Ofatumumab for Residual Disease and Maintenance Following Chemotherapy or Chemoimmunotherapy in Patients with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

Version 8

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William G. Wierda, M.D.,Ph.D.
Associate Professor of Medicine
Department of Leukemia
Division of Cancer Medicine
UT MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 428
Houston, TX 77030
(713) 745-0428 (ph)
(713) 794-1602 (fax)

Short Title: Ofatumumab for MRD and Maintenance

1.0 OBJECTIVES

Primary objective:
Response rate (CR conversion to MRD negative, PR conversion to nPR or CR, and nPR conversion to CR) with ofatumumab treatment in patients with residual disease.

Secondary objectives:
1. Determine the time-to-treatment failure and progression-free survival
2. Determine the time-to-next CLL/SLL treatment after ofatumumab
3. Evaluate the safety and tolerability of ofatumumab for residual disease
4. Evaluate pharmacokinetics of ofatumumab in this trial for residual disease and in maintenance

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 (OR) rate for FA-ref (n=59) and BF-ref (n=79) was 58% and 47%, respectively. The median time to response was 1.8 months and median response duration for both populations was 6 months. Treatment with ofatumumab was very well tolerated. 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 300 mg followed by 3 weekly doses of 2000 mg (4 total doses)[2]. This treatment was well tolerated with the most common side effect being infusion-related reactions. This human monoclonal antibody against CD20 binds to a unique epitope composed of the small- and large-loop domains of CD20 and is highly effective at fixing complement for complement-dependent cytotoxicity (CDC). *In vitro* studies demonstrated higher levels of CDC against primary CLL cells with ofatumumab compared to rituximab, especially with cells with low CD20 antigen density[3,4].

Alemtuzumab is a monoclonal antibody against CD52, approved by FDA for treatment of untreated and previously treated patients with CLL. CD52 is also present on normal T, B and NK cells; therefore these normal cells are also at risk for elimination with alemtuzumab treatment. Alemtzumab is highly effective at eliminating CLL from blood and bone marrow, the usual site of residual disease after purine analogue-based treatment. Several Phase II trials have been conducted to evaluate the efficacy of alemtuzumab at eliminating residual disease and treatment of minimal residual disease (MRD)[5-10]. While these studies that have clearly demonstrated the ability of alemtuzumab to eliminate MRD, both the safety and clinical relevance of this strategy are debated. In fact, 2 trials were terminated early owing to alemtuzumab-related infection complications with opportunistic organisms[8,10]. One of these studies demonstrated prolonged progression-free survival in patients treated with alemtuzumab[8], the other trial did not show any benefit with alemtuzumab[10]. Therefore

this strategy with alemtuzumab remains investigational and requires further clinical trial to optimize and address safety issues.

Chemoimmunotherapy (CIT) regimens, particularly fludarabine combined with cyclophosphamide and rituximab, the monoclonal antibody against CD20, are highly effective treatment for patients with CLL both frontline (CLL8)[11] and relapsed (REACH trial)[12] patients. Despite the effectiveness of this combination, many of frontline and the majority of salvage patients have residual disease present following the standard 6 cycles of FCR treatment, demonstrated by the highly sensitive 4-color flow cytometry assay done on bone marrow[13,14]. Given the high affinity of ofatumumab for CD20, highly efficient CDC, and clinical activity in FA-ref and BF-ref patients, it is an ideal antibody to treat residual disease following CIT and for maintenance. Participants in this trial will have residual disease following chemotherapy or CIT with leukemia cells expressing CD20.

Ofatumumab is an attractive option for clinical trial to treat residual disease and for maintenance in patients with CLL. CD20 is present on CLL and normal B cells, but not on T cells. Therefore, the potential for immune suppression with ofatumumab is much less than that seen with alemtuzumab. This has been confirmed also in clinical trials. In patients with residual disease, in order to be eligible for this trial, their CLL cells must express CD20, thereby providing a target for ofatumumab. The overall primary objective of this phase II trial is to evaluate the activity (response rate) of ofatumumab in treating residual disease in patients with CLL/SLL who have been treated with chemotherapy or chemoimmunotherapy (CIT) containing rituximab or ofatumumab and who have detectable residual leukemia cells expressing CD20 post-treatment.

Patients will be enrolled in 1 of 2 cohorts as follows:

1. Complete responders with evidence of minimal residual disease by 4-color flow cytometry.

2. Partial (PR) and nodular partial (nPR) responders with evidence of residual disease.

Ofatumumab is currently under development by GlaxoSmithKline and Genmab 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.

3.0 BACKGROUND DRUG INFORMATION

Ofatumumab FDA-Labeled Indication: refractory chronic lymphoid leukemia

US Trade Name: Arzerra

Dosing & Indications:

How Supplied: Intravenous solution, 20 mg/mL
*Adult Single-Agent Dosing (This dosing schedule refers to the pivotal trial. Please refer to **Section 5.0 Treatment Plan** for the dosing schedule in this trial).*

- 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 refractory CLL/SLL patient population)

- 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 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.

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 intestinal 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%)

Unused and Expired Study Drug:

Expired ofatumumab and ofatumumab left unused upon completion of the study will be destroyed and dispensed of by the MD Anderson Cancer Investigational Pharmacy.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion criteria:

1. Diagnosis of $CD20^+$ chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) treated with chemotherapy or chemoimmunotherapy:
   - Post-frontline therapy, patients must have non-progressing disease and be 4 mo to 1 yr post treatment
   - Post-treatment for relapsed CLL/SLL, eligible patients must have non-progressing disease and be 3 mo to 1 yr post treatment
2. Patients (CR, nPR, or PR at enrollment) must have measurable disease, which may include MRD by 4-color flow cytometry
3. Adequate renal and hepatic function (creatinine <2mg/dL, bilirubin <2mg/dL). Patients with renal or liver dysfunction due to organ infiltration by lymphocytes may be eligible after discussion with the study chairman. Patients with Gilbert's syndrome are eligible.
4. Age $\geq$ 18 years
5. ECOG performance status of 0-2
6. Provide informed consent indicating patient is aware of the investigational nature of this study according to the policies of the MDACC IRB
7. Patients of childbearing potential (females who have not been postmenopausal for at least 12 consecutive months or who have not undergone previous surgical sterilization or males who have not been surgically sterilized) must be willing to practice birth control during the study.

4.2 Exclusion criteria:

1. 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 subject will be excluded
2. Concurrent chemotherapy, radiotherapy, or immunotherapy, including other monoclonal antibodies. Localized radiotherapy to an area not compromising bone marrow function does not apply
3. Active infection or significant medical illness, including current active hepatic or biliary disease (with exception of patients with asymptomatic gallstones, liver involved with CLL/SLL or stable chronic liver disease per investigator assessment)
4. Pregnant and breastfeeding women are excluded.

5.0 TREATMENT PLAN

This is a single-arm, open label trial of ofatumumab. Treatment with ofatumumab will be 300 mg dose 1, then 1,000 mg weekly x 7 (referred to as “treatment”), then 1,000 mg every 2 months beginning on week 12 for a total of 2 years of treatment or until progression (referred to as “maintenance”). The “follow-up” period will be the period after completion of “maintenance”.

Ofatumumab pre-medication must be given within 30 minutes to 2 hours prior to each infusion:

Table 1. Recommended Pre-medication 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 was completed without the patient experiencing any grade 3 AE, pre-medication with corticosteroid may be reduced or omitted before the 3rd to Nth infusion at the discretion of the investigator.

First Infusion of 300 mg and 1000 mg Ofatumumab

The first dose administered of ofatumumab should be 300 mg to minimize infusion reactions. The initial rate of the **300 mg** (0.3 mg/ml) and first **1000 mg** (1.0 mg/ml) ofatumumab doses should be 12mL/hr. If no infusion reactions occur the infusion rate should be increased every 30 minutes according to Table 2, to a maximum of 200 mL/hr.

Table 2. Infusion Rate at 1st and 2nd 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. Additional corticosteroids may be given at the discretion of the treating physician. Upon restarting, 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 Infusions of 1000 mg Ofatumumab

If the previous infusion was completed without any grade ≥ 3 infusion-associated AE, the subsequent infusion of ofatumumab 1000mg (1.0mg/mL) can start at a rate of 25 mL/hour and should be doubled every 30 minutes up to a maximum of 400 mL/hr, according to

Table 3. The duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion was completed with any grade ≥ 3 infusion associated AE, the subsequent infusion should start at a rate of 12 mL/hour according to Table 2.

Table 3. Infusion Rate for Ofatumumab Infusions 3 and beyond

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 Pretreatment evaluation includes complete history and physical examination.

6.2 Laboratory studies will include CBC with differential, blood chemistries (SMA12 including: sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, albumin, alkaline phosphatase, ALT, total protein, calcium, phosphorus, uric acid, total bilirubin, lactate dehydrogenase), serum pregnancy test for women of childbearing potential, bone marrow aspirate and biopsy with diagnostic (4-color flow cytometry to demonstrate residual disease). If bone marrow evaluation is done within 3 months of enrollment and there is no intervening treatment, this will not need to be repeated. Hepatitis B (HB) serologies will be performed including HBsAg, AHBSAG, and HBcAb. For $HBcAb^{+}$ ($HBsAb^{+/-}$) individuals, HB virus DNA PCR will be performed.

6.3 Prognostic factors will be characterized including serum β2M; immunoglobulin heavy chain variable gene (*IGHV)* family and mutation status; leukemia cell expression of ZAP-70, CD38, and CD49d; 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 and there is no intervening treatment, 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 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. Optional blood samples will be obtained for pharmacokinetic (PK) analysis. See Table 5 for detailed schedule of optional PK analysis. Not all samples will be collected on all patients at all time points.

7.0 EVALUATION DURING STUDY

7.1 Monitoring will consist of biweekly (every other week ±3 days) blood counts and SMA12 during treatment (first 8 doses of ofatumumab), then every 2 months (±2 weeks) during maintenance, then every 3 months (±2 weeks) during follow-up until alternative treatment for CLL/SLL or death, whichever occurs first.

7.2 For patients who are $HBsAg^-$, $HBcAb^+$, $HBsAb^{+/-}$, and $HBV\ DNA^-$ on enrollment and proceeded with treatment, HBV DNA PCR testing will be done every 2 months while on treatment and maintenance, then every 3 months during follow-up for 6 months.

7.3 A physician will see patients at least monthly (±5 days) during treatment, then every 2 months (±2 weeks) during maintenance, then every 3 months (±2 weeks) during follow-up. A mid-level provider may evaluate patients every other week (±3 days) during treatment (8 weeks) when not seen by the physician.

7.4 Patients will be seen at MDACC for mandatory visits for enrollment, ofatumumab infusions, for response assessment after 8 weekly ofatumumab doses (Month 3), during maintenance every 6 months and for follow-up at least annually. The patients' referring physician may perform other visits and laboratories in Table 4. All patients will be followed for survival.

7.5 A letter will be sent to the local physician outlining the patient's participation in the clinical trial and will request local physician agreement to supervise the patient's care.

7.6 Protocol evaluations outside MDACC will be documented by telephone, fax, or e-mail. Fax and/ or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

7.7 Changes in schedule will be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

7.8 A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

7.9 Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

7.10 The local physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

The schedule of events is detailed in Tables 4 and 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 patients' electronic medical record. If there is a need to refer back to this, it will be available. It is not necessary to collect and record redundant information.

Table 4. Schedule of Events

Test and Evaluations	Screening Visit Day ≤ -21	Tx W1	Tx W2	Tx W3	Tx W4	Tx W5	Tx W6	Tx W7	Tx W8	MT M3-24 ****	End of MT	F/U
Informed consent	X											
Medical history	X											
Interval history		X*		X*		X*		X*		q 2mo**		q 3mo**
PE with vital signs	X	X*		X*		X*		X*		q 2mo**		q 3mo**
Serum pregnancy test	X											
Ofatumumab dose (mg)		300*	1000*	1000*	1000*	1000*	1000*	1000*	1000*	1000* q 2mo**		
CBC with diff, PLT	X	X*		X*		X*		X*		q 2mo**		q 3mo**
SMA12	X	X*		X*		X*		X*		q 2mo**		q 3mo**
Prognostic factor evaluation	X											
Bone marrow biopsy and aspiration with 4-color flow cytometry	X											
Hepatitis B (HB) surface Ag (HBsAg)and surface and core Ab (AHBSAG and HBcAb) serology	X											
$HBsAg^-$, $HBcAb^+$, $HBsAb^{+/-}$, $HBV\ DNA^-$ on enrollment, for HBcAb+ (HBsAb+/-) pts, HBV DNA PRC testing will be performed									X	q 2mo**		q 3mo** for 6 mo
PK & PD, optional samples***		X***	X***	X***	X***	X***			X***	X***	X***	X***
Response assessment (2008 IWCLL criteria) (PE, CBC with diff, optional CT chest, abd, pelvis and BM for MRD)										M3		
Monitoring for relapse and progression(2008 IWCLL criteria (PE, CBC with diff, and BM for MRD)										q 6mo**	X**	q 6mo**

Ag=antigen; Ab=antibody; BM=bone marrow evaluation; PE=physical examination; CBC=complete blood count; CR=complete remission; F/U=follow-up; PK=pharmacokinetic; PD=pharmacodynamic; IWCLL=International Working Group for CLL; M=month; MT=maintenance begins on week 12 of treatment; MRD=minimal residual disease; q="every"; SMA12=sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, albumin, alkaline phosphatase, ALT, total protein, calcium, phosphorus, uric acid, total bilirubin, lactate dehydrogenase; Tx=treatment; W=week; *indicates ± 3 days; **indicates ± 2 weeks; ***for detailed information about PK sample collection see Table 5, **** indicates cycle 9 begins at week 12 (M3).

Table 5. Detailed Schedule of Sampling for Optional PK Analyses

Time	Sampling time relative to ofatumumab infusion[1]
Week 1	Predose, End of Infusion (EOI), 1 h post-EOI
Week 2	Predose, EOI, 1 h post-EOI
Week 3	Predose
Week 4	Predose, EOI, 1 h post-EOI
Week 5	Predose
Week 6	-
Week 7	-
Week 8	Predose, EOI, 1 h post-EOI
Month 5	Predose, EOI, 1 h post-EOI
Month 7	Predose
Month 9	Predose
Month 11	Predose
Month 13	Predose
Month 15	Predose, EOI, 1 h post-EOI
Month 17	Predose
Month 19	Predose
Month 21	Predose
Month 23	Predose
Month 25	Predose
Month 27	Predose, EOI, 1 h post-EOI[2]
	1 month after last ofatumumab dose[2]
	3 months after last ofatumumab dose[2]
	6 months after last ofatumumab dose[2]

EOI = end of infusion

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

[2] Sample collected relative to last dose of ofatumumab, regardless of number of doses. Collect at any time of study day.

8.0 RESPONSE CRITERIA AND TOXICITY EVALUATION

Response assessment will be according to the 2008 International Working Group for CLL (IWCLL) guidelines[15]. Response will be formally assessed prior to the 9th dose of ofatumumab (prior to first bimonthly dose), then every 6 months thereafter while receiving maintenance ofatumumab and during the follow-up period (Table 4). During the follow-up phase, patients will be monitored for relapse and progression according to the 2008 IWCLL recommendations. Responses will be evaluated by physical examination, CBC, optional CT of chest, abdomen, pelvis, and bone marrow aspirate and biopsy with evaluation of residual disease (MRD) by 4-color flow cytometry.

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, graded, and summarized according to the

2008 IWCLL Guidelines (Table 6). Adverse events will be documented in the medical record and entered into the case report form according to the Leukemia-Specific Adverse Event Recording and Reporting Guidelines (Appendix E). PDMS/CORe will be used as the electronic case 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.

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.

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 312.32).

- 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 Sponsor.

- 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 to MDACC IND Office, regardless of attribution (within 5 working days of knowledge of the event) and GlaxoSmithKline (GSK) within 24 hours of knowledge of event.

- **All life-threatening or fatal events** with possible, probable or definite attribution to the study drug must have a written report faxed within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office (fax 713-792-9631) and to GSK within **24 hours** (next working day) of knowledge of the event. The sponsor representative should be notified by phone at 713-563-0379 to confirm receipt of the fax.

- The MDACC Internal Adverse Event Reporting Form will be used for reporting to the Sponsor (Safety Project Manager 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 test 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 the IRB and the Sponsor (Safety Project Manager IND Office). This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the Sponsor (Safety Project Manager 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.

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 on two consecutive examinations 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.

9.4 General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

9.5 Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.

10.0 STATISTICAL CONSIDERATIONS

This is a phase II, open label, single-arm study. The primary efficacy endpoint is response rate evaluated at week12 (m3). Criteria for response will be as follows:

1. For patients enrolled in CR, patients must have pretreatment evidence of residual disease in bone marrow by MRD evaluation (4-color flow cytometry). Responders will have no evidence by evaluation of the bone marrow using the enrollment test at response assessment.
2. For patients enrolled in nPR, responders must have achieved CR by the 2008 IWCLL criteria.
3. For patients enrolled in PR, responders must have achieved either nPR or CR by 2008 IWCLL criteria.

A response rate of at least 40% with this agent will be deemed promising. 42 patients will be accrued into the study (N=21 in CR and N=21 in nPR/PR).

Simon's two-stage optimal design will be used in this study for the 2 different cohorts (CR or nPR/PR), separately. In each cohort, a sample size of 21 is chosen to differentiate between a good response rate of 40% and a poor response rate of 10% at the significance level of 0.05 with 95% power. In particular, 12 patients will be enrolled at the first stage. Enrollment will be suspended until all 12 patients have completed response assessment (m3). If there is one or fewer response, the trial will be terminated due to lack of efficacy; otherwise additional 9 patients will be treated resulting in a total of 21 patients. If there are 4 or fewer responses among 21 patients, the treatment will be concluded ineffective. The probability of early termination due to futility is 0.66.

Toxicity events for purposes of safety monitoring will be defined as ofatumumab-related grade >/=4 toxicity by CTCAE V.4 that persist longer than 1 week despite holding drug and or adjusting infusion rate.

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) $\geq$ 0.9. This rule will stop the trial if [# patients with toxicity]/[# patients evaluated] $\geq$ 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 the following Table.

Table 7. Operating Characteristics Based on 1000 Simulation Study

True Prob(tox)	Pr(stop)	Median # Pts (25%, 75%)
0.05	<0.01	42 (42, 42)
0.10	0.06	42 (42, 42)
0.15	0.23	42 (42, 42)
0.20	0.47	42 (12, 42)
0.30	0.90	12 (7, 22)
0.40	>0.99	7 (7, 12)

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 time-to-progression. 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 will be evaluated at the indicated time points in Table 5 for pharmacokinetic analyses. In addition, these data will be correlated with cell counts and evaluations for minimal residual disease.

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.

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