CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER: CASE 5913

STUDY TITLE: A Phase II Study of Curcumin and Vitamin D in Previously Untreated Patients with Early Stage Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

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SPONSOR: Case Comprehensive Cancer Center

SUPPORT: Early Phase Clinical Research Support (EPCRS), Case Comprehensive Cancer Center

SUPPLIED AGENT: Pharmaceutical grade curcumin
Supplied by Sabinsa Corporation,
East Windsor, NJ

OTHER AGENT: Vitamin D3 (obtained from commercial source)

APPROVALS:

PRMC:	10/07/2013
Initial IRB:	02/20/2014
Amendment 2	09/11/2014 (protocol version date 02/17/2014)
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Amendment 3	11/13/2014 (protocol version date 10/08/2014)
CR and Amend 4	01/05/2015 (protocol version date 12/29/2014)
Amendment 5	02/22/2015 (protocol version date 02/16/2015)
Amendment 6	04/14/2015 (protocol version date 02/16/2015)
Amendment 7	n/a (protocol version date 6/26/2015)
Amendment 8	n/a (protocol version date 10/2/2018)

SUMMARY OF CHANGES:

Amendment 8, protocol v7 date 10/2/2018
Protocol: Added shipping de-identified samples to Basem William MD at OSU under a Material Transfer Agreement

Administrative Change, Consent and Protocol, no version change/IRB approval exempt
Updated Name of UHCMC to University Hospitals Cleveland Medical Center

Amendment 7, Consent v7 date 6/26/2015, Protocol v6 date 6/26/2015
Revised protocol and consent to change PI from Dr. William to Dr. Caimi

Amendment 6, Consent v date 4/3/2015
Consent: revised to clarify which activities are routine versus research related.
Protocol: no changes to protocol or protocol version date.

Amendment 5, v date 2/16/2015
Protocol: Quality of life assessments at baseline and at end of treatment added. Curcumin dose reduction adjusted to 4g daily with grade 3 diarrhea.
Consent: Consent updated to include mandatory QOL assessments.

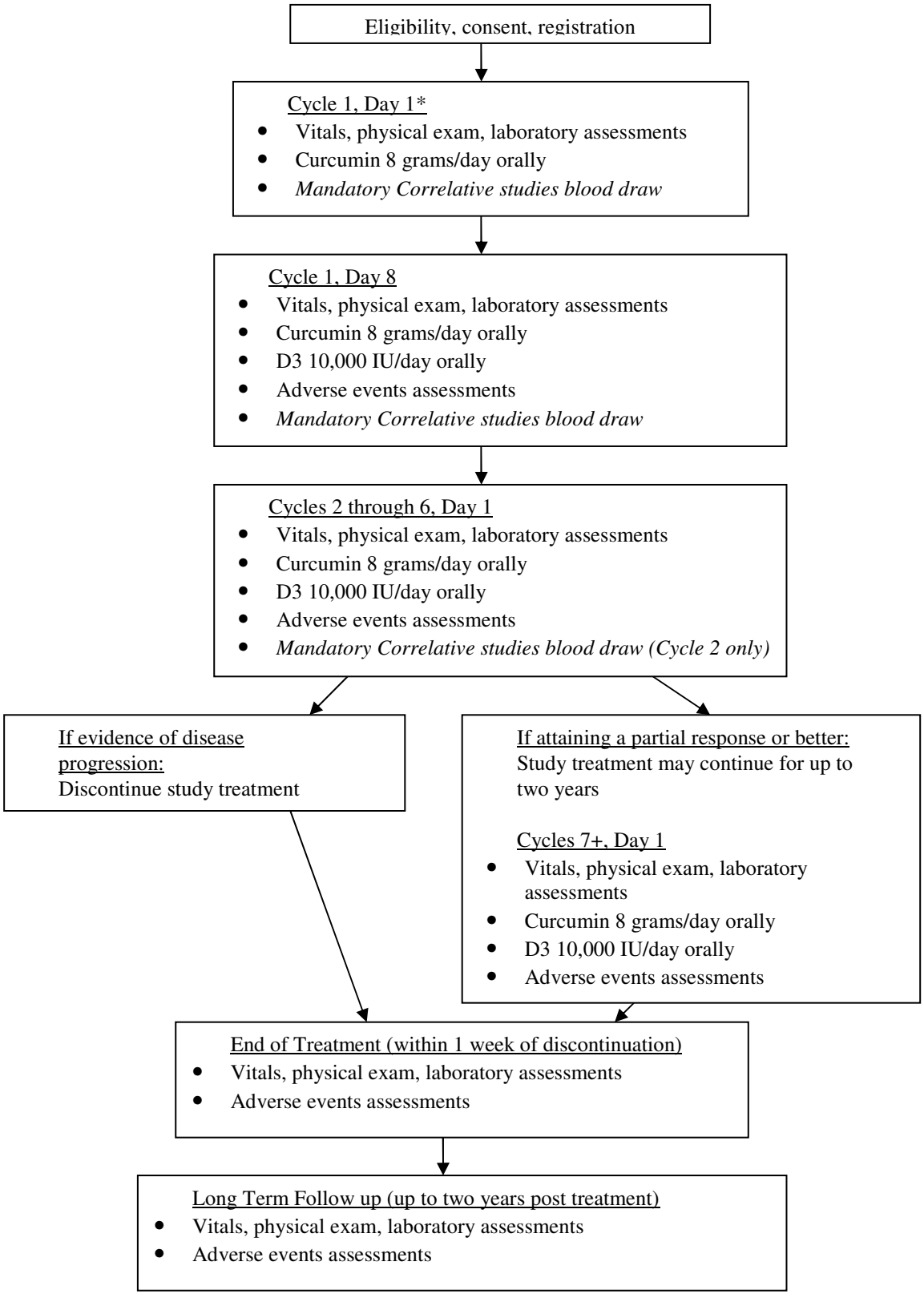
Amendment 4, v date 12/29/2014
Protocol: changes to study calendar item c to correctly indicate ALC<5000, change to section 11.2 to include a window for PE visits +/- 3 days to avoid deviations, revision to schema to indicate that all labs are mandatory.
Consent: updated to revised CCCC IRB approved template v date 12/10/2014.

Amendment 3, v date 10/08/2014

Protocol: revised timeframe for prescreening for bone marrow biopsy, flow cytometry, cytoegenics, and interphase FISH to be acceptable if completed within 5 years of enrollment.
Consent: revised to new CCCC IRB approved template, prescreening information revised to reflect protocol.

Amendment 2, v date 2/17/2014

Protocol approved with initial submission was not correctly documented with the IRB. There were no changes to the protocol with this submission. It was administrative.


Eligibility, consent, registration
Cycle 1, Day 1*
Vitals, physical exam, laboratory assessments
Curcumin 8 grams/day orally
Mandatory Correlative studies blood draw
Cycle 1, Day 8
Vitals, physical exam, laboratory assessments
Curcumin 8 grams/day orally
D3 10,000 IU/day orally
Adverse events assessments
Mandatory Correlative studies blood draw
Cycles 2 through 6, Day 1
Vitals, physical exam, laboratory assessments
Curcumin 8 grams/day orally
D3 10,000 IU/day orally
Adverse events assessments
Mandatory Correlative studies blood draw (Cycle 2 only)
If evidence of disease progression:
Discontinue study treatment
If attaining a partial response or better:
Study treatment may continue for up to two years
Cycles 7+, Day 1
Vitals, physical exam, laboratory assessments
Curcumin 8 grams/day orally
D3 10,000 IU/day orally
Adverse events assessments
End of Treatment (within 1 week of discontinuation)
Vitals, physical exam, laboratory assessments
Adverse events assessments
Long Term Follow up (up to two years post treatment)
Vitals, physical exam, laboratory assessments
Adverse events assessments
*Each cycle is 28 days

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1.0 INTRODUCTION

1.1 Early Phase Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a heterogeneous disease with an extremely variable course. Patients with ‘‘smoldering’’ CLL appear to have a life span similar to age-matched controls in the general population. Similarly, early stage asymptomatic CLL (Rai stage 0-II without active disease as defined by the National Cancer Institute Working Group [NCI-WG] Criteria) is associated with a favorable prognosis with a reported median overall survival (OS) that ranges from 8 to 12 years. Currently, management of asymptomatic early stage CLL centers on expectant surveillance for active disease warranting chemotherapy (1). However, survival outcomes vary considerably within this subset depending on prognostic factors at presentation. Early stage patients with unfavorable features are at higher risk for disease progression, and, therefore, may benefit from early intervention rather than the traditional watch-and-wait approach.

The large randomized clinical trials conducted by the French Cooperative Group in the 1980s for asymptomatic early stage CLL were limited to potentially toxic chemotherapeutics (alkylating agents). Early treatment with daily chlorambucil or intermittent chlorambucil/prednisone was associated with slower disease progression, but not longer survival when compared with the observation arms (2, 3). The lack of survival benefit was attributed to selection of resistant CLL clones due to early exposure to chlorambucil, limited availability at that time of effective salvage regimens, and excess deaths from secondary epithelial cancers. With regard to the clinical course of the disease, these randomized trials showed that at least 40% of patients with early stage CLL eventually require therapy for progressive disease, and that approximately 25% ultimately die of disease-related causes (2, 3).

1.2 Curcumin

1.2.1 History of curcumin use as a medicinal agent

Turmeric is a rhizomatous plant (Curcuma longa) consisting of approximately 3% curcumin. Turmeric use in the field of medicine was described in Asia thousands of years ago. Evidence suggests curcumin has the potential to prevent or treat various pathophysiological processes, including cardiovascular disease, carcinogenesis, wound healing and inflammation. Curcumin exists as a bright yellow powder that provides the pigmentation to turmeric, and is used in the dye industry. It carries food additive number E100. The extracted powder will typically contain 75% curcumin in addition to derivatives of the parent compound in the form of other curcuminoids; approximately16% demethoxycurcumin (DMC), 8% bisdemethoxycurcumin (bDMC) and a small amount of cyclocurcumin. BDMC and DMC possess similar molecular and biological properties. It is proposed that, within natural pathways, bDMC converts to DMC which then converts to curcumin. The powder is exported for encapsulation and subsequent distribution within world nutraceutical markets. Capsules are readily obtainable as a health food supplement (4).

1.2.2 Biochemistry of curcumin

Curcumin (or diferuloylmethane) is a poly-phenolic molecule existing as a keto-enol tautomer, with the enol isomer probably the more stable in both solid state and solution (Fig. 1) (5). The molecule is lipophilic consisting of two aromatic rings connected by two unsaturated carbonyl groups and therefore has poor water solubility. The molecule is stabilised by hydrogen-bonding associated with the central OH group. This may be one of the important functional sites responsible for the array of molecular biological activities (6). Curcumin is photosensitive and precautions should be taken to avoid exposure and subsequent degradation. Much of the interest to medical research lies within the ability of curcumin to counteract the generation and subsequent effects of reactive oxygen species and nitrogen free-radicals, typically manifesting from damaged cells. Curcuminoids can avidly donate hydrogen ions and undergo nucleophilic addition. They possess several moieties with the potential to undergo biochemical modification (6) and impart the important reduction–oxidation, anti-oxidant and proton donating properties that can combat cell damage. The mechanisms which enable curcumin to scavenge and trap radicals are numerous and complex (7). One of the key attributes of curcuminoids likely to evoke this benefit is the chain-breaking anti-oxidant activity from hydrogen atoms, most probably donated from the phenol (OH) groups (8). Curcumin is unstable under alkaline conditions and degrades in less than 30 min (9). Under acidic conditions, the rate of decomposition is significantly reduced with less than 20% of total curcumin degraded in 1 h (10). This may explain why curcumin seems to be stable within the gastrointestinal tract where the pH range is 1–6.

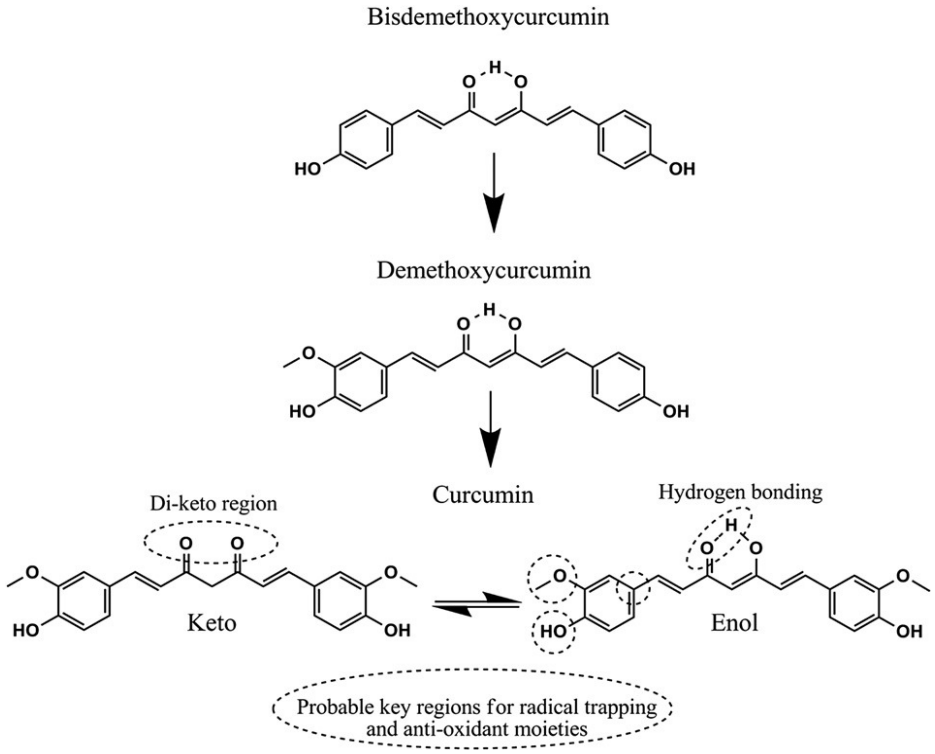

Figure-1: Proposed molecular pathway for the conversion of bDMC to DMC and finally to curcumin and the co-existence of keto and enol isomers of curcumin (4).

1.2.3 Antineoplastic properties of curcumin

Many pathways are dysregulated in cancer. Curcumin may be able to modulate multiple cellular pathways involved in carcinogenesis and thus behave as a multi-targeted drug. This is of particular interest in the management of neoplastic conditions. By not relying on a single target pathway, it may have activity across a wider population of tumor genotypes. The loss of cell cycle control can lead to the bypassing of DNA-damage checkpoints and replication of damaged cells with malignant potential. Curcumin promotes inhibition or arrest at all stages of the cell cycle. This is in part due to a curcumin-induced increase in p53 and p21 expression, however, curcumin can also inhibit G1/S mitotic arrest independently from p53 and p21 activity (11). Curcumin-induced down-regulation of cyclin D (12) prevents cells progressing from the G1 to the S phase, thus favoring apoptosis. In addition, it blocks the effect of cyclin-dependent kinases (CDK), in particular CDK4 and CDK6, the activation of which are required for cell cycle turnover. This may also be achieved by a curcumin-induced decrease in telomerase activity and by the inhibition of growth factor receptors (GFR). Apoptosis is ultimately achieved either by caspase induction or p53 signaling. Several cell line models demonstrate that curcumin promotes apoptosis via both these routes. Curcumin inhibits colorectal cancer cell growth by ~20% in vitro at concentrations as low as 5 μmol (13) and is a potent stimulator of caspase-3-induced apoptosis in hepatic cancer cell lines (14). It also increases the activation of caspase-7 (11) and (15) and caspase-8 and induces cytochrome-C release (16). Curcumin increases p53 expression, p53-driven apoptosis and subsequent p21 expression in response to DNA damage (17) and (13). In cell lines absent in p53, curcumin still enhances apoptosis via alternative pathways (e.g. death receptor dependent) utilising caspase and NF-κB signaling (18) and (16). Breast cancer cells treated with curcumin have been observed to undergo apoptosis accompanied by an increase in p53, p53 DNA binding activity and subsequent rise in Bax expression (19). C-Jun N-terminal kinases (JNK) and MAPK/p38 lie upstream from p53 in the apoptotic pathway. Curcumin may increase MAPK/p38 activation thus promoting apoptosis (20) though this has been disputed following other studies (21). This may be explained by a dose effect or differences between cancer cell lines. Curcumin also blocks the action or expression of the anti-apoptotic protein Bcl-2 in a number of cell lines (22). Curcumin inhibited NF-κB signaling, upregulated p53, and induced apoptosis in BCR-ABL acute lymphoblastic leukemia (ALL) cell lines; including cell lines driven by the T 315I BCR-ABL mutant that is resistant to tyrosine kinase inhibitors, and it prolonged survival of murine models of BCR-ABL driven ALL (23).

1.2.4 Preclinical data in CLL

As an inhibitor of NF-κB signaling, curcumin would be expected to induce apoptosis in B cell malignancies especially CLL where nuclear NF-κB is constitutively active (24). Everett and colleagues have shown that curcumin induced apoptosis in B-CLL cells from 14 patients with a mean EC(50) of 5.5 μM. In contrast, the EC(50) for whole mononuclear cells from a healthy donor was 21.8 μM confirming the fact that B-CLL are more sensitive to curcumin compared to normal lymphocytes. In a 48 hr wash-out time course, curcumin-induced apoptosis was time-dependent, with a substantial reduction in apoptosis observed when curcumin was removed after 5 hr. Curcumin treatment reduced basal nuclear NF-κB levels and 1 μM curcumin augmented both vinca alkaloid and PDE4 inhibitor-induced apoptosis in

B-CLL cells (25). Ghosh and colleagues have subsequently shown that curcumin induced apoptosis in CLL cells in a dose-dependent (5-20 μM /L) manner and inhibited constitutively active prosurvival pathways, including signal transducers and activators of transcription 3 (STAT3), AKT, and NF-κB. Moreover, curcumin suppressed expression of the anti-apoptotic proteins Mcl-1 and X-linked inhibitor of apoptosis protein (XIAP), and up-regulated the pro-apoptotic protein BIM (26). More recently, curcumin was shown to sensitize lymphoma cells to the effects of ionizing radiation through blockade of NF-κB signaling (27, 28).The in vitro efficacy of curcumin in inducing apoptosis in cell lines deficient in p53 (18), through alternative pathways like NF-κB, Akt, and spleen tyrosine kinase (Syc) (23, 25, 29, 30), makes in clinically attractive agent to develop as there it has the potential to be effective in treating CLL patients with 17p/p53 deletion which are resistant to conventional cytotoxic agents (31).

1.2.5 Clinical Data to Date

Safety of oral curcumin was demonstrated from almost 40 clinical trials involving over 800 participants (please see *toxicity* below). Dhillon and colleagues reported results of 25 patients with advanced pancreatic cancer treated with curcumin in a phase II single-institution trial (32). Patients received about 8g of oral curcumin that was well tolerated and no significant toxicities were observed. Despite poor curcumin bioavailability (see *clinical pharmacokinetics* below), steady state serum levels of 22-41 ng/ml of conjugated curcumin were achieved with such oral dosing within 3 days. All patients who donated blood samples had constitutively active NF-κB in their peripheral blood leukocytes and that was decreased after treatment with oral curcumin although such decrease wasn't statistically significant. Curcumin also led to a significant decrease in cyclooxygenase-2 in leukocytes as well. Only 2/21 evaluable patients in this study had a response. Two patients showed clinical biological activity. One had ongoing stable disease for >18 months; interestingly, one additional patient had a brief, but marked, tumor regression (73%) accompanied by significant increases (4- to 35-fold) in serum cytokine levels (IL-6, IL-8, and IL-10). Despite the absence of meaningful clinical activity in advanced pancreatic cancer, this study provided proof of concept that oral curcumin, despite its poor bioavailability, had biologic activity and is able to modulate NF-κB signaling among a myriad of other biological effects (32). Golombick and colleagues reported the results of a randomized clinical trial of oral curcumin, given also at 8g daily dose, versus placebo in 36 patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) (33). Despite small sample size, curcumin treatment resulted in a significant decrease of free light chain ratio (36% from baseline) as well as markers of bone resorbtion. Also, no toxic effects of treatment were observed. Results suggest that curcumin might have the potential to slow the disease process in patients with MGUS and SMM (33).

1.2.6 Clinical Pharmacokinetics

1.2.6.1 *Absorption and systemic bioavailability*

Clinical and in vivo studies report a limited systemic bioavailability of curcuminoids, with most of an oral dose excreted in faeces (34) and (35) and intravenous and intraperitoneal doses excreted in bile (36) and (37). Curcumin is poorly absorbed but easily detectable in the gastrointestinal tract (35), (38) and (39). Traces of parent compound have been found in rat liver and kidney (34) and (37) confirming that uptake does occur in organs distal to the

intestine albeit at low concentrations. In humans, plasma levels of curcumin reach a peak (27 nM) around 1–2 h (40) after oral administration further confirming low bioavailability. It may be that exposure to low nanomolar concentrations is sufficient, and perhaps only briefly, to exert a therapeutic effect. Despite the low bioavailability reported from animal and human studies, early evidence of both local and systemic efficacy is apparent from the reduced tumour burden that has been observed in mouse models of familial adenomatous polyposis (FAP) (41) and (42) and colorectal liver metastases (12) and some efficacy is suggested from a clinical trial of curcumin in patients with pancreatic cancer (32). Hence, in the face of very low levels of detectable curcumin at the target site, biological activity may occur. Approximately a third of faecal curcumin is excreted without being systemically metabolized (34), (36), (39) and (43). Curcumin is reduced and conjugated within the gastrointestinal tract and liver, resulting in very low amounts of the parent compound detected in the hepatic system (44).

1.2.6.2 *Detection of systemic curcumin*

Curcumin detection in plasma is variable due to poor bioavailability and a short plasma half-life. Initial studies using murine models consistently report low serum concentrations with the majority of the compounds being undetectable after 1 h following enteric (up to 2 g/kg) and parenteric (up to 40 mg/kg) administration (36) and (40). These data are mirrored by clinical trials where up to 12 g per day of oral curcumin has been given to patients and peak plasma levels occur 1–2 h following loading with trough levels at approximately 12 h (45). Only trace levels of curcumin are found in serum following oral doses less than 2 g per day. Following 4 g and 8 g of daily curcumin, serum levels of 0.51 μmol and 1.77 μmol have been reported (45) and similar values are achieved with 3.6 g per day (38).

1.2.6.3 *Urinary excretion of curcumin*

Curcumin is poorly excreted in urine (35) and (39). Murine models report negligible amounts are found in the urine even following intravenous doses of 1 g/kg (35) and (37). In humans receiving oral curcumin for four months, at doses greater than 3.6 g daily it becomes possible to detect curcuminoids in urine (43). Human renal excretion remains poor even with increasing doses (46). It is unlikely that curcumin metabolism either effects or is affected by renal function. Adverse events due to curcumin relating to renal function have not been reported in any trial and there is some evidence that curcumin may even improve function in renal disease (47).

1.2.6.4 *Toxicity*

Toxicity or changes in body weight have not been seen in pre-clinical studies of long-term curcumin use (48) and (36). Little demonstrable toxicity is observed at *in vivo* doses of up to 5 g/kg (35). No significant toxicities have been reported from almost 40 clinical trials involving over 800 participants. Patients have tolerated up to 8 g oral curcumin daily for three months (45) and escalation beyond this, although safely achievable, was limited by the volume of capsules necessary to deliver the dose. Side-effects are dose-related and typically gastrointestinal in origin, including loose stools, bloating, reflux and discomfort. Dose reduction usually leads to improvement. Trials consistently report curcumin has no effect on biochemical and haematological parameters during administration. There have been anecdotal reports of transient rises in liver enzymes although causality is unclear.

1.2.6.5 *Dosing for pharmacological effect*

The relative instability, rapid metabolism and short plasma half-life present difficulties when establishing an appropriate dose for pharmacological effect. Determining a dose that is both tolerated and efficacious is challenging. Several trials have used oral regimens of approximately 4 g daily curcumin however in vivo reports imply a daily dose of 1.6 g in humans may be enough to exert a biological effect in the lumen, achieving a colonic mucosal concentration of 0.1 μmol/g (42). Pre-clinical data is difficult to extrapolate into a human dosing regimen. Other clinical studies have required 8 g orally (45) to achieve serum levels suggested by in vivo studies to be necessary for efficacy. However, an increase in dose may not equate to a proportional increase in systemic absorption (34). Detection of curcuminoids in hepatic tissue has been demonstrated in small amounts following 3.6 g per day for one week although not with lower doses (46). Trace levels are detected in human serum at doses of 2 g. Based on that which is necessary to furnish detectable levels of curcumin in serum, portal blood or hepatic tissue, it is possible that a dose in the region of 2–4 g is the minimum required to have pharmacological effect in organs distal to the gut (46).

1.3 **Vitamin D3**

1.3.1 Vitamin D and hematological malignancies

Vitamin D is a fat-soluble vitamin that also acts as a pleiotropic hormone. There are two major forms of vitamin D. Vitamin D3 is normally produced in the skin after sun exposure and can also be acquired from diet. On the other hand vitamin D2 is only obtained exogenously. Very few foods in nature contain vitamin D but both vitamins D2 and D3 are used as dietary supplements in the United States. During exposure to solar ultraviolet B (UVB) radiation, 7-dehydrocholesterol in the skin is converted to previtamin D3, which is immediately converted to vitamin D3, which is then converted to 25-hydroxycholecalciferol [25(OH)D3] in the liver by 25-hydroxylase and consequently becomes its active form, 1,25-dihydroxycholecalciferol [1,25(OH)2D3], in the kidney by 1-α-hydroxylase; see figure-2 (49). The expression of the vitamin D receptor (VDR) in immune system cells as well as extrarenal expression of 1-α-hydroxylase and 25-hydroxylase by macrophages, dendritic cells, B- and T-cells indicates autocrine and paracrine mechanisms by which 1,25(OH)2D3 production is regulated to exert its effects on the key players of the immune system (50).

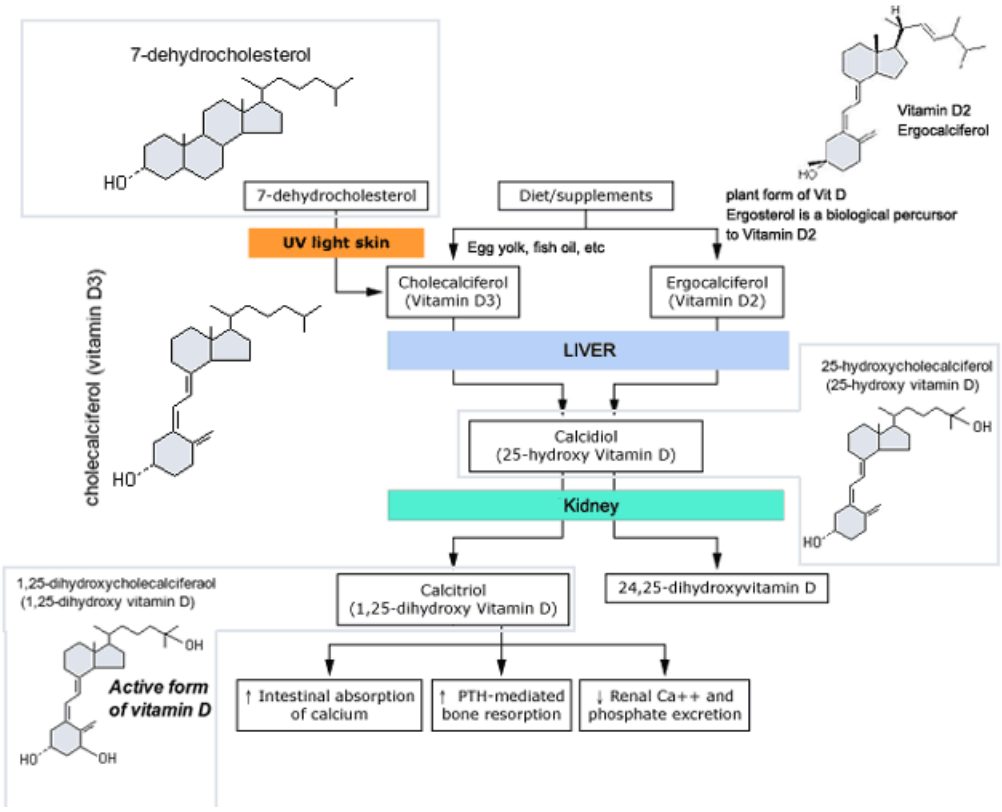

Figure-2: Vitamin D metabolism in humans

The discovery that vitamin D and its derivatives may have roles beyond the classical role of calcium absorption has led to a greater research focus on the use of vitamin D against various cancers. With epidemiological studies indicating that there is a significant correlation between vitamin D deficiency and the greater incidence of cancer (51), more evidence of the anti-tumor effects of vitamin D in various tissue types is being collected. An especially prominent focus in current literature regarding the use of vitamin D against hematological diseases is the study of acute leukemia and myelodysplastic syndrome through treatment of myeloid precursor cells. The application of vitamin D to treat other hematological malignancies, such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, and myeloma, have been under research as well. The appeal of vitamin D in treatment against these neoplastic diseases stems from the fact that vitamin D appears to halt the proliferation and induce the maturation of hematopoietic precursor cells, indicating its ability to induce terminal differentiation in the neoplastic cells that characterize hematological malignancies as well. The biochemical mechanisms through which vitamin D and its derivatives exert their effects have certainly become a topic of interest due to the implication that treatments targeting these pathways can be developed to produce desirable results, both *in vitro* and *in vivo* (52).

1.3.2 Vitamin D activity in lymphoid malignancies

With research indicating that vitamin D has anti-proliferative and pro-differentiation activities against cells possessing VDR, it is plausible that vitamin D can be used in therapy against other hematological malignancies, such as the lymphoid cancer types: Hodgkin's lymphoma, non-Hodgkin's lymphoma, and myeloma. A correlation between ultraviolet light exposure and the

decreased risk for Hodgkin's and non-Hodgkin's lymphoma has elicited studies on the possible protective role of vitamin D against the development of these lymphoproliferative diseases. One epidemiological study discovered a relationship between the season of Hodgkin's lymphoma diagnoses and the risk of death in patients, with the level of endogenous calcidiol considered to be a prognostic factor. Patients diagnosed with Hodgkin's lymphoma (HL) in autumn were found to have a lower fatality risk than those diagnosed during the winter, with serum levels of calcidiol found to be higher during summer and autumn than winter (53). A similar relationship between UV exposure and non-Hodgkin's lymphoma (NHL) has been reported in a separate epidemiological study, with lower risk of NHL associated with greater outdoor activity and sun exposure in warmer months (54). A statistical analysis of five different case-control studies led to the finding that greater sun exposure was found to significantly correlate with lower risk of both B and T cell lymphomas, although a decreasing risk for B cell lymphoma seemed to correlate more directly with greater sun exposure (55). Other efforts to discover an association between vitamin D levels and risk for NHL and HL include studies of serum levels and dietary intake of vitamin D. A study of fasting serum 25(OH)D levels revealed no significant relationship between circulating 25(OH)D and various lymphoid cancers, such as myeloma, HL, and NHL, but higher 25(OH)D did appear to have some protective effect against risk of NHL (56). The biochemical basis by which vitamin D could confer protection against Hodgkin's and non-Hodgkin's lymphoma was studied through examination of VDR polymorphisms in human populations. Single nucleotide polymorphisms in FokI, BsmI and TaqI restriction sites in the VDR gene were not found to have a clear relationship with risk for NHL and VDR polymorphism. However, the study did find certain Bsml and TaqI alleles to be associated with increased risk for diffuse large B-cell lymphoma and a FokI allele to be related to increased risk for T cell lymphoma, possibly due to decreased transactivation of VDR (57). Another study found no significant relationship between NHL risk and VDR polymorphisms, although relationships were seen with breast, skin, and prostate cancers (58).

While the relationship between VDR polymorphism and lymphoid malignancies has not been firmly established, vitamin D has been found to exert anti-proliferative and differentiating effects on VDR-expressing lymphocytes and lymphocytic precursors. 1,25(OH)2D3 as well as its analog MC903, which has a higher affinity for VDR, have been used to treat B cell lines SU-DHL4 and SU-DUL5 derived from high grade B-cell lymphoma. Results of this treatment include equal anti-proliferative effects seen in both cell lines by 1,25D and MC903, with terminal B-cell maturation indicated by the expression of markers B1, B4, and CD38 (59). Another study of vitamin D treatment on B-cells found that vitamin D suppressed proliferation and differentiation of activated B-cells while also inducing B-cell apoptosis. Up-regulation of transcription activity in B cells also led to greater expression of VDR, lymphocytic marker CD38, and cyclin kinase inhibitor p27Kip1(60). The effect of vitamin D on a malignant B-cell progenitor lineage as well as normal B and T progenitor cells was also revealed that 1,25D caused inhibition of clonal proliferation in malignant and normal lymphoid progenitor cells without any cytotoxic effects (61). The use of the vitamin D analog EB1089 on B cell progenitors has also proven to be anti-proliferative (62), as stated in the discussion on analog treatments. 1,25D was also found to be anti-proliferative in T cells by inhibiting transition from the early phase of G1 to late phase of G1 in the cell cycle; inhibition of IL-2 production was also believed to be another mechanism by which 1,25D mediates its anti-proliferative action [80].

Thus, in consideration of the suppressing effect vitamin D exerts on malignant lymphoid cells, its use for treatment of lymphoid cancers seems to be a promising area of ongoing research.

1.3.3 Vitamin D and CLL

Shanafelt and colleagues (63) evaluated the relationship of 25(OH)D serum levels with time-to-treatment (TTT) and overall survival (OS) in newly diagnosed CLL patients participating in a prospective cohort study (discovery cohort) and a separate cohort of previously untreated patients participating in an observational study (confirmation cohort). Of 390 CLL patients in the discovery cohort, 119 (30.5%) were 25(OH)D insufficient. After a median follow-up of 3 years, TTT (hazard ratio[HR] = 1.66; P = .005) and OS (HR = 2.39; P = .01) were shorter for 25(OH)D-insufficient patients. In the validation cohort, 61 of 153 patients (39.9%) were 25(OH)D insufficient. After a median follow-up of 9.9 years, TTT (HR = 1.59; P = .05) and OS (HR 1.63; P = .06) were again shorter for 25(OH)D-insufficient patients. On pooled multivariable analysis of patients in both cohorts adjusting for age, sex, Rai stage, CD38 status, ZAP-70 status, immunoglobulin heavy chain variable (IGHV) gene mutation status, CD49d status, and cytogenetic abnormalities assessed by interphase fluorescent in situ hybridization testing, 25(OH)D insufficiency remained an independent predictor of TTT (HR = 1.47; P = .008), although the association with OS was not significant (HR = 1.47; P = .07) (63). There is also anecdotal evidence that consumption of dairy products with higher vitamin D levels decreases absolute lymphocyte counts in patients with CLL (64).

1.3.4 Clinical Data to Date

Amir et al reported the results of a A phase 2 trial exploring the effects of high-dose (10,000 IU/day) vitamin D(3) in breast cancer patients with bone metastases. Forty patients were enrolled. No significant changes in bone resorption markers were seen. Despite no change in global pain scales, there was a significant reduction in the number of sites of pain. A small but statistically significant increase in serum calcium was seen, as was a significant decrease in serum parathyroid hormone (65). Most discussions of the role of vitamin D in cancer therapy express the concern that high-dose calcitriol is too toxic to be administered to patients with cancer. There are now many clinical studies that clearly establish that calcitriol can be safely administered in very high doses if an intermittent treatment schedule is used. Administration of oral calcitriol on a daily schedule (1.5–2.5 μg/d, weekly dose intensity ~10.5–17.5 μg/wk) is associated with a 20% to 30% frequency of hypercalcemia in men with PCa and in postmenopausal women.(66), (67), (68) and (69)

1.3.3 Clinical Pharmacokinetics

Calcitriol administered by mouth daily for 3 days every week (28 μg daily for 3 days) + dexamethasone (4 mg daily for 4 days) weekly is very safe and well tolerated in men with advanced prostate cancer. In 2 studies of patients with advanced prostate cancer, doses of calcitriol of 38 μg every day for 3 days weekly and 28 μg every day for 3 days monthly were safely administered together with paclitaxel and carboplatin, respectively (70). Fakih and colleagues (71) studied intravenous calcitriol (Calcijex, Roche Pharmaceutical Corporation) weekly + gefitinib and reported that very high doses of calcitriol can be administered safely. The dose-limiting toxicity of weekly intravenous calcitriol + gefitinib was grade 3 hypercalcemia at a dose of 98 μg/wk. The phase II dose of this regimen is 77 μg weekly alone and 98 μg/kg weekly when calcitriol is combined with high-dose dexamethasone.(71) and (72) The systemic exposure

of calcitriol following 98 μg is approximately 30 ng/h/24 h which is in the range of exposure we have reported in murine models in which calcitriol has clear-cut antitumor activity.(73).
Beer and colleagues (74) have studied high-dose oral calcitriol (as Rocaltrol) and concluded that 0.5 μg/kg, weekly is very safe. Studies with DN-101 demonstrated that 45 μg weekly was safe and well tolerated and that 165 μg given on week 1, followed by 45 μg weekly produced no toxicity.(75) A linear relationship between dose of DN-101 administered and area under the curve (AUC) was maintained up to 165 μg. Studies using an intermittent schedule of administration (weekly or every day for 3 days weekly) have encountered dose-limiting hypercalcemia only at doses 100 μg following intravenous administration; transient increase in serum calcium (11–13 mg/dL) does occur 1 to 3 days after completion of a single or daily for 3 days schedule. However, only at doses achieving AUC more than ~30 ng/h/ml has dose-limiting hypercalcemia been encountered. Hypercalciuria is universal following administration of high-dose calcitriol. Dietary calcium restriction is very difficult for patients to maintain and there is little evidence that it reduces hypercalciuria. There has been no deterioration of renal function in patients receiving high-dose intermittent calcitriol for more than 12 months. Radiographic monitoring for urinary tract stones (ultrasound or computed tomography) in our studies suggests that newly discovered urinary tract stones may occur in 1% to 3% of patients (69).

1.4 **Rationale**

The rationale of this study is built upon the demonstrated safety and biologic activity of both curcumin and vitamin D3 in animal models and human studies. There is no evidence of overlapping toxicities between both agents. Both curcumin and vitamin D3 have demonstrated preclinical activities in CLL and there is preclinical data to suggest potential synergism between both agents: Mosieniak and colleagues have shown that curcumin overcomes the resistance of calcitriol-differentiated HL-60 cells, an acute promyelocytic leukemia cell line, to DNA-damage-induced apoptosis by activating other cell signaling pathways leading to cell death of HL-60; such curcumin-induced cell death did not involve DNA-damage-initiated signaling pathways, to which differentiated HL-60 cells are highly resistant (76). Curcumin, in concentrations as low as 50 μMol increased the expression of VDR in BCR-ABL driven B-ALL murine cells (23). Also, curcumin was shown to directly activate VDR in colon cancer cell lines to induced VDR target genes including CYP3A4, CYP24, p21 and TRPV6 (77). Since both curcumin and vitamin D3, and its analogues, seem to induce cell death through pathways that don't require DNA damage, they have the potential to have clinical activity in 17p/TP53 deleted CLL; a disease that carries a bad prognosis because of resistance to conventional cytotoxic therapeutic agents (31).

We hypothesize that curcumin-vitamin D3 combination would have a synergistic activity against CLL beyond each agent given alone. We hypothesize that this effect is likely related to curcumin upregulating intracellular VDR cells in CLL cells rendering them more susceptible to vitamin D3. We propose to use a curcumin daily dose of 8g as this is dose was shown to have biologic activity, modulation of NF-κB signaling, and steady state pharmacokinetics, and no toxic effects after up to 9 months of therapy (32, 33). We propose to use vitamin D3 daily dose of 10,000 IU as this dose has shown safety and biologic activity in clinical trials of patients with metastatic breast cancer (65). Despite more predictable pharmacokinetics of calcitriol, which made it the more preferred agent in clinical trials for metastatic prostate cancer, we elected to choose vitamin D3 as it has a lower risk for hypercalcemia (66), (67), (68) and (69). As the impact of early

treatment of CLL on survival remains uncertain, we felt that exposing patients to 20% risk of hypercalcemia with calcitriol therapy is unacceptable under the "do no harm" principle. We propose continuous treatment with both agents analogous to prior clinical trials with curcumin to start 1 week before vitamin D3; for the theoretical advantage of attaining serum steady state of curcumin and upregulating VDR levels in CLL cells making them more susceptible to vitamin D3. We propose an initial duration of treatment of 6 months followed up observation analogous to prior clinical interventions in early stage CLL (78) and analogous to the duration of traditional chemotherapy treatments for advanced CLL (79). At least 4 studies support the concept that maximal cutaneous synthesis of vitamin D (ie, full-body, maximal exposure to sunlight) can be equivalent to an oral vitamin D3 intake of 10,000 IU/day (80-83). Furthermore, a review of data from vitamin D supplementation studies reveals a dose-response curve for vitamin D that is relatively linear up to 10,000 IU of vitamin D3 per day, suggesting that this dose may be a physiologic upper limit (84).

For more than 5 decades, chlorambucil was the standard first-line treatment for CLL and, historically, the overall response rate (ORR) to chlorambucil was 30%. Chlorambucil fell out of favor with the development of purine analogues in the early 1980 but remains an option for elderly frail symptomatic patients who cannot tolerate more forms of aggressive therapy (1). An ORR response rate of 30% had been considered a benchmark for development of CLL therapies after chlormabucil . We rationed that the curcumin/vitamin D3 combination would be worth further clinical development if we observe an ORR response of 30% or better (please refer to section 12.0 for description of response criteria).

2.0 OBJECTIVES

To determine the efficacy, and tolerability, of curcumin and vitamin D3 combination in patients with early stage, untreated, chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

2.1 Primary Objective

To determine the overall response rate (ORR) based on NCI-WG criteria in CLL or the Cheson criteria in SLL. Will also examine biologic response rate (78); defined as at least 20% reduction of absolute lymphocyte count (ALC) that is sustained over 2 months or a $\geq$ 30% reduction in palpable lymphadenopathy using this regimen.

2.2 Secondary Objective(s)

To determine the Time to first cytotoxic treatment (TFCT), progression free survival (PFS), and Overall survival (OS) using this regimen.

3.0 STUDY DESIGN

3.1 Study design

This is Case Comprehensive Cancer Center open label phase II trial.

3.2 **Number of Subjects**

We plan to enroll a maximum of 35 patients to obtain 29 evaluable patients (assuming a 20% dropout rate).

3.3 **Replacement of Subjects**

All subjects who have received at least one dose of study agent, but have discontinued study agent prior to the first scheduled response assessment are evaluable for toxicity, but are not evaluable for study endpoints. Subjects need to have received at least 2 cycles of treatment to evaluable for response. Therefore, subjects who are not evaluable for study endpoints may be replaced.

4.0 PATIENT SELECTION

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. The checklist must be completed for each patient and must be signed and dated by the treating physician.

Patient's Name _____

Medical Record # _____

Research Nurse /
Study Coordinator Signature: _____ **Date** _____

Treating Physician [Print] _____

Treating Physician Signature: _____ **Date** _____

4.1 **Inclusion Criteria**

Patients must meet all of the following inclusion criteria to be eligible for enrollment:

_____ 4.1.1 Have a diagnosis of CLL based on peripheral blood flow cytometry and/or bone marrow aspiration and biopsy OR diagnosis of SLL based on lymph node or bone marrow biopsy. Patients with SLL need to have measurable disease (see section 12.2 for definition of measurable disease)

_____ 4.1.2 Subject, age ≥ 18 years *(children are excluded from this study as CLL/SLL being exceptionally rare)*

_____ 4.1.3 Performance Status (ECOG) 0-2 (see appendix A)
ECOG PS = _____
Date: _____

_____ 4.1.4 Patients must have not received any prior treatment for CLL or SLL.

_____ 4.1.5 Patients must be stage 0-II based on Rai staging system. Must have no indication for treatment for SLL per NCI-WG criteria (see appendix B)

_____ 4.1.6 Adequate bone marrow, renal, and hepatic function, per local reference laboratory ranges as follows:

_____ 4.1.6.1 Absolute neutrophil count (ANC) ≥ 1,500/mm3
ANC= _____ Date: _____

_____ 4.1.6.2 Platelet count ≥ 100,000/mm3
Platelets= _____ Date: _____

_____ 4.1.6.3 Hemoglobin ≥ 10 g/dL
Hemoglobin= _____ Date: _____

_____ 4.1.6.4 Serum creatinine ≤ 2.0 g/dL or calculated creatinine clearance (CrCl) ≥ 60mL/min (Cockcroft-Gault method)
Creatinine= _____ Date: _____
Crcl = _____ Date: _____

_____ 4.1.6.5 AST and ALT ≤ 2.5 x institutional upper limit of normal (ULN)
AST= _____ Date: _____
ALT= _____ Date: _____

_____ 4.1.6.6 Bilirubin < 2.0 x ULN, unless subject has Gilbert's disease
Bilirubin= _____ Date: _____

_____ 4.1.6.7 Calcium <10.1 mg/dL (corrected to serum albumin as follows:
Corrected Calcium = (0.8 x (4 - patient albumin)) + serum Ca
Corrected calcium=_____ Date: _____

_____ 4.1.7 Females will be either postmenopausal for at least 1 year or surgically sterile for at least 3 months OR Females of child-bearing potential must have a negative pregnancy test at screening and agree to take appropriate precautions to avoid pregnancy (double barrier method of birth control or abstinence) from screening through 3 months after the last dose of treatment

_____ 4.1.8 Able to comprehend and willing to sign an Informed Consent Form (ICF)

_____ 4.1.9 Subjects must be off any steroids 7 days prior to the initiation of treatment.

_____ 4.1.10 Subjects must be off any curcumin, tumeric, or vitamin D supplements for 14 days prior to the initiation of treatment.

_____ 4.1.11 Subjects must be able to take oral medications

4.2 **Exclusion Criteria**

The presence of <u>any</u> of the following will exclude a patient from study enrollment.

_____ 4.2.1 Presence of malignancy (other than the one treated in this study) which required systemic treatment within the past 3 years

_____ 4.2.2 Any indication to start treatment for CLL based on NCI-WG criteria <u>(see appendix B)</u>

_____ 4.2.3 Prior therapy for CLL/SLL

_____ 4.2.4 Subjects who are pregnant or breast-feeding

Pregnant or breastfeeding women are excluded from this study because the safety of curcumin had not been established with pregnancy and is unknown. Because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with curcumin, breastfeeding should be discontinued if the mother is treated with curcumin.

_____ 4.2.5 Concurrent medical condition which may increase the risk of toxicity, including:

_____ 4.2.5.1 Hypercalcemia of any cause
_____ 4.2.5.2 Untreated hyperparathyroidism
_____ 4.2.5.3 Paget's disease of bone

_____ 4.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician; subjects receiving antibiotics that are under control may be included in the study

_____ 4.2.7 Inability to take oral medications.

_____ 4.2.8 Patients receiving other investigational agent

_____ 4.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to curcumin or vitamin D or other agents used in this study.

_____ 4.2.10 Patients on therapeutic anticoagulation, with heparin (or low-molecular weight heparin), warfarin, or a direct thrombin inhibitor as the safety of concurrent administration of curcumin has not been established

_____ 4.2.11 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with curcumin.

4.3 **Inclusion of Women and Minorities**

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

5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through University Hospitals Cleveland Medical Center and will be provided a study number.

6.0 TREATMENT PLAN

Patients will take both Curcumin and Vitamin D3 for 6 cycles (cycle = 28 days).

Patients who sustained a partial response (PR) or better can elect to extend therapy for a total of 2 years.

6.1 **Agent Administration**

As both agents are well-tolerated with no expected grade 3-4 toxicities, dose modifications are as outlined in section 7.0. Reported adverse events and potential risks of curcumin and vitamin D3 are described in Section 8.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

TREATMENT REGIMEN DESCRIPTION				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Curcumin	8 grams	PO	daily	28 day (continuous treatment)
Vitamin D3	10,000 IU	PO	Daily starting on D8 of cycle 1 and on D1 on all subsequent cycles	
The patient will be provided a Patient Pill Diary [Appendix **C** and **D**] and instructed in its use to record each dose of oral medication.				

6.1.1 Curcumin Administration

Patients will take Curcumin 8 grams/day orally with food continuously. Patients will be provided a Patient Pill Diary (Appendix C and D) and instructed in its use to record each dose of oral medication. Curcumin can be administered with other medications.

6.1.2 Vitamin D3 Administration

Patients will take vitamin D3 10,000 IU/day orally with food continuously. For cycle 1, vitamin D3 will start 1 week after curcumin (on D8) only with initiation of treatment and will be given with curcumin continuously there after. Patients will be provided a Patient Pill Diary (Appendix C and D) and instructed in its use to record each dose of oral medication. Vitamin D3 can be administered with other medications..

6.2 General Concomitant Medications and Supportive Care Guidelines

Because there is a potential for interaction of curcumin with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect CYP1A2 and CYP2A6 activity (85). Please refer to Appendix E-F for a complete list.

As patients with early stage CLL/SLL are frequently asymptomatic, have no significant cytopenias at baseline, and as both high dose vitamin D3 and curcumin were both well tolerated in clinical trials, we don't expect that study subjects will need supportive care.

6.3 Duration of Therapy

In the absence of treatment delays due to adverse events, which are not generally expected, treatment may continue for 6 cycles [or can be extended for a total of 2 years if sustained a partial response (PR) or better] until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- The investigator considers it, for safety reasons, to be in the best interest of the patient.
- Unacceptable treatment related toxicity, NCI CTC AE version 4.0. Grade 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks]
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
- Patient decision to withdraw from treatment (partial consent) or from the study (full consent),
- Pregnancy during the course of the study for a child-bearing participant
- Death

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

6.4 Duration of Follow Up

30-Day Follow-Up: Patients will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first.

Long term Follow-Up: Patients will be followed, every 3-6 months (as clinically indicated), for 2 years after discontinuation of study medications for long-term outcomes.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.0 DOSING DELAYS / DOSE MODIFICATIONS

As both agents are well-tolerated with no expected grade 3-4 toxicities, no dose modifications are planned for this study. No hematological toxicities are expected with either agent.

Event Name	**Nausea and/or vomiting**	
Grade of Event	**Management/Next Dose for curcumin**	**Management/Next Dose for vitamin D3**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Off protocol therapy	Hold * until < Grade Off protocol therapy
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
Recommended management: anti-emetics.		

Event Name	**Diarrhea**	
Grade of Event	**Management/Next Dose for curcumin**	**Management/Next Dose for vitamin D3**

≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Decrease the dose to 4 g PO daily	Off protocol therapy
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Event Name	**Hypercalcemia**	
Grade of Event	**Management/Next Dose for curcumin**	**Management/Next Dose for vitamin D3**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Off protocol therapy	Off protocol therapy
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
Recommended management: workup for hypercalcemia as per standard of care		

Event Name	**Other Unexpected toxicity**	
Grade of Event	**Management/Next Dose for curcumin**	**Management/Next Dose for vitamin D3**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Off protocol therapy	Off protocol therapy
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
Recommended management: per standard of care		

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.1 Adverse Events and Potential Risks

8.1.1 Curcumin

The most common side effects (occurs in more than 10 of 100 people) reported in clinical trials are:

- mild nausea
- vomiting
- diarrhea
- reflux
- bloating

All resolved with discontinuation of therapy.

8.1.1 Vitamin D3

Vitamin D3 is well-tolerated and no serious AEs are expected.

A rare side effect that may be expected (occurs in less than 1 of 100 people) is:

- Hypercalcemia is unusual but is recognized AEs of high-dose vitamin D3 therapy especially in individuals with unrecognized hyperparathyroidism. Hypercalcemia related to vitamin D3 resolves with discontinuation of therapy. Typical symptoms of hypercalcemia include poor appetite, nausea and vomiting, abdominal pain, generalized weakness, and frequent urination. If we observe calcium level greater than 11 mg/dL, corrected to serum albumin by as follows: corrected calcium = (0.8 x (4 - patient albumin)) + serum Ca, we plan to hold vitamin D3 and order vitamin D 25(OH) level in the clinical lab to establish such diagnosis. It is generally accepted that vitamin D 25(OH) levels greater than 80 ng/ml are considered toxic but the level on itself doesn't establish toxicity in the absence of hypercalcemia.

8.2 Definitions

8.2.1 Adverse Events

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily

have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject. In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

8.2.2 The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

> **Grades 1** are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)
>
> **Grades 2** are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).
>
> **Grades 3** are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).
>
> **Grades 4** are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).
>
> **Grades 5** are fatal adverse event resulting in death.

8.2.3 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 12 hours OR
    - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.4 Expectedness

Adverse Events can be Expected or Unexpected.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

8.2.5 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

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

8.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.
The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for AE reporting.

8.4 Serious Adverse Event Reporting Procedures

8.4.1 Reporting

Serious adverse events that occur, beginning with the signing of the informed consent form, during treatment, or within 30 days of the last dose of treatment must be reported to **Paolo Caimi, MD** (Principal Investigator).

8.4.2 FDA Reporting

The University Hospitals Principal Investigator, ***Paolo Caimi, M.D.,*** as holder of the IND, will be responsible for all communication with the FDA. In accordance with 21 CFR 312.32, the

University Hospitals Principal Investigator is responsible for notifying the FDA of SAEs that are serious, unexpected (not listed in the Investigator Brochure) and judged to be related (i.e., possible, probable, definite) to the study drug. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar Day IND Safety Report

Any unexpected fatal or life-threatening suspected adverse event represent especially important safety information and, therefore, must be reported more rapidly to FDA (21 CFR 312.32(c)(2)). Any unexpected fatal or life-threatening suspected adverse event must be reported to FDA no later than 7 calendar days after the University Hospitals Principal Investigator initial receipt of the information (21 CFR 312.32(c)(2)). University Hospitals Principal Investigator will complete a Medwatch Form FDA 3500A and notify the FDA by telephone or facsimile transmission.

15 Calendar Day IND Safety Report

The timeframe for submitting an IND safety report to FDA and all participating investigators is no later than 15 calendar days after the University Hospitals Principal Investigator determines that the suspected adverse event or other information qualifies for reporting (21 CFR 312.32(c)(1)). This includes any serious, unexpected adverse events considered reasonably or possibly related to the investigational agent. University Hospitals Principal Investigator will complete a Medwatch Form FDA 3500A and notify the FDA by telephone or facsimile transmission. If FDA requests any additional data or information, the University Hospitals Principal Investigator must submit it to FDA as soon as possible, but no later than 15 calendar days after receiving the request (21 CFR 312.32(c)(1)(v)).

Follow-up IND Safety Report

Any relevant additional information that the University Hospitals Principal Investigator obtains that pertains to a previously submitted IND safety report must be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)). The University Hospitals Principal Investigator will maintain records of its efforts to obtain additional information.

Reporting Serious Problems to FDA
Medwatch Form FDA 3500A:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
Telephone: 1-800-332-1088
Fax: 1-800-FDA-0178

IND Annual Reports

A summary of all IND safety reports submitting during the previous year will be reported to the FDA in the annual report by the University Hospitals Principal investigator, as holder of the IND.

8.5 Data Safety Toxicity Committee

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that ALL serious adverse events are reported to the Case Comprehensive Cancer Center's Data Safety Toxicity Committee. This submission is simultaneous with their submission to the Sponsor or other Regulatory body.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0. Both curcumin and vitamin D3 are available **commercially** as food supplements; both of which will be provided to study subjects free of charge.

9.1 Curcumin

Chemical Name: (1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione

Other Names: iferuloylmethane; C.I. 75300; Natural Yellow 3

Classification: Polyphenol

Molecular Formula: C21H20O6

Mode of Action: Affects multiple and complex pathways but the main mode of action is interference with activity of the transcription factor NF-κB

Metabolism: In the gastrointestinal tract and liver.

Product description: Curcumin will be provided as 1g tablets (tablet size 20 x 7 x 7 mm).

Storage requirements*:* Tablets can be stored at room temperature.

Stability*:* Tablets are stable at room temperature.

Route of administration*:* A total of 8 tablets (total dose 8g) would be given by mouth daily without regard to food intake.

Drug Procurement: Pharmaceutical grade curcumin will be provided by from Sabinsa Corporation (contact information below) free of charge.

Dr. Kalyanam Nagabhushanam Ph.D.,
President (R&D)

SABINSA CORPORATION
20 Lake Drive
East Windsor, NJ 08520
Ph: 732-777-1111 Ext 35
www.sabinsa.com
email: kalyanam@sabinsa.com

Drug will be distributed to study subjects through investigational drug services.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9.2 Vitamin D3
Chemical Name: (3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3-ol

Other Names: Cholecalciferol, activated 7-dehydrocholesterol.

Classification: Steroid

Molecular Formula: C27H44O

Mode of Action: Calcitriol, activated form of vitamin D3, binds to VDR in the nucleus andaffects multiple pathways to inhibit cellular proliferation among other mechanisms.

Metabolism: In the liver and kidneys.

Product description: Pharmaceutical grade vitamin D3 is commercially available from multiple vendors as 2000, 5000, or 10,000 IU tablets or capsules.

Storage requirements*:* Tablets can be stored at room temperature.

Stability: Tablets are stable at room temperature. Vitamin D3 is very sensitive to UV light and will be dispensed in appropriate UV-light blocking containers.

Route of administration*:* A total of 10,000 IU would be given by mouth daily without regard to food intake.

Drug Procurement: Pharmaceutical grade vitamin D3 will be obtained from a commercial vendor (as tablets or capsules). A single batch will be purchased and provided to study subjects free of charge. Drug will be dispensed to study subjects through investigational pharmacy .

For vitamin D
Dr James Grote
BTR Group, Inc.
PO Box 501
Pittsfield, Il. 62363
FAX (217) 285-6454
Phone (217) 320-1594
Email grotejames@hotmail.com
http://www.vitd3.com/healthcare_professionals.php

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

10.0 CORRELATIVE / SPECIAL STUDIES
All correlative studies are mandatory.

10.1 Vitamin D receptor expression in CLL cells
The purpose of this correlative study is to measure intracellular vitamin D receptor (VDR) levels in CLL cells compared to normal T-cells. There is preclinical evidence that curcumin increases intracellular VDR cells in clonal lymphoid cells (23).

10.1.1 Background
We hypothesize that the synergistic effect of curcumin and vitamin D3 on CLL cells is due to increased intracellular VDR levels with curcumin pretreatment (23).

10.1.2 Rationale for Analysis

We plan to assess VDR at baseline and on D8, after 1 week of treatment with curcumin, and prior to starting vitamin D3 treatment to prove this. Quantitative intracellular measurement of VDR by flow cytometry, in peripheral blood mononuclear cells, has been performed, and validated, by other investigators before (86). The purpose of this analysis is exploratory/proof of concept. Subjects with SLL with no peripheral blood lymphocytosis will be excluded from this analysis.

10.1.3 Collection of Specimens

About 4-5 ml of blood will be drawn into 1 green-topped tube (containing heparin). The tube will be kept at ambient temperature and will be delivered to the TRPC laboratory within 3 hours of venipuncture. Blood samples will be drawn at the following 3 times points:

1. Cycle 1, Day 1: pre treatment
2. Cycle 1, Day 8: prior to starting vitamin D3
3. Cycle 2, Day 1: after treatment with both curcumin and vitamin D3

10.1.4 Handling of Specimens

All specimens are to be shipped to the TRPC at the address below.

Translational Research & Pharmacology Core
ATTN Erin Hohler
University Hospitals of Cleveland
11100 Euclid Avenue
Seidman Cancer Center, Room 3608
Cleveland, OH 44106
Telephone: 216-286-3889/216-386-3890
Fax: 216-286-5772
Pager: 33471
E-mail: emh14@case.edu

TRPC Personnel will log the specimen information into the OnCore database and de-identify the specimen using a code specific for this trial.

PBMCs will be isolated by standard Ficoll-Hypaque methods, counted and re-suspended in 90% fetal bovine serum, 10% DMSO at 10 million cells/ml. Cells will be aliquoted into 3 equal portions into cryopreservation tubes and labeled with identifier, cell number, and volume. Cells will be frozen using a controlled rate freezing container and stored at -70 C (in liquid nitrogen) until analyzed.

Specimens will be transported to the Case Comprehensive Cancer Center Cytometry Core Facility Laboratory for analysis upon request of the Principle Investigator.

If the sample is collected at an outside laboratory then it should be transported at room temperature as soon as possible to the TRPC by the rapid hospital courier service.

10.1.5 Analytical Laboratory

The specimens will be analyzed in the Case Comprehensive Cancer Center Cytometry Core Facility, under the direction of Dr. James Jacobberger. Dr. Jacobberger will provide overall guidance on experimental design and interpretation of results. Personnel in the Cytometry Core Facility will perform all staining, cytometry and analysis.

Case Comprehensive Cancer Center Cytometry Core Facility
2103 Cornell Rd, WRB-3517
Cleveland, OH 44106
Contact: R. Michael Sramkoski
Telephone: (216)368-1021
Email: rms19@case.edu

10.1.6 Correlative Methods

Cells will be rapidly thawed and re-suspended in FBS.

Cells will be processed and stained using the Woost modifications of the Chow protocol without methanol.

Surface staining for CD19 will be performed to identify CLL cells. (86).

Cells will be analyzed using the following antibodies:

1. Vitamin D receptor: Cell Signaling Technology #12550 (Rabbit mab D2K6W)
2. PE-CD3
3. PerCp or V500-CD19
4. PerCp or Krome Orange CD45

10.2 **Pharmacodynamic analysis of NF-κB and bcl-2 in CLL cells**

10.2.1 Background

The purpose of this study is to evaluate the effect of curcumin and curcumin/vitamin D combination on NF-κB signaling in CLL cells. NF-κB is the main target of curcumin in cancer cells and curcumin was shown to downregulate NF-κB levels in CLL cells (25-28). Both curcumin and vitamin D3 were shown to induce apoptosis in CLL cell lines. The purpose of this analysis is exploratory/proof of concept.

10.2.2. Rationale for Analysis

Inhibition of NF-κB signaling was validated as a pharmacodynamic endpoint for curcumin treatment in prior clinical investigations (32). Bcl-2 is a master regulator of apoptosis in CLL cells (87) and would be of interest to quantitate bcl-2 expression with curcumin +/- vitamin D3 treatment as both agents may be synergistic in inducing apoptosis in CLL cells. Curcumin and 1,25-dihydroxyvitamin D3 were already shown to downregulate bcl-2 in other cellular systems leading to apoptosis (88-90). Quantitative intracellular measurement of NF-κB and bcl-2 by flow cytometry, in peripheral blood mononuclear cells, has been performed and validated by other investigators before (91, 92). This purpose of this analysis is

exploratory/proof of concept. Subjects with SLL with no peripheral blood lymphocytosis will be excluded from this analysis.

10.2.3 Collection of Specimens

About 4-5 ml of blood will be drawn into 1 green-topped tube (containing heparin). The tube will be kept at ambient temperature and will be delivered to the TRPC laboratory within 3 hours of venipuncture. Blood samples will be drawn at the following 3 times points:

1. Cycle 1, Day 1: pre treatment
2. Cycle 1, Day 8: prior to starting vitamin D3
3. Cycle 2, Day 1: after treatment with both curcumin and vitamin D3

10.1.4 Handling of Specimens

All specimens are to be shipped to the TRPC at the address below.

Translational Research & Pharmacology Core
ATTN Erin Hohler
University Hospitals of Cleveland
11100 Euclid Avenue
Seidman Cancer Center, Room 3608
Cleveland, OH 44106
Telephone: 216-286-3889/216-386-3890
Fax: 216-286-5772
Pager: 33471
E-mail: emh14@case.edu

TRPC Personnel will log the specimen information into the OnCore database and de-identify the specimen using a code specific for this trial.

PBMCs will be isolated by standard Ficoll-Hypaque methods, counted and re-suspended in 90% fetal bovine serum, 10% DMSO at 10 million cells/ml. Cells will be frozen using a controlled rate freezing container and stored at -70 C until analysis.

Specimens will be transported to the Case Comprehensive Cancer Center Cytometry Core Facility Laboratory for analysis upon request of the Principle Investigator.

If the sample is collected at an outside laboratory then it should be transported at room temperature as soon as possible to the TRPC by the rapid hospital courier service.

10.1.5 Analytical Laboratory

The specimens will be analyzed in the Case Comprehensive Cancer Center Cytometry Core Facility, under the direction of Dr. James Jacobberger. Dr. Jacobberger will provide overall guidance on experimental design and interpretation of results. Personnel in the Cytometry Core Facility will perform all staining, cytometry and analysis.

Case Comprehensive Cancer Center Cytometry Core Facility
2103 Cornell Rd, WRB-3517
Cleveland, OH 44106
Contact: R. Michael Sramkoski
Telephone: (216)368-1021
Email: rms19@case.edu

10.1.6 Correlative Methods

Cells will be rapidly thawed and re-suspended in FBS.

Cells will be processed and stained using the Woost modifications of the Chow protocol without methanol (93)
Surface staining for CD19 will be performed to identify CLL cells. (86).

Cells will be washed then analyzed by flow cytometer for quantitative estimation of for intracellular NF-κB and bcl-2 (91, 92).

Cells will be analyzed using the following antibodies:

1. NF-kB, Depending on assay need:
   a. Biolegend 616704 (A488 mouse mab) for p50
   b. CST #4886 (A488 rabbit mab) for phospho-S536-p65
   c. BD Biosci #558421 (A488 mouse mab) for phospho-S529-p65
   d. BD Biosci #610868 (mouse mab) for p65
2. Bcl2: Depending on assay:
   a. BD Biosci #610539 (mouse mab, clone 7)
   b. BD Biosci #560637 (V450 mouse mab, clone 100)
   c. Biolegend #BCL/10C4 (A647 mouse mab, clone 10C4)
3. PE-CD3
4. PerCp or V500-CD19
5. PerCp or Krome Orange CD45

10.3 Curcumin and vitamin D3 pharmacokinetics

The purpose of this study is to measure standard pharmacokinetic parameters of curcumin and vitamin D in blood in all study subjects. For subjects with CLL, this data will also be integrated with pharmacodynamic parameters described above to determine the relationship between circulating drug levels and effects on VDR, NF-κB, and bcl-2. The purpose of this analysis is exploratory/proof of concept.

10.3.1 Background

Despite the use of doses of curcumin as high as 8 g/d in humans, very little free curcumin is typically found in patient plasma samples (43, 94). Rather, curcumin is present in plasma in conjugated (glucuronide and sulfate) forms, thereby necessitating appropriate enzymatic hydrolysis of the plasma before detection of free curcumin (95).

10.3.2. Rationale for Analysis

Pharmacokinetic analysis of free curcumin with mass spectroscopy in human plasma, post oral administration, after appropriate enzymatic hydrolysis of the plasma has performed and validated before by different investigators (32, 43, 94). Since there is little or no correlation between plasma levels and effect (32, 96), there is little utility in performing intensive pharmacokinetic analysis. Vitamin D3 25OH (25-hydroxycholecalciferol) levels will be measured by liquid chromatography tandem-mass spectrometry (97). Serum levels of 25-hydroxycholecalciferol has been validated as reflective of whole-body vitamin D stores and are used clinically to define vitamin D adequacy, deficiency, and toxicity (98). As we don't know how curcumin influences vitamin D metabolism, and vice versa, will assess curcumin and 25-hydroxycholecalciferol levels in plasma before treatment, one week after treatment with curcumin and before starting vitamin D3, and 3 weeks after treatment with both agents. No adjustment in dose or stopping of vitamin D is planned based on vitamin D OH level for 3 reasons: (1) The assay used to monitor vitamin D level is for research purposes and isn't a CLIA-certified assay; (2) We are not running samples in real time to make such clinical decisions; samples will be batch-assayed; (3) There is very little correlation between vitamin D levels and actual toxicity. Vitamin D toxicity is a clinical diagnosis and a normal serum calcium level excludes the diagnosis of vitamin D toxicity (please refer to section 8.1.1 for further details).

10.3.3 Collection of Specimens

About 4-5 ml of blood will be drawn into 1 green-topped tube (containing heparin). The tube will be kept at ambient temperature and will be delivered to the TRPC laboratory within 3 hours of venipuncture. Blood samples will be drawn at the following 3 times points:

1. Cycle 1, Day 1: pre treatment
2. Cycle 1, Day 8: prior to starting vitamin D3
3. Cycle 2, Day 1: after treatment with both curcumin and vitamin D3

10.3.4 Handling of Specimens

All specimens are to be shipped to the TRPC at the address below.

Translational Research & Pharmacology Core
ATTN Erin Hohler
University Hospitals of Cleveland
11100 Euclid Avenue
Seidman Cancer Center, Room 3608
Cleveland, OH 44106
Telephone: 216-286-3889/216-386-3890
Fax: 216-286-5772
Pager: 33471
E-mail: emh14@case.edu

TRPC Personnel will log the specimen information into the OnCore database and de-identify the specimen using a code specific for this trial.

Plasma will be isolated by standard methods, aliquoted into cryovials (0.5ml/tube) and frozen at -70 C until analysis.

Specimens will be transported to the Case Comprehensive Cancer Center Pharmacology Core Facility Laboratory for analysis upon request of the Principle Investigator.

If the sample is collected at an outside laboratory then it should be transported at room temperature as soon as possible to the TRPC by the rapid hospital courier service.

10.3.5 Analytical Laboratory

All pharmacokinetic studies will be performed by the Case Comprehensive Cancer Center Pharmacology Core Facility Laboratory. Pharmacokinetic analysis of free curcumin with mass spectroscopy in human plasma, post oral administration, after appropriate enzymatic hydrolysis of the plasma has performed and validated before by different investigators (32, 43, 94). The Case Comprehensive Cancer Center Pharmacology Core Facility Laboratory has already developed, and validated, a method for analysis of 25-hydroxycholecalciferol *(Yan Xu, Ph.D. personal communication)*

The Case Cancer Pharmacology Core
11001 Cedar Avenue, Suite 200
Cleveland, OH 44106
Contact: Yan Xu Ph.D.
Telephone: (216) 832-0010
Email: y.xu@csuohio.edu

10.4 **Quality of Life Assessments**

The purpose of this correlative study is to measure the impact of curcumin and curcumin/vitamin D combination on quality of life (QOL) of patients with early stage CLL.

10.4.1 Background and Rationale

Shanafelt et al. has demonstrated that CLL, at all stages, has a negative impact on QOL; the emotional well-being scores of CLL patients were dramatically lower than that of both the general population and patients with other types of cancer in analysis of 1482 patients (99). There is no intervention that has been shown to improve QOL in CLL patients. There is anecdotal evidence that curcumin and vitamin D improve QOL in cancer patients (100-103). Patients enrolled on the trial so far have reported improvement in their fatigue and overall sense of well-being.

10.4.2 Measurement

We propose using the Functional assessment of chronic illness therapy- Lymphoma (FACT-Lym) questionnaire to assess QOL at baseline (within 2 weeks before starting C1 D1) and at end of treatment (within 2 weeks of discontinuation of study medication). Patients who are responding and will go on the 2 year continuation phase will take the FACT-Lym questionnaire within 2 weeks before starting C7 D1 and at the end of treatment. The FACT-Lym (appendix G) is a short, well-validated QOL measure has a general module (FACT-G)

with four subscales: physical, social/family, emotional and functional (104). The FACT-Lym was validated in indolent non-Hodgkin's lymphoma (which has a biology similar to CLL/SLL) and in CLL (105). Each of the four different subscales will be analyzed individually and the composite scale with 10% improvement after treatment considered significant based on prior published literature (106)

10.5 **Additional Correlative Studies**

Study has been closed to accrual on 4/12/2016 at University Hospitals. Frozen plasma/serum and peripheral blood mononuclear cells will be shipped to Dr Basem William at the Ohio State University, former PI on the trial, to undertake further analysis of inflammatory cytokines and exosomes, under a material transfer agreement (MTA). Dr William will have no access to patient identifying information and the generated research data set will be linked to clinical dataset through a unique patient number. They key linking datasets will be maintained at University Hospitals. The planned studies do not include any genetic analysis. Samples would be shipped to:

Leukemia Tissue Bank Shared Resource
334 Tzagournis Research Facility
420 W. 12th Ave.
Columbus, Ohio 43210

11.0 STUDY PARAMETERS AND CALENDAR

11.1 **Study Parameters**

11.1.1 **Screening Evaluation**

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed $\leq$ 30 days prior to administration of protocol therapy. Bone marrow biopsy, flow cytometry, cytoegenetics, and interphase FISH performed up to 5 years prior to enrollment are acceptable.

- Informed Consent
- Demographics
- Medical History
- Complete physical examination including lymph node measurements (all palpable lymph nodes will be measured in greatest dimension and documented)
- Height
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- ECOG Performance status $\leq$ 2
- Baseline Symptoms Assessment
- Laboratory Studies:

- Complete Blood Count (CBC) with differential and platelets. Absolute lymphocyte count (ALC) will be calculated from CBC and differential
- Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
- Vitamin D 25(OH) level; standard of care test (63).
- Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
- ß-HCG for women of childbearing potential

- CT scan of chest, abdomen, and pelvis (with and without contrast) will be performed in subjects with SLL who don't have ALC<5000 and non-measurable peripheral adenopathy. MRI may be performed if subject has allergy to iodinated contrast media
- Bone Marrow Biopsy is **optional** and not required prior to enrollment in study
- Peripheral blood flow cytometry (unless already performed on bone marrow biopsy)
- Peripheral blood cytogenetics including interphase FISH analysis for chromosome 11, 12, 13, and 17 abnormalities (unless already performed on bone marrow biopsy)

11.1.2 **Treatment Period**

Treatment cycles are 28 days long.
A visit window of ± 3 days is allowed for chemistry and hematology labs
A visit window of ± 7 days is allowed for 3 month and long term follow-up visits.
A visit window of ± 3 days is allowed for physical exams.

Cycle 1, Day 1

Cycle 1, Day 1 evaluations do not need to be repeated if screening evaluations were conducted within 2 weeks prior to administration of protocol therapy.

- Physical Examination including lymph node measurements (all palpable lymph nodes will be measured in greatest dimension and documented)
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- ECOG Performance status ≤ 2
- Baseline Symptoms Assessment
- **Laboratory Studies:**
  - Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
  - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
  - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
  - ß-HCG for women of childbearing potential
  - Vitamin D 25(OH) level.

- **Correlative Studies:**
    - Vitamin D receptor (VDR); by flow cytometry (only in subjects with CLL)
    - NF-κB; by flow cytometry (only in subjects with CLL)
    - bcl-2; by flow cytometry (only in subjects with CLL)
    - Curcumin and vitamin D 25(OH) plasma level [PK]
- Curcumin dispensed to start on Day 1
- Pill diary distributed on Day 1

Cycle 1, Day 8

- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- ECOG Performance status $\leq$ 2
- Adverse events assessment
- **Laboratory Studies:**
    - Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
- **Correlative Studies:**
    - Vitamin D receptor (VDR); by flow cytometry (only in subjects with CLL)
    - NF-κB; by flow cytometry (only in subjects with CLL)
    - bcl-2; by flow cytometry (only in subjects with CLL)
    - Curcumin and vitamin D 25(OH) plasma level [PK]
- Vitamin D3 dispensed to start on Day 8

Cycle 2, Day 1

- Physical Examination including lymph node measurements (all palpable lymph nodes will be measured in greatest dimension and documented)
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- ECOG Performance status $\leq$ 2
- Adverse events assessment
- **Laboratory Studies:**
    - Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium

    - Vitamin D 25(OH) level *(as clinically indicated if there are signs of vitamin D toxicity or if calcium level, corrected to serum albumin, is >11 mg/dL)*
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
- **Correlative Studies:**
    - Vitamin D receptor (VDR); by flow cytometry (only in subjects with CLL)
    - NF-κB; by flow cytometry (only in subjects with CLL)
    - bcl-2; by flow cytometry (only in subjects with CLL)
    - Curcumin and vitamin D 25(OH) plasma level [PK]
- Curcumin and vitamin D3 [4 week supply dispensed to start on Day 1]
- Pill diary collected and new diary distributed

Cycles 3-6, Day 1

- Physical Examination including lymph node measurements (all palpable lymph nodes will be measured in greatest dimension and documented)
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- ECOG Performance status $\leq$ 2
- Adverse events assessment
- **On cycle 3 D1 only** (+/- 3 days for flexibility of scheduling): CT scan of chest, abdomen, and pelvis (with and without contrast) will be performed in subjects with SLL who don't have ALC<5000 and non-measurable peripheral adenopathy. MRI may be performed if subject has allergy to iodinated contrast media. Purpose of this study is to assess response to treatment.
- **Laboratory Studies:**
    - Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
    - Vitamin D 25(OH) level *(as clinically indicated if there are signs of vitamin D toxicity or if calcium level, corrected to serum albumin, is >11 mg/dL)*
- Curcumin and vitamin D3 [4 week supply dispensed to start on Day 1]
- Pill diary collected and new diary distributed

Cycles ≥7 up to 2 years, Day 1 (for patients attaining a partial response or better)

- Physical Examination including lymph node measurements (all palpable lymph nodes will be measured in greatest dimension and documented)
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate

- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- ECOG Performance status $\leq$ 2
- Adverse events assessment
- **Laboratory Studies:**
    - Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - Vitamin D 25(OH) level *(as clinically indicated if there are signs of vitamin D toxicity or if calcium level, corrected to serum albumin, is >11 mg/dL)*
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
- Curcumin and vitamin D3 [4 week supply dispensed to start on Day 1]
- Pill diary collected and new diary distributed

End of Treatment Visit (within 1 week of discontinuation of study medications)

- Physical Examination including lymph node measurements (all palpable lymph nodes will be measured in greatest dimension and documented)
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- ECOG Performance status $\leq$ 2
- Adverse events assessment
- Pill diary collected
- **Laboratory Studies:**
    - Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
    - ß-HCG for women of childbearing potential
    - Vitamin D 25(OH) level (as clinically indicated if there are signs of vitamin D toxicity or if calcium level, corrected to serum albumin, is >11 mg/dL)

30 Day Follow-Up

- Physical Examination including lymph node measurements (all palpable lymph nodes will be measured in greatest dimension and documented)
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate

- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- ECOG Performance status ≤ 2
- Adverse events assessment
- **Laboratory Studies:**
    - Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
    - Vitamin D 25(OH) level *(as clinically indicated if there are signs of vitamin D toxicity or if calcium level, corrected to serum albumin, is >11 mg/dL)*

Long Term Follow-Up (for 2 years after discontinuation of study medications, every 3-6 months as clinically indicated)

- Physical Examination including lymph node measurements (all palpable lymph nodes will be measured in greatest dimension and documented)
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- ECOG Performance status ≤ 2
- Adverse Events Assessment
- **Laboratory Studies:**
    - Complete Blood Count (CBC) with differential and platelets
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.

11.2 Calendar

Screening studies will studies are to be conducted within 30 days prior to administration of protocol therapy. Exception: Bone marrow biopsy, flow cytometry, cytometry, cytoegenetics, and interphase FISH performed up to 5 years prior to enrollment

Study Days	Pre-Study	Cycle 1 Day 1[b]	Cycle 1 Day 8	Cycle 2 Day 1	Cycles 3-6 Day 1	Cycles 7+ Day 1[f]	End of Treatment	30 Day Follow Up[i]	Long term Follow-Up[g,i]
REQUIRED ASSESSMENTS									

Informed Consent	X								
Demographics	X								
Medical History	X								
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Vitals (blood pressure, pulse, temperature, and respiratory rate)	X	X	X	X	X	X	X	X	X
Physical Examination[i]	X	X		X	X	X	X	X	X
Concomitant Medication Assessment	X	X		X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	X	X	X
Baseline Symptoms	X	X							
Adverse Event Assessment			X	X	X	X	X	X	X
Peripheral blood flow cytometry	X								
Peripheral blood cytogenetics and FISH	X								
CBC / diff / platelets[i]	X	X	X	X	X	X	X	X	X
Serum Chemistry [a, i]	X	X	X	X	X	X	X	X	X
ß-HCG, women of childbearing potential	X	X					X		
Vitamin D 25(OH) level	X	X*		X*	X*	X*	X*	X	
DISEASE ASSESSMENT									
Lymph node measurement	X	X		X	X	X	X	X	X
CT chest/abdomen/pelvis[c]	X				X				
Bone marrow biopsy (optional)	X								
MISC ITEMS									
Pill Diary		X		X	X	X	X		
TREATMENT									
Curcumin									
Vitamin D3									
CORRELATIVE STUDIES									
Pharmacokinetic Sampling[d]		X	X	X					
Flow cytometry[e]		X	X	X					
Quality of life questionnaire	X[h]						X[h]		

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal. **[UH: Order COMP2]**
b: Cycle 1, Day 1 evaluations do not need to be repeated if screening evaluations were conducted within 2 weeks prior to administration of protocol therapy
c: In subjects with SLL who have ALC<5000 and non-measurable peripheral adenopathy
d: Plasma level of curcumin and vitamin D 25(OH)
e: For vitamin D receptor, NF-κB, and bcl-2, CLL patients only
f: For patients attaining a partial response or better
g: Every 3-6 months as clinically indicated
h: Utilizing FACT-Lym questionnaire (appendix G) within 2 weeks prior to start of treatment and within 2 weeks of discontinuation of study medications. Patients who are responding and will go on the 2 year continuation phase will take the FACT-Lym questionnaire within 2 weeks before starting C7 D1 and at the end of treatment.
i. +/- 3 day window
*: As clinically indicated if there are signs of vitamin D toxicity or if calcium level, corrected to serum albumin, is >11 mg/dL

MEASUREMENT OF EFFECT

12.1 Response Criteria for CLL; based on NCI-WG (107)

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

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4000/_L).
- Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination.
- No hepatomegaly or splenomegaly on physical exam;
- Absence of constitutional symptoms;
- Normal CBC as exhibited by polymorphonuclear leukocytes > 1500/µL, platelets > 100,000/µL, hemoglobin > 11.0 g/dl (untransfused)
- Bone marrow aspirate and biopsy must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment.
- Patients who fulfill the criteria for CR after induction with the exception of a persistent cytopenia that is believed to be treatment related will be considered a partial response. Additionally, patients who fulfill the criteria of CR with exception of having bone marrow lymphoid nodules will be considered a partial response. Patients who fulfill the criteria of CR but declined having a bone marrow biopsy will be considered be in PR.

Partial response requires a > 50% decrease in peripheral lymphocyte count from pre-treatment value, > 50% reduction in lymphadenopathy, and/or > 50% reduction in

splenomegaly/ hepatomegaly for a period of at least two months from completion of therapy. All lymph nodes will be measured bi-dimensionally and the sums of these added to determine if 50% or greater reduction has occurred.

Additionally, these patients must have one of the following:

- 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 (untransfused) or 50% improvement from pretreatment value.

Progressive Disease is characterized by any one of the following events:

- >50% increase in the products of at least two lymph nodes (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.
- >50% increase in the absolute number of circulating lymphocytes to at least 5,000/µL.
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with > 55% prolymphocytes).
- 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 and of underlying CLL. A bone marrow biopsy in such settings is strongly encouraged.

Stable Disease includes 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.

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100 000/μL	> 100 000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/μL	> 1500/μL or > 50% improvement over baseline	

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

*CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.

†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

‡These parameters are irrelevant for some response categories.

12. 2 Definitions for SLL with radiographically measurable lesions

- **Measurable disease**: the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

- **Measurable lesions** - defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (PET, CT,) or as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- **Baseline documentation of "Target" lesions** - all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (determining the product obtained from the longest diameter of two perpendicular measurements) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the products of the longest perpendicular dimensions (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

- **Non-target lesions** - All other lesions (or sites of disease) should be identified as

non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.3 Response Criteria for SLL; based on Cheson criteria (108)

The criteria for NHL are as follows (GTD = Greatest Transverse Diameter; SPD = Sum of the Products of the Greatest Diameter):

Complete Remission (CR):

- Disappearance of all evidence of disease.
- No disease related symptoms.
- Lymph nodes, nodal masses regressed to "normal" size:
  - If >1.5 cm before treatment, regressed to ≤ 1.5 cm in GTD.
  - If 1.1 to 1.5 cm before treatment, regressed to ≤ 1 cm in GTD (or >75% in SPD). If PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Spleen and all previously enlarged organs decreased to normal in size.
- If the Bone marrow was involved prior to treatment, it is clear on repeat aspirate and biopsy at the same site.

Partial Remission (PR)

- ≥ 50% decrease in SPD of six largest dominant nodes/nodal masses.
- No increase in size of other nodes, liver or spleen.
- Splenic and hepatic nodes regressed at least 50% in SPD
- No new sites of disease.
- If the PET scan was positive before therapy, the post-treatment PET is positive in at least one previously involved site.
- Patients who achieve a CR by the above criteria, but who have persistent bone marrow involvement (or those in whom pre-treatment bone marrow was involved and post-treatment bone marrow involvement was not assessed).

Relapsed Disease (RD)

- In patients previously CR or CRu:
- New lesion > 1.5 cm in any axis
- Size of previously involved site has increase ≥ 50% in GTD.
- ≥ 50% in either:
  - GTD of any previously identified node that was >1 cm in its short axis, or
  - SPD of any node or other lesion.

Stable Disease (SD)

- Patients who have achieved less than a partial remission but who have not

developed findings consistent with progressive disease.

Progressive Disease (PD)

- In patients previously PR or SD.
- ≥ 50% increase from nadir or baseline in SPD or any node or lesion
- ≥ 50% increase from nadir in GTD of any node previously >1cm in shortest diameter
- Appearance of any new lesion during or at the end of therapy.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: Patients with a global deterioration of their health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

12.4 Biologic response criteria CLL and SLL (78)

Given the favorable toxicity profile of curcumin and vitamin D3 in healthy adults and the intention to evaluate the efficacy of both agent to delay or prevent PD in patients with CLL/SLL, we also evaluated an additional response category termed ‘‘biologic response’’ among patients who did not meet standard NCI-WG criteria for CR and PR. The criteria for a biologic response were prospectively defined in a recent study of Polyphenon E, after discussion and approval of the NCI. Polyphenon E, very much like curcumin and vitamin D3, is the most active ingredient in green tea extract and it works through unique, noncytotoxic mechanisms. Biologic response was defined as a reduction in the absolute lymphocyte count (ALC) of > 20% from the pretreatment level that was sustained for at least 2 months or a ≥ 30% reduction in all palpable lymphadenopathy (78).

12.5 Duration of Response

Duration of overall response:

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease:

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.6 Progression-free survival (PFS)

Progression-free Survival (PFS) is defined as the time from entry onto study until CLL/SLL progression or death from any cause. PFS is often considered the preferable endpoint in lymphoma clinical trials, especially those involving incurable histologic subtypes (e.g., follicular and low grade, mantle cell lymphoma). PFS reflects tumor growth and, therefore, occurs prior to the endpoint of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. Whether a prolongation of PFS represents direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit ratio of the therapy under investigation. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. Where there is missing information, censoring of the data may be defined as the last date at which progression status was adequately assessed.

12.7 Time to first cytotoxic treatment (TFCT)

Time to first cytotoxic treatment (TFCT) is defined as the time from entry onto study until initiation of treatment with cytotoxic agents because of disease progression. As curcumin and vitamin D3 combination has the potential for delaying disease progression, or maintaining stable disease, TFCT is a clinically meaningful end-point of these patients.

13.0 RECORDS TO BE KEPT / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 **Data Reporting**

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

13.2 **Regulatory Considerations**

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical

information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Accessing Electronic Medical Records for University Hospitals Health System

This study will access electronic medical records systems to obtain medical information for the subjects enrolled to this study.

In order to insure patient safety, investigators and study personnel must have up-to-the-minute health information for subjects enrolled to this study. Therefore, electronic medical records must be utilized to obtain medical information in a timely manner.

The following electronic systems will be used: Athena program to access scheduling information; UH Physician Portal to access lab results and physician notes; PCOSS LITE as necessary to locate archived medical records; COPATH to locate archived pathology records; PACS to access radiological imaging results; and MySecureCare (Sunrise Clinical Manager) to access some or all of the above information when this application is fully functional.

Access to these systems is required for the life of this research study.

Information obtained from electronic systems will be copied into the Seidman Cancer Center Clinical Trials Unit research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to UH policy.

Study data will be obtained by the PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login.

13.2.4 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.5 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.2.6 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

The primary endpoint of this trial will be the overall response rate (biologic response rate+CR + PR; CR/PR are based on NCI-WG (for CLL) and Cheson criteria (for SLL). The point estimate of the overall response rate and biologic response rate along with 95% confidence intervals will be calculated using binomial distribution theory. The secondary efficacy variables of: Time to first cytotoxic treatment (TFCT), progression free survival (PFS) and overall survival (OS) will be estimated using Kaplan-Meier method and displayed graphically. Duration of response will also be calculated as a secondary variable of efficacy.

14.2 Sample Size/Accrual Rate

The sample size is calculated for a single arm, Simon optimal 2-stagephase II deign. The design to test the null hypothesis that $P \leq 0.1$ versus the alternative that $P \geq 0.3$ has a sample size of 29 and a probability of early termination of 0.74 under the null. The power is 0.8 with statistical significance declared at an alpha level of 0.05. An accrual goal of 35 patients will be enrolled in this study to allow 20% ineligibility or drop outs. According to the Simon 2-stage method, 10 patients will be accrued initially during stage I. If there is evidence of clinical benefit, the remaining 25 patients will be enrolled during stage II. For the purpose of stopping the trial for futility, clinical benefit is defined as biologic response or better (please refer to section 12.4 for the definition of biologic response).

In the planned Simon 2-Stage analysis, 10 patients will be enrolled in stage I. An interim analysis will be performed after the 10th patient completes the induction therapy period. If 1 or fewer patients exhibit clinical benefit (biologic response or better), the trial will be stopped. If 2 or more patients demonstrate clinical benefit, the study will proceed to stage II and an additional 19 patients will be enrolled and treated. If the trial goes on to the second stage, a total of 29 eligible patients will be studied. If the total number responding is less than or equal to 5, the drug combination is considered not worth further exploration. The entire study group of 35 patients will be evaluated in the final analysis.

14.3 Analysis of Secondary Endpoints

The secondary endpoints include Time to first cytotoxic treatment (TFCT), progression free survival (PFS) and overall survival (OS). For those time-to-event endpoints, Kaplan-Meier method and Cox proportional hazard model will be used for the data analysis. Potential prognostic factors will be correlated with conversion status by Fisher's exact test or Chi-square test, logistic regression will be used to assess the effect on conversion from the combination of multiple factors.

14.4 Reporting and Exclusions

14.4.1 Evaluation of toxicity:

All patients will be evaluable for toxicity from the time of their first treatment. All patients treated with curcumin and vitamin D3 will be included in safety summaries and analyses from the time of first treatment. The safety and tolerability of curcumin and vitamin D3 will be

examined by: extent of exposure to treatment (dose, duration, and number of patients), and a detailed examination of adverse events, laboratory test results, vital signs, and physical findings.

Our planned sample number is 35 evaluable patients, but if there is evidence of toxicity as high as 20% DLTs the study will be terminated within the first 20 patient cohort. If ever 2 of the initial 10 patients exhibit DLT the study will be terminated. If ever 5 of the entire 35 patients exhibit DLT the treatment will be considered too toxic. These rules imply 84% power with 9.9% type I error to distinguish a 20% DLT rate from one not over 8%. The chance of early termination under the hypothesis of 20% DLT is 37%. The chance of early termination in error is 1.8%.

14.4.2 Evaluation of response:

Subjects need to have received 2 or more cycles of treatment to be evaluable for response. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

14.4.3 Expected Accrual

Those patients are typically managed by watchful waiting and are typically under-represented in clinical trials as they are perceived to have good prognosis. We expect to enroll 10-15 patients per year on this study.

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APPENDIX A

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS CRITERIA

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

INDICATIONS FOR TREATMENT PER NCI-WG CRITERIA FOR CLL (107)

1. A minimum of any one of the following disease-related symptoms must be present:
    a. Weight loss >= 10% within the previous 6 months.
    b. Extreme fatigue (ie, ECOG PS 2 or worse; cannot work or unable to perform usual activities).
    c. Fevers of greater than 100.5°F for >= 2 weeks without evidence of infection.
    d. Night sweats without evidence of infection
2. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/ or thrombocytopenia
3. Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy
4. Massive (ie, >6 cm below the left costal margin) or progressive splenomegaly
5. Massive nodes or clusters (ie, >10 cm in longest diameter) or progressive lymphadenopathy
6. Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of less than 6 months
7. Marked hypogammaglobulinemia or the development of a monoclonal protein in the absence of any of the above criteria for active disease is not sufficient for protocol therapy

APPENDIX C
PATIENT PILL DIARY FOR CYCLE 1

Patient Name _____Protocol #_____ Patient Study ID _____
Cycle #: _____ Month #: _____

INSTRUCTIONS FOR THE PATIENT:

1. You will take 8 tablets of 1000 mg *curcumin* pills each day with or without food with a full glass (8 oz of water).
2. You will take 1 tablet of 10,000 IU *vitamin D3* pills each day with or without food with a full glass (8 oz of water) starting 1 week after you start taking curcumin and continuously thereafter.
3. Record the date, the number of tablets you took, and what time you took them.
4. If you have any comments please record them in the "Comments" column below.
5. Please bring your pill bottle and this form to your physician when you come for your next appointment.
6. Please sign your name at the bottom of the diary.

Date	Day	**8 tablets of** 1000 **mg** *curcumin* **pills and time taken**	**1 tablet of** 10,000 **IU** *vitamin D3* **pills and time taken**	Comments
	1		[redacted]	
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	13			
	14			
	15			
	16			
	17			
	18			
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	21			
	22			
	23			
	24			
	25			
	26			
	27			
	28			

Patient's Signature: _____ Date: _____

APPENDIX D

PATIENT PILL DIARY FOR CYCLES 2-6

Patient Name _____Protocol #_____ Patient Study ID _____

Cycle #: _____ Month #: _____

INSTRUCTIONS FOR THE PATIENT:

1. You will take 8 tablets of 1000 mg *curcumin* pills each day with or without food with a full glass (8 oz of water).
2. You will take 1 tablet of 10,000 IU *vitamin D3* pills each day with or without food with a full glass (8 oz of water) 3. Record the date, the number of tablets you took, and what time you took them.
4. If you have any comments please record them in the "Comments" column below.
5. Please bring your pill bottle and this form to your physician when you come for your next appointment.
6. Please sign your name at the bottom of the diary.

Date	Day	**8 tablets of** 1000 **mg** *curcumin* **pills and time taken**	**1 tablet of** 10,000 **IU** *vitamin D3* **pills and time taken**	Comments
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	13			
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	25			
	26			
	27			
	28			

Patient's Signature: _____ Date: _____

APPENDIX E
POTENTIAL CYP3A4 AND CYP2A6 INTERACTIONS

CYP1A2 Substrates	CYP1A2 Inducers	CYP1A2 Inhibitors
Alosetron	Barbiturates	Artemisinin
Caffeine	Carbamazepine	Atazanavir
Clozapine	Primidone	Cimetidine
Flutamide	Rifampin	Ciprofloxacin
Frovatriptan	Nicotine	Enoxacin
Melatonin		Ethinyl Estradiol
Mexiletine		Fluvoxamine
Mirtazapine		Mexiletine
Olanzapine		Tacrine
Ramelteon		Thiabendazole
Rasagiline		Zileuton
Ropinirole		
Tacrine		
Theophylline		
Tizanidine		
Triamterene		
Zolmitriptan		
CYP2A6 Substrates	**CYP2A6 Inducers**	**CYP2A6 Inhibitors**
Halothane	Grapefruit juice	Phenobarbital
Losigamone	Ketoconazole	Rifampicin
Methoxyflurane	Methoxsalen	
Cotinine	Pilocarpine	
Nicotine	Tranylcypromine	
Valproic acid	Isoniazid	

APPENDIX F

POTENTIAL CYP3A4 INTERACTIONS

CYP3A4 Inhibitors

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit Juice(2)	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranylcypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic Acid
Cyclophosphamide	Indinavair	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delvirdine	Itraconazole	Pilocarapine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

APPENDIX F (continued)

POTENTIAL CYP3A4 INTERACTIONS

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's Wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

When drugs classified as 'substrates' are co-administered with *(Study Agent)*, there is the potential for higher concentrations of the 'substrate'. When *(Study Agent)* is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of *(Study Agent)* is the potential outcome. The co-administration of 'inducers' would potentially lower plasma *(Study Agent)* concentrations.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.
Only major substrates and effective inducers are listed.
Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

(1) Investigator's Brochure: Dasatinib (BMS 354825). Bristol-Myers Squibb. October 2006.

(2) Malhotra *et al*. (2001). Clin Pharmacol Ther. 69:14-23.

(3) Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249.

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Updated on May 1, 2007

APPENDIX G

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

APPENDIX G (continued)

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

APPENDIX G (continued)

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin).....	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness.....	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment.....	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4