Ofatumumab Early Treatment for High-Risk, Treatment-Naïve, Early Stage (0-II) Patients with Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Leukemia (SLL)

Version 8

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Short Title: Ofatumumab for High-Risk CLL/SLL

1.0 OBJECTIVES

Primary objective:

1. Determine the response rate (2008 IWCLL/NCI-WG criteria) to treatment with single-agent ofatumumab in previously untreated, early-stage, high-risk patients with CLL/SLL.

Secondary objectives:

1. Determine the time-to-progression for high-risk patients treated with ofatumumab.
2. Determine the time-to-next chemoimmunotherapy or alternative therapy.
3. Evaluate the pharmacokinetics of single-agent ofatumumab in high-risk, previously untreated patients with CLL/SLL.
4. Evaluate for circulating $CD20^+$ cells through treatment and in follow-up in high-risk patients treated with ofatumumab.
5. Evaluate safety and toxicities of ofatumumab in previously untreated high-risk patients with CLL/SLL.

2.0 BACKGROUND

Rationale

Ofatumumab has significant single-agent activity in treating patients with CLL refractory to fludarabine and alemtuzumab (FA-ref) and fludarabine-refractory patients with bulky (>5cm) lymph nodes (BF-ref), as demonstrated by the interim analysis of the pivotal trial[1]. The overall response rate (ORR) for FA-ref (n=59) and BF-ref (n=79) was 58% and 47%, respectively. The median duration of response (median) for both populations was approximately 6 months. Treatment with ofatumumab was very well tolerated. This fully human monoclonal antibody against CD20 binds to a unique epitope composed of the small- and large-loop domains and is highly effective at fixing complement for complement-dependent cytotoxicity (CDC). *In vitro* studies demonstrated higher levels of CDC against primary CLL cells and cell lines with ofatumumab compared to rituximab[2,3]. In addition, a phase I/II trial of single-agent ofatumumab in relapsed patients with CLL demonstrated an ORR of 50% in the 26 patients treated with ofatumumab 500 mg followed by 3 weekly doses of 2000 mg (4 total doses). This treatment was well tolerated with the most common side effect being infusion-related reactions[4].

Ofatumumab was combined with fludarabine (F) and cyclophosphamide (C) (O-FC) in a multi-center, Phase II randomized trial of 2-dose levels ofatumumab (500 versus 1000 mg) for treatment of previously untreated patients with CLL[5]. First course ofatumumab was 300 mg in both dose cohorts and both cohorts received F 25 mg/m^2 and C 250 mg/m^2, both daily for 3 days of each 4-wk course. There were 31 patients and 30 patients randomized to the 500 and 1000mg cohorts, respectively. This chemoimmunotherapy regimen was active and well tolerated. There were no statistically significant differences in efficacy or safety parameters between the dose cohorts. The CR rate for the 500 and 1000 mg cohorts was 32 and 50%, respectively; the ORR for the 500 and 1000 mg cohorts was 77 and 73%,

respectively. There were no ofatumumab infusion-related reactions ≥ grade 3. Myelosuppression was the most frequent adverse event with O-FC regimen. This is a promising chemoimmunotherapy regimen and merits further study in frontline and previously treated patients with CLL.

Prior clinical trials demonstrated activity for rituximab in treating early-stage, treatment-naïve high-risk (β2M ≥ 3 mg/L) CLL[6]. The treatment was 8 weekly doses of rituximab 375mg/m^2. Patients were previously untreated, high-risk by elevated β2M (≥ 3 mg/L). There were 34 patients enrolled and treated. The CR rate was 9%, nPR was 21%, and PR was 53% (ORR 82%). The median time to treatment failure (N=34) was 27 months and the median time to progression for responders (N-28) was 43 months. Responses and response duration will be compared to this historical trial. Time to first chemoimmunotherapy will be evaluated based on observed versus expected (O/E) ratio using the MDACC CLL database and multivariable models with nomograms developed to predict time to chemoimmunotherapy based in presenting characteristics. Given the activity and tolerability of ofatumumab, it is an ideal candidate to evaluate for single-agent activity in early-stage, high-risk patients with CLL.

The overall objective of this phase II study is to evaluate the efficacy of ofatumumab in treating high-risk, watch-and-wait, treatment-naïve patients with CLL/SLL to delay time to first chemoimmunotherapy treatment. For this clinical trial, patients will be defined as high-risk for progression based on the presence of one of the following: Rai stage II, serum beta-2 microglobulin (β2M) of ≥ 3 mg/L, absolute lymphocyte count ≥ 25,000/μL, unmutated (≤ 2%) *IGHV* gene or mutated *IGHV3-21*, ZAP70 positive, CD38 positive (≥ 30%), or 11q or 17p deletion by FISH.

3.0 BACKGROUND DRUG INFORMATION

Ofatumumab FDA-Labeled Indication: refractory chronic lymphoid leukemia

Ofatumumab is currently under development by GlaxoSmithKline for the treatment of relapsed or refractory B-cell follicular lymphoma (FL) for previously untreated FL, for the treatment of relapsed or refractory B-cell chronic lymphocytic leukemia (CLL), for previously untreated CLL and for the treatment of active rheumatoid arthritis and other related autoimmune diseases.

US Trade Name: Arzerra

Dosing & Indications
How Supplied: Intravenous solution, 20 mg/mL
Adult Single-Agent Dosing

- Refractory chronic lymphoid leukemia: 300 mg IV, followed 1 week later by 2000 mg IV weekly for 7 doses (dose 2 to 8), followed 4 weeks later by 2000 mg every 4 weeks for 4 doses (dose 9 to 12); premedicate 30 min to 2 hr

before each dose with acetaminophen (1000 mg or equivalent), oral or IV antihistamine (cetirizine 10 mg or equivalent), and IV corticosteroid (prednisolone 100 mg or equivalent).
    - Corticosteroid premedication dose may be gradually reduced for doses 3 through 8, if grade 3 or greater infusion reaction did not occur with the preceding dose.
    - Corticosteroid premedication dose may be reduced to prednisolone 50 to 100 mg or equivalent for doses 10 through 12, if grade 3 or greater infusion reaction did not occur with dose 9.
    - Initiate dose 1 at an initial rate of 12 mL/hr (3.6 mg/hr), if infusion is well-tolerated, rate may be escalated in 2-fold increments at 30 min intervals to a maximum of 200 mL/hr.
    - Initiate dose 2 at an initial rate of 12 mL/hr (24 mg/hr), if infusion is well-tolerated, rate may be escalated in 2-fold increments at 30 min intervals to a maximum of 200 mL/hr
    - Initiate (dose 3 through 12) at an initial rate of 25 mL/hr (50 mg/hr), if infusion is well-tolerated, rate may be escalated in 2-fold increments at 30 min intervals to a maximum of 400 mL/hr

Mechanism of Action/Pharmacokinetics

Mechanism of Action

Ofatumumab is a human IgG1-kappa monoclonal antibody that binds to the CD20 molecule on normal B lymphocytes and on B-cell chronic lymphocytic leukemia, resulting in B-cell lysis.

Pharmacokinetics (single-agent in refractory CLL)

- Distribution: 1.7 to 5.1 L
- Excretion: total body clearance, mean: 0.01 L/hr
- Elimination half life: approximately 14 days

Administration/Monitoring

Administration

Intravenous

- Do NOT shake, mix by gentle inversion.
- Do NOT mix ofatumumab with other drugs.
- Colorless solution with small amounts of visible, translucent-to-white, amorphous, ofatumumab particles is normal; do not use if discolored, cloudy, or if foreign particulate matter is present.
- Total volume of prepared solution should be 1000 mL; withdraw appropriate volume of 0.9% sodium chloride solution to accommodate volume of ofatumumab.
- Do NOT administer as an intravenous push or bolus.
- Do NOT administer ofatumumab with other drugs.
- Administer with an infusion pump, the in-line filter supplied with product, and polyvinyl chloride administration sets.

- Infusion should be started within 12 hr of preparation; discard prepared solution after 24.
- Initiate dose 1 at an initial rate of 12 mL/hr (3.6 mg/hr), if infusion is well-tolerated, rate may be escalated in 2-fold increments at 30 min intervals to a maximum of 200 mg/hr.
- Initiate dose 2 at an initial rate of 12 mL/hr (24 mg/hr), if infusion is well-tolerated, rate may be escalated in 2-fold increments at 30 min intervals to a maximum of 200 mg/hr.
- Initiate dose 3 through 12 at an initial rate of 25 mL/hr (50 mg/hr), if infusion is well-tolerated, rate may be escalated in 2-fold increments at 30 min intervals to a maximum of 400 mg/hr

Monitoring

- Evidence of tumor response is indicative of efficacy.
- CBC regularly, including platelet count and differential.
- CBC more frequently in patients who develop grade 3 or 4 cytopenias, including platelet count and differential.
- Hepatitis B virus (HBV) infection; clinical and laboratory screening before initiation of therapy for those at high risk of HBV infection; hepatitis B carriers, signs of active HBV for 6 to 12 months after therapy.
- Infusion reaction (bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema), especially with first 2 infusions.

Dose Adjustments

- body weight: no dose adjustment is recommended
- gender: no dose adjustment is recommended
- infusion reaction, grade 1 or 2: interrupt infusion and if reaction resolves or remains less than or equal to grade 2, resume at one-half the previous infusion rate; resume infusion at normal infusion rate as tolerated
- infusion reaction, grade 3: interrupt infusion and if reaction resolves or remains less than or equal to grade 2, resume infusion at a rate of 12 mL/hr; resume infusion at normal infusion rate as tolerated
- infusion reaction, grade 4: discontinue the infusion and do not resume

Contraindications

- Specific contraindications have not been determined

Precautions

- Chronic obstructive pulmonary disease, moderate to severe (unapproved use); risk of grade 3 bronchospasm during infusion.
- Cytopenias, including prolonged severe neutropenia and thrombocytopenia may occur; monitoring recommended.
- Hepatitis B infection, carriers or at risk of infection; risk of hepatitis B reactivation with fulminant hepatitis, hepatic failure, and death; evaluate for

evidence of infection before beginning treatment and closely monitor for reactivation for 6 to 12 months following therapy; discontinue therapy if viral hepatitis occurs.

- Infusion reactions, some serious (eg. bronchospasm, dyspnea, laryngeal edema, pulmonary edema, angioedema, cardiac ischemia/infarction) have been reported; especially during first 2 infusions; premedication is recommended; depending on the severity of the reaction, adjustment in infusion rate, interruption, and/or discontinuation of therapy is recommended.
- Obstruction of small intestine may occur.
- Progressive multifocal leukoencephalopathy (PML) including fatalities, may occur; new onset or changes in preexisting neurological signs and symptoms may be indicative of PML; discontinue therapy if PML occurs.
- Viral vaccination, live; do not use in patients who recently received ofatumumab therapy.

Potential Side Effects

Common

- Dermatologic: rash (all grades, 14% to 17%; grade 3 or greater, less than 1% to 2%)
- Gastrointestinal: diarrhea (18% to 19%), nausea (11% to 12%)
- Hematologic: anemia (all grades, 16% to 17%; grade 3 or greater, 5% to 8%)
- Respiratory: bronchitis (all grades, 11% to 19%; grade 3 or greater, less than 1% to 2%), cough (19%), dyspnea (all grades, 14% to 19%; grade 3 or greater, 2% to 5%), pneumonia (all grades, 23% to 25%; grade 3 or greater, 14% to 15%), upper respiratory infection (3% to 11%)
- Other: fatigue (15%), Fever (all grades, 20% to 25%; grade 3 or greater, 3% to 5%)

Serious

- Gastrointestinal: bowel obstruction
- Hematologic: neutropenia, Grade 3 or greater (42%)
- Hepatic: relapsing type B viral hepatitis
- Immunologic: infectious disease (all grades, 70%; grade 3 or greater, 29%), sepsis (all grades, 8% to 10%; grade 3 or greater, 8% to 10%)
- Neurologic: progressive multifocal leukoencephalopathy
- Other: complication of infusion (first infusion, 44%; second infusion, 29%)

Disposition of Unused Drug

Upon termination of the study all unused materials provided by GSK shall be promptly returned at GSK's expense, or, at GSK's option, destroyed with the destruction certified in writing according to MDACC Institutional Drug Destruction Policy.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion criteria:

1. Diagnosis of chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL), previously untreated, Rai stage 0-II
2. At least 1 of the following high-risk features for previously untreated patients:
   - Rai stage II disease
   - Rai stage 0-I with disease-related fatigue
   - Serum β2M $\geq$ 3 mg/L
   - Absolute lymphocyte count $\geq$ 25,000/μL
   - Unmutated *IGHV* gene or *IGHV3-21*
   - ZAP70 positive ($\geq$ 20% by flow cytometry or positive by immunohistochemistry)
   - CD38 positive ($\geq$ 30% by flow cytometry)
   - Deletion 11q or 17p by FISH
3. ECOG PS $\leq$ 2
4. Age $\geq$ 18 years
5. Patients must have adequate renal and hepatic function (creatinine <2mg/dL, total bilirubin <2mg/dL). Patients with renal or liver dysfunction due to organ infiltration with CLL/SLL may be eligible after discussion with the study chairman
6. Provide informed consent
7. Female patients (including those <1 year post-menopausal) and male patients who have not undergone previous surgical sterilization must agree to use contraception.

4.2 Exclusion Criteria:

1. Presence of 2008 IWCLL/NCI-WG indication for CLL treatment:
   - Constitutional symptoms related to CLL/SLL:
     - Fever > 100.5°F for $\geq$ 2 weeks or night sweats for > 1 mo, both without evidence of infection
     - Unintentional weight loss of $\geq$ 10% body weight in previous 6 months
     - Extreme fatigue (ECOG PS > 2; inability to work or perform usual activities)
   - Lymphocyte doubling time of $\leq$ 6 months or 50% increase in absolute lymphocyte count within 2 months
   - Progressive anemia (Rai stage III) or thrombocytopenia (Rai stage IV)
   - Recurrent infections unrelated to hypogammaglobulinemia
   - Autoimmune phenomenon poorly responsive to corticosteroids or other standard therapy
   - Massive, progressive or symptomatic lymphadenopathy (> 10 cm in longest diameter) or splenomegaly (> 6 cm below left costal margin)
2. Prior or concurrent chemotherapy, radiotherapy, or immunotherapy for CLL

3. Active infection (febrile and requiring IV/PO antibiotics) including hepatitis C or HIV, or significant medical illness including renal, cardiac, pulmonary disease, or current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment)
4. Positive serology for Hepatitis B virus (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the patient will be excluded.
    A. Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HB positive.
5. Pregnant or breast feeding females are not eligible

5.0 TREATMENT PLAN

This is a single-arm, open label, phase II trial of single-agent ofatumumab.

Patients will receive ofatumumab 300 mg dose 1, then 1000 mg weekly for 7 additional weekly doses (8 doses). All doses will be administered at MDACC. Allopurinol 300 mg PO daily for the first 7 days of course 1 is recommended for tumor lysis prophylaxis.

There are no required prophylactic antibiotics. Herpes virus and PCP prophylaxis may be given at the discretion of the treating physician but is recommended for patients with recent or concurrent corticosteroid use.

Growth factors (neutrophil, erythrocyte, platelet) may be used at the discretion of the treating physician, if clinically indicated.

Pre-medication for each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the infusion:

Table 1. Pre-medication Requirements prior to Ofatumumab Infusions

Infusion #	**Acetaminophen (po)** or equivalent	**Antihistamine (IV or po)** diphenhydramine or equivalent	**Glucocorticoid (IV)** prednisolone or equivalent
1st	1000 mg	50 mg	50 mg
2nd	1000 mg	50 mg	50 mg
3rd -Nth	1000 mg	50 mg	0 – 50 mg[1]

1. If the 2nd infusion has been completed without the subject experiencing any grade = 3 AEs, pre-medication with corticosteroid may be reduced or omitted before the 3rd to Nth infusion at the discretion of the treating physician.

First Infusion of 300 mg ofatumumab

The first dose administered of ofatumumab will be 300 mg to minimize infusion reactions. The initial rate of the first infusion of **300 mg** ofatumumab (0.3mg/ml) should be 12mL/h. If no infusion reactions occur the infusion rate can be increased every 30 minutes, to a maximum of 200 mL/h, according to Table 2.

Table 2. Infusion rate at 1st Ofatumumab Infusion

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 – 150+minutes	200

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Hereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

Subsequent infusion of full dose (1000 mg) ofatumumab
If the previous infusion was completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of the first full dose of ofatumumab can start at a rate of 25 mL/hour and can be doubled every 30 minutes up to a maximum of 400 mL/h, according to Table 3.

Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion was completed with grade ≥ 3 infusion-associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to Table 3.

Table 3. Infusion rate at subsequent Ofatumumab Infusion

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

During infusion the patient should be monitored closely and appropriate measurements should be performed whenever judged necessary.

There are no proposed or planned ofatumumab dose reductions for toxicities. Toxicities will be addressed by escalating premedication, slowing the infusion rate or delaying planned dose as determined by the treating physician.

6.0 PRETREATMENT EVALUATION (To Be Done Day ≤ -21; TABLE 4)

6.1 Patients will have a complete history and physical examination.

6.2 Laboratory studies will include CBC, platelet count, differential count, blood chemistries (SMA 12) (bilirubin, creatinine, albumin, LDH), serum β-2 microglobulin, pregnancy test for women of childbearing potential, bone marrow aspirate (flow cytometry) and biopsy with samples sent for morphology. Hepatitis B (HB) serologies will be performed including HBsAg, HBsAb, and HBcAb. For $HBcAb^{+}$ ($HBsAb^{+/-}$) individuals, HB virus DNA PCR will be performed.

6.3 Prognostic factors will be characterized including immunoglobulin heavy chain variable gene (*IGHV)* family and mutation status; leukemia cell expression of ZAP-70, CD38, and CD49d; thymidine kinase; chromosome abnormalities by FISH (13q del, +12, 11q del, and 17p del); and p53 expression. If bone marrow evaluation is done within 3 months of enrollment, this will not need to be repeated. In these cases, if there is any prognostic factor information missing, this can be obtained from blood. If *IGHV* mutation status and ZAP70 were previously determined at any time, they do not need to be repeated.

6.4 Staging CT of chest, abdomen, and pelvis will be done within 2 months of treatment. Any other appropriate radiological and radioisotope examinations should be performed as clinically indicated.

6.5 Pretreatment optional blood (20 ml) will be taken to isolate and store mononuclear cells, DNA, RNA, and plasma. Also, pretreatment optional bone marrow will be taken (5 ml) to isolate and store cells, DNA, RNA and marrow plasma. Not all samples will be collected in all patients at all time points.

7.0 EVALUATION DURING STUDY

7.1 Monitoring during treatment will consist of weekly (±3 days) blood counts and chemistries (through C1D50), then every 3 months (±2 weeks) during follow-up until alternative treatment for CLL/SLL or death, whichever occurs first. A physician will see patients at least monthly (±5 days) during treatment. A mid-level provider may evaluate patients weekly (±2 days) during treatment (8 weeks) when not seen by the physician.

7.2 Follow-up visits will include PE with vital signs, interval history, toxicity/adverse event assessment, CBC with differential, and SMA12. Bone marrow examinations (aspirate, biopsy, and MRD evaluation) will be done at response

assessment (at least 2 months after last dose of ofatumumab) to confirm complete remission, then annually.

7.3 Patients will be followed at MDACC for all visits including follow-up, response assessment 3 months after the last ofatumumab dose, and at least annually. Patients will be considered off study when they start alternative treatment for their CLL.

7.4 For patients who are $HBsAg^{-}$, $HBcAb^{+}$, $HBsAb^{+/-}$, and $HBV\ DNA^{-}$ on enrollment and who proceeded with treatment, HBV DNA PCR testing will be done every 2 months while on treatment, then every 3 months during follow-up for 6 months. Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive. Initiate anti-viral therapy if required. If a subject's HBV DNA becomes positive during the study, notify the GSK medical monitor. For subjects who have not completed planned ofatumumab therapy, discuss with the medical monitor the risks and benefits of continuing or discontinuing ofatumumab before appropriate treatment decisions are made for that individual subject.

7.5 Information regarding concomitant medications will not be collected for patients on this study. This information is routinely collected and recorded as part of the patient's electronic record. If there is a need to refer to this, it will be available.

The schedule of events is detailed in Table 4.

Table 4. Schedule of Events

Test and Evaluations	Screening Visit Day ≤ -21	C1 D1	C1 D8	C1 D15	C1 D22	C1 D29	C1 D36	C1 D43	C1 D50 (EOT)	C1 D140	FU Q3 MO	ANNUAL FU
Informed consent	X											
Medical history	X											
Interval history, including adverse events and toxicity		X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[b]	X[c]	X[c]
PE including VS	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[b]	X[c]	X[c]
Pregnancy test	X											
β2 Microglobulin	X											
Screening BM asp/bx[d]	X											
Zap70, CD38, CD49d, thymidine kinase[e], *IGHV*, FISH (13q del, +12, 11q del, and 17p del); and p53 expression[d]	X											
Staging CT of chest, abdomen, pelvis (Day ≤-2 mo)	X											
Hepatitis B surface Ag and surface and core Ab serology	X											
CBC with diff, PLT	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[b]	X[c]	X[c]
SMA 12	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[b]	X[c]	X[c]
Ofatumumab		X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]			
For Pts $HBsAg^-$, $HBcAb^+$, $HBsAb^{+/-}$, $HBV\ DNA^-$ on enrollment, HBV DNA PCR testing will be done	X								X[a]	X[b]	X[c]	
PK & PD, optional samples	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[b]	X[c]	X[c]
Response assessment (IWCLL criteria, staging CT scan, and BM for MRD)										X[b]		X[c]

BM=bone marrow evaluation; C=course; D=day; EOT=end of treatment; FU=follow-up; MO=months; PE=physical examination; VS=vital signs; CBC=complete blood count; PK=pharmacokinetic; PD=pharmacodynamic; IWCLL=International Working Group for CLL; MRD=minimal residual disease; [a]indicates ± 3 days; [b]indicates ± 2 weeks; [c]indicates ± 4 weeks; [d]if bone marrow evaluation is done within 3 months of enrollment, this will not need to be repeated. In these cases, if there is any prognostic factor information missing, this can be obtained by blood. If *IGHV* mutation status and ZAP70 were previously determined at any time, they do not need to be repeated. [e]when testing is available at MDACC.

8.0 RESPONSE CRITERIA AND TOXICITY EVALUATION

Responses will be assessed according to the 2008 IWCLL guidelines (Table 5)[7] at MDACC. Reponses will be evaluated by physical examination; CBC; CT of chest, abdomen, pelvis; and for individuals in complete remission bone marrow aspirate and biopsy with evaluation of residual disease (MRD) by 4-color flow cytometry at least 3 months after completing ofatumumab.

Table 5. 2008 IWCLL Response Assessment

SITE	CR	PR
Nodes*†	None > 1.5 cm	Decrease ≥ 50%
Liver/Spleen	Not palpable	Decrease ≥ 50%
Symptoms	None	N/A
PMN	>1,500/μL	N/A
Platelet count	> 100,000/μL	>100,000/μl or increase ≥ 50% over baseline
Hemoglobin (untransfused)	>11.0 g/dL	>11.0 g/dl or increase ≥ 50% over baseline
Blood Lymphocytes	<4,000/μL	Decrease ≥ 50%
Bone Marrow Aspirate** Biopsy	Normocellular <30% lymphocytes No lymphocyte infiltrate or nodules	 > 50% decrease in marrow infiltrate or B lymphoid nodules

* CT scan of neck, chest, abdomen, and pelvis to confirm CR is recommended.
† Sum of the product of multiple lymph nodes.
** Evaluation for MRD will be performed either by 4-color flow cytometry or by molecular evaluation.
N/A=not applicable

Non-hematologic toxicity will be assessed, summarized and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.
Hematologic toxicity will be assessed, summarized and graded according to the 2008 IWCLL Guidelines (Table 6).

8.1 ADVERSE EVENT DOCUMENTATION

Adverse events will be documented in the medical record and entered into the case report form (CRF) according to the Leukemia –Specific Adverse Event Recording and Reporting Guidelines (Appendix E). PDMS/Core will be used as the CRF report form for this protocol. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. The Investigator will sing and date the PDMS CRF toxicity pages for each patient at the completion of each course. Following signature, the CRF will be used as source documentation for the adverse events attribution.

Table 6. 2008 IWCLL Grading for Hematological Toxicity

Grade	Decrease in PLT* or HGB** (nadir) from pretreatment value, %	Absolute neutrophil count (ANC)/μl*** (nadir)
0	≤ 10%	≥ 2000
1	11 – 24%	≥ 1500 – < 2000
2	25 – 49%	≥ 1000 – < 1500
3	50 – 74%	≥ 500 – < 1000
4	≥ 75%	< 500

Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

* PLT counts must be below normal levels for grades 1-4. If, at any level of decrease, the PLT count is < 20K/μl, this will be considered grade 4 toxicity, unless there was severe or life-threatening low initial PLT count (< 20K/μl) pretreatment, in which case the patient is not evaluable for toxicity referable to PLT count.

** HGB levels must be below normal levels for grades 1-4. Baseline and subsequent HGB determinations must be performed before any given transfusions.

*** If the absolute neutrophil count (ANC) reaches <1000/μl, it should be judged to be grade 3 toxicity. If the ANC was <1000/μl before therapy, the patient is not evaluable for toxicity referable to the ANC.

9.0 REMOVAL FROM STUDY

9.1 Progressive or Relapsed Disease

Progressive disease (PD) will be characterized by at least one of the following:

a. ≥ 50% increase in the sum of the products of at least two nodes or appearance of new palpable lymph nodes noted on two consecutive examinations at least two weeks apart (at least one node must be ≥ 2 cm).

b. ≥ 50% increase in the size of liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly which was not previously present.

c. ≥ 50% increase in absolute number of circulating lymphocytes over baseline with ≥ 5,000 B cells/μL.

d. Transformation to a more aggressive histology (Richter syndrome) documented with biopsy.

e. PLT or HGB decrease ≥ 50% from baseline secondary to CLL/SLL.

9.2 Active HBV infection or hepatitis.

9.3 Patient request.

10.0 STATISTICAL CONSIDERATIONS

This is a phase II, open label, single-arm study. Sample size calculation will be based on the CR rate. The objective is to demonstrate a 20% CR rate for patients treated with single-agent ofatumumab. A CR rate of 9% was achieved in a previous phase II clinical trial with single-agent rituximab in a similar patient population. Simon's two-stage MinMax design will be used to assess efficacy in this study. In particular, a sample size of 44 is chosen to differentiate between a good response rate of 20% and a poor response rate of 9% at the significance level of 0.10 with 80% power. In particular, 25 patients will be enrolled at the first stage. If there is 1 or fewer responders among 25, the trial will be terminated due to lack of efficacy; otherwise an additional 19 patients will be treated resulting in a total of 44 patients. If there are 6 or fewer responses among 44 patients, the treatment will be concluded ineffective. The probability of early termination due to futility is 0.33.

The probability of toxicity will be monitored based on a beta-binomial model, assuming a priori that p = Prob(toxicity) ~ beta(1, 1). The trial will be terminated if Prob(p> .15| data) ≥ .9. This rule will stop the trial if [#patients with toxicity]/[#patients evaluated] ≥ 3/7, 4/12, 5/17,6/22, 7/27, 8/32, 9/37, or 10/42. The operating characteristics for toxicity are summarized in Table 7.

Table 7. Operating characteristics based on 1000 simulation study

true Prob(tox)	Pr(stop)	Median # Pts (25%, 75%)
0.05	0.004	44 (44, 44)
0.10	0.07	44 (44, 44)
0.15	0.25	44 (44, 44)
0.20	0.49	44 (12, 44)
0.30	0.89	12 (7, 22)
0.40	0.99	7 (7, 12)

Toxicity events, for purposes of safety monitoring, will be defined as ofatumumab-related grade ≥ 4 toxicity by CTCAE V 4.0 that persist longer than 1 week despite holding drug and/or dose reduction.

Descriptive statistical analysis will be used to explore the data, including histograms or box-plots, proportions, means, standard deviations. The Fisher's exact test or Chi-square test will be used for the univariable analysis on categorical variables (response variable with Yes versus No, for example). The t-test or Wilcoxon test will be used for continuous variables. The Kaplan-Meier survival analysis will be performed to estimate the overall survival and event-free-survival. The log-rank test will be used to assess the difference of survival functions between two groups. Toxicity will be reported by type, frequency and severity.

11.0 PHARMACODYNAMIC AND PHARMACOKINETIC ENDPOINTS

Ofatumumab levels, normal blood B cell counts, leukemia cells in blood ($CD5^-$ /$CD19^+$/$CD20^{+/-}$ and light chain restricted-$CD5^+$/19^+/$20^{+/-}$) and soluble CD20 and

CD52 will be quantitated weekly during treatment (pre-dose), then at response assessment and at 6 months follow-up (3 months after response assessment).

The following is the schedule of sample acquisition for pharmacokinetic analyses. Ofatumumab levels will be measured by a central lab.

Table 8. PK/PD Sample Collections

Day	Sampling time relative to ofatumumab infusion
1	Predose, End of Infusion (EOI), 1 h and 2 h post-EOI
2	Any time of study day (+1 d)
4	Any time of study day (+3 d)
6	Any time of study day (+5 d)
8	Predose, EOI, 1 h post-EOI
15	Predose
22	Predose, EOI, 1 h post-EOI
29	Predose
36	Predose
43	Predose
50 (EOT)	Predose, EOI, 1 h and 2 h post-EOI
51	Any time of study day (+1 d)
54	Any time of study day (+4 d)
57	Any time of study day (+7 d)
	1 month after last ofatumumab dose[1]
	3 months after last ofatumumab dose[1]
	6 months after last ofatumumab dose[1]

EOT = end of treatment
[1] Collect relative to last dose of ofatumumab, regardless of number of doses. Collect at any time of study day.

The actual date and time of each sample collection will be recorded on a pharmacokinetic sample collection form.

PK, PD and bone marrow samples will be collected and sent to: Attention of Ruth LaPushin, MD Anderson Cancer Center, 1515 Holcombe Blvd., T6.3849, Houston, Texas 77030. Phone 713-792-3690. All samples will be frozen and stored for batched processing. Not all samples will be collected on all patients at all time points.

12.0 DATA CONFIDENTIALITY PLAN

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will

be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

13.0 SERIOUS ADVERSE EVENT REPORTING REQUIREMENTS

Serious Adverse Event Reporting (SAE)
A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 31+ 2.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, MDACC IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported MDACC IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in MDACC IND Office.

- **The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to MDACC IND Office.**

- **Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to MDACC IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager MDACC IND Office) according to 21 CFR 312.32.

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

All serious adverse events will also be forwarded to GSK according to their guidelines.

14.0 REFERENCES

1. Wierda WG, Kipps T Immunotherapy in Fludarabine-Refractory Chronic Lymphocytic Leukemia. J Clin Oncol. 2010;In Press.
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4. Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood. 2008;111:1094-1100.
5. Wierda WG, Kipps TJ, Durig J, et al. Ofatumumab Combined with Fludarabine and Cyclophosphamide (O-FC) Shows High Activity in Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL): Results From a Randomized, Multicenter, International, Two-Dose, Parallel Group, Phase II Trial. Blood. 2009;114:(Abstract #207).
6. Thomas DA, O'Brien S, Giles FJ, et al. Single agent Rituxan in early stage chronic lymphocytic leukemia (CLL). Blood. 2001;98:364a (Abstract 1533).
7. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111:5446-5456.