PHASE II TRIAL OF OFATUMUMAB AND FRESH FROZEN PLASMA IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

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PROTOCOL SIGNATURE PAGE

Protocol Number: UCDCC#232

Protocol Title: PHASE II TRIAL OF OFATUMUMAB AND FRESH FROZEN PLASMA IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

_____
Institution Name

_____
Date

PROTOCOL SUMMARY

Rationale

Despite progress in therapy, chronic lymphocytic leukemia (CLL) remains incurable. Response rates are promising but remain transient and all patients eventually relapse. Many patients are elderly and thus cannot tolerate multi-agent chemotherapeutic regimens. Less toxic and more effective non-chemotherapeutic approaches are needed.

An impaired complement system is thought to be involved in the pathophysiology of CLL and of its infectious complications. This study builds on the fact that the anti-CD20 monoclonal antibody, ofatumumab, effectively fixes and activates complement and complement levels in patients with CLL.

Objectives

The primary objective is to evaluate response to therapy (defined as complete, or partial response, and progression-free survival) in subjects with refractory or relapsed CLL who have relapsed after at least one prior therapy.

Secondary objectives are to evaluate toxicity, overall survival (OS), and complement levels (CH20 and C2) in subjects with refractory or relapsed CLL.

Study Design

This is an open-label, Phase II study of the combination of ofatumumab and fresh frozen plasma (FFP) in patients with relapsed or refractory CLL.

Approximately 12 subjects will be enrolled.

Treatment: 12 doses of ofatumumab as currently approved over a 24 week period with 2 units of FFP with each dose (with the exception of the first dose).

Patients will be followed for 2 years after the last dose of ofatumumab.

1.0 STUDY OBJECTIVES

Primary Objective:

- To evaluate the response to therapy (complete response (CR), or partial response (PR), and progression-free survival (PFS)) of subjects with refractory or relapsed CLL who have relapsed after at least one prior therapy.

Secondary Objectives:

- To determine the toxicity and safety of administration of the combination of ofatumumab and FFP
- To evaluate overall survival
- To evaluate complement levels in subjects with CLL receiving ofatumumab before and after the administration of FFP

2.0 BACKGROUND AND RATIONALE

2.1 Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia is the most common type of leukemia in the Western world, accounting for 40% of all leukemia types in people over the age of 65 [Oscier, 2004]. It is estimated that in the US alone 15,110 adults (8,750 men and 6,360 women) were diagnosed and 4,390 adults will die of CLL in 2008 [Jemal, 2008]. The prevalence of CLL increases with age and the median age at the time of diagnosis is 65 to 70 years [Redaelli, 2004]. Approximately 50% of patients are initially asymptomatic and are observed for several years before treatment is needed, therefore more than half of patients who finally require therapy are older than 70 years. The disease is a hematological neoplasm of unknown etiology, characterized by accumulation of monomorphic small, round mature-appearing B lymphocytes in the peripheral blood, bone marrow, and lymph nodes that aberrantly co-express T-cell (CD5+) and B-cell (CD19+, CD23+) cell surface markers, with a low expression of CD20. Over the past decade, new information suggests B-CLL originates from antigen-stimulated mature B-lymphocytes, which either avoid cell death through the effect of external signals, or die by apoptosis, but are replenished by proliferating precursor cells [Chiorazz, 2005]. CLL follows a variable clinical course with overall survival times ranging from months to decades. Median survival from diagnosis is approximately 10 years in the overall CLL population, but is only 18 months for patients with advanced disease [Nabhan, 2004]; and 9-13 months for CLL cases refractory to fludarabine [Byrd, 2004].

Clinical staging systems devised by Rai and Binet are the best validated for evaluating CLL patients [Rai, 1975; Binet, 1981]; however, there is heterogeneity in the course of the disease within defined stages. In recent years, molecular and cellular markers have been correlated with disease aggressiveness. These allow further stratification of subjects into risk groups such as: abnormal cytogenetics, CD38, ZAP-70, beta-2-microglobulin, IgVH mutational status [Oscier, 2004; Abbott, 2006; Shanafelt, 2007; Zenz, 2007]. Unfortunately, so far, these parameters have only limited use in determining when and what type of therapy to use [Binet, 2006]. One exception is that p53 deletion was shown to be predictive for non-response to purine analogues like fludarabine and for poor clinical outcome, but is not predictive for response to a particular therapy [Dohner, 1995].

2.2 Current Treatment for CLL

Over the last two decades, the treatment goal of CLL has undergone a paradigm shift changing from simple symptom palliation to attainment of maximal disease control and consequently prolonged survival [Tam, 2007]. Clinical trials assessing single agent chemotherapy were followed by studies investigating combination chemotherapies which showed no significant difference in overall survival [Shanafelt, 2007]. Subjects receiving monotherapy or combination chemotherapy experience a range of different levels of toxicity [Abbott, 2006]. Currently, fludarabine and cyclophosphamide combined with Rituxan (FCR) seems to be the most potent regimen, both in previously untreated and relapsed patients [Hallek, 2008; Tam 2008]. In general, as with most clinical studies, all these trials endorse strict eligibility criteria often excluding subjects older than 65 plus those with inferior organ function. This causes a limitation in assessing the suitability of these studied therapy regimens regarding their efficacy and tolerability for the treatment of unselected patients in practice of which the majority is older and in poor health.

Despite numerous studies with various therapies demonstrating overall and complete response rates in both previously untreated and relapsed or refractory CLL patients [Hallek, 2001; Huhn, 2001; O'Brien, 2001a; O'Brien, 2001b; Keating, 2002; Wierda, 2005], there is no curative treatment and the disease often relapses. There is no current maintenance therapy to extend the time between relapses.

The biological behavior of CLL is similar to follicular lymphoma (FL), wherein the disease is incurable and the clinical course is characterized by a high relapse rate. After relapse, both the response rate and progression-free survival after subsequent salvage regimens steadily decrease [Montoto, 2002]. Recently, in relapsed FL patients, maintenance treatment with the chimeric CD20 mAb, rituximab, resulted in a median PFS of 51.5 months versus 14.9 months with observation only ($p<.001$). Significantly improved PFS was noted regardless of induction treatment (CHOP vs R-CHOP). Additionally, rituximab maintenance also improved overall survival at 3 years (85% vs 77%, $p=.011$) [van Oers, 2006]. Similar results of improved PFS and overall survival with rituximab maintenance in FL patients have been noted [Forstpointner, 2006; Hochster, 2009].

While rituximab monotherapy is not very effective in previously untreated or relapsed CLL patients, possibly due to the relatively low CD20 expression on CLL cells [Byrd, 2001], a recent small phase II study with rituximab consolidation and maintenance treatment showed a significantly longer response duration in patients with minimal residual disease (MRD)-positive CLL in first remission after fludarabine induction [Del Poeta, 2008].

2.3 Ofatumumab

Ofatumumab is a fully human monoclonal antibody (mAb), IgG1κ, targeting a unique epitope on the CD20 molecule expressed on human B-cells, resulting in increased binding affinity to CD20, prolonged dissociation rate, and increased cell kill due to greater complement dependent cytotoxicity (CDC) activity and similar antibody dependent cell mediated cytotoxcity (ADCC) activity, especially in low CD20 expressing cells [Teeling, 2006]. Thus, depletion of B-cells by ofatumumab treatment may provide clinical benefits to subjects with CD20-expressing cell tumors. In B-CLL, the goal of treatment is to achieve complete abnormal B-cell depletion in the blood and to induce an objective tumor response in the lymph nodes.

In a Phase I dose-ranging trial of ofatumumab 500mg (n=3), 1000mg (n=3), or 2000mg (n=27) given weekly x 4, 50% PR was observed in the 2000mg dose amongst relapsed CLL patients [Coiffier, 2008]. Objective response significantly correlated with maximum observed concentration (Cmax), minimum observed concentration (Cmin), area under the concentration-time curve (AUC), and half-life (t½) and survival endpoints correlated with exposure. The maximum tolerated dose (MTD) was not reached and

treatment was well tolerated. Adverse events were limited to grade 1-2 infusion reactions and easily managed with premedication. Grade 3-4 neutropenia occurred in only 6% of patients. Non-opportunistic grade 1-2 infections were observed in 51% of patients.

Interim analysis for the pivotal trial evaluated 154 patients with refractory CLL (Study Hx-CD20-406). In the 138 evaluable patients, approximately half were refractory to both fludarabine and alemtuzumab and the other patients were refractory to fludarabine and considered inappropriate for alemtuzumab due to bulky disease of the lymph nodes. An objective response rate of approximately 50% consisting of 30 partial responses was achieved in the fludarabine and alemtuzumab refractory group and an objective response rate of approximately 44% was achieved in the fludarabine refractory group including 1 complete response and 34 partial responses. In this study, ofatumumab was generally well tolerated by the patients. The most frequently reported adverse events (>15% frequency) were pyrexia, diarrhea, fatigue, cough, neutropenia, anemia and pneumonia. There were no unexpected safety findings. Studies clearly indicate monoclonal antibodies (mAbs) play an important role in the treatment of CLL. Anti-CD20 mAbs with a low toxicity can be applied advantageously in subjects who cannot tolerate highly toxic treatments (i.e. advanced age), in combination with chemotherapy and as maintenance treatment. Ofatumumab preclinical data demonstrates superior CDC activity in CLL compared to rituximab. Based on this, therapeutic combinations that may exploit the enhanced CDC potential would be hypothesized to improve outcome.

2.4 Fresh Frozen Plasma (FFP)

FFP is the fluid portion of one unit of human blood that has been centrifuged, separated, and frozen solid at −18 °C (−0 °F) or colder within eight hours of collection. FFP contains the labile as well as stable components of the coagulation, fibrinolytic and complement systems. In addition, fats, carbohydrates and minerals are present in concentrations similar to those in circulation. Although well-defined indications exist for the use of FFP in single or multiple coagulation deficiencies, indications for many of its other uses may be empiric. These indications generally are limited to the treatment of deficiencies of coagulation proteins for which specific factor concentrates are unavailable or undesirable. In addition, circumstances exist in which FFP has been employed and is believed to be of therapeutic value, but data supporting its efficacy are limited or unavailable (e.g., multiple coagulation protein deficiencies in the uncontrollably bleeding patient). Because such patients are often critically ill and satisfactory alternative therapy may not be at hand, FFP may be appropriate. FFP is efficacious for treatment of deficiencies of factors II, V, VII, IX, X, and XI when specific component therapy is neither available nor appropriate. FFP is also a rich source of complement proteins and previous studies have demonstrated effective replacement in patients with hereditary complement deficiencies, autoimmune disease and cancer. Complement is crucial for the physiological processing of immune complexes and the beneficial effect of reconstituting the deficient complement component is likely to be at least in part the result of temporarily restoring this biological role. Evidence to support this includes the demonstrations that: (i) the uptake of immune complexes by the spleen is absent in complement C2 deficiency but restored after the administration of FFP; and (ii) circulating levels of immune complexes fell in a C2-deficient individual following plasma infusion [Rudmann, 2005].

2.5 Rationale

While there have been significant advances in the understanding of the pathogenesis of CLL and innovative new strategies are being explored, few have resulted in a significant change in the survival. The vast majority of patients with this disease are elderly and often they cannot tolerate standard multi-agent chemotherapeutic or biochemotherapeutic approaches. Based on this, less toxic and more effective treatment options are needed. Ofatumumab has proven to be effective in patients with relapsed and/or refractory CLL. A phase II study found that patients treated with ofatumumab that were refractory to fludarabine and alemtuzumab had an overall response rate of 42% with a median duration

of response of 6.5 months. While this is a significant improvement in this patient population, improvements in efficacy without substantially increasing toxicity are needed. Previous studies have shown that ofatumumab is more effective than rituximab at activating complement and utilizing complement-dependent cytotoxicity (CDC) [Pawluczkowycz, 2008]. It has been also shown that patients with CLL are complement deficient, especially those that are heavily pretreated [Varga, 1995l, Schlesinger, 1996]. While not thoroughly examined, it is hypothesized that complement levels drop even lower after treatment with large doses of humanized antibodies. Based on this principle, a previous study gave 5 highly refractory CLL patients two units of FFP (as a source of complement) with rituximab (375 mg/m^2) as a single agent, repeated every 1-2 weeks, as needed. All 5 patients had a "rapid and dramatic clinical and laboratory response." In fact, 3 of the patients were rituximab refractory [Kelpfish, 2008]. Toxicity was minimal and the treatment was well-tolerated in all cases. Based on these principles, we propose treating relapsed/refractory CLL patients with FFP in combination with ofatumumab.

3.0 SUBJECT SELECTION

3.1 Number of Subjects

Subjects who meet all the following inclusion/exclusion criteria will be eligible for enrollment into the study. Approximately 42 subjects will be screened to obtain 12 evaluable subjects (assuming 15 % screen failure and 5 % drop out rates).

3.2 Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Patients must have a pathological diagnosis of B-cell CLL

2. Patients must have received prior rituximab therapy and must have recovered from all non-hematologic toxicities. (Previous radiation is allowed as long as patients have recovered from all treatment related toxicities)

3. Patients must meet the following laboratory values:

    - Hgb $\geq$ 9.0 g/dl
    - Platelets $\geq$ 50,000/mm^3
    - Creatinine $\leq$ 2.0 times the institutional upper limit of normal
    - SGOT/SGPT $\leq$ 2.5 times the institutional upper limit of normal (unless due to disease involvement of liver)
    - Total Bilirubin $\leq$1. 5 times the institutional upper limit of normal
    - Alkaline phosphatase $\leq$2.5 times upper limit of normal (unless due to disease involvement of the liver or bone marrow)

4. Patients must be at least 18 years of age.

5. Patients must have a performance status of 0-2 by ECOG criteria (see Appendix I).

6. All patients must be informed of the investigational nature of this study and must sign and give written consent in accordance with institutional and federal guidelines.

3.3 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Subjects who have current active hepatic or biliary disease (with the exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment).

2. Having received rituximab within the prior 2 months

3. Treatment with any known therapeutic or experimental therapy within 4 weeks prior to enrollment, or currently participating in any other interventional clinical study

4. Other past or current malignancy. Subjects who have been free of malignancy for at least 5 years, have a history of completely resected non-melanoma skin cancer, successfully treated in situ carcinoma, adequately treated basal or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer for which the patient has been disease-free for 5 years are eligible.

5. Prior treatment with anti-CD20 monoclonal antibody or alemtuzumab within 2 months prior to start of therapy.

6. Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis C.

7. History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms or sequelae

8. Known HIV positive

9. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to randomization, congestive heart failure (NYHA III-IV), and arrhythmia unless controlled by therapy, with the exception of extra systoles or minor conduction abnormalities.

10. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease which in the opinion of the investigator may represent a risk for the patient.

11. Positive serology for Hepatitis B (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. HBsAg negative, HBsAB negative, HBsAB positive subjects can be included, * See Monitoring criteria for HBcAb+ and HBV DNA negative subjects on next page.
    - Consult with a physician experienced in care & management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive

12. Positive serology for hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a HC RIBA immunoblot assay on the same sample to confirm the result

13. Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test at screening. **women of child bearing potential must undergo pregnancy testing prior to each dose if the previous pregnancy test was greater than 14 days prior and a pregnancy test at 6 months after the last dose.

14. Women of childbearing potential, including women whose last menstrual period was less than one year prior to screening, unable or unwilling to use adequate contraception from study start to one year after the last dose of protocol therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence.

15. Male subjects unable or unwilling to use adequate contraception methods from study start to one year after the last dose of protocol therapy.

16. Receiving warfarin

*Monitoring criteria for HBcAb+ and HBV DNA negative subjects:

- If HBV DNA is negative, subject may be included but must undergo at least every 2 month HBV DNA PCR testing from the start of treatment during the treatment course.

- Monitoring during the follow-up period will be performed during routine study visits for a minimum follow-up period of six months after the last dose, as long as the subject remains on study. Monitoring frequency during follow-up should occur at a minimum of every 2-3 months. Whenever possible, the monitoring should occur as part of the routine follow-up visit (Note: for most studies, the follow-up visits are 1 month post-dose, 3 months post-dose and 6 months post-dose.

- Prophylactic antiviral therapy may be initiated at the discretion of the investigator.

3.4 Withdrawal Criteria

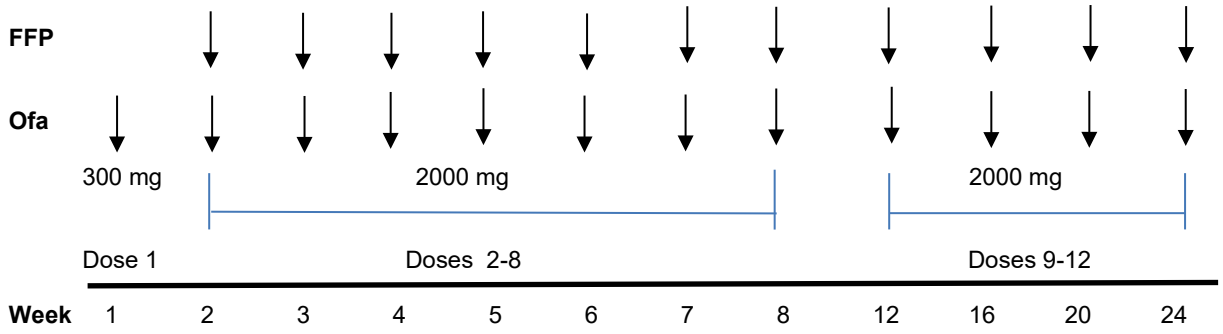
Subjects may be withdrawn from the study at any time if it is the wish of the subject (or their legally acceptable representative) for any reason, the investigator judges it necessary due to medical reasons including disease progression or the subject becomes pregnant. (See also Section 7.4.7) The subject will be evaluated for disease status and survival per the follow-up visit schedule outlined in Section 7.1.

The reason for withdrawal from study participation must be documented.

4.0 INVESTIGATIONAL PLAN

Study Design

TREATMENT SCHEMA



This is an open-label, Phase II study of ofatumumab in patients with relapsed or refractory CLL. Twelve doses of ofatumumab as currently approved over a 24 week period with 2 units of FFP with each dose (with exception of the first dose) will be administered. Ofatumumab will be infused intravenously on day 1 (300 mg initial dose), followed one week later by 2000 mg weekly for 7 doses, followed 4 weeks later by 2000 mg every 4 weeks for 4 doses. Two units (approximately 200 or 250 ml) of FFP will be administered prior to ofatumumab.

The study period will consist of screening, treatment, and follow-up (see Section 7.1 for study calendar and assessments schedule).

5.0 STUDY TREATMENT

5.1 Ofatumumab

Novartis will supply ofatumumab vials presented as 100 mg – acetate formulation, 20 mg/mL, 5 mL fill vials, and 1000 mg – acetate formulation, 20 mg/mL, 50 mL fill vials.

The study medical product, ofatumumab, is a liquid concentrate for solution for infusion presented in glass vials. Ofatumumab will be infused intravenously on day 1 (300 mg initial dose), followed one week later by 2000 mg weekly for 7 doses, followed 4 weeks later by 2000 mg every 4 weeks for 4 doses.

The ofatumumab infusions will be prepared in 1000 mL NaCl sterile, pyrogen free 0.9% NaCl to yield a 0.3 mg/mL, or 2 mg/mL ofatumumab concentration for infusions of 300 mg or 2000 mg, respectively.

Ofatumumab vials must be stored at 2-8°C. Protect from light and do not freeze. No special packaging components, other than the outer white cardboard carton in which the vials are placed, will be used to afford light protection.

Ofatumumab open-labeled product will be for intravenous infusion. Our site is responsible for labeling individual vials for study use.

All items required for administration of study medication (e.g., infusion bags, filters, etc.) will be provided by University of California Davis Comprehensive Cancer Center.

5.1.1 Ofatumumab Pre-Medication

Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment (Table 5-1).

Table 5-1 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*

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

5.1.2 Composition of Ofatumumab Injection 20 mg/mL

The quantitative composition of acetate formulation is 20 mg/mL. This is available in two fill volumes, 5 mL / vial (100 mg/vial) and 50 mL/vial (1000 mg/vial).

Ingredient	**Quantity/ mL**
Ofatumumab	20.0 mg
Sodium Acetate, Trihydrate	6.80 mg
Edetate Disodium, Dihydrate (EDTA)	0.019 mg
Polysorbate 80	0.20 mg
L-Arginine	10.0 mg
Sodium Chloride	2.98 mg
Hydrochloric Acid	to give pH 5.5
Water for Injection	*q.s.* to 1.0 mL

5.1.3 Preparation of Ofatumumab Infusion

Ofatumumab will be prepared as 1000 mL dilution of ofatumumab in sterile, pyrogen-free 0.9% NaCl. The exact time of dilution into the 0.9% NaCl must be written on the label of the infusion bag.

Once diluted into saline, the product is stable for up to 24 hours at ambient temperature. However, the product contains no preservative and should be used as soon as possible after dilution.

Preparation of drug solution for intravenous injection by the site pharmacist or designee will be done in accordance with the protocol, and in these dilution instructions. Ofatumumab intravenous solution will

be prepared using standard dilution methods and following general aseptic practice standard to preparation of IV medications. Eyes and hands should be protected when handling ofatumumab.

For intravenous administration, compatibility of the following components for ofatumumab in clinical studies (i.e., not for commercial product) has been established:

Table 5-2 Dosing Components for Ofatumumab in Clinical Studies

Dosing component	Material of construction	Suggested Vendor
1L Saline Bags	Polyvinyl Chloride (PVC)	Baxter
	Polyolefin [polyethylene* (PE)/polypropylene (PP)]	Baxter, B. Braun
Administration Set	PVC	Baxter
	PVC lined with Polyethylene	B. Braun
Filter Extension Set	Sterilizing-grade (0.22 μm) hydrophilic filter	Durapore brand by Millipore
	Lines made of PVC, filter membrane material polyether sulfone	Baxter
	Lines made of PVC lined with Polyethylene, filter membrane material polyether sulfone	Alaris/Cardinal Health

Preparation of the 1000 mL infusion bags should be done on the day of planned infusion.

* polyethylene (IUPAC name: polyethene)

5.1.3.1 Materials for Preparation and Administration of Infusion

The following materials are needed when preparing and administering the infusion:

1000 mL sterile pyrogen free 0.9% saline (NaCl) infusion bag(s). The solution can be kept at ambient temperature for a maximum of 24 hours after preparation; however, the product does not contain a preservative and dosing should begin as soon as possible after dose preparation.

Ofatumumab 100 mg and 1000 mg vials (supplied by Novartis)

Needles and syringes (50 mL sterile syringe) not supplied by Novartis

Intravenous (IV) cannula (not required if subject has central venous access) [not supplied by Novartis]

Infusion pump and infusion tubing set (not supplied by Novartis)

In-line low protein binding, polyether sulfone filter 0.2 μm (please make sure a spare filter is available in case the filter needs to be changed) [not supplied by Novartis]. Please note that the commercial filters are sterilizing-grade (0.22 μm) hydrophilic Durapore by Millipore.

5.1.3.2 Dilution of Ofatumumab

- Ensure the correct container number is used.
- Take a 1000 mL infusion bag (sterile pyrogen free 0.9% saline), remove and dispose of the appropriate amount of saline according to Table 5-3 or Table 5-4
- Draw the required amount of ofatumumab according to Table 5-3 (100 mg vials) or Table 5-4 (1000 mg vials) below
- Inject ofatumumab into the saline bag
- Invert the infusion bag slowly 3 times, avoiding formation of any foam
- Label the infusion bag with the completed label

Table 5-3 Preparation of Ofatumumab Infusion: 100 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
300 mg	1000 mL	15 mL	15 mL (3 vials, 5 mL/vial)
2000 mg	1000 mL	100 mL	100 mL (20 vials, 5 mL/vial)

Table 5-4 Preparation of Ofatumumab Infusion: 1000 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
2000 mg	1000 mL	100 mL	100 mL (2 vials, 50 mL/vial)

5.1.4 Ofatumumab Infusion Set up

Ofatumumab must be administered by i.v. infusion through an in-line filter and through a well-functioning i.v. catheter (i.v. cannula) into a vein in the arm (or other venous access) by an infusion pump.

Please Note: It is mandatory to use an in-line low protein binding 0.2 micron polyether sulfone filter for all IV dosing of ofatumumab drug product.

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Ofatumumab should not be mixed with any other medication. If ofatumumab is to be dosed through an in-dwelling catheter, then, any previous medication should be removed by flushing with normal saline prior to dosing with ofatumumab.

- Check subject ID against the label on the infusion bag and ensure the expiry of the solution. The solution must be administered in its entirety to the subject within 24 hours from time of preparation.
- Attach the 1000mL infusion bag to the infusion set (if not done at the pharmacy).
- Attach the in-line filter to the infusion set (closest to the subject; see Figure 1). **Note: The in-line filter must be used during the entire infusion.**
- Prime the infusion set and filter with ofatumumab (if not done at the pharmacy).
- In case of a problem with the filter (i.e. clogging/blockage), please change, re-prime the new filter, and continue the infusion.
- In case of problem with infusion set, follow local procedures.
- Check the backflow from the i.v. cannula according to routine practice at site
- Set the pump at the initial infusion rate 12mL/hr for the first infusion and 25mL/hr for the subsequent infusions (if no grade ≥ 3 infusion-associated AEs were observed in the previous infusion)
- Start the infusion using the following infusion rates

Table 5-5 Infusion rate of 1st ofatumumab infusion (300 mg)

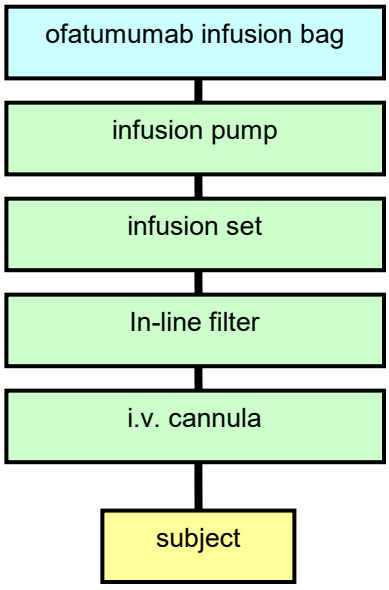
Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

Table 5-6 Infusion rate of 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

No ofatumumab dose modifications are permitted.

Figure 1 Infusion Set-Up Schematic



6.0 FRESH FROZEN PLASMA ADMINISTRATION

Fresh frozen plasma will be administered per University of California Davis Health System GUIDELINES FOR ADULT TRANSFUSION (Patient Care Standards, XIII-12) (Approved by Medical Staff Executive Committee 11/06).

7.0 STUDY ASSESSMENTS AND PROCEDURES

7.1 Study Calendar and Assessment Schedule

All visits should be +/- 7 business days with the exception of day 1 of cycle 1.

Procedures	**≤ 14 days prior to registration†**	**Treatment**				**Follow-up**	
		Doses 1-4 (Every week – Week 1, 2, 3, 4)	Doses 5-8 (Every week – Week 5, 6, 7, 8)	Doses 9-12 (Every 4 weeks - - Week 12, 16, 20, 24)	Treatment withdrawal	1,3, 6 months following last ofatumumab dose	9, 12, 15, 18, 21, 24 months following last ofatumumab dose
Medical History	**X**						
Disease History	**X**						
Therapy History	**X**						
Efficacy Assessments							
[1]Bone marrow/ aspirate biopsy	**X**					**X**	
[2]CT/PET	**X**					**X**	**X**
Safety Assessments							
[3]Physical Exam or Evaluation	**X**	[3]**X**	[3]**X**	[3]**X**		**X**	**X**
[3]ECOG	**X**	[3]**X**	[3]**X**	[3]**X**		**X**	**X**
Height	**X**						
Weight	**X**					**X**	**X**
Vital Signs	**X**	**X**	**X**	**X**		**X**	
12-lead ECG	**X**						
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**
[4]FFP (2 units)		[4]**X**	**X**	**X**			
Dispense Study Medication							
Ofatumumab		**X**	**X**	**X**			
Lab Assessments							
[5]Hematology	**X**	**X**	**X**	**X**		**X**	**X**
[6]Chemistry	**X**	**X**	**X**	**X**		**X**	**X**
[7]Liver chemistry	**X**	**X**	**X**	**X**			
[8]Complement levels	**X**	**X**		**X**		**X**	**X**

Procedures	≤ 14 days prior to registration†	Treatment				Follow-up	
		Doses 1-4 (Every week – Week 1, 2, 3, 4)	Doses 5-8 (Every week – Week 5, 6, 7, 8)	Doses 9-12 (Every 4 weeks - - Week 12, 16, 20, 24)	Treatment withdrawal	1,3, 6 months following last ofatumumab dose	9, 12, 15, 18, 21, 24 months following last ofatumumab dose
[9]B-cells, IgG, IgA and IgM	**X**					**X**	
[10]HIV Test	**X**						
[11]Serum Pregnancy Test	**X**						
Hepatitis B&C*	**X**						**X**
Survival	**X**					**X**	**X**
***REQUIRED- Subjects who are HBcAb positive** must undergo at least every 2 month HBV DNA PCR testing during the treatment course. Monitoring must also occur during the follow-up period for a minimum of 6 months after the last dose as long as the subject remains in the study at a minimum frequency of every 2 to 3 months.							

† Bone marrow/aspirate biopsy and CT/PET performed within 28 days of registration.

1. BM biopsy will be performed for staging at baseline and if clinically warranted after completion of therapy. If the BM biopsy is positive at baseline it must be repeated once to confirm CR. This will include flow cytometry for minimal residual disease (MRD) status. Bone marrow (or peripheral blood if bone marrow is unavailable must be sent to the cytogenetics laboratory for analysis. If the BM biopsy is negative at baseline, it will not be repeated.
2. CT/PET will be performed for staging at baseline and if clinically warranted after completion of therapy.
3. Patient will see treating physician for physical exam/evaluation and ECOG evaluation every 4 weeks.
4. Two units of FFP will be given with each dose of ofatumumab with the exception of the first dose of ofatumumab.
5. During the treatment phase, obtain hematology pre-treatment and every 2 weeks for the first month, then every month thereafter for at least 6 months after the last dose of ofatumumab.
6. Chemistries include electrolytes, BUN, creatinine and lactate dehydrogenase (LDH). During the treatment phase, obtain chemistries pre-treatment and every 2 weeks for the first month, then every month thereafter for at least 6 months after the last dose of ofatumumab or up to discretion of investigator.
7. Liver chemistries consist of albumin, INR, ALT, AST, total bilirubin, and alkaline phosphatase. During the treatment phase, obtain liver chemistries pre-treatment and every 2 weeks for the first month, then every month thereafter for at least 6 months after the last dose of ofatumumab.
8. Complement will be measured at baseline, before and after the first and second dose of ofatumumab, at week 12, 16, 20 and 24, at completion of therapy, and at follow up only in patients with low complement levels at baseline or after treatment.
9. B-cells, IgG, IgA and IgM will be monitored until they return to baseline or up to two years after the last dose of ofatumumab, or until the subject starts other B-cell depleting therapy.
10. Human Immunodeficiency Virus (HIV) test; If status is unknown.
11. Women of childbearing potential must have a negative pregnancy test at screening. **women of child bearing potential must undergo pregnancy testing prior to each dose if the previous pregnancy test was greater than 14 days prior and a pregnancy test at 6 months after the last dose.

7.2 Efficacy

Efficacy analyses will be performed on data from the Intent-to-Treat Population.

Definition of Response

Response criteria	NCI-WG National Cancer Institute – Working Group	IWCLL International Workshop on Chronic Lymphocytic Leukemia
Complete Response (CR):		
Physical exam (nodes, and/or liver, spleen)	Normal	Normal
Symptoms	None	None
Lymphocytes (x 10^9/L)	$\leq$4	<4
Neutrophils (x 10^9/L)	$\geq$1.5	
Platelets (x 10^9/L)	> 100	
Hb (g/dL)	>11 (untransfused)	Not stated
Bone marrow lymphocytes (%)	>30; no nodules	Normal, allowing nodules or focal infiltrates
Partial Response (PR):		
Physical exam (nodes, and/or liver, spleen)	$\geq$50% decrease	Downshift in stage
Plus $\geq$1 of:		
Neutrophils (x 10^9/L)	$\geq$1.5	
Platelets (x 10^9/L)	>100	
Hemoglobin (g/dL)	>11 or 50% improvement	
Duration of CR or PR	$\geq$2 months	Not stated
Progressive disease (PD):		Upshift in stage
Physical exam (nodes, liver, spleen)	$\geq$50% increase or new	
Circulating lymphocytes	>50% increase	
Other	Richter's syndrome	
Stable disease (SD):	All others	No change in stage

Bone Marrow Examination

A bone marrow aspirate and biopsy are generally not required to make the diagnosis of CLL. Nevertheless, CLL is a disease of the bone marrow, and it is appropriate to evaluate a major site of involvement. The aspirate smear must show >= 30% of all nucleated cells to be lymphoid. A bone marrow examination also provides useful prognostic information by determining whether there is diffuse or non-diffuse involvement, and permits an assessment of the erythroid precursors and megakaryocyte **.**

7.3 Safety Assessments

7.3.1 Liver chemistry stopping and follow-up criteria

Liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology. The sponsor-investigator will review all events which meet liver chemistry stopping criteria to determine if the event was due to:

- tumor lysis, disease related liver involvement
- other identified cause and to exclude drug induced liver injury (DILI) due to ofatumumab

The criteria are relevant for all Ofatumumab studies because transient elevations in LFTs may be due to tumor lysis which is of clinical benefit, disease related liver involvement or due to other chemotherapy rather than drug induced liver injury from ofatumumab.

If the event is determined to be due to causes other than ofatumumab DILI and improvement is observed after withdrawal of ofatumumab, rechallenge may be attempted if deemed appropriate by the sponsor-investigator and in addition to consent of the subject.

7.3.1.1 Liver chemistry interruption/stopping criteria

1. ALT >3xULN **and** bilirubin > 2 x ULN (>35% direct bilirubin; bilirubin fractionation required*)

2. ALT >8xULN

3. ALT >5xULN for more than 2 weeks

*__NOTE__: If *serum bilirubin fractionation not immediately available, study drug should be discontinued if ALT > 3 x ULN and bilirubin > 2 X ULN. Serum bilirubin fractionation should be performed if testing is available. . If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.*

When any of the liver chemistry stopping criteria is met, do the following:

- Immediately stop study treatment
- Hold Ofatumumab for two weeks, repeat liver chemistry testing at least twice weekly, and report to sponsor-investigator to discuss the possibility of re-challenging with ofatumumab*. Note: The 2 week time point for stopping medication was chosen because it will distinguish from LFT elevations due to tumor lysis which should have resolved within this time period. Medication is interrupted and it is a clinical and patient decision if ofatumumab may be re-started. The risk: benefit ratio is different in an oncology setting and an efficacious therapy may be life-saving.*
- Report SAE to Novartis within 24 hours

- All events of ALT > 3xULN **and** bilirubin > 2xULN (>35% direct bilirubin) (or ALT>3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
- NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT > 3xULN **and** bilirubin > 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

Liver chemistry follow-up assessments are to be followed until liver chemistries resolve, stabilize or return to baseline values.

7.3.1.2. Liver Chemistry Follow-up Assessments

Chemistry tests/ assessments below are to be performed at the time of the event and then continued and/or discontinued at the discretion/judgment of the sponsor-investigator; please refer to stopping criteria within this document.

Viral hepatitis serology including:

- Hepatitis A IgM antibody;
- Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
- Hepatitis C RNA;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
- Fractionate bilirubin, if total bilirubin >2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins
- Increased alcohol use

The following assessments are required for subjects with ALT >3xULN and bilirubin >2xULN (.35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Stopping Criteria:

- For subject meeting liver stopping criteria 1:
    - A repeat of liver chemistries within 24 hours, liver event follow-up assessments and close monitoring
    - A specialist or hepatology consultation is recommended
    - Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.
- For subjects meeting criteria 2 or 3:
    - A repeat of liver chemistries within 24 to 72 hours for repeat liver chemistries and liver event follow-up assessments
    - Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values
- After holding ofatumumab for two weeks:
    - If the treatment is exhibiting efficacy **and** the subject wants to continue therapy after being informed of the results of liver chemistry testing, then the ofatumumab may be re-started.
    - Liver chemistries and follow-up assessments should be monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to baseline values, at which point monitoring should be continued per protocol
- Subjects with ALT >3xULN **but** <5xULN **and** bilirubin <2xULN without hepatitis symptoms or rash, and who may be monitored weekly for at least 4 weeks, then the following actions should be taken:
    - Subjects can continue ofatumumab
    - Weekly repeat of liver chemistries until they resolve, stabilize, or return to baseline values, then monitor liver chemistries as per protocol assessment schedule

If at any time the subject meets any of the liver chemistry stopping criteria, then proceed as described above.

If after 4 weeks of monitoring, ALT<3xULN and bilirubin<2xULN monitor twice monthly until liver chemistries normalize or return to within baseline values

7.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1 Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication (overdose per se will not be reported as an AE/SAE)

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- B cell depletion and hypogammaglobulinemia due to ofatumumab treatment

7.4.2 Definition of a SAE

A serious adverse event is an undesirable sign, symptom or medical condition which:

a. Results in death

b. Is life-threatening

c. Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

   - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
   - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
   - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- social reasons and respite care in the absence of any deterioration in the patient's general condition

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.4.3 Toxicity Assessments of AEs and SAEs

The investigator is required to make an assessment of the toxicity grade of each AE or SAE reported. In this protocol, the maximum toxicity grade of each non-hematologic AE/SAEs will be evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

It is important to consider low blood counts at the initiation of therapy when evaluating hematologic toxicity of CLL subjects.

7.4.4 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator **are** to be recorded as AEs or SAEs.

- All events meeting liver stopping criteria must be recorded as an SAE.

- However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

- B cell depletion, IgG below LLN, low CD19+ count, and hypogammaglobulinemia due to treatment with ofatumumab are **not** to be reported as AEs or SAEs.

- Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is **not** to be reported as a SAE.

7.4.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

7.4.6 SAE Reporting

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

Reporting to the FDA

All serious, unlabeled, (unexpected) adverse events will be reported to the FDA as required by 21 CFR 312.32. (Investigational New Drug) https://www.accessdata.fda.gov/scripts/medwatch/. All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Cancer Center Clinical Trial Support Unit (CTSU) or participating site policies. The UC Davis IRB can be reached at (916) 703-9151.

Reporting to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring

- after the patient has provided informed consent and up to a minimum of 6 months after the last dose of study product or until the end of the follow-up period whichever is longer. All SAEs regardless of causality will be collected until the end of the follow-up period. SAEs are no longer required to be reported if a subject begins treatment with another therapy.
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. This includes serious, related, not related, labeled (expected) and, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within24 hours.

Send SAE Reports to Novartis via Fax:

Novartis Drug Safety and Epidemiology
Fax: 877-778-9739

Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: [redacted]

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation. If the SAE is not previously documented in the Ofatumumab Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.

Subjects who are HBsAg negative, anti-HBc positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring. Consult with a physician experienced in care & 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 Novartis Clinical Team. 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.

7.4.7 Pregnancy

Any pregnancy that occurs during study participation must be reported to Novartis. To ensure subject safety, each pregnancy must be reported to Novartis within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study product, must be promptly reported to Novartis.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Novartis as described above.

Novartis Drug Safety and Epidemiology
Fax: [redacted]
Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: [redacted]

8.0 STATISTICAL CONSIDERATIONS

8.1 Datasets to be Analyzed

The primary study endpoint is response to therapy (defined as a CR, or PR, and progression free survival). The secondary endpoints are toxicity, overall survival, complement levels (CH50 and C2 levels) will be measured from the time of entry into the clinical trial.

Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

8.2 Statistical Methodology

Thirty-six patients will be treated with ofatumumab and FFP at dose levels previously established to be safe. Objective response (CR + PR) will be monitored using Simon's optimal 2-stage minimax design. This study design is optimal in that sense that it minimizes the expected sample size among competing designs. The OR rate of ofatumumab in patients that have failed fludarabine and alemtuzumab is approximately 42% respectively. However, patients enrolled on this study will have received prior rituximab therapy and the objective response rate in such patients retreated with rituximab is estimated to be 25%. A 20% increase in the objective response rate with the addition of FFP to 45% would justify evaluation of this regimen in larger, more definitive trials. We assume a one-sided type I error rate of 5% and desire at least 80% power to conclude that this regimen elicits and objective response rate significantly greater than 25% if the true response rate of this regimen is 45% or higher. Under these assumptions, if 4 or fewer OR's are observed in the first 17 patients, the principal investigator may conclude that the regimen is insufficiently active to warrant further study. Otherwise, accrual will continue to a total of 12 patients. If 14 or more OR's are observed in 36 patients, this regimen will be deemed sufficiently active to warrant further study.

8.3 Analysis Plan

Continuous variables (e.g., age, hematology values, complement levels) will be summarized using the mean (s.d.) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of patient characteristics (e.g., low/high complement levels) on the objective response rate. The distribution of time-to-event endpoints (e.g., CR duration, overall survival) will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups of patients (based on known prognostic factors, e.g cytogenetics, CD38, Ig mutational status) will be made using the logrank test. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes.

8.4 Safety Evaluation

Data from all subjects who receive any study drug will be included in the safety analyses. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. Unacceptable toxicity (> grade 3) experienced in patients will be monitored according to guidelines for monitoring toxicity in pilot/phase II trials using sequential probability ratio test based criteria. The guidelines will be used to raise a flag if the number of patients who experience unacceptable toxicity is greater than 20%. Toxicity information recorded will include the type, severity, date of onset, date of resolution, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity. Baseline information (e.g. the extent of prior therapy, extent of disease) and demographic information will be presented, as well, to describe the patients treated in this Phase II study.

9.0 STUDY CONDUCT CONSIDERATIONS

9.1 Registration Guidelines

9.1.1 Study Registration

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Clinical Trials Support Unit (CTSU) policy. To register a patient, the data manager must complete the Eligibility Checklist and the Patient Registration Form. A patient accession number will then be assigned. Administration of study product may not be initiated until the patient is registered.

9.1.2 Protocol Deviations

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center CTSU policies or participating site policies.

9.2 Minority and Gender Statement

Recruitment is open to all minorities and both genders. Although distributions may vary by disease type, our recruitment procedures have been developed to enroll patients who are representative of the respective target population.

9.3 Ethical and Regulatory Considerations

All patients will have signed an informed consent for participation in research activities in accordance with all institutional, NCI and Federal regulations, and will have been given a copy of the Experimental Subject's Bill of Rights.

9.4 Quality Assurance

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring Plan.

Quality control will be maintained by the CTSU Quality Assurance team according to CTSU policy.

9.5 Record Retention

9.5.1 Confidentiality of Records

The original data collection forms will be stored in secure cabinets in the UCD Clinical Trials Support Unit.

9.5.2 Patient Consent Form

In accordance with UCD CTSU policy, an original signed and dated participant Informed Consent document will reside in a secured location within the UCD CTSU. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System

Information Management for inclusion in the participant's UCD Health System Medical Record or participating site's medical record.

9.5.3 Registration Eligibility Worksheet

At the time of registration, the information requested on the Eligibility Checklist will be submitted to the Protocol Coordinator.

9.6 Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in Section 7.4, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) Clinical Trials Support Unit (CTSU) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator (CRC), meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable.

According to the UCDCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drug being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC Scientific Review Committee (SRC) determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

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11.0 APPENDICES

Appendix 1: Performance Status Scale

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

Appendix 2: Arzerra® (Ofatumumab) Prescribing Information

(The hyperlink below is to the revised Prescribing Information document, Revised: 04/2015)

http://www.pharma.us.novartis.com/product/pi/pdf/arzerra.pdf

Appendix 3: Data Submission Schedule

All data will be collected using UC Davis data collection forms. Copies of the completed forms will be submitted to UC Davis data coordinating center for data entry and storage in a secure location. The original data collection forms will reside at the originating institution in secure location.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form

- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  In-House Pre-Study Evaluation Form (IH-102)

- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form

- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  Adverse Event/Drug Relationship Form

- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  In-House Treatment Cycle Form (IH-201)

- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:
  Tumor Measurement Log

- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Clinical Trials Support Unit: Notice of Protocol Deviation

- SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:
  Follow-Up Form (IH-302)

- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL.

Appendix 4: Drug Request Form
Drug Supply Request Form

PI: Joseph Tuscano, MD
Novartis Study Number: COMB157AUS19T

Title of Study: PHASE II TRIAL OF OFATUMUMAB AND FRESH FROZEN PLASMA IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Read carefully. For Investigator Sponsored Studies (ISS), the PI may need to hold an IND. You are responsible for following CFR and GCP for labeling and dispensing (21 CFR 312.6) study medication.

Novartis will provide content labeled-Ofatumumab vials presented as either 100mg – acetate formulation, 20mg/mL, 5mL fill vials or 1000mg – acetate formulation 20mg/mL, 50mL fill vials.

Ofatumumab vials must be stored at 2-8°C. Protect from light and do not freeze. No special packaging components, other than the outer white cardboard carton in which the vials are placed, will be used to afford light protection. The prepared solution remains stable for up to 24 hours at ambient temperature. Since the product contains no preservative, it should be used as soon as possible after dilution.

Ofatumumab open-labeled product will be for intravenous infusion. The site is responsible for labeling individual vials for study use. All other items required for administration of study medication, e.g. infusion bags, filters etc, are to be provided by the site.

PLEASE NOTE: UPON NOVARTIS RECEIPT OF ALL REQUIRED DOCUMENTION, IT MAY TAKE UP TO 2 WEEKS FOR DRUG TO BE SENT TO YOU.

The *full shipping address* for drug supply:

Pharmacist: Name, (shipping) address, contact info (email and phone) of the pharmacist or person handling the study drug	**add contact info here**

Please complete the following 3 items.

Step 1:

Total Number of Subjects	**Best Estimate of Patient accrual/mo**	**Dose(s) in mg**	**Total dose (mg) per patient; Life of Study**	**Total # vials (100mg/vial); per patient**	**Total Duration of study (mos)**
_____	_____		_____	_____	_____

Step 2:
TOTAL VIALS REQUIRED FOR STUDY (# subjects x total # vials per patient) _____

Step 3:

Specific number of vials for initial study shipment (i.e., 3 month supply)	**Estimated # of patients (3 months) =** _____ **1. Total # vials requested for first shipment =** _____ **(NB: 1 vial x 5 mL fill = 100mg dose)** **2. Total # vials requested for first shipment =** _____ **(NB: 1 vial x 50 mL fill = 1000mg dose)**

Best estimate of Study Start (First Subject First Visit)_____(dd/mmm/yyyy)

SEND TO:

[redacted]