,500/μL or 50% improvement from pre-treatment value;
- Platelets >100,000/μL or 50% improvement from pre-treatment value;
- Hemoglobin >11.0 g/dl (un-transfused) or 50% improvement from pre-treatment value.

Progressive Disease: Characterized by any one of the following events:

- ≥50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥2 cm); appearance of new palpable lymph nodes.
- ≥50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥56% prolymphocytes).
- *During therapy,* patients not fulfilling the above criteria for progressive disease but demonstrating a decrease in hemoglobin >2 gm/dL, decrease >50% in platelet or granulocyte count will not be rated as progressive disease because these may occur as both a consequence of therapy. A bone marrow biopsy in such settings is strongly encouraged.
- *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 (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100 000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable Disease: Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

7.1.1 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment until objective tumor progression or death.

7.2 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of non-hematologic adverse events and modified iwCLL criteria for hematologic adverse events (Appendix B).

8.0 ADVERSE EVENTS

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

8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins after initiation of study treatment and ends 28 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier.

All patients experiencing an adverse event, regardless of its relationship to study drug (or at least possibly related to the drug), will be monitored until:

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

8.2 Severity

Hematologic adverse events will be graded using a modified iwCLL criteria (appendix 2).

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

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

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

8.3 Seriousness

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death.
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening.
   (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

8.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

8.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current product label.

8.6 Reporting Requirements for Adverse Events

8.6.1 Expedited Reporting

- The **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The **UCSD Human Research Protections Program (HRPP)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or

others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

- The **FDA** will be notified within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

8.6.2 Routine Reporting Requirements

- The UCSD HRPP will be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
- The FDA will be notified of all non-serious adverse events annually at the time of the annual report.

9.0 AGENT INFORMATION

9.1 Dimethylfumarate

Please refer to package insert / prescribing information for more comprehensive information.

Other names for the drug: Tecfidera

Mechanism of action (or Product description): The mechanism of action of DMF is unknown. DMF and its metabolite, monomethyl fumarate (MMF) have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. Preliminary studies in CLL have demonstrated inhibition of the Wnt pathway and other pro-survival pathways (eg: NFKB, JAK) in cancer cells, including CLL cells.

Availability: commercially available, will be provided for 8 weeks by the clinical trial.

How supplied: Available as hard gelatin delayed-release capsules in two strengths containing either 120 mg or 240 mg of dimethyl furcate. The green and white 120 mg capsules are printed with "BG-12 120 mg" in black ink. The green 240 mg capsules are printed with "BG-12 240 mg"

in black ink.

Storage and stability: Store at 15 degrees C to 20 degrees C (59 to 86 degrees F). Protect the capsules from light. Store in original container. Once opened, discard bottles after 90 days.

Route of administration for this study: oral

Side effects:

Adverse reactions occurring in >10% of patients:
Cardiovascular: Flushing (40%)
Gastrointestinal: Abdominal pain (18%), diarrhea (14%), nausea (12%)
Infection: Infection (60%; placebo: 58%)

Adverse reactions occurring in 1% to 10%:
Dermatologic: Pruritus (8%), skin rash (8%), erythema (5%)
Gastrointestinal: Vomiting (9%), dyspepsia (5%)
Genitourinary: Proteinuria (6%)
Hematologic: Lymphocytopenia (2% to 6%)
Hepatic: Increased serum AST (4%)

Adverse reactions occurring in <1% (Limited to important or life-threatening): Eosinophilia (transient)

There are no contraindications listed within the manufacturer's U.S. product labeling.

Concerns related to adverse effects:

- Dermatitis/irritation: May cause rash, pruritus, or erythema. There are case reports of contact dermatitis resulting from dimethyl fumarate (DMF) exposure after use as a fungicide and desiccant in the shipping of furniture (Bruze, 2011; Giménez-Arnau, 2011; Ropper, 2012).
- Flushing: Commonly causes mild-to-moderate flushing (eg, warmth, redness, itching, burning sensation); flushing generally appears soon after initiation, and improves or resolves with subsequent dosing. Administration with food may decrease flushing incidence. The Canadian labeling suggests that a temporary dosage reduction or short-term (≤4 days) administration of aspirin (nonenteric coated) 30 minutes prior to dimethyl fumarate may also reduce the incidence and severity of flushing. Use of aspirin > 4 days has not been studied; long-term use of aspirin is not recommended.
- Gastrointestinal events: GI events (eg, nausea, vomiting, diarrhea, abdominal pain, dyspepsia) commonly occur with use; GI events generally occur in the first month of use and decrease thereafter. To improve tolerability, the Canadian labeling recommends administering with food or temporarily reducing the dosage.
- Hepatic effects: Transaminase elevations (usually <3 times ULN) were observed, generally occurring in the first 6 months of treatment.
- Lymphopenia: Decreased lymphocyte counts may occur with use. Prior to initiation, a recent CBC (within 6 months) should be reviewed to identify patients with preexisting low lymphocyte counts. Obtain CBC at least annually (or more frequently if indicated) during use. In trials, mean lymphocyte counts decreased ~30% over the first year of therapy (then stabilized), and lymphocyte counts increased (but did not return to baseline) 4 weeks following discontinuation. No difference in incidence of infection or series infections has

been observed in treated patients when compared to placebo; consider temporarily discontinuing therapy in patients with serious infections. Has not been studied in patients with preexisting low lymphocyte counts. Canadian labeling recommends treatment not be initiated in patients with signs/symptoms of a serious infection.

- Proteinuria: In clinical trials, proteinuria was reported at a slightly higher incidence than that observed with placebo; significance of these findings is unknown.

9.1.1 Return and Retention of Study Drug

Remaining drug is to be destroyed according to Moores Cancer Center Investigational Drug Services destruction policy.

9.1.2 Drug Accountability/Subject Compliance

Records of study medications used, dosages administered, and intervals between visits will be kept during the study. Patients will be asked to fill out a pill diary and bring with them for review after each cycle of study treatment. Drug accountability will be noted at the completion of the trial. Patients will be asked to return all unused medication at the end of the study.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a single arm, open-label, non-randomized phase I study, to evaluate the tolerability, safety, and clinical activity of DMF. Relapsed/refractory CLL patients will be recruited. The primary endpoint is the maximum tolerated dose or biologically active dose and the rate of DLTs.

Secondary endpoints include the rate of adverse events including infections, the proportion of patients able to complete 2 months of therapy without intolerance or disease progression, the objective response rate (including partial response, complete response, or nodular complete response) by international working group in CLL guidelines (iwCLL), progression free survival, the change of expression of LEF1, c-myc, Wnt pathway, STAT pathway, and STAT1 phosphorylation.

10.1.1 Statistical Design

A standard 3+3 dose escalation design will be used. There are two test dose levels with a potential de-escalation dose. A minimum of three subjects will be treated at each dose level. All three subjects in a cohort will be evaluated for DLT in the defined DLT evaluation period (within 56 days of starting study treatment) before enrollment of subjects at the next dose level may begin. For all dose levels, if no DLTs are observed during the evaluation period among the three treated patients, escalation to the next dose level may begin. If a DLT is observed in one of the first three subjects in the cohort, the cohort will be expanded to six subjects. If zero or one of six subjects in the cohort experiences a DLT within the evaluation period, escalation to the next dose level will occur. If a DLT is seen in two or more subjects in a cohort, escalation will be stopped and the Maximum Tolerated Dose (MTD) will be considered to have been exceeded. The next lower dose will be considered as MTD if six patients have already been treated at that dose. Otherwise if only three patients have been treated at the next lower dose, then an additional three patients should be enrolled at the next lower dose level for a total of six

patients. If zero or one has DLTs among the 6 patients, then this dose is declared as MTD. Otherwise, there is further de-escalation according to the same scheme. As a result, the MTD is the highest dose where at most one-sixth of the patients developed DLT. If MTD is not reached, the higher dose will be selected. As with MTD, another 3 subjects will be treated at this dose if only 3 subjects have been treated.

1 additional cohort with 3 patients will be recruited at the selected dose to further evaluate the safety. The sample size of 9 subjects is considered to be sufficient to support preliminary tolerability, safety, and DLTs based on the established safety profile of this compound.

10.2 Sample Size and Accrual

15 to 21 patients may be recruited.

10.3 Evaluable Cohort and Subject Replacement

A subject will be considered evaluable for assessment of DLT if the subject receives at least 7 days of DMF and completes the safety follow-up through the DLT evaluation period, or the subject experiences a DLT at any time during the DLT evaluation period. Any non-evaluable subject will be replaced in the same dose cohort to complete the number of evaluable subjects for the MTD analysis.

Any subject who receives at least one dose of DMF is evaluable for safety. The safety population will be used to evaluate baseline characteristics as well as all descriptive endpoints for safety.

All patients who undergo at least one dose of the study treatment will be included in the efficacy analysis. If the response for a patient cannot be assessed (for example, a patient dies early) prior to 2 months assessments, it will be considered to be an event that does not favor the study therapy (e.g., non-response).

10.4 Data Analyses Plans

Primary Analysis

The rate of DLTs will be estimated along with its exact 95% confidence interval using the patients treated at the selected dose in Phase I.

Secondary analyses

The adverse events from the treatment beginning to 56 days after treatment completion or study discontinuation will be recorded for all patients. Incidence of adverse events will be summarized by event type,grade and relatedness, separately for the two dose levels.

The proportion of patients that received the selected dose and are able to complete 2 months of therapy without intolerance or disease progression will be reported. The reason for patient discontinuing treatment early will be recorded.

The objective response rate (including partial response, complete response, or nodular complete response) based on iwCLL will be estimated along with its exact 95% confidence interval.

If follow-up is available, median progression-free survival and overall survival will be estimated using the Kaplan-Meier method.

The expressions of LEF1, c-myc, Wnt pathway, STAT pathway, and STAT1 phosphorylation will be measured over time. The trajectories will be showed by graphs. We will test if the average level of these measurements throughout the treatment is significantly changed from the pre-treatment level by a paired t-test at 5% significance level. We will use the methods of Smyth (2005) to fit linear models to assess differential expression between pre- and post-treatment measurements. As we plan to conduct a large number of hypothesis tests within the gene expression outcome, we will use the Benjamini-Hochberg method to control the false discovery rate (FDR), setting it to 5%.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

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

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

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

11.3 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

11.4 Data and Safety Monitoring/Auditing

In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, quality assurance of the study will be performed by the clinical trials office

internal monitor. Monitoring intervals will be dependent upon the number of patients enrolled and the complexity of the study.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported after every 6 patients or sooner if required for clinical study stopping rules, and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the date of first and most recent patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

11.5 Adherence to the Protocol

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

11.5.1 Emergency Modifications

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

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

11.5.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

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

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

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

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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APPENDICES

Appendix A. Performance Status

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

Appendix B. Hematologic AE grading scale

Taken from iwCLL guidelines, Hallek et al, 2008.

Table 5. Grading scale for hematologic toxicity in CLL studies

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

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

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

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

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