A phase II study of intensive consolidation and stem cell mobilization therapy with ofatumumab, etoposide, and high-dose ara-C (OVA), followed by autologous stem cell transplantation in high-risk patients with relapsed/refractory Diffuse Large B-Cell Lymphoma

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Table of Contents

Study Summary

Title	A phase II study of intensive consolidation and stem cell mobilization therapy with Ofatumumab, etoposide, and high-dose ara-C (OVA), followed by autologous stem cell transplantation in high-risk patients with relapsed/refractory Diffuse Large B-Cell Lymphoma
Study Design	*Phase II, single institution pilot study*
Study Duration	*24 months accrual, 24 months followup*
Objectives	Primary Objective: To demonstrate the ability of Ofatumumab in combination with etoposide and cytarabine to mobilize peripheral blood stem cells and lead to a high compelte metabolic response rate prior to autologous stem cell transplantation in rituximab pre-treated patients with high-risk relapsed or refractory DLBCL. Secondary Objectives: 2.2.1 To evaluate stem cell engraftment following successful mobilization. 2.2.2 To determine PFS following treatment with Ofatumumab in combination with etoposide and high-dose ara-C (OVA) and subsequent autologous stem cell transplantation. 2.2.3 To measure the effect of OVA on other clinically meaningful endpoints. 2.2.4 To measure the FDG-PET conversion rate from PR to CR following OVA and its association with clinical outcomes. 2.2.5 To examine potential relationships between Ofatumumab concentration and clinical outcomes. 2.2.6 To study the safety and tolerability of OVA. 2.2.7 To store tumor tissue for future molecular subtyping. 2.2.8 To evaluate minimal-residual disease testing in the setting of transplantation.
Number of Subjects	*24 patients*
Main Eligibility Criteria	KEY INCLUSION CRITERIA Diagnosis of CD20+ WHO diffuse large B-cell lymphoma or primary mediastinal B-cell lymphoma. Transformation of previously-diagnosed low-grade lymphoma is excluded. Refractory to or relapse following a rituximab/anthracycline first-line regimen High-risk disease as defined by one of the following: • First relapse after CR within 12 months of initiation of front-line therapy • Less than CR to front-line therapy • sAAIPI of 2 or higher at the time of relapse (see attachment 14.2) Receipt of no more than three prior chemotherapy regimens. Monoclonal antibody therapy and involved field radiotherapy are not included in this number. Prior use of ofatumumab is allowed if there has been no disease progression following that therapy (i.e. ofatumumab-based salvage regimens allowed) KEY EXCLUSION CRITERIA Progression following prior ofatumumab salvage therapy

	Active central nervous system or meningeal involvement by lymphoma. Patients with a history of CNS or meningeal involvement must be in a documented remission by CSF evaluation and contrast MRI imaging for at least 3 months prior to study entry. Bone marrow involvement with more than or equal to 15% lymphoma cells following salvage therapy. Evidence of myelodysplasia on any bone marrow biopsy prior to initiation of therapy. Known HIV infection Positive serology for Hepatitis B (HB) defined as a positive test for HbsAg and a detectable HBV DNA viral load. If negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HBV DNA test will be performed and if positive the subject will be excluded. 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. Prophylactic antiviral therapy may be initiated at the discretion of the investigator. Positive serology for hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a HCV PCR to confirm the result Receipt of live virus vaccination within 4 weeks prior to planned initiation of study treatment.
Study Product, Dose, Route, Regimen	*Ofatumumab 1000 mg IV on days 0,7,14,21* *Given concurrently with:* *Etoposide 10 mg/Kg IV over 24 hours daily, days 1-4* *Cytarabine 2000 mg/m2 IV twice daily, days 1-4*
Statistical Methodology	This is a single-institution, single-arm, open-label Phase II study of Ofatumumab in combination with etoposide and high-dose cytarabine as an intensive consolidation and stem cell mobilization regimen in patients with relapsed/refractory diffuse large B-cell lymphoma. The primary efficacy endpoint of the study is the mobilization-adjusted complete response rate (maCR) which is defined as the proportion of patients achieving complete response to the treatment upon successful stem cell mobilization, defined as at least 2 x10^6 CD34+cells/Kg of actual body weight. Secondary endpoints include time to neutrophil and platelet engraftment following ASCT, PFS in this high-risk patient population and other survival-time measures of clinical efficacy, i.e. OS, TTP, EFS, and CR/Pr proportion at day +90. Our study will also measure the FDG-PET conversion rate from PR to CR following OVA and correlate post-OVA PET results with PFS, TTP, and OS. We will examine potential relationships between Ofatumumab concentration at selected time points and PFS, TTP, OS. We will perform MRD testing at baseline, at the time of stem cell collection, and following ASCT, and will correlate the results to clinical endpoints. Finally, safety will be evaluated with regard to infusion-related reactions, B-cell number, hypogammaglobulinemia, and long-term hematologic toxicity. Patients who have received a single infusion of study drug (day 0 of OVA) will be included in the statistical analyses. We are planning to accrue 24 subjects over the course of 2 years with an additional 2-year follow-up. In terms of the

composite primary endpoint, the historical CR rate after 2 cycles of salvage therapy among high risk, rituximab refractory patients is between 25% and 50% of the overal responses (i.e CR/(CR+PR).[8, 19, 20] Furthermore, the chance of a mobilization failure among complete an dpartial responders observed in the CORAL study is 15%.[9] We thus expect the null value of the composite endpoint of maCR to be 25% (~40% CR-15% mobilization failure). Given the excellent historical CR rates with intensive consolidation and the very low risk of mobilization failures, we expect the alternative maCR rate to be 50%. Based on the exact probability with type I error of 10% and 1-sided test, a sample size of N=24 in the single arm study will have > 80% power to detect the maCR rate for the following hypothesis: H0: p0<25% (40%CR/15%mobilization-failure) vs Ha: p1>50% (55%CR/5%mobilization-failure under OVA). The following table shows statistical power for the test of the null hypothesis under the assumed maCR of 25% and for various mobilization-adjusted complete response rates with 24 subjects (alpha=10% under 1-sided exact test):

maCR rate	**Statistical Power**
25% vs 40%	51%
25% vs 45%	70%
25% vs 50%	**84%**
25% vs 55%	93%
25% vs 60%	97%

An interim analysis for futility and safety will be performed when 12 subjects are enrolled. We will define the futility as >50% stem cell mobilization failure as excessive and unacceptable. If six or fewer (< 50%) subjects have adequate stem cell mobilization, the enrollment will not continue and the study will be closed for treatment futility. Otherwise we will enroll 12 additional patients to complete study for full maCR efficacy analysis. At the same time as the interim analysis for futility, we will also perform an interim evaluation for safety, which is defined as >30% SAE as too toxic and unacceptable. If 4 or more (>30%) of the first 12 patients treated are observed to have protocol-defined unacceptable toxicity, the study will be closed for lack of safety. If the stem cell collection success rate is less than 50%, the probability of early stopping due to futility is 61%. If the toxicity rate is greater than 30%, the probability of early stopping due to safety is 64%.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 DLBCL

Diffuse Large B-cell Lymphoma (DLBCL) is the most common lymphoma worldwide. Even though rituximab/anthracycline-containing chemotherapy (e.g. R-CHOP) can cure a significant proportion of patients with this disease in the modern era, approximately 40% are either refractory to front-line treatment or relapse following therapy.[1-3] The standard of care for these relapsed/refractory patients involves salvage chemotherapy (e.g. R-ICE, R-DHAP, R-ESHAP, etc) followed by autologous stem cell transplantation (ASCT) in patients who are chemosensitive to salvage.[4]

The obstacles to curing patients following a relapse are several. These include: 1) poor response to salvage therapies, and thus ineligibility for subsequent ASCT; 2) inadequate mobilization of stem cells in these densely pre-treated patients; and 3) residual disease following salvage therapy.[5, 6] Historically, patients at high-risk for treatment failure include those refractory to initial therapy or relapsed within 12 months of treatment initiation [7] and those with a high age-adjusted international prognostic index at the time of relapse (sAAIPI). [8] More recently, the international CORAL study has also identified prior treatment with rituximab to be significantly associated with inferior response rates to rituximab-containing salvage therapy and inferior long-term survival outcomes after ASCT.[9] This effect appears to be limited to those patients who relapse within 12 months of initiation of therapy, and 2-year PFS in this population starting from initiation of salvage therapy was only 15%. Out of the 187 patients in that group, only 68 (36%)made it to transplantation, and this subgroup had a 2-year PFS of 39% following ASCT. [9] Additionally, 15% of responding patients didn't make it to ASCT solely due to inadequate stem cell collection.

1.2 Intensive Mobilization

We have developed an intensive approach for treating relapsed patients with high-risk aggressive lymphoma prior to transplantation. [10] Following 2-3 cycles of salvage therapy at relapse, high-risk patients undergo an additional cycle of therapy with either etoposide, cyclophosphamide, and rituximab (CER) or etoposide, cytarabine, and rituximab (EAR) to further decrease tumor burden and to provide in-vivo purging of the stem cell graft. Stem cells are then collected following this regimen as opposed to standard mobilization (high-dose cyclophosphamide or R-ICE) used for the low-risk patients. In our reported cohort, treatment with intensive mobilization was well-tolerated and resulted in excellent stem-cell mobilization with no collection failures. Moreover, event-free survival among the high-risk patients with DLBCL going to ASCT after CER or EAR was comparable to that of low-risk patients treated with standard mobilization (Figure 1a) and overall survival was significantly improved (Figure 1b). In this high-risk cohort, our observed 4-year EFS and OS rates are 67% and 76% respectively, comparing very favorably to the reported rates from CORAL (4-year PFS 39%).[10]

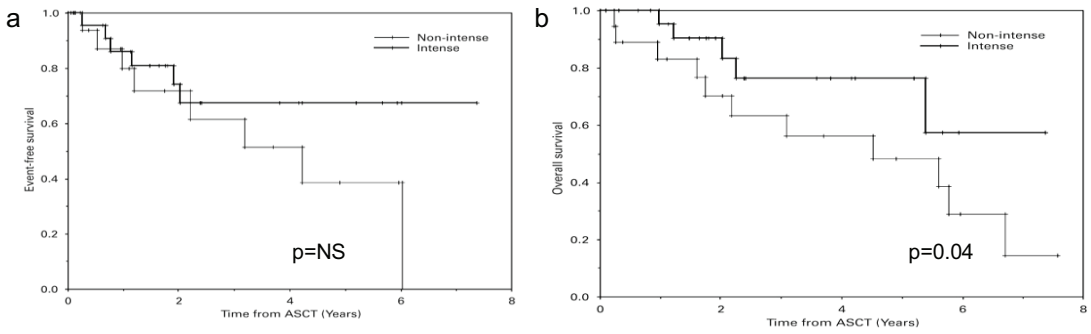


Figure 1: Event-free (a) and overall (b) survival among 43 patients with DLBCL who underwent autologous stem cell transplantation per protocol. Reproduced from Damon *et al* [10]

1.3 FDG-PET as a predictive marker in relapse

PET imaging using fluorodeoxyglucose (^{18}F) has been conclusively shown to predict response duration, progression-free, and overall survival at the completion of first-line therapy in patients with DLBCL and other lymphomas.[11] It has consequently been incorporated in the response assessment criteria for lymphoma and has become the standard of clinical care.[12] Several studies are underway to address the utility of interim PET in tailoring frontline therapy for selected groups of patients.

In the relapse setting, there is evidence to suggest that FDG-PET assessment following salvage therapy is also predictive of outcomes following ASCT. [13-18] Specifically, patients in PET+ PR prior to ASCT have long-term disease-free survival rates in the order of 30-40% compared to 70-80% for the PET- CR patients. Historically, PET response data are limited in the setting of salvage therapy for high-risk patients with DLBCL. Based on the available studies, we believe the PET-negative CR rate following 2 cycles of salvage to be between 25% and 50% among overall responders in this high-risk group of patients [CR/(CR+PR)= 25-50%].[8, 19, 20] We hypothesize that if we can improve the PET- CR rate with intensive consolidation therapy and thus achieve a PET-negative response prior to ASCT, we will improve long-term outcomes in this group of patients. The ability of tailored therapy for PET+ patients to improve long-term transplantation-related outcomes has been validated in relapsed Hodgkin Lymphoma. [21]

1.4 Ofatumumab

Ofatumumab is a type I, human IgG_1k antibody that binds to a novel epitope of CD20 that encompasses the small extracellular loop and the N-terminal region of the second large extracellular loop.[22] It binds to a different epitope from rituximab and because of the avidity and proximity of CD20 binding, it may lead to better complemet-dependent cytotoxicity (CDC).[22, 23] Although the mode of action of the two mAbs is similar, nonclinical data indicate that ofatumumab may have a greater potential for effector activity, particularly on tumor cells expressing low levels of CD20. Another potential advantage is the predicted low level of immunogenicity for a human anti-human antibody (HAHA) response to ofatumumab in comparison to the human anti-chimeric antibody (HACA) response to rituximab. An *in vitro* human tissue cross-reactivity study has confirmed that ofatumumab binding is restricted to B cells within the peripheral blood circulation and human lymphoid tissues, suggesting there is little likelihood of non-pharmacologically mediated effects.[24]

1.4.1 Safety

1.4.1.1 Preclinical Studies

Intravenous (IV) administration to monkeys for up to 7 months profoundly decreased circulating B cells and resulted in moderate germinal center and follicular atrophy in the lymph nodes, Peyer's patches and spleen. Following clearance of ofatumumab, repletion of B cell counts and a reversal of the tissue changes noted during the study were observed. There were no other ofatumumab-related systemic effects (including effects on the delayed type hypersensitivity response) or histopathological changes in monkeys following chronic exposure to ofatumumab. However, a minor reduction in the magnitude of the immunoglobulin G (IgG) response to the keyhole limpet haemocyanin (KLH) antigen was noted in monkeys dosed at 20 and 100 mg/kg.

There were 5 unscheduled deaths in the intravenous 7-month repeat dose study. Three out of 42 monkeys succumbed to a probable C. jejuni infection; a common yet problematic fecal-oral transmitted pathogen in monkeys. This infection was not considered to be ofatumumab treatment-related and no increase in susceptibility to infection has been reported in the clinical studies. Haemolytic anaemia occurred in 2 out of 42 monkeys in the 7-month study. Both of these monkeys had a positive direct Coombs' test indicative of the presence of anti-drug antibodies (ADAs). It is most likely that the hemolytic anemia was due to a strong ADA response to ofatumumab, which induced immune complex formation. Binding of immune complexes to the surface of the red blood cells is thought to have resulted in sequestration of the coated red cells in the spleen causing the hemolytic anemia. ADAs have been detected in several monkey toxicity studies following both IV and SC administration. However, no toxicities directly associated with the ADAs have been reported and an ADA response in monkeys is not considered indicative of an ADA response in humans.[25]

No maternal toxicity, adverse effects on embryofetal development or teratogenicity occurred in the monkey embryofetal development study at doses up to 100 mg/kg. The effect on human pregnancy is unknown. Precautions will be undertaken to avoid pregnancy and adequate contraception will be used while using ofatumumab.

1.4.1.2 Clinical Studies in Humans

Over 1000 patients have been exposed to ofatumumab in hematologic malignancy clinical trials. Infusion reactions in the IV program are common adverse events (AEs) that are generally mild to moderate in severity, and have been mitigated by premedication and slower IV administration. Severe infusion reactions have been reported, and have occasionally led to temporary interruption or withdrawal of ofatumumab.

Infectious events including lower respiratory tract infections and cytopenias that include neutropenia, anemia, and thrombocytopenia have been observed in oncology trials with ofatumumab, but these events are commonly reported with the diseases under study and/or other concomitant therapies. Neutropenia and serious infections have also been reported in RA studies, but these generally occurred at a similar frequency between the ofatumumab and placebo groups.

A total of 59% (48/81) of patients had infusion-related reactions after the start of and up to 24 hours after any of the 8 ofatumumab infusions. Investigators considered infusion reactions to be drug-related in 44% (36/81) of patients. Infusion reactions primarily occurred during Infusion 1 (40%) and Infusion 2 (22%), and decreased with subsequent infusions. The most common infusion-related reactions, regardless of causality, were rash (10%), anaphylactoid events (9%), hypersensitivity (7%), edema (7%), anorexia (6%), nausea (6%), and cardiac events (6%). Infusion-related reactions were predominantly (96%) Grade 1-2 in severity. Four subjects (5%) experienced infusion-related reactions ≥ Grade 3 in severity (2 subjects anaphylactoid events, 1 subject bradycardia and convulsion 1 subject facial edema, rash, nausea, and altered taste). All subjects recovered.[24]

In study GEN415 [26], a total of 81 subjects diagnosed with DLBCL were treated with 8 weekly infusions of ofatumumab (1st dose: 300 mg; 2nd – 8th dose: 1000 mg). All subjects received oral acetaminophen and IV antihistamine prior to each infusion and IV glucocorticoid prior to the first and second infusions. The protocol defined AE reporting period was from the first infusion (Visit 2/Week 0) to Visit 18 (Month 24 of follow-up) or time of withdrawal (treatment and follow-up). SAEs were reported through Month 60 (treatment, follow-up and extended follow-up). The safety cut-off for the interim safety analysis was 28 Feb 2010.

Of all 81 subjects, 78 (96%) experienced AEs during treatment and follow-up. The most commonly reported AEs are shown below. The most common AEs experienced overall were diarrhea (14 subjects, 17%), fatigue (12 subjects, 15%), edema, peripheral (each 12 subjects, 15%), neutropenia (11 subjects, 14%), abdominal pain, constipation, nausea (each 10 subjects, 12%), pyrexia, anemia, leukopenia (each 9 subjects, 11%), and dyspnea, anorexia (each 8 subjects, 10%).

AEs experienced by Greater than or equal to 10% of DLBCL

System Organ Class Preferred Term	Ofatumumab N=81
Any AEs, n (%)	**78 (96)**
Diarrhea	14 (17)
Fatigue	12 (15)
Edema, peripheral	12 (15)
Neutropenia	11 (14)
Abdominal Pain	10 (12)
Constipation	10 (12)
Nausea	10 (12)
Pyrexia	9 (11)
Anemia	9 (11)
Leukopenia	9 (11)
Dyspnea	8 (10)
Anorexia	8 (10)

Note: AEs reported up to the date of the interim safety analysis

1.4.1.3 Pharmacokinetics, Product Metabolism, and Pharmacodynamics in Humans

Pharmacokinetic data are currently available from four completed studies (Study 001, Study 402, Study 403, and Study 148), three concluded studies (Study 405, Study 407, and Study GEN414/OMS115102 [48-week interim analysis completed]), and four ongoing studies (Study 406, Study 409, Study GEN410/OFA110635 [completed to 24 weeks], and Study OFA110867 [Day 169 interim analysis completed]). Ofatumumab was administered by IV infusion in all studies except Study OFA110867, in which it was given by SC injection.

Measurable concentrations of ofatumumab were detected in all actively treated subjects, except for some subjects who received low doses in Study OFA110867. After repeated IV administration, clearance and volume of distribution values were low, and half-life values were long for ofatumumab, as seen with other monoclonal antibodies. Statistically significant increases in AUC, Cmax, and t½ values and decreases in CL values were found between the first and the last infusion. These findings are likely due to the rapid and sustained depletion of CD20+ B cells after first infusion, leaving a reduced number of B cells available for the antibody to bind at the following infusions. Subcutaneous administration of a single dose of ofatumumab ≥30 mg in subjects with RA similarly resulted in rapid and sustained B-cell depletion.

1.4.2 Efficacy

1.4.2.1 Follicular Lymphoma

As of 21 December 2010, efficacy results are available from one completed study (Study Hx-CD20-001) and 2 concluded studies in Follicular Lymphoma (FL); Study Hx-CD20-405 and Study Hx-CD20-409 [24].

In Study Hx-CD20-001 (N=40), overall response (OR) in evaluable subjects with FL in all ofatumumab dose groups was 41% (300 mg, n=10: 63%; 500 mg, n=10: 33%; 700 mg, n=10: 20%; and 1000 mg, n=10: 50%) and included 4 (10%) subjects with complete response (CR), 3 (8%) subjects with complete response unconfirmed (CRu), and 8 (20%) subjects with partial response (PR). A total of 19 (48%) subjects had stable disease (SD), and 3 subjects had progressive disease (PD). The median time to progression (TTP) for all subjects was 8.8 months and the median duration of response was 29.9 months. The median time to next FL therapy was not reached during the study.

In Study Hx-CD20-405, 116 subjects were treated with two dose levels (500 mg, n=30; 1000 mg, n=86) of single-agent ofatumumab. The overall response rate (ORR) in the total population was 11%. This group of subjects was highly refractory with 65% refractory to their last chemotherapy. Subjects in the study had previously received a median of 4 prior treatment regimens. The 1000 mg dose group (n=86) demonstrated an ORR of 10% (1 CR, 8 PR). In addition, 50% of subjects in the 1000 mg treatment arm had SD. The ORR among subjects in both treatment arms who were refractory to prior rituximab monotherapy (n=27) was 22%. The ORR rate in subjects refractory to rituximab in combination with chemotherapy was 7%, and the ORR among subjects refractory to rituximab maintenance was 9%. The median duration of response was 6 months, and the median progression free survival (PFS) for all subjects was 6 months.

In Study Hx-CD20-409 (N=58), subjects with previously untreated FL were randomized to two dose levels of ofatumumab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone): 300 mg of ofatumumab (cycle 1) followed by 500 or 1000 mg of ofatumumab (cycles 2-6), in combination with CHOP, every 3 weeks for 6 cycles. Results demonstrated an ORR of 90%, CR 24%, and CRu 45% in the 500 mg group (n=29). In subjects treated with 1000 mg of ofatumumab (n=29), the ORR was 100% including 38% CR and 17% CRu. Two subjects had SD and 1 subject had PD.

1.4.1.2 Diffuse large B-cell lymphoma

Cilessen *et al* demonstrated that DLBCL cell lines and rituximab-resistant DLBCL cells from 10 patients were effectively killed by ofatumumab. [27] As of 21 December 2010, efficacy results are available from 1 conculded study in relapsed Diffuse Large B-Cell Lymphoma (DLBCL) (GEN415/OMB111776). In study GEN415 [26], patients (n=81) with relapsed DLBCL, ineligible for transplant or relapsed after autologous transplant were treated with 300mg, followed by seven weekly 1000mg infusions of ofatumumab as single agent. Notably, the median number of prior therapies in that study was 3 and 96% of the patients had received prior treatment with rituximab. The ORR for the single agent was 11% (3 CR and 6 PR). [26]

1.5 Study Rationale and Selection of Primary Endpoint

Patients with relapsed DLBCL who are refractory to or relapse within 12 months of first-line rituximab-based therapy, have poor outcomes with conventional approaches to autologous stem cell transplantation as detailed above. We hypothesize that the intensive mobilization strategy developed at our institution can overcome some of the obstacles to successful ASCT by both eliminating residual disease following salvage therapy and by facilitating stem cell collection. Even though there is clinical experience in the cooperative group setting with intensive pre-ASCT mobilization, it has never been prospectively validated in DLBCL and concerns exist as to its ability to improve outcomes with ASCT in this high-risk, and heavily pretreated group of patients. Furthermore, most patients in our registry treated with intensive mobilization were rituximab-naïve and the findings may not translate in the rituximab-refractory population. We also believe that ofatumumab, a novel monoclonal antibody against a distinct CD20 epitope may in fact overcome rituximab resistance in DLBCL patients and through more effective CDC may eliminate minimal residual disease in the patient and contaminating tumor cells in the stem cell graft.

We thus propose a pilot phase II study that will incorporate ofatumumab instead of rituximab in combination with etoposide and cytarabine (OVA) as an intensive mobilization regimen in high-risk patients with DLBCL undergoing ASCT. We have chosen our primary endpoint, mobilization-adjusted PET negative CR rate, as a criterion for maximum benefit prior to ASCT, i.e. improving mobilization rates compared to traditional mobilization and increasing the depth of response. This is consistent with the primary endpoint of the CORAL study, i.e. mobilization-adjusted response rate. If our approach is

successful, we would plan to validate this strategy in a multi-institution / cooperative group setting in this patient population.

2 Study Objectives

2.1 Primary Objective: To demonstrate the ability of Ofatumumab in combination with etoposide and cytarabine to mobilize peripheral blood stem cells **and** lead to a high complete metabolic response rate prior to autologous stem cell transplantation in rituximab pre-treated patients with high-risk relapsed or refractory DLBCL.

2.2 Secondary Objectives:

2.2.1 To evaluate stem cell engraftment following successful mobilization.
2.2.2 To determine PFS following treatment with Ofatumumab in combination with etoposide and high-dose ara-C (OVA) and subsequent autologous stem cell transplantation.
2.2.3 To measure the effect of OVA on other clinically meaningful endpoints.
2.2.4 To measure the FDG-PET conversion rate from PR to CR following OVA and its association with clinical outcomes.
2.2.5 To examine potential relationships between Ofatumumab concentration and clinical outcomes.
2.2.6 To study the safety and tolerability of OVA.
2.2.7 To store tumor tissue for future molecular subtyping.
2.2.8 To evaluate minimal-residual disease testing in the setting of transplantation.

3 Study Design

3.1 General Design

This is a single-institution, single-arm, prospective phase II study. Patients with high-risk DLBCL (defined as either achieving less than CR to initial rituximab-containing therapy or relapsing within 12 months of initial therapy) will be enrolled on this study and will undergo staging prior to receiving intensive mobilization with ofatumumab, etoposide, and high-dose ara-C (OVA). Following successful stem cell collection, patients will proceed to standard autologous transplantation with cyclophosphamide, BCNU, and etoposide (CBV) preparative regimen. Response evaluation will occur after salvage therapy, following intensive mobilization therapy (d42), at day +90 after ASCT, and at 6, 12 and 24 months thereafter. Event-free, progression-free, and overall survival will also be assessed until 48 months. The primary study endpoint is mobilization-adjusted complete metabolic response rate (maCR) following OVA. Subjects who are not chemosensitive to salvage therapy (i.e. do not achieve a PR or CR) will be re-evaluated after an additional salvage regimen. If they are still not chemosensitive at this point, they will be withdrawn from the study and replaced.

3.2 Primary Study Endpoints

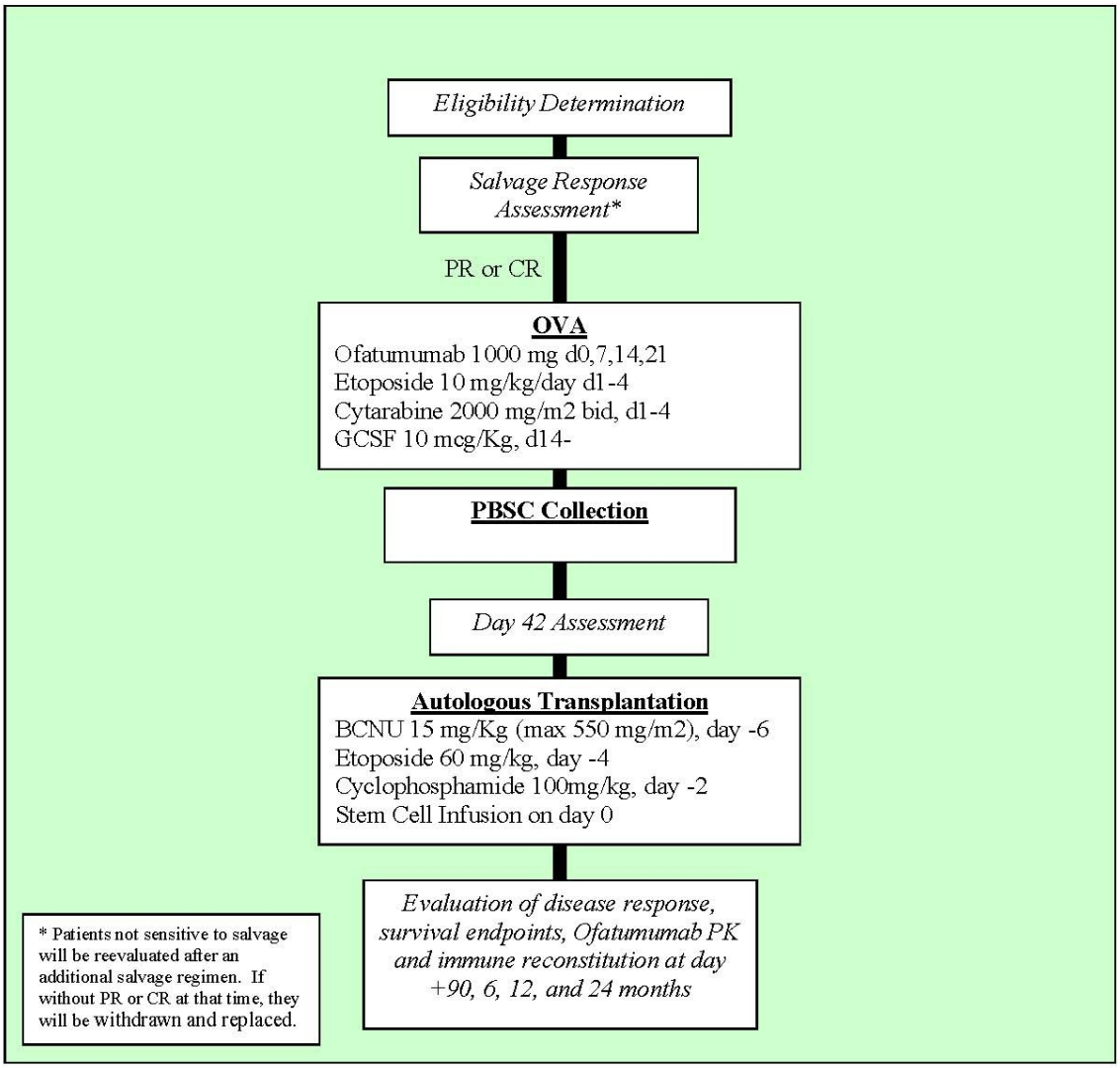
To demonstrate the ability of OVA to **both**:

i) mobilize at least 2 x10^6 CD34+cells/Kg of actual body weight peripheral blood stem cells, and
ii) result in a metabolic CR on day 42 assessment

3.3 Secondary Study Endpoints

3.3.1 Estimate additional mobilization parameters: Percent of patients collecting ≥2, ≥5 and ≥10 x10^6 CD34+cells/Kg with one collection; median # collections to achieve ≥2, ≥5 and ≥10 x10^6 CD34+cells/Kg; Time to neutrophil and platelet engraftment following ASCT.
3.3.2 To determine PFS following treatment with Ofatumumab in combination with etoposide and high-dose ara-C (OVA) and subsequent autologous stem cell transplantation.
3.3.3 To measure the effect of OVA on other clinically meaningful endpoints including OS, time to progression or relapse (TTP), EFS, CR/PR proportion at day +90.

3.3.4 To measure the FDG-PET conversion rate from PR to CR following OVA and correlate post-OVA PET results with PFS, TTP, OS.
3.3.5 To examine potential relationships between Ofatumumab concentration at selected time points and PFS, TTP, OS.
3.3.6 To study the safety and tolerability of OVA including: infusion-related reactions, B-cell number, hypogammaglobulinemia, and long-term hematologic toxicity.
3.3.7 To store tumor tissue for future molecular subtyping.
3.3.8 To evaluate minimal-residual disease testing in the setting of transplantation.



4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Patients fulfilling ALL of the following criteria are eligible for entry to the study:

4.1.1 Diagnosis of refractory or relapsed biopsy-proven CD20+ diffuse large B-cell lymphoma or primary mediastinal B-cell lymphoma.

4.1.2 Age 18 years or older

4.1.3 Refractory to or relapse following a rituximab/anthracycline first-line regimen

4.1.4 High-risk disease as defined by one of the following:

- First relapse after CR within 12 months of initiation of front-line therapy
- Less than CR to front-line therapy
- sAAIPI of 2 or higher at the time of relapse (see attachment 14.2)

4.1.5 Receipt of no more than three prior chemotherapy regimens. Monoclonal antibody therapy alone and involved field radiotherapy are not included in this number. Prior use of ofatumumab is allowed if there has been no disease progression following that therapy (i.e. ofatumumab-based salvage regimens are allowed)

4.1.6 ECOG performance status ≤ 2.

4.1.7 Patient must be consented to the study prior to salvage assessment

Eligibility to proceed to OVA

a. Chemosensitive disease as defined by at least a partial response to salvage therapy by PET/CT criteria.
b. Bone marrow with less than 15% lymphoma cells following salvage therapy. No evidence of myelodysplasia.
c. Patients must have adequate organ function with serum creatinine <2.0 mg/dL, total bilirubin ≤2X ULN, and AST ≤3X ULN.
d. Neutrophils >1,000/μL and platelets >100,000/μL prior to day 0
e. No active uncontrolled infection.

4.2 Exclusion Criteria

Patients fulfilling ANY of the following criteria are NOT eligible for entry to the study:

4.2.1 Presence of disease transformation from a previously diagnosed low-grade lymphoma.

4.2.2 Progression following prior ofatumumab-based therapy.

4.2.3 Active central nervous system or meningeal involvement by lymphoma. Patients with a history of CNS or meningeal involvement must be in a documented remission by CSF evaluation and contrast MRI imaging for at least 3 months prior to study entry.

4.2.4 Evidence of myelodysplasia on any bone marrow biopsy.

4.2.5 Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half-lives or 4 weeks prior to enrollment, whichever is longer, or currently participating in any other interventional clinical study.

4.2.6 Other past or current malignancy. Subjects who have been free of malignancy for at least 3 years, or have a history of completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma are eligible.

4.2.7 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.

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

4.2.9 Known HIV infection.

4.2.10 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.

4.2.11 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.

4.2.12 Positive serology for Hepatitis B (HB) defined as a positive test for HbsAg and a detectable HBV DNA viral load. If negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HBV DNA test will be performed and if positive the subject will be excluded. 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. Prophylactic antiviral therapy may be initiated at the discretion of the investigator.

4.2.13 Positive serology for hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a HCV PCR to confirm the result.

4.2.14Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test at screening.

4.2.15Women 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.

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

4.2.17 Subjects who have received live virus vaccination within the 4 weeks prior to planned initiation of study treatment.

4.3 Subject Recruitment and Screening

Patients will be identified by the principal investigator and sub-investigators in the malignant hematology/BMT clinic at UCSF and be registered on this study. Subjects can enter the study any time after a documented relapse.

4.4 Early Withdrawal of Subjects

UCSF retains the right to terminate the study at any time.
UCSF retains the right to terminate an individual study patient's participation in the study due to the following:
1. Noncompliance with study procedures
2. Concomitant use of any study drug or procedure without prior approval from the Principal Investigator
3. Unanticipated adverse medical experiences in this or other studies indicating a potential health hazard caused by the study

4. Study patient's withdrawal from protocol
5. No evidence of response (PR or CR) to salvage therapy. Subjects will be allowed to proceed to a different salvage regimen and will be re-evaluated following this. If still without a PR or CR, they will be withdrawn for this reason and replaced.

4.5 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws consent to participate in the study prior to day 0 of OVA, he or she will be replaced. If a subject withdraws consent on day 0 of OVA or later, attempts will be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period qt 24 months. For the latter subjects, we will continue to record disease-specific data, adhering to the protocol as much as possible. This data will be obtained (with the subject's permission) from local treating physicians if the subject is no longer followed at UCSF.

5 On Study Evaluation

5.1 Registration

5.1.1 History including demographics, detailed description of prior anti-lymphoma therapy, complications associated with therapy (i.e. infections, liver toxicity) and any ongoing medical problems. Complete medication list. Complete physical examination including vital signs and ECOG performance status.

5.1.2 Laboratory studies:
- a. Hematology: CBC, differential, platelets.
- b. Chemistries: Bilirubin, AST, ALT, alkaline phosphatase, creatinine, electrolytes, LDH, glucose, albumin, total protein.
- c. PT/PTT
- d. Serum Pregnancy Testing
- e. Serologies: HBsAb, HBcAb, HbsAg, HCAb.
- f. **Subjects who are HBcAb positive** must undergo HBV DNA PCR testing.

5.1.3 20 unstained slides or tissue block from the time of relapse (preferred) or initial diagnosis, if either available, will be acquired. Ten slides will be used for minimal-residual disease (MRD) test calibration and the rest will be stored for future DLBCL subtyping.

5.1.4 10 cc of peripheral blood for baseline MRD testing

5.2 Salvage Response Assessment

TO BE COMPLETED AFTER SALVAGE THERAPY
Salvage therapy is standard treatment for relapsed diffuse large cell lymphoma patients. These regimens can consist of different agents, such as R-ICE, R-DHAP, R-Gem/Ox, and others. Salvage therapy is done outside of this protocol***;*** however, a response to salvage therapy is required prior to proceeding with OVA therapy, per eligibility criteria.

5.2.1 Interim history, concomitant medications, and complete physical examination including vital signs.

5.2.2 Laboratory studies:
- a. Hematology: CBC, differential, platelets.
- b. Chemistries: Bilirubin, AST, ALT, alkaline phosphatase, creatinine, electrolytes, LDH, glucose, albumin, total protein.

5.2.3 Bone marrow aspirate and biopsy within 8 weeks of the end of salvage therapy, and before the start of OVA. This should include morphology and standard cytogenetics. Required to proceed to OVA.

5.2.4 Lumbar puncture with cell count, differential and protein within 8 weeks **IF** patient has had prior CNS involvement or has suspicion of CNS disease.

5.2.5 FDG-PET and CT Neck, Chest, Abdomen, Pelvis with PO/IV contrast or PET/CT within 4 weeks from initiation of last cycle of salvage therapy.

5.2.6 12-lead EKG

5.2.7 Cardiac ejection fraction by Echo or MUGA within 8 weeks of salvage response assessment. Required to proceed to transplant, but not to OVA.

5.2.8 Pulmonary function testing with DLCO within 8 weeks of salvage response assessment. Required to proceed to transplant, but not to OVA.

5.2.9 10cc of peripheral blood for MRD testing. Sendout.

OVA STEP

5.3 Day 0 of OVA

OVA therapy will begin within 2 weeks following Salvage Response Assessment.

5.3.1 Interim history, concomitant medications, and complete physical examination including vital signs.

5.3.2 Laboratory studies:

a. Hematology: CBC, differential, platelets.

b. Chemistries: Bilirubin, AST, ALT, alkaline phosphatase, creatinine, electrolytes, calculated creatinine clearance, glucose, albumin, uric acid, LDH. PT and Fibrinogen. Quantitative IgG, IgA, IgM.

c. Peripheral blood CD19+ B-cell determination by flow cytometry.

5.3.3 Ofatumumab administration (see section 6.1.1)

5.4 All other days of OVA

5.4.1 Laboratory studies until completion of apheresis:

Daily	CBC, differential, platelets, electrolytes, creatinine.
Twice-weekly	Bilirubin, alkaline phosphatase, AST, ALT.

5.4.2 Etoposide and Cytarabine administration on days 1-4 (see sections 6.1.2 – 6.1.4)

5.4.3 Ofatumumab administration on days 7,14,21 (see section 6.1.1)

5.4.4 GCSF administration daily, starting on day 14 and continued until stem cell collection (see section 6.1.5)

5.4.5 Ofatumumab pharmacokinetic evaluation within 24 hours after end of infusion on day 21

5.4.6 4 PBMC cryovials will be stored at the time of first leukapheresis for future studies. 4 cc of apheresis product on day 21 or later will be used for MRD testing.

5.5 Day 42 Evaluation (+/- 4 days)

5.5.1 History and complete physical examination including vital signs and ECOG performance status.

5.5.2 Laboratory studies:
a. Hematology: CBC, differential, platelets.
b. Chemistries: Bilirubin, AST, ALT, alkaline phosphatase, creatinine, electrolytes, LDH, glucose, albumin, and total protein, and quantitative IgG, IgA, IgM.
c. Peripheral blood CD19+ B-cell determination by flow cytometry.
d. Ofatumumab pharmacokinetic evaluation
e. **Subjects who are baseline HBcAb positive** must undergo HBV DNA PCR testing.

5.5.3 Bone marrow aspirate and biopsy **IF** positive for lymphoma at baseline. This should include morphology and standard cytogenetics.

5.5.4 FDG-PET and CT Neck, Chest, Abdomen, Pelvis with PO/IV contrast or PET/CT.

5.5.5 10 cc of peripheral blood for MRD testing.

5.6 CBV Administration

Laboratory studies:

Daily	CBC, differential, platelets, electrolytes, glucose, creatinine.
Twice-weekly	Bilirubin, alkaline phosphatase, AST, ALT.

TREATMENT PER INSTITUTIONAL STANDARD OF CARE. See Section 14.3 for UCSF recommended Standard of Care.

5.7 Day +30' and +60' Evaluation (+/- 4 days)

5.7.1 History and complete physical examination including vital signs and ECOG performance status.

5.7.2 Laboratory studies:
a. Hematology: CBC, differential, platelets.
b. Chemistries: Bilirubin, AST, ALT, alkaline phosphatase, creatinine, electrolytes, LDH, glucose, albumin, and total protein.
c. **Subjects who are baseline HBcAb positive** must undergo HBV DNA PCR testing.

5.8 Day +90' Evaluation (+/- 4 days)

5.8.1 History and complete physical examination including vital signs and ECOG performance status.

5.8.2 Laboratory studies:
a. Hematology: CBC, differential, platelets.
b. Chemisties: Bilirubin, AST, ALT, alkaline phosphatase, creatinine, electrolytes, LDH, glucose, albumin, and total protein, and quantitative IgG, IgA, IgM.
c. Peripheral blood CD19+ B-cell determination by flow cytometry.
d. Ofatumumab pharmacokinetic evaluation
e. **Subjects who are baseline HBcAb positive** must undergo HBV DNA PCR testing.

5.8.3 Bone marrow aspirate and biopsy within 2 weeks **IF** positive for lymphoma at baseline. This should include morphology and standard cytogenetics.

5.8.4 FDG-PET and CT Neck, Chest, Abdomen, Pelvis with PO/IV contrast or PET/CT within 2 weeks.

5.8.5 Pulmonary Function Testing with DLCO within 2 weeks.

5.8.6 10 cc of peripheral blood for MRD testing.

5.9 Month 6, 12, and 24 Evaluation (+/- 4 weeks)

5.9.1 History and complete physical examination including vital signs and ECOG performance status.

5.9.2 Laboratory studies:
a. Hematology: CBC, differential, platelets.
b. Chemistries: Bilirubin, AST, ALT, alkaline phosphatase, creatinine, electrolytes, LDH, glucose, albumin, and total protein, and quantitative IgG, IgA, IgM.
c. Peripheral blood CD19+ B-cell determination by flow cytometry.
d. Ofatumumab pharmacokinetic evaluation at 6 months or time of relapse, whichever occurs earlier.
e. **Subjects who are baseline HBcAb positive** must undergo HBV DNA PCR testing at month 6.

5.9.3 FDG-PET **IF** positive on day+90' will be repeated at month 6.

5.9.4 CT Neck, Chest, Abdomen, Pelvis with PO/IV contrast or PET/CT.

5.9.5 10 cc of peripheral blood for MRD testing.

5.10 At Time of Suspected Relapse/Progression

5.10.1 History and complete physical examination including vital signs and ECOG performance status.

5.10.2 Laboratory studies:
a. Hematology: CBC, differential, platelets.
b. Chemistries: Bilirubin, AST, ALT, alkaline phosphatase, creatinine, electrolytes, LDH, glucose, albumin, and total protein.

5.10.3 FDG-PET and CT Neck, Chest, Abdomen, Pelvis with PO/IV contrast or PET/CT.

5.10.4 Bone marrow aspirate and biopsy **IF** indicated. This should include morphology and standard cytogenetics.

5.10.5 Tumor tissue (20 unstained slides or tissue block) from biopsy confirming relapse, if feasible, will be acquired and stored for future testing.

5.10.6 10 cc of peripheral blood for MRD testing.

6 Follow-up Phase

I. If a subject has progressive disease prior to day 0 of OVA, he/she will be replaced.
II. If patients progress between day 0 of OVA and day -6 of CBV, and the intent is to proceed to an autologous stem cell transplant in the future, they will be followed at regular intervals starting on day +90 as specified in the protocol for post-transplant follow-up (Sections 5.8,5.9,5.10).
III. If patients progress between day 0 of OVA and day -6 of CBV and the intent is not to proceed with transplant **or** if they progress any time after day -6 of CBV, they will be followed for survival only every 3 months for up to 2 years or death, whichever occurs sooner.

IV. Patients who do not progress in the first 24 months, will be followed for disease status and survival every 6 months, until 5 years.

7 Treatment Regimen

7.1 Intensive Mobilization Regimen (OVA)

7.1.1 Ofatumumab Administration at 1000mg IV on days 0,7,14, and 21.

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

Table 1 Pre-medication Requirements prior to Ofatumumab Infusions

Infusion #	**Acetaminophen (po)** or equivalent	**Antihistamine (iv or po)** diphenhydramine or equivalent	**Glucocorticoid (iv)** prednisolone or equivalent
1st	1000 mg	50 mg	50 mg
2nd	1000 mg	50 mg	50 mg
3rd and 4th	1000 mg	50 mg	0 – 50 mg[1]

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 or 4th infusion at the discretion of the investigator.

First Infusion of 1000 mg Ofatumumab, day 0

The initial rate of the first infusion of **1000 mg** ofatumumab (1 mg/mL) should be 12 mL/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/h, according to Table 2. If this schedule is followed, the infusion duration will be approximately 4.6 hours.

Table 2: Infusion rate at 1st ofatumumab infusion (1000 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

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Thereafter, 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, days 7,14, and 21

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of the 1000 mg of ofatumumab (1 mg/mL) can start at a rate of 25 mL/hour

and should be doubled every 30 minutes up to a maximum of 400 mL/h, according to Table 3. Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with grade ≥ 3 infusion-associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to Table 2.

Table 3: Infusion rate at subsequent ofatumumab infusions

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.

7.1.2 **Etoposide 10 mg/kg IV continuous infusion over 24 hrs for 4 days (total course dose 40 mg/kg).**

Dose should be based on corrected weight, calculated as follows: Ideal + 25% of the difference between actual and ideal weight. If actual is less than ideal weight, use actual weight.

Etoposide infusion should be mixed in normal saline at a concentration of 0.4-0.5 mg/ml. The infusion volume will be approximately 1.39 ml/kg/hour and should be rounded to the nearest 500-1000 ml and infused through a central venous catheter.

7.1.3 **Cytarabine (ara-C) 2,000 mg/m^2 IV over 2 h q 12 h x 8 doses Days 1-4.**

Cytarabine dosage should be based on corrected weight, calculated as follows: Ideal weight + 25% of the difference between actual and ideal weight. If actual weight is less than ideal weight, use actual weight.

Begin first cytarabine infusion at the end of first hour of etoposide. Cytarabine doses should be mixed in 250 ml of D_5W.

7.1.4 To prevent neurotoxicity from high-dose cytarabine (HDAC), cytarabine doses will be adjusted according to renal function.

- **The dose of cytarabine will be reduced to 1000 mg/m^2/dose** if creatinine is 1.5-1.9 mg/dL or if there is an increase from baseline creatinine at start of cytarabine of 0.6-1.1 mg/dL (example: baseline creatinine 0.8 mg/dL increase to 1.4 mg/dL (difference of 0.6 mg/dL)), decrease cytarabine to 1000 mg/m^2/dose.
- **The dose of cytarabine will be reduced to 100 mg/m^2/day by continuous infusion** if creatinine $\geq$ 2.0 mg/dL or if there is an increase from baseline $\geq$ 1.2 mg/dL and 4 or fewer cytarabine doses have been administered. The infusion will end at the completion of the 96-hour etoposide infusion. If 5 or more cytarabine doses have been administered, then **discontinue cytarabine.**
- **If cytarabine** neurotoxicity develops or is suspected (dysmetria, dysdiadochokinesis, truncal/gait ataxia, dysarthria, and/or cerebral/psychiatric abnormalities not explainable by other medications), **stop cytarabine immediately**. If 4 or fewer of 8 planned high-dose cytarabine doses have been delivered, cytarabine should be changed to 100 mg/m2/day as continuous IV infusion to end at the conclusion of the 96-hour etoposide infusion. If 5 or more high-dose cytarabine doses have been delivered, then give no more cytarabine**.**

7.1.5 Supportive Care Measures:

- **G-CSF 10 mcg/kg** (actual body weight) SQ daily beginning day 14 and should be continued until the peripheral blood stem cell collection has been completed. **Do not skip or dose reduce for bone pain.** All G-CSF doses should be rounded up to a convenient dose based on vial sizes of 300 mcg and 480mcg.
- **Fluoromethalone** 0.1% ophthalmic solution (or equivalent medication) 2 drops qid to each eye Days 1-6.
- **Voriconazole** 4 mg/Kg (corrected weight) rounded to the nearest 50 mg will be administered PO Q12 hours beginning the day after completion of chemotherapy (Day 6). Dose may be modified or omitted due to toxicity and equivalent anti-fungal prophylaxis with fluconazole, itraconazole, posaconazole or Liposomal-based amphotericin (1mg/kg) may be used instead.
- Prophylaxis against bacterial infections should begin when the ANC is < 500/uL and continue until the ANC is > 1000/uL. **Moxifloxacin** 400 mg daily or an equivalent antibiotic is appropriate.
- **Acyclovir** 400 mg PO bid or valcyclovir 500 mg PO qd beginning day 6. Continuing antiviral prophylaxis following hospital discharge is recommended. Patients unable to take oral medication should receive acyclovir 2 mg/kg IV q12 h.
- **Trimethoprim/Sulfamethoxazole** DS PO bid (or IV equivalent dose) every Saturday and Sunday as Pneumocystis carinii prophylaxis. For sulfa allergy, substitute Dapsone 100mg PO once every Monday-Wednesday-Friday. If intolerant to dapsone, substitute aerosolized Pentamidine 300 mg Q month.
- Patients should be hospitalized in private rooms when possible.
- Showers are strongly encouraged twice a day during days 1 to 6 to minimize skin toxicity.
- Strict low bacteria diet should be used when ANC < 500 cells/uL.
- Recommended mouth care: salt and soda swish tid
- **Transfusions**: Institution standards should be followed for blood product support. In lieu of standards, packed RBCes should be given to maintain the hemoglobin $\geq$8.5 gm/dl or hematocrit >25%. Platelet should be transfused to keep the platelet count $\geq$10-20 x 10^9/l. Blood should be filtered and irradiated (3000 cGy).

7.2 PERIPHERAL BLOOD STEM CELL (PBSC) COLLECTION

7.2.1 Begin collections when the total white blood count exceeds 10,000/µl or when appropriate based on peripheral CD34+ cell counts (institutional standard)

7.2.2 Aim for a **minimum CD34 cell dose of > 2 x 10 x 10^6/kg** (actual body weight) and an **optimal target CD34 cell dose of > 5 x 10^6/kg (actual body weight).**

7.2.3 Stem Cell Collection: Process 18-20 L of whole blood over 3-4 hours according to institutional standards.

7.2.4 PBSC Processing: The buffy coat is concentrated by centrifugation. Cells are suspended in Normosol media with 5% autologous plasma and 10% DMSO to a final cell concentration of 2.5 x 10^8/ml. Seventy ml aliquots are placed in polyolefin bags and frozen in a controlled rate freezer. Bags are labeled then stored in the liquid phase of a liquid nitrogen freezer. Institutional standard for PBSC processing should be followed.

7.2.5 Four 2 ml aliquots of PBSC will be frozen in liquid nitrogen for future analysis. 4 mL of PBSC will be used for MRD testing, if baseline test was informative.

7.2.6 Increased GCSF dosing or plerixafor (Mozobil) supplementation may be utilized after consultation with the principal investigator to augment CD34+ cell yield. Use of plerixafor constitutes a **failure of mobilization** with OVA.

7.2.7 **Failure to Collect Peripheral Blood Stem Cells**. Should the minimum number of CD34 cells not be reached, remobilization of peripheral blood stem cells or pelvic bone marrow harvest is permitted. The study PI needs to be consulted regarding re-mobilization or bone marrow harvest and the PI needs to grant permission for this to proceed.

7.3 High-Dose Therapy with Stem Cell Rescue (CBV)

Drug administration and supportive care performed per institutional standard.

7.4 Optional Radiotherapy

Radiation therapy of a single site of residual disease **or** progression is allowed following OVA before **or** after transplant at the investigator's discretion.

8 Measurement of Effect

8.1 Definition of Adequate Stem Cell Collection

Acceptable stem cell collection is defined as a minimum **CD34 cell dose of > 2 x 10 x 10^6/kg** (actual body weight) and **optimal stem cell collection** as a **CD34 cell dose of > 5 x 10^6/kg (actual body weight).** Use of plerixafor or an autologous bone marrow harvest are considered mobilization failures.

8.2 Definition of Engraftment

Neutrophil engraftment is defined as the first day of 3 consecutive days with absolute neutrophil count of >500 cells/uL. Platelet engraftment will be defined as the first of three consecutive measurements for which the platelet count was > 20,000/uL, and must be at least 24 hours following the last platelet transfusion.

8.3 Lymphoma response assessment (revised IWG criteria [12])

PET or PET/CT scans acquired prior to study entry will be utilized in evaluating the response to salvage therapy and the day 42 assessment. Semi-quantitative and qualitative PET analysis will be performed at our center using SUV, mediastinal blood pool, and liver uptake. We recommend that all PET scans be performed at the same instrument at our institution.

CR: The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
2. A post-treatment residual mass of any size is permitted as long as it is PET negative.
3. The spleen and/or liver, if enlarged before therapy on the basis of the physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR.

PR: The designation of PR requires all of the following:

1) The post-treatment PET should be positive in at least one previously involved site.

2) At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
3) No increase should be observed in the size of other nodes, liver, or spleen.
4) Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
5) With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
6) Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
7) No new sites of disease should be observed.

Stable Disease: Stable disease (SD) is defined as the following:
1) A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2) The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD):
Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.
1) Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities.
2) At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
3) At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4) Lesions should be PET positive unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).
Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

8.4 Survival-time parameters

- **Overall Survival** is defined as the time from day 0 until death as a result of any cause. Patients will be censored at the time of last followup.

- **PFS** is defined as the time from day 0 until lymphoma progression, receipt of anti-lymphoma therapy (except for planned post-ASCT radiotherapy), or death as a result of any cause. Patients will be censored at the time of last followup.

- **Time to Progression**: Time to progression (TTP) is defined as the time from study entry until documented lymphoma progression or receipt of anti-lymphoma therapy (except for planned post-ASCT radiotherapy) or death due to lymphoma. Patients are to be censored at the time of last followup or death due to another cause.

- **Event-Free Survival**: Event-free survival (time to treatment failure) is measured from day 0 to any treatment failure including disease progression, discontinuation of treatment for any reason, initiation of new therapy without documented progression, incidence of secondary AML or MDS, or death related to treatment. Patients are censored at the time of last followup or death unrelated to treatment or disease.

9 Safety and Adverse Events

9.1 Safety Definitions

9.1.1 Adverse Events:

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 medial 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 investigational 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 investigational 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

9.1.2 Grading: AEs and toxicities will be graded using the NCI Common Toxicity Grading Scale (Version 4.0; http://ctep.cancer.gov/reporting/ctc.html) included in Appendix 1. AEs that are not included in the NCI Common Toxicity Criteria will be graded as follows:

1. **Mild** (Grade 1) – near the lowest intensity (or within the lower one-third) typically seen with the observed sign or symptom
2. **Moderate** (Grade 2) – average intensity typically seen with the observed sign or symptom
3. **Severe** (Grade 3) – near the highest intensity (or within the top third) typically seen with the observed sign or symptom
4. **Life-threatening** (Grade 4) – any AE that places the patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not refer to an event that hypothetically might have caused death if it were more severe.
5. **Fatal** (Grade 5)

9.1.3 Causality: The association or relationship of the AEs to targeted busulfan will be defined according to the NCI Common Toxicity Criteria guidelines as follows:
1. **Definite** – The AE is clearly related to the study product, e.g., an event that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of drug
2. **Probable** – The AE is likely related to the study product, e.g., an event that follows a reasonable temporal sequence from administration of the drug, that follows a known or expected response pattern to the suspected drug, that is confirmed by stopping or reducing the dosage of the drug, and that could be reasonably explained by the known characteristics of the subject's clinical state
3. **Possible** – The AE may be related to the study product, e.g., an event that follows a reasonable temporal sequence from administration of the drug, that follows a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors
4. **Unlikely** – The AE is doubtfully related to the study product
5. **Unrelated** – The AE is clearly not related to the study product
6. **Not applicable** – The AE occurred prior to administration of the study product
7. **Unknown** – No evaluation for causality can be made

9.1.4 Definition of a SAE
A serious adverse event is any untoward medical occurrence that, at any dose:
a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other

serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Hospitalizations or procedures performed for the routine purpose of chemotherapy administration will not be collected as adverse events and will not be reported as serious adverse events. This would include any elective hospitalization for the administration of radiation and/or chemotherapy, or hospitalization for the placement of central venous catheters to be used for chemotherapy administration.

d. Results in disability/incapacity

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. 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.

9.1.5 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.

9.1.6 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 investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

9.2 Time Period and Frequency of Detecting and Reporting SAEs

Once an investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to NOVARTIS within 24 hours of being notified of the event. All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product to after the last dose of investigational product (minimum of 6 months or until the end of the follow-up period which ever is longer). All SAEs regardless of causality will be collected until the end of the follow-up period.

From the time a subject consents to participate in and completes the study all SAEs assessed **as related to study participation** (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or **related to NOVARTIS concomitant medication**, will be reported promptly to NOVARTIS.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to NOVARTIS.

You should report safety data to Novartis by fax to:

- U.S. Drug Safety & Epidemiology at Fax #: 877-778-9739

o (Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: clinicalsafetyop.phuseh@novartis.com)

- The attached Coversheets must be attached to all SAE submissions
- SAE Submissions must reference your Novartis Study Code: COMB157DUS22T

Reporting Process to UCSF IRB

Serious and **unexpected** adverse events should be reported to the UCSF IRB within 10 working days of the occurrence. This includes any adverse experience which is fatal or life-threatening, permanently disabling, requires inpatient hospitalization or prolongs hospitalization, or has not been identified in nature, severity or frequency in the literature. Should a serious or unexpected toxicity occur please contact:

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 investigational 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.

9.3 Special Reporting Considerations

9.3.1 Intensive Consolidation and Stem Cell Mobilization with OVA

The following adverse events are expected, based on experience with Etoposide and High-Dose Cytarabine in this patient population. They will be documented in the patient medical record but will ONLY be recorded in the Case Report Form if they are grade 3-5.

Neutropenia: expect ANC < 500/μL for approximately 14 days with recovery to >500/μL by day 28.

Thrombocytopenia: expect platelets <20,000/μL for 10-14 days with recovery to >25,000/μL without transfusion support by day 28.

Anemia: Expect to transfuse approximately 6 units of packed RBC.

Stomatitis: most patients do not need narcotic analgesia or TPN, but both are possible.

Diarrhea: enterocolitis is uncommonly seen.

Skin: diffuse erythema is expected and common shortly after chemotherapy. Exfoliative dermatitis with blistering is uncommon. It would be unusual to need >7 days of narcotic analgesia for skin toxicity.

Fatigue/Performance Status: patients require hospitalization for all or most of OVA and may be unable to fully care for themselves for 1-2 weeks following hospitalization.

9.3.2 High-Dose Therapy with CBV and Stem Cell Rescue

The following adverse events are expected, based on experience with CBV in this patient population. They will be documented in the patient medical record but will ONLY be recorded in the Case Report Form if they are grade 3-5.

Neutropenia: absolute neutropenia is expected for 7-10 days. Neutrophils begin to engraft around day +8 to +10. Lack of neutrophil engraftment by day +21 IS REPORTABLE.

Thrombocytopenia: Grade 4 thrombocytopenia is expected for 7-14 days. Platelet transfusion-independence usually occurs by day +9 to +12. Expect approximately 3 platelet transfusions. Reportable platelet recovery would be failure to reach transfusion independence by day +28.

Anemia: expect to transfuse 4-6 units of packed RBC.

Stomatitis: Grade 4 stomatitis can occur but is uncommon, usually between day +3 to +10. Some patients will require narcotic analgesia and possibly TPN (depending on institutional practices).

Diarrhea: enterocolitis is uncommon, but may occur. It generally requires narcotic analgesia, anaerobic antibiotics, and TPN.

Skin: exfoliative dermatitis requiring local skin care (including blistering and weeping wounds) may occur and may require narcotic analgesia; palms and soles and intertriginous areas are most common. Skin breakdown > 2 weeks would be considered distinctly unusual.

Fatigue & Performance Status: patients will be hospitalized for most or all of this therapy. They are unlikely to be able to fully care for themselves for 1-2 weeks post-hospital discharge.

10 Study Drug and Chemotherapeutic Agents

10.1 Ofatumumab (Arzerra)

Pharmaceutical Presentation
Ofatumumab is formulated at two strengths, 20 mg/mL
and 100 mg/mL, for IV and SC administration.

Formulation Presentation
20 mg/mL, acetate buffer 100 mg/vial (5 mL/vial)
20 mg/mL acetate buffer 1000 mg/vial (50mL/vial)
100 mg/mL, acetate buffer 500 mg/vial (5 mL/vial)
100 mg/mL, acetate buffer 100 mg/vial (1 mL/vial)

All drug product presentations are prepared aseptically and filled into clear glass, stoppered vials. The products are formulated without a preservative and are supplied as a single use vial.

Physical, Chemical and Biological Properties of the Drug Substance
Approved Name: INN: Ofatumumab
Chemical Name (Chemical Abstracts): Immunoglobulin G1, anti-(human CD20 (antigen)) (human monoclonal HuMax-CD20 heavy chain), disulfide with human monoclonal HuMax-CD20 κ-chain, dimer (CAS number: 679818-59-8)
Other Names: Genmab Product code: HuMax-CD20
Genmab Laboratory Code: 2F2

Biochemical and Structural Information: Ofatumumab is a fully human immunoglobulin G1 antibody (IgG1-kappa) against human CD20 molecule expressed on B cells. The antibody consists of two heavy IgG1 chains and two light kappa chains. The heavy chains are connected to each other by two interchain disulfide bonds and one light chain is attached to each heavy chain by a single interchain disulfide bond. The light chain has two intrachain disulfide bonds and the heavy chain has four intrachain disulfide bonds. The C-terminal lysine on the heavy chain is subject to partial post-translational cleavage, resulting in antibody populations which contain 0, 1, or 2 C-terminal lysine residues. The majority of the C-terminal heavy chains are clipped. There is a single N-linked glycosylation site on each heavy chain. The major glycans present are fucosylated biantennary structures with varying amounts of terminal galactose.
Molecular Weight 149 kDa (including carbohydrate residues approximately 2%).
Physical Form Clear, colourless liquid (at 20 mg/mL).
Clear to hazy, colourless to pale yellow liquid (at 100 mg/mL).

Summary of Manufacturing Process and Quality Assurance
Ofatumumab Injection presentations were prepared according to current Good Manufacturing Practice (cGMP) and tested according to International Conference on Harmonization (ICH) and Food and Drug Administration (FDA) Guidelines for monoclonal antibodies and products derived from recombinant DNA technology. The cell banks used to manufacture ofatumumab have been extensively tested to demonstrate freedom from adventitious virus contamination. Ofatumumab is produced by a recombinant mammalian cell line, and no animal derived raw materials are used in the manufacture of Ofatumumab Injection. The antibody is purified by a multi-step sequential chromatography and filtration process, which has been validated to demonstrate removal and inactivation of a range of viruses in compliance with ICH guidelines.

Storage and Handling
The recommended storage conditions and expiration date, where required, are stated on the product label for Ofatumumab Injection 20 mg/mL and 100 mg/mL.

Administration and Compatibility
Ofatumumab Injection, 20 mg/mL and 100 mg/mL for intravenous administration must be diluted with 0.9% w/v Sodium Chloride for Injection. Directions for administration are provided in section 6.1.1. Ofatumumab must be administered separately from other medications.

Toxicity: Infusion reactions, neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections. Detailed above.

10.2 Etoposide (Vespid®; VP-16)

Action: inhibition of Topoisomerase II results in metaphase arrest, predominantly G2.
Availability: commercially available.
Preparation: supplied as a liquid in mutli-dose vials (100 mg/5ml; 150 mg/7.5 ml; 500 mg/25 ml; 1,000 mg/50 ml).
Storage and Stability: unopened vials are stable for 24 months at room temperature. Vials opened and diluted to a concentration of 0.2-0.4 mg/ml are stable for 96 and 24 hours, respectively, at room temperature in glass or plastic containers.
Administration: Can be administered undiluted intravenously over 4 hours with NS piggyback.
Toxicity: fever, hypotension, bronchospasm, acidosis, and hypersensitivity reactions during administration, bone marrow suppression, stomatitis and enteritis, skin reactions, elevated liver tests, rarely paresthesias, nausea, vomiting, and alopecia.

10.3 G-CSF (Filgrastim; Neupogen®)

Action: stimulates the proliferation and differentiation of myeloid progenitor cells, stimulates their end-cell functional activation, and mobilizes hematopoietic stem cells into the peripheral circulation.
Availability: G-CSF is commercially available.

Preparation: Supplied in 300 and 480 mcg vials containing 1.0 and 1.6 ml of sodium acetate, respectively.
Storage and Stability: Vials should be stored at 2-8° C. Avoid freezing or shaking of vials. Vials are stable at room temperature for 6 hours.
Administration: SQ or IV administration is permitted.
Toxicity: mild to severe bone pain, leukocytosis, pain at injection site, anaphylaxis, Sweet's syndrome, hypotension, splenomegaly, splenic pain.

10.4 Cytarabine (Cytosar-U®; Ara-C; Cytosine arabinoside)

Action: as a pyrimidine analog, cytarabine is incorporated into DNA and competitively inhibits DNA polymerase and thus inhibits DNA synthesis.
Availability: commercially available.
Preparation: supplied as 100, 500 mg, 1,000 mg, and 2,000 mg vials.
Storage and Stability: diluted solutions are stable for at least 192 hours at room temperature.
Administration: dilute with 0.9% benzyl alcohol (5 ml for 100-1,000 mg cytarabine; 20 ml for 2,000 mg cytarabine) plus 50-100 ml D5W or NS for 1-2 hour IV infusions or in 500-1,000 ml D5W or NS for longer IV infusions. May be given SQ (10-30 mg) in 1 ml NS.
Toxicity: myelosuppression, central nervous system toxicity (doses ≥500 mg/m2, especially when creatinine clearance is <60 cc/min; see Sections 9.4.3 and 10.6.2), stomatitis, nausea, emesis, non-cardiogenic pulmonary edema, keratoconjunctivitis, cutaneous toxicity, alopecia, hepatic dysfunction.

11 STATISTICAL CONSIDERATIONS

This is a single-institution, single-arm, open-label Phase II study of Ofatumumab in combination with etoposide and high-dose cytarabine as an intensive consolidation and stem cell mobilization regimen in patients with relapsed/refractory diffuse large B-cell lymphoma. The primary efficacy endpoint of the study is the mobilization-adjusted complete response rate (maCR) which is defined as: the proportion of patients achieving complete response to the treatment upon successful stem cell mobilization, defined as at least 2 x10^6 CD34+cells/Kg of actual body weight. Secondary endpoints include time to neutrophil and platelet engraftment following ASCT, PFS in this high-risk patient population and other survival-time measures of clinical efficacy, i.e. OS, TTP, EFS, and CR/Pr proportion at day +90. Our study will also measure the FDG-PET conversion rate from PR to CR following OVA and correlate post-OVA PET results with PFS, TTP, and OS. We will examine potential relationships between Ofatumumab concentration at selected time points and PFS, TTP, OS. We will perform MRD testing at baseline, at the time of stem cell collection, and following ASCT, and will correlate the results to clinical endpoints. Finally, safety will be evaluated with regard to infusion-related reactions, B-cell number, hypogammaglobulinemia, and long-term hematologic toxicity.

11.1 Sample Size

Patients who have received a single infusion of study drug (day 0 of OVA) will be included in the statistical analyses. We are planning to accrue 24 subjects over the course of 2 years with an additional 2-year follow-up. In terms of the composite primary endpoint, the historical CR rate after 2 cycles of salvage therapy among high risk, rituximab refractory patients is between 25% and 50% of the overal responses [i.e CR/(CR+PR].[8, 19, 20] Furthermore, the chance of a mobilization failure among complete and partial responders observed in the CORAL study is 15%.[9] We thus expect the null value of the composite endpoint of maCR to be 25% (~40% CR-15% mobilization failure). Given the excellent historical CR rates with intensive consolidation and the very low risk of mobilization failures, we expect the alternative maCR rate to be 50%. Based on the exact probability with type I error of 10% and 1-sided test, a sample size of N=24 in the single arm study will have > 80% power to detect the maCR rate for the following hypothesis: H0: p0<25% (40%CR/15%mobilization-failure) vs Ha: p1>50% (55%CR/5%mobilization-failure under OVA). The following table shows statistical power for the test of the null hypothesis under the assumed maCR of 25% and for various mobilization-adjusted complete response rates with 24 subjects (alpha=10% under 1-sided exact test):

maCR rate	Statistical Power
25% vs 40%	51%
25% vs 45%	70%
25% vs 50%	**84%**
25% vs 55%	93%
25% vs 60%	97%

An interim analysis for futility and safety will be performed when 12 subjects are enrolled. We will define the futility as >50% stem cell mobilization failure as excessive and unacceptable. If six or fewer (< 50%) subjects have adequate stem cell mobilization, the enrollment will not continue and the study will be closed for treatment futility. Otherwise we will enroll 12 additional patients to complete study for full maCR efficacy analysis. At the same time as the interim analysis for futility, we will also perform an interim evaluation for safety, which is defined as >30% SAE as too toxic and unacceptable. If 4 or more (>30%) of the first 12 patients treated are observed to have protocol-defined unacceptable toxicity, the study will be closed for lack of safety. If the stem cell collection success rate is less than 50%, the probability of early stopping due to futility is 61%. If the toxicity rate is greater than 30%, the probability of early stopping due to safety is 64%.

11.2 Statistical Methods

The results of this single-institution study will be evaluated and reported as follows. Proportions will be compared with the chi square test. Time-to-event variables will be analyzed with the Kaplan-Meier method and compared across subgroups with the log-rank test.

Primary Analysis

For primary efficacy analysis, the proportion of stem cell mobilization, the proportion of complete response and the proportion of mobilization-adjusted complete response will be analyzed and reported separately and collectively. Descriptive statistics with frequency and proportion with exact 95% confidence intervals will be reported for the study. The acceptable stem cell collection is defined as a minimum CD34 cell dose of > 2 x 10 x 10^6/kg (actual body weight) and optimal stem cell collection as a CD34 cell dose of > 5 x 10^6/kg (actual body weight). Subjects who require use of plerixafor or an autologous bone marrow harvest are considered mobilization failures and will be treated as non-responders, ie. they will be included in the denominator when calculating the percentage for the primary efficacy analysis. The CR rate will be calculated based on the PET/CT scan following 2 cycles of salvage therapy.

Secondary Analyses

Progression free survival (PFS), defined the time from day 0 until lymphoma progression, receipt of anti-lymphoma therapy (except for planned post-ASCT radiotherapy), or death as a result of any cause, will be summarized using Kaplan-Meier quartile estimates along with two-sided 95% confidence intervals. If a subject receives subsequent anti-lymphoma therapy prior to the date of documented progression or death, progression free-survival will be censored at the last adequate assessment prior to the initiation of that anti-cancer therapy. Otherwise, if the subject does not have a documented date of progression or death, progression-free survival will be censored at the date of the last adequate assessment. No formal hypothesis test will be performed for significance.

Stem cell engraftment rate will be evaluated for neutrophil and platelet following successful mobilization. Failures of stem cell collection will be considered as non-responders. Neutrophil engraftment is defined as the first day of 3 consecutive days with absolute neutrophil count of >500 cells/uL. Platelet engraftment will be defined as the first of three consecutive measurements for which the platelet count was > 20,000/uL, and must be at least 24 hours following the last platelet transfusion. Engraftment rate will be reported separately for neutrophil and platelet. Descriptive statistics with proportion and frequency will be

used and 95% confidence intervals will also be reported. No formal hypothesis test will be performed for significance.

The **Time to progression,** defined as the time from study entry until documented lymphoma progression or receipt of anti-lymphoma therapy or death, will be summarized descriptively using Kaplan-Meier quartiles, along with two-sided 95% confidence intervals, for each of the cohorts. Only the subset of subjects who show a complete or partial tumour response will be included in this analysis. Censoring rules follow the rules for PFS. No formal hypothesis test will be performed for significance.

Overall survival (OS): OS, defined as the time to death for any reason, will be summarized using Kaplan-Meier quartile estimates along with two-sided 95% confidence intervals. OS will be censored using the date of last known contact for those who are alive at the time of analysis. No formal hypothesis test will be performed for significance.

Other secondary analyses will include the association between FDG-PET conversion, Ofatumumab concentration, the effect of OVA and the clinical outcomes such as PFS, OS and Time to progression (duration of response).

11.3 Accrual and Estimated Duration of Study

As a tertiary care referal BMT center in Northern Califronia, we perform approximately 15 such transplants in this patient population annually and we expect to enroll most of our patients on this study. There are no competing studies currently, in development, or planned. Thus the study should complete accrual within 24-30 months of initiation.

11.4 DLBCL Subtyping

Tumor tissue and peripheral blood stem and mononuclear cells will be collected for DLBCL subtyping. The best way to subtype DLBCL is currently in evolution. For this study, a combination of gene expression profiling (GEP) and immunohistochemistry (IHC) will be utilized to distinguish different disease entities.

11.5 Minimal Residual Disease Testing

MRD assessments will take place in collaboration with Sequenta (South San Francisco, CA). For each patient the cancer-specific IgH rearrangement will be identified through the assessment of a diagnostic sample. The diagnostic sample will be the positive lymph node (frozen or archived FFPE) or bone marrow aspirate sample (whole aspirate, frozen cells, or clots) in patients with an involved marrow. All the IgH sequences are amplified from the diagnostic samples and the product is subjected to DNA sequencing. The cancer-specific sequence is expected to be present at high frequency (>10%) in contrast to most other sequences present at very low level (<0.1%). The cancer-specific sequence is then readily measured for each patient by determining the level of that sequence in a subsequent sample. This is done by amplifying all the IgH sequences from the relevant samples and subjecting the product to deep sequencing (1M reads or more). The level of the cancer-specific sequence can then be determined at very high sensitivity (due to the depth of sequencing) and specificity (due to the uniqueness of each IgH sequence). We will determine the feasibility of this methodology in our patient population. We will measure the MRD conversion rate following OVA and correlate this with clinical outcomes. Additionally, we will perform MRD surveillance following ASCT and correlate it with Ofatumumab pharmacokinetics and relapse.

11.6 Data Safety Monitoring Plan:

The study data will be reviewed twice a month by the PI and study coordinator. Safety data and specifically SAEs and grade 3-5 AEs will be reviewed at the Hematology Site Committee twice a month.

Monitoring and Reporting Guidelines
Investigators will conduct continuous review of data and patient safety at weekly Transplant Meeting or Site Committee meetings where the results of each patient's treatment are discussed. The discussion will include, the number of patients enrolled, significant toxicities, stem cell mobilization, and observed responses. The study coordinator will keep a log of subject(s) on study and grade 3-5 AE's and SAE's will be entered in the HDFCC Oncore database.

Interim Analysis
An interim analysis for futility and safety will be performed when 12 subjects are enrolled. We will define the futility as >50% stem cell mobilization failure as excessive and unacceptable. If six or fewer (< 50%) subjects have adequate stem cell mobilization, the enrollment will not continue and the study will be closed for treatment futility. Otherwise we will enroll 12 additional patients to complete study for full maCR efficacy analysis. At the same time as the interim analysis for futility, we will also perform an interim evaluation for safety, which is defined as >30% SAE as too toxic and unacceptable. If 4 or more (>30%) of the first 12 patients treated are observed to have protocol-defined unacceptable toxicity, the study will be closed for lack of safety. If the stem cell collection success rate is less than 50%, the probability of early stopping due to futility is 61%. If the toxicity rate is greater than 30%, the probability of early stopping due to safety is 64%.

Serious Adverse Event Reporting
Serious Adverse Event reporting will be in accordance with the UCSF-Committee on Human Research Regulations and Code of Federal Regulation Title 21 Volume 5 Part 312.32. In addition, SAEs will be entered into the Oncore database.

UCSF CHR website for guidance in reporting serious adverse events
http://www.research.ucsf.edu/chr/Guide/chrA_AE.asp

FDA website for guidance in reporting serious adverse events
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

MedWatch forms and information:
http://www.fda.gov/medwatch/getforms.htm

Serious Adverse events will be reported on the MedWatch form. A copy of the MedWatch report and CHR forms must be sent to CCC-DSMC at Box 1297. The date the SAE was sent to all required reporting agencies will be documented on Oncore; hard copies of the report will be maintained in the regulatory files.

12 Data Management and Study Termination

12.1 Data and Protocol Management

1. Data Management**:** All patients enrolled on trial will be given a study-specific registration number. The registration number will be used to identify all patients on trial.
2. Protocol Compliance: Patients and their medical records will be reviewed every other week until the first 30 days post-transplantation and otherwise monthly by the study investigators. Study endpoints will be reviewed and documented. Any questions regarding serious adverse events and toxicity should be discussed with the study chairman directly.

3. Case Report Forms: Clinical data will be recorded on case report forms. CRF's should be completed on a timely basis. The principal investigator will review all CRF's.
4. Accuracy of Data Collection: The UCSF Cancer Center DSMB, UCSF CHR, IBMTR or individual government board may review the data from this study for accuracy. The UCSF DSMB will be the final arbiter of eligibility, toxicity and other endpoints should a difference of opinion exist.

12.2 Termination of Study

UCSF retains the right to terminate the study at any time.

UCSF retains the right to terminate an individual study patient's participation in the study due to the following:

1. Noncompliance with study procedures
2. Concomitant use of any study drug or procedure without prior approval from the Principal Investigator
3. Unanticipated adverse medical experiences in this or other studies indicating a potential health hazard caused by the study
4. Study patient's withdrawal from protocol

13 Study Finances

13.1 Funding Source

This study is financed by NOVARTIS.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. Subject Stipends or Payments

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15 Attachments

15.1 Study Procedures

Procedures	Registration	Salvage Assessment	OVA						Post ASCT Follow-up		Long term follow-up		
Days:			0	1-4	7	14	21	42	Days +30', +60' post ASCT	Day +90' post ASCT	Month 6 post ASCT	Month 12 post ASCT	Month 24 post ASCT[13]
Informed Consent	X												
Demography	X												
Medical History	X	X	X					X	X	X	X	X	X
Disease History	X												
Therapy History	X												
Efficacy Assessments													
Bone marrow biopsy		X						X[1]		X[1]			
CT		X						X		X	X	X	X
PET		X						X		X	X[7]		
LP[2]		X											
Disease Status & survival		X						X		X	X	X	X
Safety Assessments													
Physical Exam	X	X	X					X	X	X	X	X	X
ECOG	X							X	X	X	X	X	X
Height	X												
Weight	X												
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X											
Echo or MUGA		X											
PFTs with DLCO		X								X			
Adverse Events			X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication													
Ofatumumab			X		X	X	X						
Etoposide				X									
Cytarabine				X									
G-CSF					X[3]	X[3]	X[3]						

Procedures	Registration	Salvage Assessment	OVA						Post ASCT Follow-up		Long term follow-up		
Days:			0	1-4	7	14	21	42	Days +30', +60' post ASCT	Day +90' post ASCT	Month 6 post ASCT	Month 12 post ASCT	Month 24 post ASCT[13]
Lab Assessments													
Hematology	X	X	X	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X	X
Chemistry	X	X	X	X[5]	X[5]	X[5]	X[5]	X	X	X	X	X	X
Coags	X		X										
Serum Pregnancy Test	X												
Hepatitis B&C antibodies[6]	X												
HBV DNA PCR[6]	X							X	X	X	X	X	X
CD19+ B-Cells			X					X		X	X	X	X
Quant Igs			X					X		X	X	X	X
Ofa PK							X[8]	X		X	X	X	X
Tumor Tissue Collection	X[9]												
PBMC Aliquot							X[10]						
MRD Testing on Blood	X[11]	X[11]						X[11]		X[11]	X[11]	X[11]	X[11]
MRD Testing on PBMC from apheresis							X[12]						

1:BM performed on day 42 and +90' If positive at salvage assessment
2: LP performed only if previously positive or for suspected CNS involvement
3: Starts day 14 and stops when stem cell collection complete
4: Daily CBC with differential until leukapheresis completed.
5: Daily: electrolytes, creatinine. Twice weekly: bilirubin, alkaline phosphatase, AST, ALT, LDH. Stop when leukapheresis completed
6: 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.
7: PET will be repeated at 6 months if positive at day +90' evaluation
8: Within 24 hours after end of infusion on day 21.
9: 20 unstained slides or tissue block from the time of relapse (preferred) or initial diagnosis, if available.
10: 4 cryovials with PBMC aliquot will be stored at time of first apheresis. Apheresis may occur on or after day 21.
11: MRD determination will be performed on 10 mL of peripheral blood at the timepoints indicated.
12. Some apheresis product (4cc) will be sent for MRD testing.
13: Patients who do not progress in the first 24 months, will be followed for disease status and survival every 6 months, until 5 years. See Section 6.0.

15.2 Calculation of sAAIPI

This is calculated at the time of progression or relapse and prior to initiation of second-line (salvage) chemotherapy.

-Serum LDH > upper limit of normal

-ECOG PS ≥ 2

-Stage ≥ III

15.3 High Dose Therapy with Stem Cell Rescue (CBV)

Carmustine 15 mg/kg IV (maximum dose, 550 mg/m2) on Day -6.

a. Carmustine dose should be calculated based on corrected weight calculated as ideal weight plus 25% of the difference between actual and ideal weight. Use actual weight if it is lower than ideal weight.
b. Each Carmustine vial is reconstituted with 3 ml absolute ethanol and 27 mL sterile water. Total Carmustine dose is diluted in 1000 ml D5W or NS.
c. Administer over 2-3 hours in a light-protected glass bottle or Excel bag. Maximum infusion rate is 180 mg/m2/hour.
d. Premedication with diphenhydramine 50 mg IV 30 minutes prior to Carmustine is recommended.

Etoposide 60 mg/kg IV over 4 hours on Day -3.

a. Etoposide dose should be calculated based on corrected weight calculated as ideal weight plus 25% of the difference between actual and ideal weight. Use actual weight if it is lower than ideal weight.
b. Etoposide should be given undiluted over 4 hours and piggybacked into NS at 1000 ml/hour.
c. Premedication with hydrocortisone 100 mg IV to be repeated in 2 hours during the infusion, acetaminophen 650 mg PO, and cetirizine 10 mg PO is recommended. Meperidine 25 mg IV q1 hour prn for rigors may be administered up to 3 doses.
d. Febrile reactions should be treated with hydrocortisone and diphenhydramine as is necessary.
e. Hypotension may occur during the Etoposide administration. If this happens, first pause the infusion and restart when the blood pressure recovers. If hypotension persists or recurs, then give Dopamine IV to maintain the blood pressure in order to complete the Etoposide infusion. If hypotension persists, **abort** the Etoposide infusion.
f. **Etoposide Phosphate (Etopophos)**: may be substituted for etoposide for patients > 60 years old or for younger patients as clinically indicated. Etopophos 60 mg/kg IV over 3-4 hours. Mix in 250-500 milliliters 0.9%NaCl for concentration > 0.1 mg/ml. Hydrocortisone 100 mg IV and cetirizine 10 mg PO will be given prior to infusion. Febrile reactions should be treated with additional hydrocortisone and diphenhydramine as is necessary.

Cyclophosphamide 100 mg/kg IV over 2 hours day -2.

a. Cyclophosphamide and Mesna dose should be calculated based on corrected weight calculated as ideal weight plus 25% of the difference between actual and ideal weight. Use actual weight if it is lower than ideal weight.
b. One hour before cyclophosphamide begin IV NS plus KCl 20meq/L to run at 250 cc/hour to continuefor 20 hours after end of cyclophosphamide infusion, for a total of 24 hours.
c. **MESNA** 120 mg/kg (corrected weight) in 1 liter D5W IV over 24 hours should begin one hour prior to cyclophosphamide infusion for a total of 24 hours.
d. Cyclophosphamide should be infused over 3 hours in 500 mL D5W.
e. Cyclophosphamide-related gross or microscopic **hematuria** correlates with the concentration of drug metabolites in the bladder. Adequately hydrate patients and ensure frequent voiding. If hemorrhagic cystitis occurs, consider adding bladder irrigation (500 cc/hour sterile urologic saline via a 3-way Foley catheter for 48 hours after cyclophosphamide administration).
f. Furosemide may be used for volume management per institutional protocol.

Autologous peripheral blood stem cell infusion will take place on Day 0.

Peripheral blood stem cells should be thawed in a 37˚ water bath and immediately infused intravenously.

Supportive Care

- **G-CSF 5 mcg/kg SQ daily (actual body weight, rounded up to vial size) starting Day +6'.** G-CSF should continue daily until the absolute neutrophil count exceeds 1500/µl for 2 consecutive days or > 5000/uL for one day. It should then be stopped but should be resumed if the ANC falls to < 1000/µl. If G-CSF is resumed it should then be continued until the ANC > 5000/µl.
- **Fluconazole** 400 mg PO will be given daily starting from day +1' and will continue until the neutrophils are at least > 500/uL. Equivalent anti-fungal prophylaxis with itraconazole or liposomal-based amphotericin product may be used.
- Prophylaxis against pneumocystis carinii will be used. The regimen of choice is **trimethoprim/sulfamethoxosole (Septra)** DS po bid 2 days/week starting after engraftment (ANC >1500/uL, and Platelets >30,000/uL). An alternative regimen is dapsone 100 mg po daily. Prophylaxis will continue until at least day +90' after transplant.
- Prophylaxis against bacterial infections should begin when the ANC is < 500/uL and continue until the ANC is > 1000/uL. **Moxifloxacin** 400 mg daily or an equivalent antibiotic is appropriate.
- Prophylaxis against herpes simplex and herpes zoster with **acyclovir** 400 mg po bid from day –2 until 1 year post-transplant or as per institutional standard. Patients unable to take oral medication should receive acyclovir 2 mg/kg IV q12 h.
- Patients should be hospitalized in private rooms with positive pressure ventilation and filtered air systems, when possible.
- Strict low bacteria diet should be used when ANC < 500/uL.
- Recommended mouth care:

    a. Salt and soda swish tid
    b. Gel clear is allowed

- **Transfusions**: Institution standards should be followed for blood product support. In lieu of standards, packed RBCes should be given to maintain the hemoglobin $\geq$8.5 gm/dl or hematocrit >25%. Platelet should be transfused to keep the platelet count $\geq$10-20 x 10^9/l as per institution standards. Blood should be filtered and irradiated (3000 cGy).