Phase I/II Study of Bendamustine in Combination with Ofatumumab, Carboplatin and Etoposide for Refractory or Relapsed Aggressive B-cell Lymphomas.

AUTHORS

Principal Investigator
Joanne Filicko-O'Hara, MD

Co-Investigators
S. Onder Alpdogan, MD
Matthew Carabasi, MD
Jerald Gong, MD
Margaret Kasner, MD
Neal Flomenberg, MD
Ubaldo Martinez, MD
John L.Wagner, MD
Dolores Grosso, DNP, CRNP
Avnish Bhatia, MD
Andrew Chapman, DO
Michael Ramirez, MD
Lewis Rose, MD
Atrayee Basu-Mallick, MD
Allison Zibelli, MD
Christina Brus, MD
Sameh Gaballa, MD
Pierluigi Porcu, MD
Neil Palmisiano, MD
Lindsay Wilde, MD

Biostatistician
Inna Chervoneva, PhD

Division of Hematologic Malignancies and
Hematopoietic Stem Cell Transplantation
Department of Medical Oncology
Kimmel Cancer Center
Thomas Jefferson University
834 Chestnut Street, Suite # 320,
Philadelphia, Pa 19107
Phone (215) 503-5894

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STUDY SUMMARY

List of Abbreviations

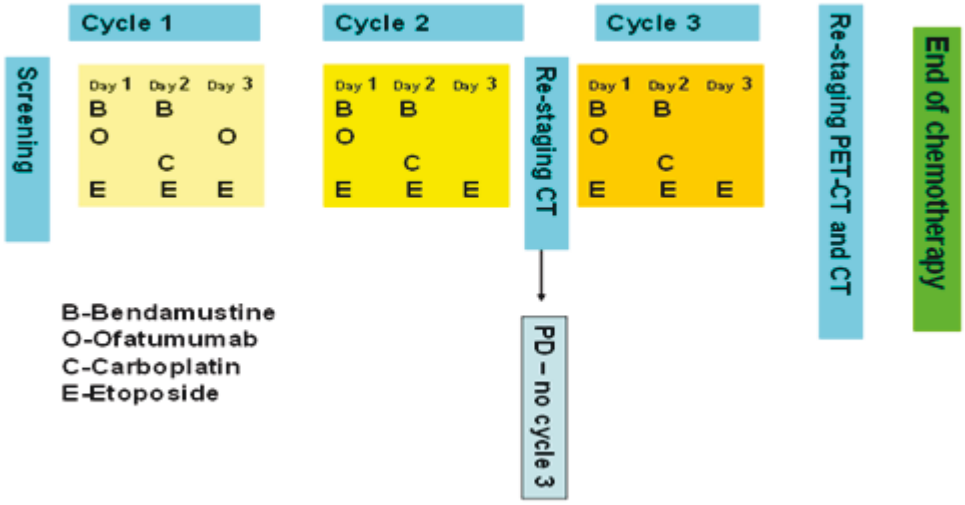
ABC	Activated B-cell–Type
AE	Adverse Event
ANC	Absolute Neutrophil Count
ASCO	American Society of clinical Oncology
ASCT	Autologous Stem Cell Transplant
AUC	Area Under the Curve
BOCE	Bendamustine, Ofatumumab, Carboplatin and Etoposide
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CCRRC	Clinical Cancer Research Review Committee
CDC	Complement Dependent Cytotoxicity
CD	Cluster of Differentiation
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
CLL	Chronic Lymphocytic Leukemia
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRMO	Clinical Research and Management Office
DLBCL	Diffuse Large B cell Lymphoma
D5W	5% Dextrose in Water
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
EFS	Event Free Survival
EBER	Epstein Barr Encoded RNA
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
FISH	Fluorescence In Situ Hybridization
FLIPI	Follicular Lymphoma IPI score
GCB	Germinal-Center B-cell–like
GFR	Glomerular Filtration Rate
HAART	Highly active Antiretroviral Therapy
HB	Hepatitis B
HC	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus

ICE	Ifosfamide, Carboplatin, Etoposide
IHC	Immunohistochemistry
IRB	Institutional Review Board
IWG	International Working Group
FC	Fludarabine, Cyclophosphamide
IgG 1k	Immunoglobulin G1 kappa
IWG	International Working Group
KCC	Kimmel Cancer Center
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
M-BACOD	Methotrexate with Leucovorin, Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine, and Dexamethasone
MACOP-B	Methotrexate with Leucovorin, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone, and Bleomycin
MCL	Mantle Cell Lymphoma
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non Hodgkin Lymphoma
NIH	National Institute of Health
NS	Normal Saline
OPRR	US Dept of Health & Human Serv./Office for Protection from Research Risk
OS	Overall survival
ORR	Overall Response Rate
ProMACE-CytaBOM	Prednisone, Methotrexate, Doxorubicin, Cyclophosphamide, Etoposide-CytaBOM: Cytarabine, Bleomycin, Vincristine, Methotrexate
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PHI	Protected Health Information
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Response
PS	Performance Status
RICE	Rituximab, Ifosfamide, Carboplatin, Etoposide
RT	Radiotherapy
SAAIPI	Second line Age Adjusted International Prognostic Index
SAE	Serious Adverse Event
SEER	Surveillance Epidemiology and End Results
SLL	Small Lymphocytic Lymphoma
SWOG	South Western Oncology Group
ULN	Upper Limit of Normal

Title	**Phase I/II Study of Bendamustine in Combination with Ofatumumab, Carboplatin and Etoposide for Refractory or Relapsed Aggressive B-cell Lymphomas.**
Short Title	BOCE in Relapsed/Refractory Aggressive Lymphomas
Protocol Number	*11D.404*
Phase	Phase I/II
Methodology	Phase I – 3x3 design, open label. Phase II - Single arm, open label.
Study Duration	2 years
Study Center(s)	Single center
Objectives	**Primary objective for Phase I part of the study:** Safety and toxicity profile of bendamustine in combination with ofatumumab, carboplatin and etoposide for refractory or relapsed aggressive B cell lymphomas. **Secondary objective for Phase 1:** To determine the Overall Frequency of Response with combination bendamustine, ofatumumab, carboplatin and etoposide for refractory or relapsed aggressive B cell lymphomas. **Primary objective for Phase II study:** Determine the Overall Frequency of Response with combination bendamustine, ofatumumab, carboplatin and etoposide for refractory or relapsed aggressive B cell lymphomas. **Secondary objectives for Phase II study**: • To determine CR rate • To determine 1 and 2 year progression free survival. • To determine 1 and 2 year overall survival. • To define safety and toxicity of the combination of ofatumumab, bendamustine, carboplatin and etoposide for refractory or relapsed aggressive B cell lymphomas. • To evaluate the level of CD20 expression in the various biologic types of relapsed aggressive B cell lymphomas and to correlate that with response to the study regimen.
Number of Subjects (max)	36
Diagnosis and Main Inclusion Criteria	Relapsed/refractory aggressive B cell Non-Hodgkin's lymphoma

<table>
<tr><td>Study Product, Dose, Route, Regimen</td><td>In the Phase I part of the study a standard 3+3 design will apply to identify dose limiting toxicities (DLT) and to define maximum tolerated dose (MTD) of combination bendamustine, ofatumumab, carboplatin, and etoposide in refractory and relapsed aggressive B cell lymphomas.
The Phase II part of the study will be a single-arm, open-label study in which all patients will receive combination bendamustine, ofatumumab, carboplatin and etoposide at the MTD dose defined in phase I
Patients will be followed on the study until disease progression, unacceptable toxicity, or withdrawal of consent or for total of 2 years post completion of therapy (whichever is earlier).
<table>
<tr><th>Agent</th><th>Dose</th><th>Route</th><th>Schedule</th></tr>
<tr><td>Ofatumumab</td><td>Cycle 1: 300 mg on day 1 (or up to 3 days prior to day 1), 1000 mg on day 3.
Cycles 2 and 3: 1000 mg on day 1.</td><td>IV</td><td>Cycle 1: days 1 (or up to 3 days prior to day 1) and day 3.
Cycle 2 and 3: day 1</td></tr>
<tr><td>Bendamustine</td><td>Phase I: as per escalating dose protocol.
Phase II: MTD achieved in Phase I</td><td>IV</td><td>Day 1 and 2</td></tr>
<tr><td>Carboplatin</td><td>AUC 5</td><td>IV</td><td>Day 2</td></tr>
<tr><td>Etoposide</td><td>100 mg/m²</td><td>IV</td><td>Day 1, 2 and 3</td></tr>
</table>
</td></tr>
<tr><td>Duration of administration</td><td>3 cycles approximately every 3 weeks or upon blood cell recovery, whichever is later</td></tr>
<tr><td>Reference therapy</td><td>RICE (rituximab, ifosfamide, carboplatin, etoposide).</td></tr>
<tr><td>Statistical Methodology</td><td>A total of 9 to a maximum of 18 patients will be enrolled in Phase I part of the trial. Twenty four patients will be enrolled in Phase II part of the trial. This is based on the Simon Optimal Two-Stage Design with the assumption that an ORR rate of 25% indicates that the treatment is not effective and an ORR rate of 50% indicates that the treatment is effective with alpha (type I error) 0.05 and 80% power. The last 6 patients enrolled at the MTD level in Phase I will be included in the Phase II part of the study. Thus the estimated maximum sample size will be 36 patients.</td></tr>
</table>

Study Schema
Figure 1



1. INTRODUCTION

1.1 Background:

Epidemiology

According to the Surveillance, Epidemiology and End Results (SEER) data, around 65,540 people in the United States will be diagnosed with and 20,210 will die of non-Hodgkin lymphomas (NHL) in 2010. Aggressive B cell lymphomas consist of diffuse large B cell lymphoma (DLBCL), the single largest category of all lymphomas, primary mediastinal large B cell lymphoma, T cell rich B cell lymphoma, transformed low grade B cell lymphomas and a variant of mantle cell lymphoma (MCL). All the above lymphomas are unified by their B cell origin, aggressive behavior and similar standard treatment approach. Burkitt lymphoma has a highly aggressive clinical course and is thus treated with different, more aggressive regimens and will not be discussed here.

First Line Treatment

In the early 1970's Levitt and DeVita initially described potentially curative combination chemotherapy for large cell lymphomas (1, 2). Since then, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) has been widely used in the treatment of aggressive NHL. Its superiority over other second and third generation combination chemotherapy (m-BACOD, ProMACE-CytaBOM, and MACOP-B) was established by the historic Phase III SWOG trial (Fisher RI et al 1993) which showed equal efficacy and superior safety profile of CHOP with an overall survival of 54% at three years (3).

The addition of Rituximab to chemotherapy for patients with aggressive B cell lymphoma has significantly improved outcome. The use of rituximab in combination with CHOP (RCHOP) vs. CHOP in young patients with good prognosis DLBCL has resulted in better PFS and OS. Pfreundschuh et al evaluated RCHOP vs. CHOP in young patients (age 18-60) with good prognosis DLBCL (4). The 3 year event free survival was 79% in the RCHOP arm vs. 59% in the CHOP arm. Similar improved results were seen in the elderly population. A 10 year follow up study of elderly (age 60-80) patients with DLBCL showed that, 10 year PFS was 36.5% in RCHOP arm vs. 20% in the CHOP alone arm (5). Ten year OS was 43.5% in RCHOP compared to 26.7 % in CHOP arm.

Relapsed/Refractory Aggressive B cell NHL

Up to 50% of patients with aggressive B cell lymphomas will relapse after CHOP-like chemotherapy with rituximab. There is no standard salvage regimen for patients with relapsed or refractory disease and at least 75% of patients are expected to succumb to their condition with the commonly used rescue regiments.

Prognostic Factors for Relapsed/Refractory NHL:

There are various factors that predict outcome in relapsed/refractory lymphomas. These include Second Line Age Adjusted International Prognostic Index (sAAIPI), (see Table 1 and Appendix 1), initial remission lasting more than 12 months and use of Rituximab in initial therapy. Prognostic factors are useful to assess the efficacy of new treatment regimens compared to previous approaches. They are also helpful in identifying groups which have a poor prognosis with existing regimens and may benefit from alternative therapies. sAAIPI assessed at the

initiation of second line therapy, predicts the outcome after Autologous Stem Cell Transplant (AutoSCT) in patients with relapsed/refractory lymphomas (6).

Table 1-sAAIPI assessed at the time of second line therapy

Risk factors:	**Score**
LDH >ULN	1
Stage III or IV	1
KPS <80%	1

Low risk (L) with 0 factors, low intermediate (LI) risk with 1 factor, high-intermediate risk (HI) with 2 factors, and high risk (H) with all 3 factors present.

Treatment of Relapsed/Refractory NHL

For patients with relapsed/refractory disease, there is no standard salvage regimen. For patients that are eligible for transplant the National Comprehensive Cancer Network (NCCN) recommends a rescue regimen followed by high dose therapy and AutoSCT or high dose therapy followed by AlloSCT in selected patients.

Salvage Regimens:

There are a number of regimens that have been described for relapsed/refractory aggressive lymphomas in the era of monoclonal antibodies. No regimen has shown clear superiority to the other and response rates have ranged between 35-78% depending on prior rituximab use in frontline setting; uniformly there were inferior outcomes among patients who had relapsed after a rituximab containing frontline therapy. See table 2. These inferior clinical outcomes apply to our current relapsed patient population who overwhelmingly had previously been treated with rituximab containing frontline regiments.

Table 2

Regimen	**Previous rituximab use**	**sAAIPI≥2**	**CR/Cru**	**ORR**	**OS**	**Author**
R-ICE	0%	47.2%	53%	78%	N/A	Kewalramani , 2004 (7)
	62%	**37.1%**	**36%***	**63.5%*,**	**47% *(at 3 years)**	**Gisselbrecht, 2010 (8)**
DHAP	0%	N/A	31%	55%	25% at 2 years	Velasquez, 1988 (9)
R-DHAP	**62%**	**38.1%**	**40%***	**62.8%***	**51%* (at 3 years)**	**Gisselbrecht, 2010 (8)**
R-ESHAP	56%	35%	45%	73%	55.8% at 29 months	Martin, 2008 (10)
R-EPOCH	16%	58%	28%	68%	35%projected OS at 3 yrs	Jermann M, 2004 (11)
GEMOX-R	N/A	69%	34%	43%	41% at 1 yr	Lopez A, 2008 (12)

*CR, ORR and OS **Significantly lower in patients who had prior rituximab**

RICE (Rituximab, Ifosfamide, carboplatin and Etoposide) is the most frequently used salvage regiment in the United States and DHAP is widely used in Europe. RICE has been developed and investigated at the Memorial Sloan-Kettering Cancer center. Kewalramani et al investigated the RICE regimen in 36 patients with aggressive lymphomas that had relapsed after or were refractory to single standard anthracycline based chemotherapy (7). The ORR was 78% and CR was 53%. Among 25 patients who underwent transplantation after RICE 2 year progression free survival was 54%.

DHAP (high dose cytarabine with cisplatin and dexamethasone) was studied by Velasquez et al in 90 patients with relapsed/refractory lymphomas (9). The ORR was 55% and the CR was 31%. Both these regimens were also investigated in a randomized Phase III trial (CORAL study) comparing RICE vs. RDHAP followed by high dose therapy and autologous transplant in patients with relapsed/refractory DLBCL (8). The ORR of 63% and 62% with RICE and RDHAP, respectively, and the 3 year event free survival was 26% and 35%, respectively (p=0.6). Three-year EFS was affected by prior rituximab treatment versus no prior rituximab (21% *v* 47%, respectively).

R-ESHAP (rituximab with etoposide, cytarabine, cisplatin and methylprednisolone) is another salvage regimen in relapsed/refractory aggressive lymphomas. Martine et al retrospectively evaluated the efficacy of R-ESHAP in 163 patients as a salvage regimen (10). In the rituximab naïve group the CR and ORR was 56% and 81% respectively. In comparison, the 94 patients who had been treated with rituximab earlier the CR and ORR was 37% and 67%. These data strongly indicated that rituximab containing salvage regimens were less effective in the patients who were previously treated with a rituximab containing frontline therapy.
R-EPOCH (rituximab with doxorubicin, etoposide, vincristine, cyclophosphamide and prednisone) was evaluated by Jermann et al in 50 patients with relapsed/refractory large B cell lymphomas and mantle cell lymphomas (11). The ORR was 68% and CR was 28%.
GEMOX-R (rituximab with gemcitabine and oxaliplatin) when studies in 32 patients with relapsed/refractory lymphomas had a ORR of 43% and a Cr of 34% (12).

1.2 Investigational Agent- Ofatumumab:
Ofatumumab is a fully human IgG1κ monoclonal anti-CD20 antibody. It recognizes a distinct epitope encompassing both the large and the small extracellular loops on the human CD20 molecule expressed on B cells. Binding of ofatumumab causes clustering of CD20 on the cell surface and promotes cell death through the induction of complement mediated cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). It has been approved by FDA for use in relapsed/refractory CLL and has been extensively investigated in indolent and aggressive B cell NHLs.

1.2.1. Preclinical Data
In *in-vitro* studies, Ofatumumab has shown more complement dependent cytotoxicity (CDC) than rituximab (13). It has similar binding to CD20 as rituximab, but has a slower off rate which contributes to increased CDC (13). Ofatumumab targets an epitope on the small extracellular loop of CD20 in contrast to rituximab which targets only the large extracellular loop of CD20

(14). This proximity of target may also contribute to increased CDC. Importantly, Ofatumumab is able to lyse cells that are insensitive to rituximab due to their low CD20-expression (13).

1.2.2. Clinical Data

Coiffier et al demonstrated the safety and efficacy of ofatumumab in 33 patients with relapsed/refractory B cell CLL (15). They dose escalated ofatumumab to initial 500 mg infusion followed by three 2000 mg infusions. The response rate was 50%. The majority of adverse effects occurred at the time of first infusion and decreased with subsequent infusions. 51% of patient's experienced infectious complication and majority (88%) were Grade 1 or 2. Hagenbeek et al reported use of ofatumumab in 40 patients with relapsed/refractory low grade (Grade 1 or 2) follicular lymphoma (16). They escalated the dose to 4 weekly infusions of 1000 mg. As seen by Coiffier et al, the majority of adverse effects occurred on the first infusion day and declined with subsequent infusions, which was similar to the infusion reactions observed with rituximab. Twenty infectious adverse effects were noted and 2 were Grade 3.The clinical response ranged from 20%-63%. Based on these studies, it has been established that ofatumumab is safe to give as a single agent in B cell lymphomas.

1.2.3. Adverse Events Noted in Follicular Lymphoma Subjects:

Gastrointestinal: nausea, vomiting, abdominal pain.
Respiratory: pharyngolaryngeal pain, dyspnoea, cough, bronchospasm.
Skin: rash, pruritus, urticaria, flushing.
General and Administration Site Conditions: hypotension, influenza-like illness, fatigue, fever, chills, headache, dizziness, hyperhidrosis, cytokine release syndrome, infusion-related reaction.
Musculoskeletal: arthralgia, myalgia.
Immune System: hypersensitivity.

1.2.4. Ofatumumab Combination Therapy

Ofatumumab has been evaluated in combination with chemotherapy for treatment of chronic lymphocytic leukemia (CLL) and other lymphoid malignancies. Czuczman et al presented (ASCO 2010 Abstract No 8042) clinical data of combination ofatumumab with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy in previously untreated 59 patients with follicular lymphoma (17). Patients were randomized to 2 groups: Ofatumumab dose 500 mg (Group A) or 1,000 mg (Group B). The combination was well tolerated and had a CR/CR unconfirmed of 76% in patients with FLIPI (Follicular lymphoma IPI score) of 3-5 at a median follow up of 9.7 months. Ofatumumab infusion-related reactions were primarily Grade 1-2; 2 patients had Grade 3 reactions during first dose, but were able to receive subsequent doses. The most common Grade 3-4 adverse events were leukopenia and neutropenia (31 and 28%, Group A; 28 and 17%, Group B). Incidences of Grade 3-4 leukopenia and neutropenia were 83 and 90% in Group A and 72 and 90% in Group B, respectively. Grade 3-4 infections occurred in 10% of pts in Group A and 3% in Group B, with febrile neutropenia in 7 and 3% of pts, respectively. No deaths have been reported.

Wierda et al (ASCO 2010, abstract 6520) reported preliminary results of a phase II trial investigating the efficacy and safety of two dose levels of Ofatumumab-FC (fludarabine, cyclophosphamide) in previously untreated patients with CLL (18). Sixty one patients were randomized to ofatumumab 500 mg (Group A) or 1,000 mg (Group B) Day 1, with FC

chemotherapy. Due to the short follow up (8 months) at the time of presentation, response rates were not reported. The same group published preliminary results in 2011 (19). A total of 61 patients were treated in the study. Treatment response was assessed using the 1996 NCI Guidelines. The CR rate was 32% in patients who received 500 mg of ofatumumab (n=31) and 50% in patients who received 1000 mg of ofatumumab (n=30). The overall response rate was 77% in the 500 mg treatment group and 73% in the 1000 mg treatment group. There were no unexpected safety findings reported during treatment and within 30 days after last infusion. The most common adverse event reported was neutropenia at 48%. Other common adverse events (greater that 15 percent) were nausea, leukopenia, rash, vomiting, pyrexia, headache and thrombocytopenia. The number of patients, who experienced adverse events, including serious adverse events, was similar between the two dose groups. One death was reported and was judged by the investigator as unrelated to ofatumumab.

The safety of ofatumumab combinations has been addressed in multiple studies.
There are several ongoing trials that are registered on the clinicaltrials.gov website looking at the safety and efficacy of ofatumumab in combination with chemotherapy in patients with lymphoma. NCT01014208 is a randomized trial 'Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy Followed by ASCT in Relapsed or Refractory DLBCL". This study plans to enroll 380 patients with relapsed/refractory DLBCL and has been enrolling since March 2010. Patients are randomized to ofatumumab plus chemotherapy- DHAP (cisplatin, cytarabine and dexamethasone) or DVD (DHAP Cycle 1 and 3, VIM-etoposide, ifosfamide and methotrexate Cycle 2) or rituximab plus chemotherapy-DHAP or DVD. The primary endpoint of this trial is PFS. Another Phase II trial is "A Single Arm, Safety and Efficacy Study of Ofatumumab in Combination With ICE or DHAP Chemotherapy in Relapsed or Refractory Aggressive Lymphoma Prior to Autologous Stem Cell Transplantation" NCT00823719. In this Phase II trial, patients with relapsed/refractory DLBCL, transformed follicular lymphoma or Grade 3b follicular lymphoma will be treated with ofatumumab in combination with ICE chemotherapy or DHAP chemotherapy prior to autologous stem cell transplantation. The primary endpoint of this study is ORR. This study has been opened and accruing since May 2009 and is expected to be completed by December 2011. The Ofatumumab-ICE arm in this trial is comparable to our proposed study, except for a novel alkylating agent bendamustine which in our trial will substitute ifosfamide.

1.3 Bendamustine

On October 31, 2008, the U.S. Food and Drug Administration (FDA) approved bendamustine hydrochloride (TREANDA®, Cephalon, Inc.), an intravenously administered alkylating agent, for the treatment of patients with indolent B-cell NHL that progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. The recommended dose for NHL is 120 mg/m2 on day 1 and 2 of each cycle. Bendamustine is an alkylator/purine analogue hybrid cytotoxic drug with a distinct pattern of activity, different from other alkylators (20).Bendamustine has demonstrated single agent activity in lymphomas refractory to other alkylating agents, such as cyclophosphamide. Friedberg et al showed the safety and efficacy of single agent Bendamustine in 76 patients with indolent or transformed NHL that was refractory to rituximab (21). Patients were treated with bendamustine 120 mg/m2 on day 1 and 2 every 3 weeks for 6 cycles as long as they had a response or stable disease. Fifteen patients required dose reduction to 90 mg/m2 and 4 needed reduction to 60 mg/m2. The most common adverse effects

were hematological. Grade 3 or 4 neutropenia occurred in 54%, thrombocytopenia in 25% and anemia in 12%. The overall response rate was 77% in this study. In another multicenter study, Kahl et al evaluated the response to a single agent Bendamustine in 100 patients with rituximab refractory indolent B cell lymphoma (22). Treatment consisted of bendamustine 120 mg/m2 on day 1 and 2 every 3 weeks for 6-8 cycles as long as response or stable disease occurred. Twenty four patients had dose reductions, 20 patients to 90 mg/m2 and 4 to 60 mg/m2. They achieved a similar overall response rate of 75%. Grade 3 or 4 hematological toxicities included neutropenia (61%), thrombocytopenia (25%) and anemia (10%).

In *in vitro* studies, rituximab has shown chemosensitizing effect when used in combination with bendamustine in lymphoma cell lines (23). Based on this, Robinson et al investigated the efficacy of combination of Bendamustine and Rituximab in 67 patients with relapsed indolent lymphoma and mantle cell lymphoma (24). In this study patients received rituximab 375 mg/m2 on day 1 and bendamustine 90 mg/m2 days 2 and 3 of a 28-day cycle for 4-6 cycles. An additional dose of rituximab was administered 1 week before the first cycle and 4 weeks after the last cycle. The combination was well tolerated and the primary toxicity was hematological; Grade 3 or 4 neutropenia (36%), Grade 3 or thrombocytopenia (9%) and anemia (2%). Ten episodes of Grade 3 or 4 infections occurred. Overall response rate was 93% in indolent lymphomas and 92% in mantle cell lymphomas.

Bendamustine has also been used in combination with mitoxantrone and rituximab. Weide et al from the German Lymphoma study group used this combination in 57 patients with relapsed and refractory indolent lymphomas and mantle cell lymphomas (25). Treatment consisted of bendamustine 90 mg/m2 on days 1 and 2, mitoxantrone 10 mg/m2 on day 1 rituximab 375mg/m2 on day 8; repeated every 4weeks for four cycles. Grade 3 or 4 adverse events included anemia (10%), thrombocytopenia (16%), and neutropenia (46%). ORR was 89%, 92% in follicular lymphoma and 78% in mantle cell lymphoma. Vacirca et al presented preliminary data of bendamustine and rituximab combination in aggressive B cell lymphomas at 2010 ASCO meeting (26). Bendamustine was given at 120 mg/m2 on day 1 and 2 and rituximab 375mg/m2 on day 1 of a 28 day cycle for 6 cycles. Efficacy data showed ORR of 53% in 17 evaluable patients. The combination was safe, in 76 cycles 1 Grade 4 neutropenia and 9 additional Grade 3 events. Thus, bendamustine combinations have shown to be effective and can be given safely in patients with relapsed lymphomas.

1.4 Ofatumumab and Bendamustine Combinations

A total of 10 phase I/II and phase III studies of ofatumumab and bendamustine combination regiments have been registered to date on the 'clinicaltrials.gov' site and at least 5 of them have been actively recruiting patients with NHL and CLL. Among them are the following trials:

- A Phase II study of Ofatumumab and Bendamustine for Previously Treated CLL and small lymphocytic lymphoma (SLL) has been accruing patients since 2009. Ofatumumab is given at 300-mg IV on Day 1 of week -1 and then 1000 mg on Day 1 of each cycle for 6 cycles and Bendamustine is given at 70 mg/m2 IV on days 1 and 2 of each cycle for 6 cycles. The primary outcome of the study is the overall response rate. Clinical trial identifier: NCT01010568.
- A Phase I/II Trial of Dexamethasone, Ofatumumab and Bendamustine as first-line treatment of Mantle-cell Lymphoma (MCL) in the elderly has been recruiting patients

since 2010.The starting dose of the 2 main component drugs is the MTD of each drug as single agent. Ofatumumab infused iv on day 1 at 300 mg during the first cycle, followed by infusions of 1000 mg on day 1 of each subsequent cycle Bendamustine infused iv at the dose of 120 mg/m2 (days 2, 3 every 21 days) or 120 mg/m2 (days 2, 3 every 28) or 90 mg/m2 (days 2, 3 every 28 days) depending on toxicity Dexamethasone administered i.v. at 40 mg (days 1, 2, 3, 4). The primary endpoint of the phase II part of the study is the complete remission rate. Clinical trial identifier: NCT 01221103.

- A Phase III study of ofatumumab plus bendamustine versus bendamustine alone has been opened for patients with indolent B-cell NHL who did not respond to rituximab or progressed on a rituximab-containing regimen during or within six months of the last rituximab treatment. A total of 338 patients in this open label study will be randomized to receive either ofatumumab in addition to bendamustine or bendamustine alone. Each group will receive up to eight cycles of bendamustine while the combination group will be given ofatumumab on day one of each cycle. Once patients in the combination group have completed bendamustine therapy, they will continue to receive ofatumumab monthly until 12 doses have been given. The primary endpoint of the study is progression free survival. Clinical trial identifier: NCT01077518.

1.5. Study Rationale:

Bendamustine in combination with ofatumumab containing therapy may present a novel attractive salvage regimen for relapsed aggressive B cell lymphomas. We propose a novel RICE-like salvage combination regimen in which rituximab is substituted with ofatumumab and ifosfamide with bendamustine in combination with carboplatin and etoposide for refractory or relapsed aggressive B cell lymphomas. We hope to avoid the substantial well recognized ifosfamide mediated bladder toxicity (incidence of Grade 3 and 4 hemorrhagic cystitis in 8-12%) and neurologic toxicity (incidence 10-30%; namely, somnolence, confusion, psychosis and seizure) by substituting ifosfamide for bendamustine. Bendamustine has a single agent activity in relapsed aggressive lymphomas, including those refractory to other alkylating agents, and has shown a favorable safety profile in combination with other chemotherapeutic agents, as noted above. The proposed regimen is convenient and, unlike RICE, can be administered on the outpatient basis which presents an additional benefit to the patients and to the providers.

We will first determine safety and toxicity of escalating dose bendamustine in combination with fixed doses of ofatumumab, carboplatin and etoposide. We recognize that the commonly used doses of bendamustine in lymphoid malignancies range from 70-120 mg/m2. The recommended dose of bendamustine in NHL is 120 mg/m2 and a dose of 90 mg/m2 has been commonly used in combination regimens. Thus, we propose to initiate bendamustine in combination at a dose of 70mg/m2 and escalate to a dose of 120 mg/m2.

We will determine maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT) of the combination by using dose escalation of bendamustine from 70mg/m2 in a standard 3 by 3 design. We will then assess efficacy of the combination regiment at MTD in relapsed and refractory aggressive B-cell lymphomas.

1.6 Rationale for the Correlative Studies:

1.6.1. Analysis of the Surface Expression of CD20 on Malignant Cells in Relapsed

Aggressive B-cell Lymphomas

CD20 is a mature B cell marker and is present on the surface of most B cell lymphomas with variable level of expression. Rituximab which is a human/mouse chimeric monoclonal antibody is widely used in the treatment of B cell neoplasms. *In-vitro* studies have shown a transient decrease in CD20 expression after treatment with rituximab (27). When B cell lymphomas relapse, the CD20 expression may be decreased, thus making rituximab less effective in the relapsed setting. In *in-vitro* studies, Ofatumumab has shown more complement dependent cytotoxicity (CDC) than rituximab (12). Importantly, Ofatumumab is able to lyse cells that are insensitive to rituximab due to their low CD20-expression (see section 1.2). Based on these data ofatumumab may be more effective at targeting B cells in the relapsed setting. The level of CD 20 expression on malignant B cells is variable and we will assess the level of CD20 expression in patients with relapsed B cell lymphomas. In addition, we will prospectively evaluate if the level of CD20 expression correlates with the response to the Ofatumumab based combination chemotherapy. To assess the level of CD20 expression we will use IHC based scoring system in all studied paraffin tissues. In addition, flow cytometry analysis for CD20 expression distribution will be performed in all available fresh tissue samples.

1.6.2. Biologic Profile of Relapsed and Refractory Aggressive B-cell Lymphomas

DLBCL is a group of aggressive B cell lymphomas which encompass a variety of biologic entities with variable clinical and prognostic features. Based on cDNA microarray analysis (Rosenwald 2002), DLBCL have been subdivided into two large prognostic subgroups that include germinal-center B-cell– (GCB) and activated B-cell–type (ABC) DLBCL (28). When treated with standard chemotherapeutic regiments, the GCB group has significantly better prognosis as compared to the ABC. Hans et al used immunohistochemistry techniques to further characterize the above two prognostic categories (29). They identified **GCB** type as CD10 positive, Bcl-6 positive and MUM-1 negative or as CD10 negative, Bcl-6 positive and MUM-1 negative and **non-GCB** type as CD10 negative, Bcl-6 negative and MUM-1 positive or CD10 negative, Bcl-6 postive and MUM-1 positive. In concert with the data presented by Rosenwald et al, the GCB type had an improved overall survival as compared to non-GCB type. In addition, Hans et al. assessed Bcl-2 expression in studied samples and Bcl-2 positive subjects had a significantly shorter overall survival as compared to Bcl-2 negative. We will evaluate the rate of ABC and GCB type among the accrued patients with relapsed or primary refractory lymphomas and will follow them for responses to the investigational regimen.

Novel prognostic subcategories have recently been identified among aggressive B cell lymphomas. Among them EBV positive B cell lymphoma of the elderly is an increasingly recognized biologic entity. Based on morphology and immunophenotype these cases overwhelmingly fall into DLBCL category, however, they have distinct clinical presentation and tend to relapse or show resistance to R-CHOP-like therapy. It is seen in immunocompetent elderly subjects and is associated with a worse clinical outcome (30). In our study, we will assess the rate of EBV positive cases among the studied patients with relapsed and refractory aggressive B cell lymphomas. We will evaluate EBER expression in tumor tissue using in-situ hybridization technique and will evaluate response rate to the investigational rescue therapy in this poor prognostic group.

'Double hit' lymphomas (DH) is a subset of DLBCL with chromosomal breakpoint in cMYC locus in combination with another breakpoint, usually Bcl-2, but also BCL-6 (31). These lymphomas were recognized in the 2008 WHO classification as a provisional entity entitled "B cell lymphoma unclassifiable with features intermediate between DLBCL and BL." They have an adverse prognosis when treated with RCHOP based chemotherapy (31). Cyclin D1+/MYC+ represents a variant of mantle cell lymphoma also with a very poor response to standard chemotherapy and dismal outcome.

We hypothesize that a high prevalence of the above newly recognized biologic entities will be identified in the studied group of patients. We propose to evaluate the rate of the above biologic markers in this unfavorable group of patients who have presented with relapsed or primary refractory disease. We will assess all available tissue samples for CD10, Bcl 6 and MUM1, expression by immunohistochemistry; EBER expression by in-situ hybridization and Bcl-2, Bcl-6+, Cyclin D1 and cMYC by FISH analysis. We will prospectively assess patients' clinical characteristics and objective responses to the investigational chemotherapy in these biologically determined subgroups.

1.6.3. Validation of Oligonucleotide-based Microarray Platform for NHL Risk Stratification

The combination of karyotype analysis and fluorescence in situ hybridization (FISH) has revealed key chromosomal abnormalities in various hematologic malignancies, such as acute myelogenous and acute lymphocytic leukemias, chronic lymphocytic leukemias, myelodysplastic syndrome and multiple myeloma. In contrast, NHL is associated with only a few unique chromosomal abnormalities, such as c-Myc, t(11;14), t(14;18) and little is known yet if other key aberrations may be identified and used to risk-stratify large NHL groups, such as DLBCL. A novel genome-wide microarray technology reveals submicroscopic chromosome aberrations, which can't be picked by conventional cytogenetic analysis and FISH studies (32). We propose to identify submicroscopic chromosome aberrations in patients with well-defined diagnoses of the selected clinically unfavorable group of B cell NHL. We will perform a comprehensive biologic profiling of the biopsy samples of the study group as described above and will use OncoChip cytogenetcs platform to determine if there are identifiable unique biologic and cytogenetic features upon which risk-group stratification may develop. The Cancer Microarrays Signature OncoChip technology (Signature Genomic Laboratories) has the ability to detect clinically relevant copy-number imbalances as well as submicroscopic gains and losses not seen by conventional cytogenetics. By using microarray platform the OncoChip™ can simultaneously identify balanced translocations as well as the translocation breakpoints and their partners. We will use this comprehensive system to analyze DNA from cryopreserved or fresh diagnostic NHL samples. We will assess these submicroscopic chromosomal aberrations in parallel with the conventional karyotype and FISH studies. We will determine the feasibility of incorporating a newly developed oligonucleotide-based microarray platform into NHL risk stratification analysis.

2 STUDY OBJECTIVES

2.1 Primary Objective for Phase I Part of the Study:

To determine the safety and toxicity profile of bendamustine in combination with ofatumumab, carboplatin and etoposide for patients with refractory or relapsed aggressive B cell lymphomas.

2.2 Secondary Objective for Phase 1:
To determine the overall frequency of response; overall response will include all subjects with complete response (CR) and partial response (PR).

2.3 Primary Objective for Phase II Study:
To determine the overall frequency of response with combination bendamustine, ofatumumab, carboplatin and etoposide for refractory or relapsed aggressive B cell lymphomas.

2.4 Secondary Objectives for Phase II Study:

- To determine CR and PR rate
- To determine 1 and 2 year progression free survival.
- To determine 1 and 2 year overall survival.
- Among transplant eligible patients to determine the proportion of patients who are able to undergo stem cell transplant.
- To define safety and toxicity of the combination of ofatumumab, bendamustine, carboplatin and etoposide for refractory or relapsed aggressive B cell lymphomas.
- To evaluate the level of CD20 expression in the various biologic types of relapsed aggressive B cell lymphomas and to correlate that with response to the study regimen.

3 STUDY DESIGN

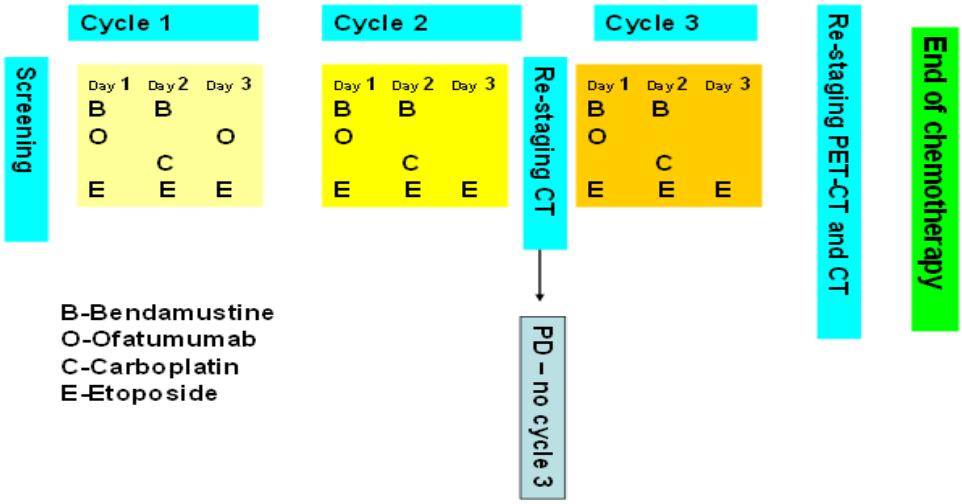


Figure 1

3.1 General Design Phase 1
The Phase I study is designed to identify dose limiting toxicities (DLT) and to define maximum tolerated dose (MTD) of bendamustine in combination with ofatumumab, carboplatin and etoposide in refractory and relapsed aggressive B cell lymphomas. Dose escalation will allow the identification of maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT) for bendamustine given i.v. on day 1, 2 schedule in combination with fixed doses of ofatumumab,

carboplatin and etoposide. At each dose level DLT will be assessed during a minimum of one cycle period.

Schema for Phase 1

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. If ≥2 DLT at (-1) dose level, the study will be terminated.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 additional patients experience DLT, proceed to the next dose level. • If 1 or more of the 3 additional patients suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This will be the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Dose Escalation Schedule:

Dose level	Dose of Bendamustine
Level 1	70 mg/m²
Level 2	90 mg/m²
Level 3	120 mg/m²
Level -1	50 mg/m²

3.2 General Design for Phase II

After MTD of the combination is established from the Phase 1 part of the study, patients with relapsed/refractory aggressive B cell-NHL will be enrolled in the Phase II study to determine the efficacy of the combination regimen. The Phase II study will be a single-arm, open-label study in which all patients will receive combination bendamustine, ofatumumab, carboplatin and etoposide (at the MTD dose defined in phase I) for a maximum of 3 cycles.

Patients will be followed on the study until disease progression, unacceptable toxicity, or withdrawal of consent or for total of 2 years post completion of therapy (whichever is earlier).

3.3 Primary Study End Point for Phase I

Maximum tolerated dose which is determined using a dose escalation protocol for bendamustine in combination with fixed doses of ofatumumab, carboplatin and etoposide.

3.4. Secondary Study End Point for Phase I

Overall response frequency which is determined as cumulative complete response (CR) and partial response (PR) in the studied group

3.5 Primary Study End Point for Phase II

Overall Response which is determined as cumulative CR and PR in the studied group. The 2007 Revised Cheson Criteria for NHL will be used to assess response (33); see appendix 5.

CR will be determined if meets all of the following requirements:

- PET positive prior to therapy: mass of any size permitted if PET negative. Variably FDG-avid or PET negative prior to therapy: regression to normal size on CT (≤ 1.5 cm in their greatest transverse diameter for nodes ≥ 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to <1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
- The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination.
- If bone marrow is known to be involved before treatment, then repeat biopsy documents clearance

PR will be determined if meets the following requirements**:**

1. ≥ 50% decrease in SPD of up to 6 largest dominant masses
   a. FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved site
   b. Variably FDG-avid or PET negative: regression on CT
2. No new sites of disease or increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.

3.6. Secondary Study End Points for Phase II

1. CR and PR, assessed per the 2007 Revised Cheson Criteria for NHL (33)
2. 1 and 2 year progression free and overall survival
3. Safety and toxicity of the combination of bendamustine, ofatumumab, carboplatin and etoposide for refractory or relapsed aggressive B cell lymphoma. Toxicity will be

assessed according to the NIH CTCAE version 4.0 (http://ctep.cancer.gov/reporting/ctc.html). Toxicity refers to toxic events during the full course of treatment that are attributed as possibly, probably or definitely due to treatment. For details of toxicity assessment see Section 8.0.

4. Tolerability of the combination of bendamustine, ofatumumab, carboplatin and etoposide for refractory or relapsed aggressive B cell lymphomas.
    - Tolerability of this regime will be compared to historical controls who received RICE protocol
    - Subjects who discontinue therapy prior to Cycle 3 in order to undergo stem cell collection and transplant are considered to have successfully completed therapy.
5. Among transplant eligible patients, the frequency of subjects who undergo autologous or allogeneic stem cell transplant.

3.7 Primary Safety End Points

Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria (CTCAE version 4.0). DLT will be defined as any Grade 4 infection, or Grade >/= 3 non-hematologic toxicity that persists for 7 days or more

4. Subject Selection and Withdrawal

4.1 Inclusion Criteria:

1. Age 18 and above
2. Patients with histologically confirmed aggressive B cell lymphoid malignancy, such as DLBCL, including primary mediastinal large B cell lymphoma, T cell rich B cell lymphoma, "double hit" DLBCL, mantle cell lymphoma, any transformed low grade B cell lymphomas or Grade 3 follicular lymphoma (Grade 3a or 3b) who were refractory to RCHOP-like or any anthracycline based chemotherapy or relapsed after at least one prior combination chemotherapeutic regimen and who are deemed candidates for a salvage type chemotherapy.

    Relapsed disease:

    - Progressive disease after a CR for at least 28 days. Progression will be defined according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007 (33).

    Refractory disease:

    - Subjects must meet one of the following criteria:
    - Persistent or progressive lymphoma with a CR of <28 days duration or with a PR of any duration. Subjects must have received at least 3 cycles of RCHOP-like or any anthracycline base chemotherapy or at least 2 full cycles of HyperCVAD – like chemotherapy.
    - Persistent lymphoma and stable disease after at least 2 cycles of RCHOP-like or any anthracycline base chemotherapy or at least 1 full cycle of HyperCVAD – like chemotherapy (part A and B).
    - Progressive disease despite at least 1 cycle of RCHOP-like or any anthracycline base chemotherapy or at least 1 cycle (part A or A and B) of HyperCVAD – like chemotherapy
3. Measurable disease, defined by the revised lymphoma criteria (Cheson 2007).

4. Absolute neutrophil count ≥1,500 and platelet count ≥ 75,000, unless due to underlying lymphoma.
5. Left ventricular ejection fraction estimated by MUGA scan or 2D-echocardiogram of at least 45% Cardiology consult is recommended prior to enrolment if a history of coronary artery disease, CHF with estimated LVEF of <50% or clinically significant arrhythmia.
6. Estimated glomerular filtration rate (GFR) must be ≥ 50 mL/min
7. Serum bilirubin ≤ 1.5 × upper limit of normal (ULN) unless deemed elevated secondary to lymphoma involvement of the liver or known Gilbert's syndrome.
8. Aspartate transaminase (AST)/alanine transaminase (ALT) ≤ 2.5 × ULN; unless elevated secondary to lymphoma involvement of the liver
9. Alkaline phosphatase ≤ 2.5 × ULN; unless elevated secondary to lymphoma involvement of the liver.
10. Performance status of ECOG 0-2.
11. Both potentially AutoSCT or AlloSCT candidates and those who are not transplant candidates are eligible for the study.
12. Capable of understanding the investigational nature, potential risks and benefits of the study, and able to provide valid informed consent and HIPAA consent.
13. Female patients of childbearing potential must have a negative serum pregnancy test within 3 days prior to enrollment.
14. Male and female patients of reproductive potential must use an effective contraceptive method during the study and for a minimum of 1 year after the after study treatment**.**
15. Must be able to comply with study and follow up requirements

4.2 Exclusion Criteria:

1. Current concomitant chemotherapy, radiation therapy, or immunotherapy other than as specified in the protocol. Concomitant use of corticosteroids is permitted as clinically indicated.
2. Use of investigational agents within 4 weeks prior to enrollment.
3. Any anticancer therapy within 3 weeks before study entry. This exclusion does not apply to corticosteroid therapy. The patient must have recovered from all acute toxicities from any previous therapy.
4. Radioimmunotherapy (i.e. Zevalin) within 8 weeks of enrollment.
5. Prior treatment with anti-CD20 monoclonal antibody or alemtuzumab within 4 weeks prior to start of therapy.
6. Autologous stem cell rescue within 12 weeks before study enrollment or those who underwent allogeneic stem cell transplant within one year of enrollment.
7. Known leptomeningeal or parenchymal brain involvement with lymphoma unless in complete remission after treatment for at least 12 weeks with negative CSF cytology within 2 weeks. Prophylaxis of CNS disease using intrathecal or intraventricular dosing of cytotoxic regimens is permitted and should be performed according to the discretion of the treating physician.
8. History of serious organ dysfunction or disease involving the heart, kidney, liver or other organ system that may place the patient at undue risk to undergo treatment.
9. Systemic fungal, bacterial, viral, or other infection if not controlled. Defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment. (May be enrolled if controlled on

treatment).

10. Significant concurrent disease, illness, or psychiatric disorder that would compromise patient safety or compliance, interfere with consent, study participation, follow up, or interpretation of study results.
11. Subjects who have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment)
12. History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms.
13. 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 extrasystoles or minor conduction abnormalities.
14. Other malignancy, unless the patient has been disease-free for at least 3 years following the completion of curative intent therapy, with the following exceptions: treated non-melanoma skin cancer, any *in situ* carcinoma, or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed. Organ-confined prostate cancer with no evidence of recurrent or progressive disease based on prostate-specific antigen (PSA) values are also eligible for this study if hormonal therapy has been initiated, or radical prostatectomy or definitive prostate irradiation has been performed.
15. Positive test for the Human Immunodeficiency Virus (HIV), unless undetectable viral load within 3 months of enrollment (HIV RNA less than 48 copies/mL) on HAART therapy.
16. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. . Patients with prior history of Hepatitis B infection, but immune, with only IgG Hepatitis core antibody + (HBcAb +) must be checked for hepatitis B virus titers by PCR and if the viral load is undetectable may be enrolled. These patients must receive anti-viral prophylaxis, such as lamivudine 100 mg po daily (or an equivalent) starting at least one week prior to cycle 1 and continued through the completion of treatment and for 9 months after the last dose of ofatumumab. Hepatitis B virus titers by quantitative PCR and HBsAg should be checked every month (+/- 1 week) while on therapy and every 3 months (+/- 1 month) thereafter for 9 months after the last ofatumumab dose. In the event of an early termination of the clinical trial for any reason, a treating physician will be determining the frequency and the length of follow up studies of hepatitis B virus titers and HBsAg status. It is recommended that the patient remains on prophylactic lamivudine or an equivalent, as above, regardless of whether the study was continued or terminated. In addition, if appropriate consultation with a hepatologist should be obtained.
17. Positive serology for hepatitis C (HC) defined as a positive test for HCAb if confirmed by HC RIBA immunoblot assay (for positive HCAb reflexively perform a HC RIBA immunoblot assay on the same sample)
18. Pregnant or lactating women.

Inclusion of Women and Minorities

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

4.3 Subject Recruitment and Screening

Subjects will be recruited from the practices of the Department of Medical Oncology, Thomas Jefferson University. Patients who meet eligibility criteria will be invited by their physician to participate in the study. All therapeutic options will be discussed with the patient and the patient's questions will be answered to the patient's satisfaction. Patients will be asked to read, comment/ask questions about the study and then sign the informed consent form before study procedures are to take place.

Subjects will be screened based on review of previous diagnostic workup including diagnostic tissue biopsy and other laboratory parameters. Another tissue biopsy will be obtained to confirm the relapse, if possible and if patient is agreeable. The diagnosis will be confirmed on the basis of review of initial diagnostic pathology by our institutional hemato-pathologist. Screening laboratory work to be performed will include blood chemistries, viral serologies (for HIV, Hepatitis B and Hepatitis C), pregnancy testing (if applicable), physical assessment and other tests as per section 6.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients will be withdrawn from the study if any of the following occurs:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient noncompliance.
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.
- Initiation of alternative therapy by the treating physician
- Stem cell transplant prior to completion of 3 cycles of treatment. Of note, stem cell collection is allowed after 2 or 3 cycles upon discretion of TJU bone marrow transplant group and study PI or her designee and patients will continue on the trial until initiation of a conditioning regimen and SCT, unless excluded due to other conditions as listed above.

After withdrawal from the study further treatment for the subject will be per the discretion of the treating physician.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

In case of early withdrawal of study, attempts will be made to collect data on subjects who have received at least 1 cycle of treatment. Survival data will be gathered from the treating physician of the subject. If a subject withdrew consent to participate, but allow survival and disease status follow up, attempts will be made to record the data up to the protocol-described end of follow-up period. Patients will be followed for disease status and survival at Months 3, 6, 9, 12, 18 and 24 months post treatment or post ASCT with a window of ± 1 month.

5 Study Drug

5.1 Ofatumumab

Other Names : Arzerra™

Classification : Antineoplastic Agent, Monoclonal Antibody

Mode of Action: Ofatumumab is an anti-CD20 monoclonal antibody and binds specifically to both the small and large extracellular loops of the CD20 molecule. The Fab domain of ofatumumab binds to the CD20 molecule and the Fc domain mediates immune effector functions to result in B-cell lysis in vitro. Data suggest that possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity.

Incompatibilities: Do not mix drug with or administer as an infusion with other medicinal products.

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

Storage: Refrigerate between 2° to 8°C (36° to 46°F). Do not freeze. Vials will be protected from light. Start infusion within 12 hours of preparation. Discard prepared solution after 24 hours.

Preparation: Prepare all doses in 1,000 mL of 0.9% Sodium Chloride Injection, USP. The solution will be a colorless and may contain a small amount of visible translucent-to-white, amorphous, ofatumumab particles.

Route of Administration: iv infusion

Pre-medications

Antiemetics (ondansetron 24 mg IV or equivalent) will be administered prior to chemotherapy. Acetaminophen 650 mg po, diphenhydramine 50 mg po/iv and dexamethasone 20 mg iv (or equivalent) will be given within 30 minutes to 2 hours prior to ofatumumab treatment. If the 2nd infusion has been completed without the subject experiencing any Grade 3/4 adverse events (AEs), pre-medication with glucocorticoid may be reduced or omitted before the 3rd infusion at the discretion of the investigator.

Ofatumumab Infusion

The first dose of ofatumumab will be 300 mg to minimize infusion reactions. The initial rate of the first infusion of 300 mg ofatumumab (0.3 mg/mL) will be 12 mL/h. If no infusion reactions occur the infusion rate will be increased every 30 minutes, to a maximum of 400 mL/h, according to Table below. If this schedule is followed, the infusion duration will be approximately 4.6 hours.

Infusion rate at 1st ofatumumab infusion (300 mg)

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25

61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

If an infusion reaction develops, the infusion will be temporarily slowed or interrupted. Upon restart, the infusion rate will 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 will be restarted at 12 mL/hour. Thereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described.

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 will be doubled every 30 minutes up to a maximum of 400 mL/h, according to Table 4. 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 will start at a rate of 12 mL/hour according to Table 2.

Infusion rate at subsequent ofatumumab infusion (1000 mg)

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 subject will be monitored closely and appropriate measurements should be performed whenever judged necessary.

Side Effects of Ofatumumab:

Hematologic: Neutropenia (≥ Grade 3: 42%; Grade 4: 18%; may be prolonged >2 weeks), anemia (16%; Grades 3/4: 5%). Prolonged (≥1 week) severe neutropenia and thrombocytopenia can occur with ofatumumab. Complete blood counts (CBC) and platelet counts will be monitored at regular intervals as described in section 6

Common: (>10% Frequency)**: Pneumonia,** Upper respiratory tract infection, bronchitis, anemia, cough, dyspnea, diarrhea, nausea, rash, pyrexia and fatigue. **Infusion Reactions** Ofatumumab can cause significant infusion reactions, including serious. Please see above section regarding premedications and ofatumumab infusion.

Occasional: (5-10% Frequency): sinusitis, sepsis, nasopharyngitis, herpes zoster, insomnia, headache, hypertension, hypotension, tachycardia, urticaria, hyperhidrosis, back pain, muscle spasms, peripheral edema, chills.

Rare but Serious (<5% frequency):

Severe Infusion Reactions
Ofatumumab can cause serious infusion reactions. Please see above section regarding premedications and ofatumumab infusion

Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML), including fatal PML, can rarely occur with ofatumumab. PML diagnosis will be considered in any patient with new onset of changes in pre-existing neurological signs or symptoms. Ofatumumab will be discontinued if PML is suspected, and subject will be evaluated for PML including consultation with a neurologist, brain MRI, and lumbar puncture.

Hepatitis B Infection and Reactivation
Fulminant and fatal hepatitis B virus (HBV) infection can occur in patients newly exposed to HBV following treatment with ofatumumab. Subjects will be screened for HBV infection before initiation of treatment and if positive will be excluded. If subjects develop Hepatitis B during treatment, ofatumumab will be discontinued and subjects will be taken off study.

Intestinal Obstruction
Obstruction of the small intestine was reported in two patients receiving ofatumumab. Subjects will have a diagnostic evaluation if obstruction is suspected.

Nursing/Patient Implications:
Advise patients to contact a healthcare professional for any of the following:

- Signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion
- Bleeding, easy bruising, petechiae, pallor, worsening weakness, or fatigue
- Signs of infections including fever and cough
- New neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems
- Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes
- New or worsening abdominal pain or nausea
- Pregnancy or nursing
- Advise patients of the need for:
- Periodic monitoring for blood counts
- Avoiding vaccination with live viral vaccines.

Immunizations
The safety of immunization with live viral vaccines during or following administration of ofatumumab has not been studied. Live viral vaccines will not be administered to subjects within 1 month of ofatumumab administration.

5.2 Bendamustine
Other Names: Treanda®

Classification : Antineoplastic Agent, Alkylating Agent; (Nitrogen Mustard)

Mode of Action: Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown

Reconstitution: Use appropriate precautions for handling and disposal. Reconstitute 25 mg vial with 5 mL and 100 mg vial with 20 mL of sterile water for injection to a concentration of 5 mg/mL; powder usually dissolves within 5 minutes. Prior to administration, dilute appropriate dose in 500 mL NS (or $D_{2.5}{}^1/_2NS$) to a final concentration of 0.2-0.6 mg/mL; mix thoroughly.

Storage:
Bendamustine may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F). Retain in original package until time of use to protect from light

Preparation: Bendamustine will be aseptically reconstituted with Sterile Water for Injection, USP per manufacturer's guidelines. The volume needed for the required dose (based on 5 mg/mL concentration) will aseptically withdrawn from the vial and transferred to a 500 mL infusion bagof 0.9% Sodium Chloride Injection, USP (normal saline), or a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 – 0.6 mg/mL. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. The admixture should be a clear and colorless to slightly yellow solution. Any unused solution should be discarded according to institutional procedures for antineoplastics.

Route of Administration: iv

Contraindications: Known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine or mannitol.

Availability: Bendamustine hydrochloride for Injection is available commercially and is supplied in individual cartons as follows:
NDC 63459-390-08 Bendamustine hydrochloride for Injection, 25 mg in 8 mL amber single-use vial
NDC 63459-391-20 Bendamustine hydrochloride for Injection, 100 mg in 20 mL amber single-use vial

Drug Interactions: Inhibitors of CYP1A2 may increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 may decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites. Caution should be used, if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

Side Effects of Bendamustine
Common (>20% Frequency): Nausea, Vomiting, Diarrhea, constipation, fatigue, fever, anorexia, headache, cough.

Hematological: leukopenia, neutropenia, lymphopenia, anemia, thrombocytopenia occur in majority of patients.

Occasional (5-20% Frequency): Tachycardia, Stomatitis, abdominal pain, dyspepsia, gastroesophageal reflux, dry mouth, abdominal distention, chills, edema, asthenia, infusion site pain, pain, herpes zoster infection, upper respiratory infection, sinusitis, pneumonia, febrile neutropenia, oral candidiasis, nasopharyngitis, weight loss, dehydration, hypokalemia, back pain, arthralgia, bone pain, pain in extremities, dizziness, dysgeusia, insomnia, anxiety, depression, dyspnoea, pharyngolaryngeal pain, wheezing, nasal congestion, rash, pruritis, dry skin, night sweats, hyperhidrosis and hypotension.

Rare but Serious (< 5% Frequency): hyperglycemia (3%), elevated creatinine (2%0, hyponatremia (2%), hypocalcemia (2%). Severe hypersensitivity reactions, including Steven-Johnson syndrome may occur.

Nursing/Patient Implications:

1. Allergic (Hypersensitivity) Reactions: Patients will be informed of possibility of severe allergic reactions including Steven-Johnson syndrome when the drug is used concomitantly with allopurinol and other medications known to cause these syndromes. Patients should immediately reports any rash, facial swelling, or difficulty breathing.
2. Myelosuppression. Monitor CBC. Advice patients of increased risk of infection with absolute neutrophil count less than 500 cells/mm³ and increased risk of bleeding with platelet counts less than 20,000 cells/ mm³. Advise patients to call the office if they develop a fever above 100.4ºF or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
3. Pregnancy and nursing. The drug can cause fetal harm. Women who are pregnant or become pregnant will be excluded from the study and will be advised to avoid becoming pregnant throughout treatment and for 12 months after treatment. Men receiving the drug should use reliable contraception for the same time period. Any pregnancy will be reported. Nursing mothers will be excluded from study.
4. Fatigue. Patients will be advised to avoid driving and operating heavy machinery as the drug may cause fatigue.
5. Nausea and Vomiting. Advise patients that the drug may cause nausea and/or vomiting. Antiemetics will be administered as indicated.
6. Diarrhea. Advise patients that the drug may cause diarrhea.
7. Rash. Advise patients to immediately report severe or worsening rash.

5.3 Etoposide

Other Names: VP 16

Classification: Podophyllotoxin derivative, topoisomerase II inhibitor

Mode of Action: Two different dose-dependent responses are seen. At high concentrations (10 mcg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 mcg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular

assembly. The predominant macromolecular effect of etoposide appears to be DNA synthesis inhibition.

Storage and Stability: Store at controlled room temperature 15° to 30°C. Unopened vials are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 to 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25° C) under normal room fluorescent light in both glass and plastic containers.

Preparation: Etoposide Injection will be diluted with either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP to give a final concentration of 0.2 to 0.4 mg/mL.

Route of Administration: i.v

Availability: Etoposide is available commercially for intravenous use as a sterile 20 mg/mL solution in 5 mL, 25 mL, or 50 mL sterile multiple dose vials. Each mL contains 20 mg Etoposide. Etoposide Injection 20 mg/mL is supplied as follows:
NDC Number Size
0703-5643-01 100 mg 5 mL Multiple Dose Vials
0703-5643-03 100 mg 5 mL Multiple Dose Vials
0703-5646-01 500 mg 25 mL Multiple Dose Vials
0703-5646-03 500 mg 25 mL Multiple Dose Vials
Also available as:
0703-5667-01 1 gram 50 mL Multiple Dose Vials
5 mL and 25 mL vials are available individually or packaged 10 per shelfpack.
50 mL vials are individualy packaged.

Side Effects of Etoposide
Common (>20% frequency): Alopecia (8% to 66%), Nausea/vomiting (31% to 43%), Leukopenia (60% to 91%; Grade 4: 3% to 17%; nadir: 7-14 days; recovery: by day 20), thrombocytopenia (22% to 41%; Grades 3/4: 1% to 20%; nadir 9-16 days; recovery: by day 20), anemia (≤33%).

Occasional (5-20% frequency): anorexia (10% to 13%), diarrhea (1% to 13%)

Rare but Serious (< 5% Frequency): Hypotension (1% to 2%; due to rapid infusion), Stomatitis (1% to 6%), abdominal pain (up to 2%), Hepatic toxicity (up to 3%), Peripheral neuropathy (1% to 2%), Anaphylactic-like reaction (I.V. infusion 1% to 2%; oral capsules <1%; including chills, fever, tachycardia, bronchospasm, dyspnea).

<1% (Limited to important or life-threatening): Amenorrhea, blindness (transient/cortical), cyanosis, extravasation (induration/necrosis), facial swelling, hypersensitivity, hypersensitivity-associated apnea, interstitial pneumonitis, laryngospasm, maculopapular rash, metabolic acidosis, MI, mucositis, optic neuritis, perivasculitis, pruritus, pulmonary fibrosis, radiation-recall dermatitis, rash, seizure, Stevens-Johnson syndrome, tongue swelling, toxic epidermal necrolysis weakness.

5.4 Carboplatin
Classification: Platinum analog

Mode of Action: Produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links.

Storage and Stability: Unopened vials of carboplatin injection are stable for the life indicated on the package when stored at 20° to 25°C (68° to 77°F). **Protect from light.**

Dose Specifics: Doses will be calculated by the target AUC using the Calvert formula, where **Total dose (mg) = Target AUC x (GFR + 25)**. If estimating glomerular filtration rate (GFR) instead of a measured GFR, the GFR will be capped at a maximum of 125 mL/minute to avoid potential toxicity. In this study an AUC of 5 will be used for carboplatin dosing.

Preparation: Carboplatin injection is a premixed aqueous solution of 10 mg/mL. Carboplatin injection can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection. When prepared as directed, carboplatin injection is stable for 8 hours at room temperature 25°C (77°F). It is recommended that carboplatin injection be discarded 8 hours after dilution.

Route of Administration: iv

Compatibility: Stable in $D_5\ ^1/_4NS$, $D_5\ ^1/_2NS$, D_5NS, D_5W, NS.

Availability: Carboplatin Injection, 10 mg/mL, is available commercially and is supplied as follows:
NDC 55390-153-01, 50 mg/5 mL aqueous solution in multidose vials, individually boxed.
NDC 55390-154-01, 150 mg/15 mL aqueous solution in multidose vials, individually boxed.
NDC 55390-155-01, 450 mg/45 mL aqueous solution in multidose vials, individually boxed.

Side Effects of Carboplatin
Common (>20% frequency): Pain (23%), Hyponatremia (29% to 47%), hypomagnesemia (29% to 43%), hypocalcemia(22% to 31%), hypokalemia (20% to 28%), Vomiting (65% to 81%), Myelosuppression (dose related and dose limiting; nadir at ~21 days; recovery by ~28 days), anemia (71% to 90%; Grades 3/4: 21%), leukopenia (85%; Grades 3/4: 15% to 26%), neutropenia (67%; Grades 3/4: 16% to 21%), thrombocytopenia (62%; Grades 3/4: 25% to 35%), Alkaline phosphatase increased (24% to 37%), AST increased (15% to 19%), Creatinine clearance decreased (27%), BUN increased (14% to 22%)

Occasional (5-20% Frequency): abdominal pain (17%), nausea (without vomiting: 10% to 15%), Weakness (11%), Hypersensitivity/allergic reaction (2% to 16%), Neurotoxicity (5%), Constipation (6%), diarrhea (6%), Bleeding (5%), hemorrhagic complications (5%), Bilirubin increased (5%), Peripheral neuropathy (4% to 6%), Creatinine increased (6% to 10%), Infection (5%).
Rare but Serious (< 5% Frequency): Alopecia (2% to 3%), stomatitis/mucositis (1%), taste

dysgeusia (1%), Visual disturbance (1%), Ototoxicity (1%).

<1% (Limited to important or life-threatening): Anaphylactic reaction, bronchospasm, cardiac failure, cerebrovascular accident, dehydration, embolism, erythema, hemolytic uremic syndrome (HUS), hyper-/hypotension, injection site reactions (pain, redness, swelling), necrosis (associated with extravasation), neutropenic fever, pruritus, rash, secondary malignancies, urticaria, vision loss.

Contraindications
History of severe allergic reaction to cisplatin, carboplatin, other platinum-containing formulations, mannitol, or any component of the formulation.

5.5 Treatment Regimen
5.5.1 Chemotherapy Regimen

Agent	Dose	Route	Infusion duration	Schedule
Ofatumumab	Cycle 1: 300 mg on day 1 (or up to 3 days prior to day 1), 1000 mg on day 3. Cycles 2 and 3: 1000 mg on day 1.	IV	Per section 5.1	Cycle 1: Days 1 and 3. Cycle 2 and 3: Day 1.
Bendamustine	Phase I: per the dose level. Phase II: MTD achieved in Phase I	IV	30 minutes	Days 1and 2
Carboplatin	AUC 5	IV	1 hour	Day 2
Etoposide	100 mg/m²	IV	1 hour	Day 1-3

Cycles will be repeated approximately every 3 weeks or when counts recover, whichever is later. Count recovery is defined as ANC >1000/ μl, Platelets >50,000/ μl.

The patients will be admitted to Thomas Jefferson University (TJU) hospital and treated as inpatient for the first cycle. If no unexpected Grade ≥3 toxicities occur during infusion of the first cycle all subsequent treatments will be administered in the outpatient infusion center of Kimmel Cancer Center of TJU or as inpatient at TJUH, as per discretion of the treating physician

5.5.2 Supportive Care:
5.5.2.1 Pre-medications
Antiemetics (ondansetron 24 mg IV or equivalent) will be administered prior to chemotherapy. Acetaminophen 650 mg po, diphenhydramine 50 mg po/iv and dexamethasone 20 mg iv (or equivalent) will be given within 30 minutes to 2 hours prior to ofatumumab treatment. If the 2nd infusion has been completed without the subject experiencing any Grade 3/4 adverse events (AEs), pre-medication with glucocorticoid may be reduced or omitted before the 3rd infusion at the discretion of the investigator.

5.5.2.2 Ofatumumab Infusion
Will be infused as per Novartis protocol. See section 5.1.

5.5.2.3 Tumor Lysis Prophylaxis
All patients will receive allopurinol 300 md PO daily starting at least 24 hours prior to the initiation of the first cycle of therapy or the day of therapy and continued for at least the first week of the initial cycle of therapy. In case of an allergic reaction to allopurinol tumor lysis prophylaxis will include aggressive IV hydration and close monitoring of tumor lysis markers. Rasburicase may be administered as per discretion of the treating physician. For all patients additional measures will include aggressive IV hydration and rasburicase administration at the discretion of the treating physician. Patients will also be assessed for laboratory markers of tumor lysis syndrome.

5.5.2.4 Growth Factor Support
A granulocyte colony stimulating factor (either filgrastim or peg-filgrastim) is mandatory and will be administered at least 24 hours but not later than 96 hours after completion of each cycle of chemotherapy.

5.5.2.5 Prophylaxis of Pneumocystis jirovecii (previously known as Pneumocystis carinii)
It is recommended that patients receive prophylaxis for Pneumocystis during chemotherapy of Trimethoprim/sulfamethoxazole 1 DS PO daily or 2 DS tablets PO Monday, Wednesday, Friday. Patients allergic to the drug may receive Dapsone 100 mg/day or Pentamidine at the discretion of the treating physician.

5.5.2.6 Anti-Fungal Prophylaxis
It is recommended that patients receive anti fungal prophylaxis with fluconazole 400 mg daily or per the discretion of the treating physician.

5.5.2.7 Antiviral Prophylaxis
Patients may be given anti viral prophylaxis with acyclovir 400 mg twice daily or per the discretion of the treating physician.

5.5.2.8 Prophylaxis of CNS Disease
Prophylaxis of CNS disease using intrathecal dosing of cytotoxic regimens is permitted but not required by protocol and should be performed according to the discretion of the treating physician and/or study PI or her designee.

5.6 Method for Assigning Subjects to Treatment Groups
This is an open label study of a single therapy regimen.

5.7 Preparation and Administration of Study Drug
Ofatumumab will be delivered to the Investigational Drug Service at TJUH from Novartis. The Investigational Drug Service will then provide the doses in the inpatient and outpatient oncology infusion setting per the treatment schedule (Cycle 1:Days 1 and 3. Cycle 2 and 3: Day 1). Bendamustine, carboplatin and etoposide will be obtained commercially by the qualified

personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in an appropriate environment.

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

5.8 Subject Compliance Monitoring
Only dose delays or modifications by the investigators or treating physician are permissible.

5.9 Prior and Concomitant Therapy

1. Information of prior cytotoxic regimens will be collected.
2. All concomitant medical therapy will be collected as part of the history.
3. All concomitant medicines/therapies are permitted during the study except for those noted in the exclusion criteria in section 4.2.

5.10 Receiving, Storage, Dispensing and Return
5.10.1 Receipt of Drug Supplies
Ofatumumab will be supplied by Novartis to the Investigational Drug Service (IDS) at Thomas Jefferson University hospital. Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.10.2 Storage
See section 5.1 through 5.4

5.10.3 Dispensing of Study Drug
Ofatumumab will be dispensed by the IDS pharmacy; all other drugs, pre-meds, etc will come from commercial supply from the regular pharmacy. Regular study drug reconciliation will be performed to document drug assigned, drug administered, and drug remaining. For ofatumumab, this reconciliation will be logged by the Investigational Drug Service on the drug reconciliation form.

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

the study files. The remaining drug will be shipped back to the supplier. If the supplier requests that the drug be destroyed on site, it will be documented in the study files.

6 Study Procedures

6.1 Schema

Prior to enrollment (within 28 days) each eligible subject will have a detailed medical history, comprehensive physical examination, vital signs and baseline laboratory parameters (including CBC, CMP (including liver function tests, kidney function tests, electrolytes), Uric acid, LDH, Hepatitis B&C screen, HIV screen, IgG, IgM and IgA. Based on these and a pathological review of initial diagnostic biopsy, subjects will be evaluated for study eligibility. Serum pregnancy test will be done if applicable in eligible subjects at the time of study enrollment. We will attempt to get a repeat lymph node/mass/bone marrow biopsy of a site involved at the time of relapse to confirm the diagnosis and for correlative studies. If another biopsy is unobtainable, either due to location of disease, risk of procedure or patient preference, the diagnosis will be confirmed on the basis of initial diagnostic pathology.

See Appendix 4 for Study Procedures Schedule.

Pathology Review

If diagnostic biopsy was performed at another institution it is required that diagnostic material from the original tumor biopsy must be submitted to TJU hemato-pathology for review and classification.

Protocol Deviations

Protocol coordinator must be notified of any deviations to protocol.
Any deviations to protocol or unanticipated problems to be reported to the IRB via an OHR-20.

6.2. Stem Cell Mobilization and Stem Cell Transplant

This section is relevant to potential transplant candidates.

Mobilization of stem cells will be performed after Cycle 2 or Cycle 3 upon discretion of TJU hematopoietic stem cell transplant group and in agreement with the study PI or her designee from the key study personnel. Stem cells will be mobilized according to TJU hematopoietic stem cell transplant group policy using filgrastim, pegfilgrastim or/and prelixafor (Mozobil). Use of other agents for mobilization may be approved following consultation with the study PI or her designee.

Restaging CT scan should be performed after Cycle 2 and prior to stem cell mobilization and restaging whole body PET/CT scan should be performed after Cycle 3; it should be performed after Cycle 2 if patient is proceeding to autologous SCT after 2 cycles of the study regimen (see section 6).

A patient may proceed to high dose chemotherapy and autologous SCT after 2 cycles of BOCE trial or a third cycle of BOCE regimen may be given after stem cell collection and before autologous SCT upon discretion of TJU hematopoietic stem cell transplant group and in agreement with the study PI or her designee. Stem cell collection should be completed within 8

weeks following Cycle 2 in order to proceed to Cycle 3. A whole body PET/CT scan will be performed in addition to CT scan or MRI if patient is proceeding to autologous SCT after 2 cycles.

Allogeneic stem cell transplant will be performed in selected cases upon discretion of TJU hematopoietic stem cell transplant group and in agreement with the study PI or her designee.

If restaging studies after 2 cycles and before stem cell mobilization reveal progressive disease the patient will be withdrawn from the study and no stem cell collection will be attempted at that point.

6.3. Dose Delays and Dose Reductions

6.3.1 Cycle Delays

Cycles should typically be administered at 3 week intervals. Minor variations, up to 3 days, are permissible for logistical reasons; longer delays, up to 8 weeks are allowed for cytopenias, Grade ≥3 AEs or for stem cell mobilization. Subjects will be withdrawn if dosing is delayed for more than 8 weeks due to an AE. Dose reductions may be approved following consultation with the protocol coordinator and study PI or her designee.

Administration of Cycle 2 or 3 of the investigational regimen will be delayed if the absolute neutrophil count is $<1.0x10^9$/L or the platelet count is $<50x10^9$/L. However, for subjects with counts below these levels at baseline, the start of Cycles 2 and 3 should be delayed until neutrophil and platelet counts have recovered to 80% of the baseline values. A granulocyte colony stimulating factor (either filgrastim or pegfilgrastim) is recommended at least 24 hours but not later than 96 hours after completion of each cycle of chemotherapy.

It is recognized that occasionally mild neutropenia (ANC 0.5-1,0x 109/L) may persist in some responding patients in whom further delay in administering treatment is not medically appropriate. Such patients whose counts do not further improve following a 1-2 week delay may receive the next cycle of therapy after conferring with the PI (or her designee).

6.3.2 Dose Reduction of Bendamustine

In case of Grade 4 infection, or Grade ≥ 3 non-hematologic toxicity that persists for 7 days or more, dose of bendamustine should be reduced with the following cycle of chemotherapy according to the following schema:

Initial dose	Decrease dose to:
120 mg/m²	90 mg/m²
90 mg/m²	70 mg/m²
70 mg/m²	50 mg/m²
50 mg/m²	Withdraw from the study

6.3.3 Dose Modifications of Carboplatin, Etoposide and Ofatumumab

Dose reductions of carboplatin and etoposide should be avoided but, if medically appropriate, a 25% dose reduction may be approved following consultation with the PI of the study or with her designee.

There is no dose reduction for Ofatumumab, only infusion rate adjustment or discontinuation.

Liver Chemistry Interruption/Stopping Criteria (see section 8.4 for more information).
The sponsor-investigator is to review all events which meet liver chemistry stopping criteria to determine if the event was due to;

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

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

6.4. Disease Response

Response Criteria

Baseline imaging studies such as CT scans of the thorax, abdomen and pelvis or MRI (may include other sites, such as head, neck or extremities, if clinically indicated) and the whole body PETCT will be performed prior to the start of study therapy. If at any time point starting from month 3 post chemotherapy, a problem occurs with precertification of a particular PET/CT scan (documentation is required for each time point), a diagnostic quality CT scan (as described above) or/and MRI (if done at baseline), are acceptable for restaging purposes. Patients will be assessed for response based on the revised response criteria by the Revised Response Criteria for Malignant Lymphoma [Cheson, 2007] (see appendix 5) incorporating CT scans of the thorax, abdomen and pelvis and whole body PET/CT (33). Response will be first assessed after 2 cycles using CT scan or/and MRI (if relapse was confirmed by MRI before treatment). Restaging studies will be performed 2-8 weeks after Cycle 2 but before Cycle 3. Restaging PET/CT scan will be performed after 3 cycles of treatment (3-8 weeks post treatment but before high dose chemotherapy and ASCT, if applicable). Additional studies, such as CT scan of chest, abdomen and pelvis (or MRI) will be performed after 3 cycles upon discretion of treating physician or study PI. Imaging may be submitted for retrospective review.

Bone marrow biopsies will be repeated after completion of 3 cycles or before stem cell mobilization if they were abnormal before treatment.

PET/CT Scans

The International Working Group (IWG) recommends the use of pretreatment PET with a low resolution CT (PETCT) scan in evaluation of patients with DLBCL and other aggressive lymphomas when response rate is a major end point (33). Thus in the current study we will assess patients with PETCT pretreatment and post treatment if initial PETCT was positive. Post treatment PETCT will be performed 3-8 weeks after completion of therapy. Of note, the CT portion of PET/CT should not be counted as diagnostic CT scan and a high resolution CT scan or MRI should be done in addition to PET/CT when required by protocol (see Appendix 4: Study Procedures Schedule). Follow up PET/CT scans will be done per institutional guidelines post treatment or post transplant. A diagnostic quality, contrast enhanced CT scan of the chest, abdomen and pelvis (and neck, if done at baseline or if a new suspected area of involvement)

or/and MRI of any site can be added at any restaging time point upon discretion of the study PI, a co-investigator or a treating physician. If at any time point starting from month 3 post chemotherapy, a problem occurs with precertification of a particular PET/CT scan (documentation is required for each time point), a diagnostic quality CT scan (as described above) or/and MRI (if done at baseline), are acceptable for restaging purposes.

Response Evaluation for Transplant Candidates

Restaging CT scan (or/and MRI if positive before treatment) should be performed after Cycle 2 and prior to stem cell mobilization and restaging PET/CT scan should be performed after Cycle 3 (see section 6). A patient may proceed to high dose chemotherapy and ASCT after 2 cycles of BOCE trial or a third cycle of BOCE regiment may be given after stem cell collection and before ASCT upon discretion of TJU hematopoietic stem cell transplant group and in agreement with the study PI or her designee. Stem cell collection should be completed within 8 weeks following Cycle 2 in order to proceed to Cycle 3. A PET/CT scan should be performed in addition to CT scan or/and MRI if patient is proceeding to ASCT after 2 cycles

6.5 Correlative Studies

6.5.1 Flow Cytometry for CD20 Expression

CD20 expression will be assessed by flow cytometry as per standard protocol on fresh tissue biopsy, if available. If bone marrow is involved, or if there are circulating lymphoma cells in peripheral blood flow cytometry analysis for CD20 will be also performed on aspirated bone marrow or peripheral blood cells (if available). The intensity of CD20 expression will be determined in 3 levels in reference to negative isotope controls: Strongly positive: significant shift of abnormal cell population from negative control with no overlap of two populations. Weakly positive: shift of abnormal cell population from negative control but overlap is present. Negative: no significant shift of abnormal population from negative control.

6.5.2 Immunohistochemistry (IHC) Studies

Various panels of IHC will be performed based on disease type. The following antibodies will be performed on all available tissue samples: CD20, CD3, Ki-67. Additional selected antibodies including CD5, CD10, CD23, BCL1, BCL2, BCL6, and MUM1 will be performed according to specific disease type. CD20 expression will be assessed on paraffin sections by IHC in all available tissue Three levels of CD20 expression intensity are determined using light microscopy: strongly positive, weakly positive or negative.

6.5.3 FISH Studies

Fluorescence in situ hybridization (FISH) will be performed on formalin fixed, paraffin embedded tissue or/and on touch-preps, if available. The panel selection is based on specific disease type:

Diffuse large B-cell lymphoma	BCL2, BCL6, cMYC
Mantle Cell Lymphoma	BCL1 (also cMYC for blastoid variant)
Transformed lymphoma	BCL2, BCL6, cMYC

6.5.4 Analysis of Epstein Barr Encoded RNA (EBER)

Presence of Epstein Barr virus will be assessed using in situ hybridization for Epstein Barr Encoded RNA (EBER) on tumor tissue sections in all available tissue samples.

6.5.5 Submission of Blood and Bone Marrow Samples

In the consent section, subjects will be asked if they are willing to participate in correlative studies. Tissues from the subjects who answer "Yes" to "I allow my blood or bone marrow to be tested for additional laboratory research studies as a part of the clinical trial" will be utilized for correlative studies. Of note, blood samples will be collected for correlative studies only if suspected circulating lymphoma cells, based on routine CBC studies or flow cytometry data.

6.5.6 Freezing and Storage

After adequate tissue has been utilized for the correlative studies, the remained of the fresh tissue (lymph node tissue, bone marrow or other tissue obtained for diagnostic purposes and correlative studies) will be frozen and stored to be utilized for additional tests as per study protocol or for future IRB approved studies. Subjects will be asked if they allow storage and future use of their tissue for research purposes. If they refuse, the remained of tissue will not be stored and utilized for future studies. See Appendix 3.

6.6 Duration of Therapy

Treatment may continue for ***3 cycles*** or until one of the following criteria applies:

- Stem Cell Transplant after 2 cycles of the study regimen
- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.7 Duration of Follow Up

Patients will be followed for disease status and survival at 3, 6, 9, 12, 18 and 24 months (with a window of ± 1 month) post treatment, post ASCT, removal from the study, or until death, whichever occurs first. Patients removed from the study for unacceptable adverse event(s) will have AE(s) followed until resolution or stabilization.

6.8 Follow up/monitoring

After completion of treatment, patients will be followed at a minimum of every 3 months with a window of +/- 1 month) for the first year and then at least every 6 months for the second year. Patient will be seen and examined by their treating physician along with a research nurse. Imaging studies per protocol will be obtained (see Appendix 4: Study Procedures Schedule). Whenever possible, the monitoring will occur as part of the routine follow-up visit.

7 Statistical Plan

7.1 Sample Size Determination

A total of 9 to 18 patients will be enrolled in Phase I part of the trial. Twenty four patients will be enrolled in Phase II part of the trial. This is based on the Simon Optimal Two-Stage Design with

the assumption that an ORR rate of 25% indicates that the treatment is not effective and an ORR rate of 50% indicates that the treatment is effective with alpha (type I error) 0.05 and 80% power. The last 6 patients enrolled at the MTD level in Phase I will be included in the Phase II part of the study. Thus the estimated maximum sample size will be 36 patients.

7.2 Statistical Methods

Phase I Design

In Phase I, three doses and 3-6 subjects per dose with the total of 9-18 subjects will be studied (please see the study design table below). We will use a two-stage accrual design at each dose considered. We will initially enter 3 subjects at each dose. If none of the three experiences a dose-limiting toxicity we will proceed to the next dose. If one of the three experiences a dose-limiting toxicity, we will accrue 3 more subjects at that dose. If at any time there are two or more dose-limiting toxicities (in the 3-6 subjects) on a given dose, dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. If >2 DLT at (-1) dose level, the study will be terminated. No patient will be treated at a higher dose until the 3 or 6 patients have completed their toxicity evaluation period at the current dose. With this plan, a dose with a 50% or greater probability of causing a dose-limiting toxicity has at most a 12.5% chance of satisfying the conditions for dose escalation after the first 3 subjects and at least a 50% chance of stopping at 3. With the two-stages (3-6) together, there is at most a 17.2% chance of escalation. The MTD will then be the last dose studied or the previous dose, based on clinical judgment of the degree of toxicity seen at the last dose. While waiting for the 3 or 6 subjects accrued according to plan to complete their toxicity evaluation period, additional subjects may be accrued at the current dose. These additional subjects will not count towards the formal plan of stopping at two or more toxicity occurrences, but will contribute to the judgment as to the MTD. For determination of Dose Limiting Toxicity please see section 8.1

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
$\geq$2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. If $\geq$2 DLT at (-1) dose level, the study will be terminated.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 additional patients experience DLT, proceed to the next

	dose level. • If 1 or more of the 3 additional patients suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This will be the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Phase I Data Analyses

Data analysis of phase I studies is descriptive. At each dose level DLT will be assessed during a minimum of one cycle period. A dose escalation will be allowed only when all 3 or 6 patients have completed at least one cycle of the studied regimen. All estimates of dose-specific rates (e.g., response and toxicity) will be presented with corresponding confidence intervals using the exact method. The method of Atkinson and Brown will be used for any rate related to definition of dose limiting toxicity, due to two-stage sampling. The method of Conover will be used otherwise.

After all the patients have been accrued to the Phase I part of the study, the study investigators and sponsor will convene to assess safety and toxicity. If there are concerns over the safety of the combination therapy, the investigators and the sponsor may terminate the study. Also, if there are >2 DLT at (-1) dose level during accrual period, the study will be terminated.

Phase II Design and Sample Size

We design this trial with the potential for early termination in the case of a poor ORR rate. The design will be a two-stage design using the approach of Simon, selecting among admissible choices (Jung et al.). Choice of design is guided by a desire to stop the trial early if the actual ORR rate is 25% or less. If the ORR rate is 50% or greater, we would like to have a low probability of failing to conclude effective.

Since the Phase I subjects will be treated and followed the same as the Phase II subjects, the Phase I subjects (6) accrued at the chosen MTD will be considered as accrued to the Phase II study as well.

Our chosen design is:

Look after this number of patients:	**Stop if number of successes is less than:**
9	3
24	10

After testing the treatment on 9 patients in the first stage, the trial will be terminated if 2 or fewer respond. After the first 9 patients have been accrued the trial will be on hold for a response

analysis. Once there are confirmed 3 or more responses (PR or CR) the accrual will continue. The trial will be terminated if less than 3 responses were achieved among first 9 accrued patients. If the trial goes on to the second stage, a total of 24 patients will be studied. If the total number responding is less than or equal to 9, the treatment is rejected.

With this design, we have no more than a 20% chance of concluding ineffective (≤25% ORR rate) when the ORR rate is at least 50%. Similarly, we have no more than a 5% chance of concluding effective (≥50% ORR rate) when it is ineffective. If the actual ORR rate is 25% or worse, we have at least a 0.60 probability that the trial will stop after the first 9 subjects. Phase II design requires a maximum of 24 patients. Thus, including 6 patients from Phase I at MTD with Phase II patients, the total of 30 to 36 patients is required for combined Phase I/II study.

7.3 Subject Population(s) for Analysis

All patients who were enrolled in the study and received any clinical trial material will be included in the intent-to-treat analysis. All safety analyses will be performed on the intent-to treat population. The efficacy analysis will include any patient who has received at least one dose of the investigational drug Ofatumumab. All estimates of rates (e.g., response and toxicity) will be presented with corresponding confidence intervals. For ORR rates, the method of Atkinson and Brown will be used to allow for the two-stage design; otherwise the method of Conover will be used.

7.4 Analysis of Missing Data

Subjects with unknown or missing responses will be considered as non-responders.
For endpoints which determine the percentage of responders, subjects with unknown or missing response will be assumed to be non-responders, and will be included in the denominator when calculating the percentages.

8.0 Safety and Adverse Events

8.1 Definitions

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious.

A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening

- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 except for hematologic toxicity.

Hematologic toxicity will be assessed using the NCI working group grading scale as proposed by Hallek et al (34). Hematologic toxicity is expected and a grade of cytopenia will be recorded but it is not a dose limiting toxicity in this study. Grade 3 and 4 neutropenia, grade 3 and 4 thrombocytopenia and Grade 4 anemia are expected desirable targets and should not be considered SAEs in this trial. Only clinically significant events such as neutropenic fever will be captured as an SAE; similarly, grade 4 thrombocytopenia, complicated by bleeding is a reportable event. In terms of cytopenias, only persistent grade 4 neutropenia or/and thrombocytopenia lasting longer than four weeks as measured by twice weekly CBC measurements will be considered an SAE.

Dose-Limiting Toxicity (DLT)
DLT will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTCAE, Version 4.0). DLT will be defined as any Grade 4 infection, or Grade $\geq$ 3 non-hematologic toxicity that persists for 7 days or more. Inability to restart therapy in greater than 8 weeks after previous cycle due to investigational agent-related toxicity or a delayed count recovery will be considered dose limiting. Toxicity must be considered related or possibly related to study drug in order to be classified as a DLT or treatment-related Grade 3 or greater toxicity.

The following adverse events will <u>NOT</u> be considered dose limiting:
- anemia
- thrombocytopenia
- neutropenia
- Alopecia
- Nausea, vomiting, anorexia
- Grade 3 fatigue resolving before the next scheduled dose
- Pain at tumor site due to obvious progression of disease

Infusion reactions to Ofatumumab or Bendamustine which last less than 48 hours.

Hypersensitivity reactions (Grade ≤ 3 only) without use of prophylactic pre-medications

Adverse Event and Serious Adverse Event Reporting Period
All Adverse Events (AEs) regardless of relationship to the study drug regimen will be collected from the initiation of any study procedures until 60 days following the last administration of study treatment. AEs are no longer required to be reported if a subject begins treatment with another therapy, including transplant.

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 Serious Adverse Events (SAEs) regardless of relationship to the study drug regimen will be collected from the initiation of any study procedures until the end of the follow-up period. SAEs are no longer required to be reported if a subject begins treatment with another therapy, including transplant. SAEs related to underlying disease or progression of disease do not need to be reported to NOVARTIS.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality will be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization will be documented

and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Slow infusion rate of ofatumumab (due to infusion reaction) needing overnight hospitalization to complete the infusion will not be recorded as a serious adverse reaction. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery will be reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery will ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though will be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event (SAE) brought to the investigator's attention after the subject has completed the study and is considered by the investigator as possibly related to the study treatment or study participation will be recorded and reported immediately.

The investigator must determine if an AE/SAE is in some way related to the study drug regimen. The relationship should be described as: Unrelated, Unlikely, Possibly, Probably or Definitely Related.

8.3 Stopping Rules

Accrual to the Phase II trial will be stopped if the actual ORR rate is 25% or less. We will evaluate the ORR after 9 subjects have been treated and the trial will be terminated if 2 or fewer respond. Please see section 7.2 for more information.

8.4 Liver Chemistry Interruption/Stopping Criteria

The sponsor-investigator is to review all events which meet liver chemistry stopping criteria to

determine if the event was due to;

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

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

Liver Chemistry Interruption/Stopping Criteria:

1. ALT >3 times upper limit of normal (ULN) **and** bilirubin >2 times ULN (>35% direct bilirubin; bilirubin fractionation required)
2. ALT >8 times ULN
3. ALT >5 times ULN for more than 2 weeks

When any of the liver chemistry stopping criteria is met, following will be done:

- Immediately stop study treatment
- Hold Ofatumumab for two weeks, repeat liver chemistry testing at least twice weekly, and report to sponsor-investigator to discuss the possibility of re-challenging with Ofatumumab.
- Report SAE to NOVARTIS within 24 hours
- All events of ALT > 3xULN **and** bilirubin > 2xULN (>35% direct bilirubin) (or ALT>3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

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

Liver Chemistry Follow-up Assessments

The chemistry tests/ assessments below are to be performed at the time of the event and then continued and/or discontinued at the discretion/judgment of the sponsor-investigator.

- Viral hepatitis serology including:
    - Hepatitis A IgM antibody;
    - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
    - Hepatitis C RNA;
    - Cytomegalovirus IgM antibody;
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
    - Hepatitis E IgM antibody
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
- Fractionate bilirubin, if total bilirubin >2xULN
- Obtain complete blood count with differential to assess eosinophilia

- Record the appearance or worsening clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins
- Increased alcohol use

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

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

Stopping Criteria:

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

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

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

8.5 Data and Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the compliance and implementation of the KCC data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events by both the assigned Medical Monitor and the KCC DSMC.

8.5.1 Medical Monitoring and AE/SAE Reporting

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

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

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

- after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment
    - must be reported to Novartis U.S. Drug Safety and Epidemiology within 24 hours of learning of its occurrence.

      Report to Novartis via Fax:
    - **U.S. Drug Safety & Epidemiology at Fax #: 877-778-9739**
    - Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: clinicalsafetyop.phuseh@novartis.com
    - **Attach Novartis Coversheet to all SAE submissions**
    - **Reference Novartis Study Number COMB157DUS09T**

This includes serious, related, not related, labeled (expected) and, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within24 hours.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

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

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Ofatumumab Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

For medical emergencies, the contact is:

Gaetano Bonifacio MD
Medical Director
US CD MA Hematology
Novartis Pharmaceuticals Corporation
One Health Plaza, 345/4th
East Hanover, NJ 07936-1080
Mobile +1 610 427 3613
gaetano.bonifacio@novartis.com

A Medical Monitor is assigned to this study at the Thomas Jefferson University. This is a physician/pharmacist who is not directly involved in the trial, and is not currently collaborating with the sponsor/investigator on any other trial. The role of the Medical Monitor is to review all reportable AEs/SAEs (in real-time) including grading, toxicity assignments, non-reportable AEs (quarterly), protocol violations/deviations, as well as all other safety data and activity data observed in the ongoing clinical trial occurring at Thomas Jefferson University. The Medical Monitor may recommend reporting of adverse events and relevant safety data, and may also recommend suspension or termination of the study to the DSMC and TJU IRB.

Every KCC investigator initiated protocol includes requirements for reporting of adverse events based on CTC 4.0. All events are reported to the IRB and Medical Monitor using a password protected web-site. In addition all serious adverse events (SAEs) are reported to the TJU IRB Investigator/Study Sponsor will be responsible for reporting SAEs to the Food and Drug Administration (FDA) if applicable. The investigator is required to submit all serious adverse events to the TJU IRB and the Medical Monitor within the timeframes outlined in the below table. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, if the Medical Monitor determines corrective action is necessary, an “ad hoc” DSMC

meeting will be called. ***Fatal adverse events related to treatment which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.*** A summary of the reporting procedure is presented below.

	Grade 1	**Grade 2**	**Grade 2**	**Grade 3**		**Grade 3**		**Grades 4 and 5**
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 - 48 Hours (Death: 24 Hours) Phase 2 - 5 Working Days
Possible Probable Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 working days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase 1 - 48 Hours Phase 2 - 5 Working Days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 and Phase 2 - 48 Hours (Death: 24 Hours)

**NOTE: This table is based on the NCI AE/SAE reporting Guidelines and the TJU IRB Policy and Procedures. Please follow the individual protocol AE/SAE reporting guidelines if more stringent reporting procedures are specified.
***See section 8.1 for exceptions to this monitoring plan.

8.5.2 Data and Safety Monitoring Committee

Data and Safety Monitoring Committee (DSMC) is the Data and Safety Monitoring Board (DSMB) for the KCC. The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials at the Thomas Jefferson University KCC. The committee meets quarterly to review the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

- The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC

meets (by conference call) within 24 hours following the notification of an unexpected adverse event felt to be related to the study drug.

- Prior to each DSMC meeting, each board member, is provided a printout of all reported AEs and SAEs occurring during the reporting period for this clinical trial. The principal investigator provides a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment, a written report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol, as well as recommendations from the Medical Monitor. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.
- A summary of the board's action is sent to each investigator, the CCRRC and TJU IRBs. The DSMC actions may include recommendations/requirements that will lead to improved patient safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC may also take note of slow accrual or lack of scientific progress, and refer such issues to the CCRRC. The DSMC provides the investigator with the rationale for any decision made.

9.0 Data handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the completion and termination of the protocol.

10.0 Study Monitoring, Auditing and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

KCC Investigator Initiated Phase I Studies

Phase I studies require continuous monitoring by the PI of the study with quarterly safety and monitoring reports submitted to the CRMO and the DSMC. Each protocol is assigned to a medical monitor (a physician or other member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial). The medical monitor reviews all adverse events (in addition to unexpected adverse events), safety data and activity data observed in the ongoing clinical trial at each new dose level, prior to dose escalation.

The PI provides a report to the DSMC of all AE/SAEs, safety and toxicity data, and any corrective action that occurred on a quarterly basis. The medical monitor also provides a summary of their review. The summary of all discussions of adverse events are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place quarterly. Patients are only identified by initials, and no other personal health information (PHI) is included in the reports.

The medical monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data observed throughout the life of a clinical trial. In such circumstances, and "ad hoc" DSMC meeting will be called to discuss corrective action with the PI. If for any reason the PI of the trial disagrees with the conclusions of the Medical Monitor or DSMC, the issue will be referred to the Associate Director of Clinical Investigations, who will be responsible for dispute resolution.

The summary of all discussions of adverse events are included in the KCC investigator's reports to the TJU IRBs as part of its annual progress report. The DSMC and the TJU IRBs may, based on the monitor's recommendation suspend or terminate the trial. The quarterly safety and monitoring reports include a statement as to whether this data has invoked any stopping criteria in the clinical protocol.

KCC Investigator Initiated Phase II Studies
Phase II studies require monthly monitoring by the PI of the study with quarterly safety and monitoring reports submitted to the CRMO, and the DSMC. Each protocol is assigned to a medical monitor (a physician or other member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial). The medical monitor reviews all adverse events (in addition to unexpected adverse events), safety data and activity data observed in the ongoing clinical trial.

The PI provides a report to the DSMC of all AE/SAEs, safety and toxicity data, and any corrective action that occurred on a quarterly basis. The medical monitor also provides a summary of their review. The summary of all discussions of adverse events are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place quarterly. Patients are only identified by initials, and no other PHI is included in the reports.

The medical monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data observed throughout the life of a clinical trial. In such circumstances, and "ad hoc" DSMC meeting will be called to discuss corrective action with the PI.

The summary of all discussions of adverse events are included in the KCC investigator's reports to the TJU IRBs as part of its annual progress report. The DSMC and the TJU IRB may, based on the monitor's recommendation suspend or terminate the trial. The quarterly safety and monitoring reports include a statement as to whether this data has invoked any stopping criteria in the clinical protocol.

10.2 Auditing and Inspecting
The investigator will permit study-related monitoring, audits, and inspections by the IRB, the funding sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.2.1 Independent External and Internal Audits
In addition to review by the DSMC, all studies initiated by KCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, CCRRC and/or the Director

of Clinical Investigations, KCC. Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or CCRRC based on prior findings, allegations of scientific misconduct and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CRMO randomly audits at least 10 percent of all patients entered into therapeutic KCC trials and other trials as necessary, on at least a bi-annual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the CCRRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

11.0 Ethical Considerations

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.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.0 Study Finances

12.1 Funding Source

The study was supported by GSKand remaining support to be provided by Novartis

12.2 Conflict of Interest

None to report

13. Publication Plan

We intend to publish our results in a peer reviewed journal and to present our data at a reputable National or International meeting. The primary responsibility for publication lies with the PI and

statistician.

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APPENDICES

Appendix 1: Second Line Age Adjusted International Prognostic Index (sAAIPI)

Risk factors:	**Score**
LDH >ULN	1
Stage III or IV	1
KPS <80%	1

Low risk (L) with 0 factors, low intermediate (LI) risk with 1 factor, high-intermediate risk (HI) with 2 factors, and high risk (H) with all 3 factors present.

Appendix 2: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Ref:
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Appendix 3: Tissue Freezing and Storage Procedure

After adequate tissue has been utilized for the diagnostic and correlative studies, the remained of the fresh tissue (lymph node tissue, bone marrow or other tissue obtained for diagnostic purposes and correlative studies) will be frozen and stored to be utilized for additional correlative tests as per protocol (section 6.5) or for future IRB approved studies. Subjects will be asked to sign a consent form if they allow their tissue to be stored for additional tests as per current correlative protocol and also if they allow it to be used for future research purposes. If they refuse, the remained of the collected tissue will not be stored to be utilized for current or for any future studies.

Tissue Freezing Procedure
1. The tissue, approximately 3-5mm thickness or more will be placed into a plastic container labeled with the specimen number, person ID number and source of tissue.
2. The container will be wrapped in foil and a specimen number sticker is placed on the outside of the foil. The container with the foil is then put into the liquid nitrogen flask to be snap frozen..
3. The sample will then be transferred to the –70°C freezer and stored until used for research..
4. A log of the sample stored will be maintained in the tissue bank and in the CRMO. The following information will be recorded in the log:

- Specimen ID
- Name
- Date of Birth
- Tissue type
- Consent form
- Date Tissue Taken
- Time to freeze/fix tissue
- Date blocks processed
- Number of tumor pieces frozen
- Additional specimens taken
- Storage of additional specimens
- Relevant additional information/comments

Appendix 4: Study Procedures Schedule

Procedures	Screening[1]	Treatment[10]					Follow-up Procedures[11]	
		Cycle 1	Cycle 2	Cycle 3	Post treatment assessment[12]	Treatment withdrawal or disease progression	3 months post treatment or post ASCT	6, 9, 12, 18 and 24 months post treatment or post ASCT
Informed Consent	X							
Demography	X							
Medical History	X							
Disease History	X							
Therapy History	X							
Efficacy assessment								
Bone Marrow biopsy	X[2]				X[14]			
Lymph node/mass biopsy	X[3]				X[3]	X[3]		
CT (or MRI)	X[4]		X[4]		X[4]		X[13]	X[13]
PET/CT	X[4]		X[4]		X[4]		X[13]	X[13]
Clinical disease assessment	X	X	X	X	X	X		
Disease assessment and survival							X	X
Safety Assessments								
Physical Exam	X	X	X	X	X			
ECOG performance[5]	X				X			
Height	X							
Weight	X	X	X	X	X			
Vital Signs	X	X	X	X	X			
12-lead ECG	X							
MUGA or ECHO	X[6]							
Toxicity Assessment		X	X	X	X			
Concomitant Medications	X	X	X	X				

Procedures	Screening[1]	Treatment[10]					Follow-up Procedures[11]	
		Cycle 1	Cycle 2	Cycle 3	Post treatment assessment[12]	Treatment withdrawal or disease progression	3 months post treatment or post ASCT	6, 9, 12, 18 and 24 months post treatment or post ASCT
Lab								

Assessments								
Hematology (CBC with differential)	**X**	**X**	**X**	**X**		**X**		
Chemistry (CMP-12), Uric acid, LDH, B2M	**X**	**X**	**X**	**X**		**X**		
Serum Pregnancy Test	**X**[7]	**X**[7]	**X**[7]	**X**[7]		**X**[7]		
Hepatitis B&C screen[8]	**X**							
HIV screen	**X**							
IgG, IgM, IgA	**X**				**X**	**X**		
Dispense Study Medication								
Ofatumumab		**X**	**X**	**X**				
Bendamustine		**X**	**X**	**X**				
Carboplatin		**X**	**X**	**X**				
Etoposide		**X**	**X**	**X**				
Correlative studies[9]								
Flow cytometry for CD20	**X**							
IHC including CD20, Bcl-2, Bcl-6, Cyclin D1	**X**							
FISH: FISH for Bcl-2, Bcl-6 and MYC rearrangement	**X**							
EBER by in situ hybridization	**X**							
Cryopreservation and storage of malignant cells from diagnostic tumor biopsy	**X**							

1 To be done within 28 days of initiation of Cycle 1, unless otherwise noted. Such screening studies as

2 To be done if involved at the time of initial diagnosis or if clinically indicated

3 It is strongly recommended (but not mandatory) that additional diagnostic tissue biopsies are performed, when possible, to confirm diagnosis, relapse or tumor progression

4 **Imaging studies** will be performed before therapy (within 4 weeks of initiation of treatment). If patient had a PET/CT scan done within 6 weeks of starting treatment all efforts should be made to have a new study done within 4 weeks of starting treatment, however, if rejected by the insurance company the patient will still be eligible for the trial and the PET/CT that was done with 6 weeks will be counted as baseline study.CT or MRI should be done within 4 weeks of initiation of treatment. CT and MRI (if patient had a

positive MRI before treatment) will be repeated after 2 cycles and PET/CT scan will be performed after 3 cycles of therapy. Restaging PET/CT will be performed after Cycle 2 (in addition to other restaging studies) if stem cell transplant is planned after 2 cycles or if tumor progression is suspected based on other restaging studies. CT or/and MRI may be repeated after 3 cycles in addition to PET/CT upon discretion of study PI or a treating physician.

5 See Appendix 2 for ECOG performance status assessment

6 MUGA or ECHO can be performed up to 3 months prior to start of treatment

7 For women of childbearing age: Serum pregnancy testing should be performed within 3 days prior to enrollment, prior to each cycle if last test was more than 30 days prior and at 6 months after last cycle of the study regimen.

8 Hepatitis B screen should include HepBcAb, HepBsAg, and HepBsAb. If HepBsAg is negative and HepBcAb is positive a quantitative PCR analysis for HepB DNA should be performed.(see study exclusion criteria)

9 Strongly recommended but not mandatory

10 Day 1 study procedures of each cycle can be done up to 72 hours prior to Day 1.) In the event of a prolonged ofatumumab infusion (> 8 hours) it is acceptable to reschedule the rest of day 1 chemotherapy to the following day. In that case day 2 and day 3 chemotherapy will be rescheduled to day 3 and 4, respectively.

11 Follow up procedures should be performed at Months 3, 6, 9, 12, 18 and 24 months post treatment or post ASCT with a window of ± 1 month

12 Post treatment assessment should be completed between 3-8 weeks post treatment

13 Follow up PET/CT scans will be done per institutional guidelines post treatment or post transplant. A diagnostic quality, contrast enhanced CT scan of the chest, abdomen and pelvis (and neck, if done at baseline or if a new suspected area of involvement) or/and MRI of any site can be added at any restaging time point upon discretion of the study PI, a co-investigator or a treating physician. If at any time point starting from month 3 post chemotherapy, a problem occurs with precertification of a particular PET/CT scan (documentation is required for each time point), a diagnostic quality CT scan (as described above) or/and MRI (if done at baseline), are acceptable for restaging purposes

14 To be done if positive at screening

Appendix 5

Revised Response Criteria for Malignant Lymphoma.
Cheson BD, Pfistner B, Juweid ME, et al.. J Clin Oncol 2007;25:579–86

CR
1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a 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 until data become available demonstrating a clear difference in patient outcome.

CRu
The use of the above definition for CR and that below for PR eliminates the category of CRu.

PR
The designation of PR requires all of the following:

1. 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.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. 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.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

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. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

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 × ≤ 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. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

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 × 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 if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy 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.