Phase II Study of the Dose Adjusted EPOCH Regimen in Combination with Ofatumumab/Rituximab as Therapy for Patients with Newly Diagnosed or Relapsed/refractory Burkitt Leukemia or Relapsed/refractory Acute Lymphoblastic Leukemia

1.0 Objectives

1.1 Primary Objective: To evaluate the clinical efficacy of the combination of DA-EPOCH + ofatumumab in patients with newly diagnosed or relapsed/refractory Burkitt leukemia or relapsed/refractory ALL defined by complete response rate

1.2 Secondary Objective: To evaluate the safety of this combination, the overall survival and event-free survival rates.

2.0 Background

2.1 Burkitt Leukemia

Historically, adult patients with mature B-ALL had a very poor prognosis [1-5]. With conventional induction chemotherapy (vincristine and steroids), the complete response (CR) was about 60%. In addition, one-third of the patients presented with central nervous system (CNS) leukemia or most of them developed CNS leukemia during the course of the disease if they did not succumb earlier to their leukemia. With the previous intensive regimens used for ALL (2-3 years of intensifications + maintenance) the long-term disease free survival was less than 10% to 20%.

Patients with B-ALL may be divided into 1) Burkitt's L3 ALL or 2) non-Burkitt's B- ALL. The latter category is characterized by the presence of mature B cell markers (surface or cytoplasmic immunoglobulin [sIg or cIg] positivity) but without the French-American-British (FAB) L3 morphology or typical Burkitt's karyotype [t(8;14) or the variants t(8;2) or t(8;22)]. While the prognosis of Burkitt's leukemia was extremely poor with conventional therapy, the patients with non-Burkitt's B-ALL appeared to have a slightly better prognosis, and did not seem to require long-term maintenance therapy [1-10].

Subsequent studies emphasized the use of hyperfractionated cyclophosphamide, high-dose cytarabine and high-dose methotrexate in the management of B-ALL and Burkitt's lymphoma (BL). The treatments were intensive but only for 6-8 months. This treatment regimen united the treatment of B-ALL and advanced-stage Burkitt's NHL. The rationale was that B-ALL (L3 sIg positive) in most cases represents an extreme form of

stage IV Burkitt's NHL with marrow replacement, and that the clinical behavior of B-ALL and stage IV Burkitt's NHL are virtually identical in their aggressiveness.

Despite the advancements made in the treatment ALL most of them will relapse and essentially the outcome is very poor. In fact, in patients who relapse the median survival is only 5 months. The dose adjusted EPOCH regimen has shown significant activity in Burkitt Leukemia and therefore would like to extend the treatment to patients with adult ALL with relapse/refractory disease. We believe that this treatment will benefit this patient population where there are no minimal options available with a very poor outcome.

2.2 Treatment with Hyper-CVAD and immunotherapy

Murphy et al. designed an intensive, multi-agent chemotherapy program based on the concept of delivery of agents in rapid sequence in children with Burkitt's leukemias and lymphomas [4]. Because it was recognized that these lymphomas/leukemias have high growth fractions and doubling times as short as 25 hours, cyclosphosphamide was fractionated in the induction phase in an attempt to encompass the entire generation time of the tumor as well as to provide a smoother induction with fewer metabolic complications [5]. The Total B regimen consists of cycles of fractionated high-dose cyclophosphamide (300mg/m2 q 12 hours for six doses), vincristine, and doxorubicin alternating with high dose methotrexate (1g/m2) and escalating doses of ara-C. Kantarjian et al modified this program, and developed the regimen of hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and ara-C) [11-12]. This regimen has significant activity in the treatment of Burkitt's disease, mantle cell lymphoma, multiple myeloma, lymphoblastic lymphoma, and aggressive chronic lymphocytic leukemia with or without Richter's transformation. Of the 2004 patients with de novo ALL who were treated with hyper-CVAD protocol, 91% achieved a complete remission. The median time to achieve CR was 21 days with 81% of patients achieving CR after one course of chemotherapy. The estimated five-year survival was 39%, and the estimated median survival time was 35 months.

The addition of rituximab to the hyper-CVAD program in patients with CD20 expression (≥20%) improved outcome compared to historical experience, with 3-year CRD rates (68% vs 28%, $p<0.001$) and OS rates (65% vs 35%, $p=0.01$) approaching those of the CD20 negative counterparts [13].

We have recently reviewed the outcome of fifty-one patients with newly diagnosed non-HIV Burkitt leukemia/lymphoma treated at our institution with R-HCVAD [14]. The overall CR rate in 41 evaluable non-HIV patients (10 in CR at start either due to one course of prior therapy or resected disease) was 95%; 2 patients achieved partial

response. All 11 patients aged 60 years or older achieved CR. One induction death was observed in the younger group. CR rate was 64% in the HIV-positive group (5 failures). After a median follow-up of 48 months (range, 2-114+ months) in the non-HIV group, 3 relapses were observed. Nine patients died in CR related to infections (n=3), secondary malignancies (n=3), or other causes (n=3). For the non-HIV group, in comparison with 48 historical patients treated with hyper-CVAD alone, the 4-year rates for OS (77% vs 50%, p=.03), age <60 years (78% vs 70%, p=NS) and age 60 years or older (75% vs 19%, p=.002) were superior for hyper-CVAD with rituximab. Over 90% of non-HIV patients were beyond 1 year of follow-up without disease recurrence. Toxicity profile was similar to hyper-CVAD alone. Three patients developed secondary dyscrasias (acute myelogenous leukemia [AML] at 7 years, myelodysplastic syndrome at 3-1/2 years, AML with t(8;21) at 3 years).

2.3 DA-EPOCH-R in BL

Based on the hypothesis that DA-EPOCH-R may be effective in BL, given its established efficacy in DLBCL and its ability to overcome highly proliferative tumors, pilot studies had assessed whether DA-EPOCH-R could maintain the high cure rates of standard therapy in BL while minimizing treatment related toxicity in HIV negative patients. A total of 30 patients with BL have been treated at the NCI on two protocols using EPOCH and rituximab [15] [#93-C-0133 (DA-EPOCH-R in untreated DLBCL and BL), #01-C-0030 (DA-EPOCH-RR in untreated ARL)]. Characteristics of all 25 patients included median age 30 years (range, 18-66); male sex 20 (80%); median ECOG PS 1 (range, 1-3); stage III/IV 54%; LDH > N 56%; extranodal sites 79% and ileocecal disease 54%. 8/25 (32%) had low-risk disease and 17/25 (68%) had high-risk disease. No patients had CNS involvement at diagnosis. All patients achieved a CR/CRu with one patient receiving consolidative radiation to a site of residual disease. OS and PFS are both 100% and EFS 96% at a median potential follow-up of 28 months. Significant toxicities included tumor lysis syndrome (TLS) in only one patient and fever/neutropenia in 16% of cycles. There were no treatment related deaths. These pilot results suggested that DA-EPOCH-R is effective regimen in newly diagnosed BL and is associated with low toxicity and low rates of TLS compared to “standard” high dose regimens used in BL. Hence, these results suggest that DA-EPOCH-R may significantly advance the therapeutic index in the treatment of BL [15].

2.3 Ofatumumab

Ofatumumab (HuMax-CD20) is a human monoclonal antibody that targets a unique small-loop epitope on CD20 and elicits potent *in vitro* complement-dependent cytotoxicity (CDC), even in malignant B cells with low CD20 expression levels. Ofatumumab was found to be more effective than rituximab in promoting lysis of opsonized B cells via classical pathway complement CDC. Classical pathway CDC is initiated by binding of C1q to aggregated IgG bound to cells. Taylor and colleagues have recently reported on the higher capacity of ofatumamab when compared to rituximab in promoting CDC [16]. In fact, their results indicated that binding of very small amounts of C1q to mAb-opsonized cells, far below the maximal C1q binding capacity of the cells, was sufficient to promote CDC. Greater CDC induced by ofatumumab compared with rituximab might be due in part to a higher level of binding of C1q to OFA-opsonized B cells. Also, cell-bound C1q was found to be more closely associated with ofatumumab (based on the co-localization studies), likely functioning more effectively to activate the classical C pathway and promote CDC.

Ofatumumab has been shown to be safe and active in chronic lymphocytic leukemia (CLL). In a phase I/II study, 12 of 26 relapsed patients who had received 4 weekly infusions of up to 2,000 mg of ofatumumab responded [17]. Time to progression and time to next therapy was 161 and 366 days, respectively. The interim results of a non-randomized phase III registration trial in patients with CLL who progressed after fludarabine and alemtuzumab (DR) or who are refractory to fludarabine and have bulky adenopathy (BFR) have been recently reported. The objective response rate ORR was 51% (34, 68%) for the DR group and 44% (30, 59%) for the BFR group. Median time to next CLL therapy was 9 months for the DR group and 8 months for the BFR group. The median OS was about 14 months for the DR group and 15 months for the BFR group [18]. A phase II study of ofatumumab combined with cyclophosphamide and fludarabine in previously untreated patients recently completed accrual.

To date, we have treated 17 patients with de novo ALL and 2 patients in CR previously treated with HCVAD-ofatumumab [19]. Median age was 50 years (39–71). Median WBC at diagnosis was 5.5 x 109/L (1 -189 x 109/L). CD20 expression above 20% was found in 11 patients (58%), between 10 and 20% in 1 (5%) and below 10% in 7 (37%). 2 patients (11%) had concomitant CNS disease at diagnosis. Among the 15 patients with evaluable baseline cytogenetic analysis, 10 (67%) were abnormal. All but one patient (94%) achieved a CR after cycle 1. All eighteen (100%) patients achieved minimal residual disease (MRD) negativity as assessed by FCI; of whom 12 (67%) achieved MRD negativity after induction. Grade ≥ 3 toxicity included increase of LFT's in 7 patients (37%), increase of bilirubin in 5(26%), thrombotic events in 1 (5%) and neuropathy in 1 (5%). With a median follow up of 8 months (1-23), 18 patients are alive in CR. The 1-year CRD and overall survival rates were 100% and 95% respectively.

3.0 Background Drug Information

3.1 Drug information for the following agents is attached as an appendix to the back of this protocol (Appendix D).

- Cyclophosphamide
- Doxorubicin
- Vincristine
- MESNA
- Methotrexate
- Cytarabine (Ara-C)
- Filgrastim Product (G-CSF)
- Prednisone
- Etoposide

3.2 Ofatumumab [20]

Ofatumumab is a clear colorless liquid concentrate intended for intravenous infusion after dilution in sterile, pyrogen free 0.9% sodium chloride. During its infusion, ofatumumab will be filtered using a 0.2 mm in-line filter. Ofatumumab is formulated at 20 mg/mL adjusted to pH 6.5 and supplied in 5 mL and 50 mL glass vials. The 5 mL vial of ofatumumab (20 mg/mL) contains a total of 100 mg. The 50 mL vial of ofatumumab (20 mg/mL) contains a total of 1000 mg.

3.2.1 Ofatumumab IMP composition: (ingredient Quantity per mL Function)

Ofatumumab drug substance 20 mg Active ingredient
Sodium acetate, trihydrate 6.8 mg
Edetate disodium, dihydrate (EDTA) 0.019 mg
L-arginine 10 mg
Sodium chloride 2.98 mg
Hydrochloric acid to give pH 5.5
Water for injection q.s. to 1 mL

3.2.2 Ofatumumab preparation:

All doses of ofatumumab will be prepared in 1000 mL of 0.9% Sodium Chloride Injection, USP.

- 300 mg dose: withdraw and discard 15 mL from a 1000 mL polyolefin bag of 0.9% Sodium Chloride Injection, USP. Withdraw 5 mL from each of 3 vials of ofatumumab (each vial containing 100 mg) and add to the bag. Mix diluted solution by gentle inversion.
- 2000 mg dose: Withdraw and discard 100 mL from a 1000 mL polyolefin bag of 0.9% Sodium Chloride Injection, USP. Withdraw 50 mL from each of 2 vials (each vial containing 1000 mg) of ofatumumab and add to the bag. Mix diluted solution by gentle inversion

Table 1

Dose of ofatumumab	**Infusion bag size**	**Volume of Sodium chloride 0.9% to be removed from infusion bag**	**Volume ofatumumab (number of ofatumab vials)**
300 mg	1000 mL	15 mL	15 mL (3 vials, 5 mL/vial)
2000 mg	1000 mL	100 mL	100 mL (2 vials, 50 mL/vial)

For intravenous administration, compatibility of the following components for ofatumumab in clinical studies has been established:

Table 2

Dosing component	**Material of construction**	**Suggested vendor**
1L sodium chloride 0.9% bags	Polyvinyl chloride (PVC) Polyolefin [polyethylene* (PE)/polypropylene (PP)]	Baxter Baxter, B. Braun
Administration set	PVC PVC lined with polyethylene	Baxter B. Braun
Filter extension set	Sterilizing-grade (0.22 μm) hydrophilic filter	Durapore brand by Millipore
	Lines made of PVC, filter membrane material polyether sulfone	Baxter
	Lines made of PVC lined with polyethylene, filter membrane material polyether sulfone	Alaris/Cardinal Health
*polyethylene (IUPAC name: polyethene.		

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

- 1000 mL sterile pyrogen free 0.9% saline (NaCl) infusion bag(s).

- Ofatumumab 100 mg and 1000 mg vials (commercial supply)
- Needles and syringes (50 mL sterile syringe)
- Intravenous (IV) cannula (not required if subject has central venous access) Infusion pump and infusion tubing set
- In-line low protein binding, polyether sulfone filter 0.2 μm

Preparation of the 1000 mL infusion bags should be done on the day of planned infusion. Store diluted solution between 2° C and 8° C. Start infusion within 12 hours of preparation. Discard prepared solution after 24 hours.

3.2.3 Ofatumumab administration:

Ofatumumab is to be administered using an infusion pump with a polyvinyl chloride (PVC) administration set and an in-line filter set provided with the product. It is mandatory to use an in-line low protein binding 0.2 micron polyether sulfone filter for all IV dosing of ofatumumab drug product. The line should be flushed with 0.9% Sodium Chloride Injection, USP before and after each dose.

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

Table 3 - Pre-medication Requirements prior to Ofatumumab Infusions

Infusions #	Acetaminophen (po) or equivalent	Antihistamine (iv or po) diphenhydramine or equivalent	Glucocorticoid (iv) Prednisolone or equivalent
1st	1000 mg	25 mg	100 mg
2nd	1000 mg	25 mg	100 mg
3rd –Nth	1000 mg	25 mg	0-50 mg[1]

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

Ofatumumab dosing recommendation for combination therapy in ALL: the first cycle of ofatumumab in combination with chemotherapy should consist of an infusion of 300 mg on Day 1 and an infusion of 2000 mg of Days 2 and 11 for Cycle 1. For subsequent cycles, a dose of 2000 mg should be infused on Day 1 and 8 of Cycle 2 and 4, and day 1 and 11 of Cycle 3.

First Infusion of 300 mg of ofatumumab

The first dose administered of ofatumumab should be 300 mg to minimize infusion reactions. The initial rate of the first infusion of 300 mg (0.3 mg/mL) ofatumumab and the second infusion of 2000 mg ofatumumab (2 mg/mL) should be 12 mL/h. If no infusion reactions occur the infusion rate should be increased every +/- 30 minutes, to a maximum of 200 ml/h, according to the table below:

Table 4 - Infusion rates of ofatumumab.

Interval after start of infusion (min)	Dose 1 (mL/hr)	Dose 2 (mL/hr)	Dose 3 and beyond (mL/hr)
0-30	12	12	25
31-60	25	25	50
61-90	50	50	100
91-120	100	100	200
>120	200	200	400

Interrupt infusion for infusion reactions of any severity. For grade 4 infusion reactions, do not resume the infusion. For grade 1, 2 or 3 infusion reactions, if the infusion reaction resolves or remains less than or equal to grade 2, resume infusion with the following modifications according to the initial rate of the infusion reactions.

- Grade 1 or 2: infuse at one-half the previous infusion rate
- Grade 3: infuse at a rate of 12 mL/hr

If the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Hereafter, the infusion rate may be increased according to the table above and judgment of the investigator.

Subsequent infusion of full dose of ofatumumab

If the previous infusion has been completed without grade ≥ 3 infusion associated AEs, the subsequent infusion of the first full dose of ofatumumab can start at a rate of 25 mL/hour and should be increased every 30 minutes up to a maximum of 400 mL/h, according to Table 4. If the previous infusion has been completed with grade ≥ 3

infusion associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to Table 4.

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

3.2.4 Dose Reduction:

No dose reduction is planned for ofatumumab, its administration will be held for grade 3 or higher hepatic toxicity and can be omitted if clinically indicated.

3.3. Rituximab

Rituximab is a chimeric IgG1 kappa monoclonal antibody (with murine light- and heavy-chain variable region sequences and human constant region sequences) that recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas [24,25]. It is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD.

The CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35), important in cell cycle initiation and differentiation [26], is expressed strongly in over 90% of B-cell lymphomas, including hairy cell leukemia. It is a hydrophobic trans-membrane protein which is not shed from the cell surface or internalized with antibody binding. CD20 is not found on hematopoietic stem cells, pro-B cells, or normal plasma cells. Rituximab shows specificity for the CD20 antigen and binds with an apparent affinity of 5.2 x 10-9 M.

3.3.1 Storage/Preparations

3.3.1.1 Clinical Formulation

Rituximab (sterile, clear, colorless, preservative-free liquid concentrate) will be provided to the clinical sites packaged in single use 10 ml (100 mg) and 50 ml (500 mg) Type I glass vials at a concentration of 10 mg of protein per ml. The product is formulated for intravenous administration in 7.35 mg/ml sodium citrate dihydrate, 0.7 mg/ml polysorbate 80, 9.0 mg/ml sodium chloride and Sterile Water for Injection. The pH is adjusted to 6.5.

Rituximab may be produced by the mammalian (Chinese Hamster Ovary) cell suspension culture in a nutrient medium containing 100 mg/ml of the antibiotic gentamicin. The antibiotic is not detectable in the final product. The antibody is purified

by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures.

3.3.1.2 Storage

Rituximab for clinical use should be stored in a secure refrigerator at 2-8oC.

3.3.1.3 Reconstitution and Dilution of rituximab

Using a sterile syringe and a 21 gauge or larger needle, transfer the necessary amount of Rituximab from the vial into a partially filled IV pack containing sterile, pyrogen-free 0.9% Sodium Chloride, USP (saline solution). The final concentration of Rituximab should be 1 mg/ml. Mix by inverting bag gently.

Caution should be taken during the preparation of the drug. Parenteral drug products should be inspected visually for particulate matter prior to administration. Preparations of Rituximab containing visible particles should not be used. As with all parenteral drug products, aseptic procedures should be used during the preparation and administration of Rituximab.

4.0 Patient Eligibility

4.1 Inclusion Criteria:

1. Burkitt's or Burkitt-like leukemia/lymphoma, either previously untreated, or relapsed/refractory, or HIV-related. Patient with double or triple hit high-grade leukemia/lymphoma are eligible also. Patients HIV positive will be described and reported separately; or relapsed/refractory acute lymphoblastic leukemia (ALL)
2. All ages are eligible
3. Zubrod performance status ≤ 3 (ECOG Scale, Appendix E)
4. Adequate organ function with creatinine less than or equal to 2.0 mg/dL (unless considered tumor related), bilirubin less than or equal to 2.0 mg/dL (unless considered tumor related).
5. Adequate cardiac function defined as no history of clinically significant arrhythmia, or history of MI within 3 months prior to study enrollment. Cardiac function will be assessed by history and physical examination.

4.2 Exclusion criteria:

1. Pregnant or nursing women.
2. Active and uncontrolled disease/infection as judged by the treating physician
3. Unable or unwilling to sign the consent form

4. 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)

5.0 Treatment Plan

5.1 All patients will be registered through CORe.

5.2 General considerations

All patients will receive 8 cycles of EPOCH-O/R (2 doses of ofatumumab or rituximab per cycle for the first 4 cycles, except for Cycle 1, where it is necessary to administer one additional dose of ofatumumab to prevent infusion reactions). Rituximab will be administered instead of ofatumumab if insurance does not cover ofatumumab. In patients requiring emergent treatment, patients may be started on ofatumumab before insurance approval is received and switched to rituximab if it is determined that insurance will not cover ofatumumab.

Pegfilgrastim / pegfilgrastim biosimilar 6 mg (flat dose) within 72 hours after completion of chemotherapy. Filgrastim product10 µg/kg/day (rounded) until neutrophil recovery 1 x 10^9/L or higher can be substituted or can be added to Pegfilgrastim if neutrophils have not recovered to 1 x 10^9/L by day 21.

• The next course may be started when granulocytes are more than or equal to 1.0 x 10^9/L and platelets are more than or equal to 50 x 10^9/L. Therapy may start earlier or later depending on the clinical situation, with a minimum of 14 days between cycles. Courses may be started with dose reductions prior to full platelet recovery, if the treatment is delayed (e.g., greater than 28 days from last course).

• Prophylactic antibiotics may be given with each course. Prophylactic antibiotics will vary based on patient tolerance and allergy status. Suggestions include:

Levofloxacin 500 mg p.o. daily or other appropriate prophylactic antibacterial agents.

Fluconazole 200 mg p.o. daily or other appropriate antifungal agent.

Valacyclovir 500 mg p.o. daily or other appropriate antiviral agent.

No maintenance phase chemotherapy will be planned. Patients who are unable to complete all 8 courses of planned chemotherapy will be monitored for disease-free and overall survival only, and will not be considered off-protocol. An end-of-treatment date will indicate completion of therapy.

Serial measurements of minimal residual disease will be obtained, and depending on the results, post remission or maintenance therapy programs for high risk patients may be developed.

Patients with HIV disease will not be excluded, but should be evaluated for highly active antiretroviral therapy (HAART), in addition to antibiotic prophylaxis for Pneumocytis carini (PCP), cytomegalovirus, and Mycobacterium avium-intracellulare. An infectious disease consultation will be obtained for those patients not followed by an HIV specialist.

No dose escalations beyond those specified in the protocol are allowed. Other variations to the treatment plan as outlined are allowed if felt to be in the best clinical interest of the patient. Examples of these clinical scenarios include:

- Treatment delays (> 14 days from recovery) despite hematologic recovery for reasons of patient request or unavoidable social situations. Treatment delays to allow recovery from infections or other toxicities of therapy will not be considered deviations, as these are expected complications of the therapy.

- Dose reductions or alterations in the chemotherapy administration beyond those specified in the protocol for reasons of patient request or unavoidable social situations. Dose reductions performed for clinical reasons will not be considered deviations, as patients may have unique toxicities or tolerance not accounted for by standard dose reductions.

- Other clinical scenarios after approval by the Principal Investigator.

The induction chemotherapy and follow up will be at M. D. Anderson Cancer Center for the first 3-4 weeks. Other courses can be given at M. D. Anderson Cancer Center whenever possible. Subsequent courses of intensive chemotherapy can be given at M. D. Anderson or by the local oncologist after review of the outside laboratory data, discussion with the local physician, and preparation of the sample orders by the Principal Investigator and Research Nurse assigned to the protocol. Supportive care, intrathecal chemotherapy, ofatumumab, and vincristine may be given by the local physician in all cases.

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule. All dose adjustments will be made according to the protocol unless otherwise specified.

5.3 EPOCH-O/R

Ofatumumab 300 mg (FLAT DOSE) IV on day 1 (before infusions) and 2,000 mg (FLAT DOSE) on days 2 and 11 (plus or minus 3 days) during Cycle 1 only. Starting with Cycle 2, patients will receive Ofatumumab 2,000 mg (FLAT DOSE) IV on days 1 and 8 (+/- 3) of Cycles 2 and 4, and day 1 and 11 (+/- 3) of Cycle 3 for a total of 9 injections of ofatumumab; see Section 3.2.6 for administration instructions

Etoposide 50 mg/m^2/day CIV infusion days 1- 4 (96 hour infusion) +/- 4 hours

Doxorubicin 10 mg/m^2/day CIV infusion days 1-4 (96 hour infusion) +/- 4 hours

Vincristine 0.5 mg (FLAT DOSE) CIV infusion days 1-4 (96 hour infusion) +/- 4 hours

Cyclophosphamide 750 mg/m^2 IV day 5 over approximately 1 to 2 hours

Prednisone 60 mg PO BID days 1-5

Rituximab 375 mg/m^2 IV days 1 and 11 (+/- 3) of Cycle 1 and 3 and days 2 and 8 (+/- 3) of Cycle 2 and 4 replaces ofatumumab if insurance does not approve ofatumumab.

Variations in infusion times due to minor differences in IV bag overfill/underfill and institutional procedure on flushing chemotherapy lines will not result in protocol deviation. All infusion times are considered approximate.

5.3.1 Dose adjustments for inadequate myelosuppression between cycles

Recent studies using the EPOCH regimen have enacted a dose adjustment strategy for the cytotoxic agents according to an individual's level of myelosuppression experienced in the previous cycle. Myelosuppression is a surrogate marker of anti-leukemia/lymphoma activity, so this strategy allows for the chemotherapy doses to be tailored to an individual patient's "pharmacodynamic" response. We are suggesting a similar, yet simplified dose-adjustment policy for the present study.

A patient's starting dose level will depend on their age and performance status according to the table below as follows:

< 60 years of age: dose level 1

60 – 74 years of age and PS of 0 – 2: dose level -1

> 74 years of age or > 60 years of age with PS 3: dose level -2 (In addition, vincristine dose will be reduced by 50%)

-Patients will have a CBC with differential performed at least weekly between chemotherapy cycles

-The definition of adequate myelosuppression is an ANC nadir of less than 500/microliter

-If the patient experiences an ANC nadir of less than 500/microliter, doses of chemotherapy will not be increased during the subsequent cycle

-If a patient's ANC nadir is above 500/microliter, doses of cyclophosphamide, etoposide, and doxorubicin should be increased by one dose level according to the table below

-If a treating physician cannot determine the ANC nadir for a given cycle, there will be no dose increases in chemotherapy unless discussed with the PI

-If the treating physician feels it is in the best interest of the patient to not have their chemotherapy doses increased despite a qualifying nadir ANC, this would be allowed

-Further dose reductions of 20-25% are allowed as indicated below.

Table 5 - Drug Dose Levels

Drugs		Drug Dosing per Dose Level		
	-2	-1	1	2
Doxorubicin ($mg/m^2/day$)	6	8	10	12
Etoposide ($mg/m^2/day$)	30	40	50	60
Cyclophosphamide ($mg/m^2/day$)	500	600	750	900

5.4 Central Nervous System Management

5.4.1 For previously untreated patients, treat with standard CNS prophylaxis with methotrexate and cytarabine for 2 intrathecal treatments (IT) with each course if no evidence of CNS disease.

5.4.2 Total number of prophylactic intrathecal treatments for previously untreated patients will be 16 (2 with each course). Missed intrathecals (e.g., related to failed procedure attempts, scheduling issues, patient social situations) can be made up with later courses or upon completion of therapy to achieve

the planned number of intrathecal treatments to prevent CNS relapse based on available data. IT prophylaxis consisted of cytarabine 100 mg alternating with methotrexate 12 mg.

If CNS disease: give methotrexate alternating with cytarabine twice weekly until CSF clear; then once weekly for 4 weeks, then back to prophylactic schedule. Consider XRT to the base of the skull, with cranial nerve root involvement (cranial nerve palsies), except for instances where intrathecal therapy alone is expected to produce a response (e.g., mental neuropathy, isolated lateral rectus nerve palsy).

5.5 Suggested Dose Modifications

5.5.1 Etoposide

- For estimated creatinine clearance between 31 – 50 mL/min: reduce dose by 25%
- For estimated creatinine clearance $\leq$ 30 mL/min: reduce dose by 50%
- Doses can be re-escalated if creatinine clearance improves at the discretion of the treating physician
- For total bilirubin > 2: reduce dose by 50%

5.5.2 Vincristine 0.25 mg (FLAT DOSE) via IV continuous infusion for 4 days on days 1 – 4

- Bilirubin > 2.0 mg/dL and $\leq$ 3.0 mg/dL.
- Grade 2 persistent peripheral neuropathy.
- Eliminate vincristine for grade 3-4 neurotoxicity, including ileus suspected to be related to vincristine, bilirubin > 3.0 mg/dL, peripheral neuropathy

5.5.3 Doxorubicin:

- Reduce by 50% for bilirubin 2 to 3 mg/dL, by 75% for bilirubin >3 to 5 mg/dL. Eliminate if bilirubin > 5 mg/dL

5.6 Administration of Rituximab

CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS

5.6.1 Suggested premedication (two tablets [375 mg or 500 mg] of acetaminophen orally and 25 to 100 mg of diphenhydramine hydrochloride orally or intravenously) 30 to 60 minutes prior to starting each infusion of Rituximab. Other alternative prophylactic measures may be appropriate, such as hydrocortisone or Solu-Medrol.

5.6.2 The drug may be administered via a peripheral or central intravenous line. The rate should be slowly escalated as tolerated.

5.6.3 Rituximab is associated with hypersensitivity reactions (hypotension, bronchospasm, or angioedema) which may respond to adjustments in the infusion rate. Transient fever and rigors may occur. Rituximab should be interrupted for severe reactions and resumed at a reduced rate when symptoms have improved or resolved. Supportive care such as IV saline, diphenhydramine, hydrocortisone, and acetaminophen should be considered as the clinical situation dictates.

6.0 PRETREATMENT EVALUATION

6.1 History and physical examination.

6.2 CBC, platelet count, differential, creatinine, bilirubin, uric acid, LDH.

6.3 Bone marrow aspirate and cytogenetics within 2 weeks.

6.4 Echocardiogram or MUGA prior to doxorubicin for course 1 in patients with history of congestive heart failure or myocardial infarction. Cardiology consultation recommended in patients with reduced ejection fractions (< 40%).

7.0 EVALUATION DURING STUDY

7.1 At least once weekly CBC, platelet count, and differential (when granulocytes > 1.0 x 10^9/L) for course 1, then at least every 2 weeks during courses 2-8 of chemotherapy. Then every 2-4 months for the first year, then every 4-8 months for the next 2 years

7.2 Creatinine, bilirubin, uric acid, LDH at least every 2 weeks for course 1, then creatinine and bilirubin at least every 4 weeks during courses 2-8 of chemotherapy. Then every 2-4 months for the first year, then every 4-8 months for the next 2 years

7.3 Bone marrow aspiration on day 14 +/- 5 days of the first course of chemotherapy for patients with involvement of marrow prior to initiation of therapy, then in 1-2 weeks +/- 5 days later to confirm response status (or at the time of hematologic recovery). Then every 2-4 months for the first year, then every 4-8 months for the next 2 years.

7.4 Minimal residual disease assays (for patients with bone marrow involvement prior to initiation of therapy) at the time of CR, then every 2-4 months for the first year and every 4-8 months for the next 2 years.

8.0 Long-Term Follow-Up

After last study visit, patients will be called by the study staff and asked about their health every 3-6 months for 1 year. These calls should last about 5 minutes each. For

patients registered on our long-term follow-up umbrella protocol DR09-0223, survival follow-up may be conducted under that protocol

9.0 CRITERIA FOR RESPONSE

9.1 Burkitt's Leukemia or ALL

9.1.1 Complete Remission: Normalization of the peripheral blood and bone marrow with 5% or less blasts in a normocellular or hypercellular marrow with a granulocyte count of 1 x 10^9/L or above and platelet count of 100 x 10^9/L or above. Complete resolution of all sites of extramedullary disease is required for CR.

8.1.2 Partial Response: as above except for the presence of 6-25% marrow blasts.

9.2 Burkitt's or Burkitt's like Lymphoma

9.2.1 Objective response of bi-dimensionally measurable and unidimensionally measurable parameters.

- **Complete Response (CR)**. Complete disappearance of all known disease.
- **Partial Response (PR)**. ≥ 50% decrease in tumor size using the sum of the product (bi-perpendicular dimensions when available). This includes a 50% volume decrease in lesions measurable in three dimensions.
- **No Response (NR)**. No significant change (includes stable disease). Lesions decreased in size but < 50% or lesions with slight enlargement but < 25% increase in size.
- **Progressive Disease (PD)**. Appearance of new lesions. □ 25% increase in size of existing lesions (increase ≥ 50% if only one lesion is available and is □ 2 cm in size).

9.2.2 Objective response for non-measurable parameters.

- CR, NR, and PD same as above but estimated.
- PR definite improvement estimated to be ≥ 75% of lesion but not quantifiable by measurement.

10.0 EVALUATION OF TOXICITY

9.1 Toxicities will be graded according to the current NCI Expanded Common Toxicity Criteria.

11.0 CRITERIA FOR REMOVAL FROM THE STUDY

11.1 Progressive disease.

11.2 Non-compliance by the patient with protocol requirements or patient's request to be removed from the study.

12.0 STATISTICAL CONSIDERATIONS

General description

This is a phase II study of dose adjusted EPOCH regimen in combination with ofatumumab/rituximab as therapy for patients with newly diagnosed or relapsed/refractory Burkitt leukemia or relapsed/refractory ALL. Up to 25-30 newly diagnosed patients and 10-15 relapsed/refractory patients will be enrolled in the study. The primary objective is to determine the efficacy of the study treatment, and the primary endpoint is defined as the complete response (CR) during the first two treatment cycles. The two treatment groups will be analyzed separately.

New diagnosed patient cohort

Up to 25-30 newly diagnosed patients will be enrolled in the study. The historical data indicated that the CR rate is 73% for newly diagnosed patients under standard treatment. It is expected that the proposed combination study can achieve a CR rate of 87%, an increase of 14% in CR rate over the standard therapy. The study will monitor futility and toxicity using a Bayesian method to stop the study early if there is evidence to suggest that the experimental treatment is too toxic or the response rate is low.[21] If the study is not stopped early and a maximum of 30 patients are enrolled, and assuming that we observe 22 (73%) patients have CR, then the 95% confidence interval for the CR rate will be (57.1%, 88.9%). Assuming that we observe 26 (87%) patients have CR, the 95% confidence interval for the CR rate will be (75%, 99%).

<u>Futility and toxicity monitoring</u>

The accrual in the newly diagnosed cohort will be stopped early if the data suggested that:

1) $Pr(\theta_E < 0.14 + \theta_S \mid data) > 0.95$ or
2) $Pr(T_E > 0.30 \mid data) > 0.85$

Where θ_E represents the CR rate for experimental drug in this study and θ_S represents the CR rate for the standard practice, and T_E denotes the probability of toxicity, which is defined as treatment related grade 3 or higher non-hematological toxicity. The first rule is for futility monitoring. That is, if at any time during the study we determine that there is 95% or more chance that the CR rate is less likely to improve by 14% than that under the standard treatment, we will terminate the study in this cohort. We assume that θ_S has a distribution of beta (73, 27) to reflect the information on 100 patients for the historical data, which has a mean response rate of 0.73 and a variance of 0.002. We

also assume that θ_E has a non-informative flat prior beta(1.46, 0.54) with mean of 0.73 and variance of 0.0657. The second rule is for toxicity monitoring. Toxicity will be monitored closely and toxicity monitoring for stopping rules will apply to cycle 1 only. We will stop the trial if, at any time during the study, we determine that there is more than 85% probability that the Toxicity rate is more than 30%. We assume T_E has a prior distribution of beta(0.6, 1.4).

The stopping boundaries for futility monitoring based on the above rule and assumptions are listed in table 6. The monitoring will begin after the first 5 patients are treated and thereafter when every 5 patients are treated. For example, accrual will cease if only two or fewer patients experience achieve a CR among the first 5 patients treated.

Table 6. Stop accrual if the number with CR is less than or equal to indicated (i.e., # patients with CR) among the number of patients evaluated

# patients evaluated	5	10	15	20	25
# patients with CR	0-2	0-6	0-10	0-14	0-17

The stopping boundaries for the toxicity monitoring based on above toxicity monitoring rule are listed in table 7. For example, accrual will cease if 3 or more patients experience toxicities among the first 5 patients treated or if 5 or more patients experience toxicities among the first 10 patients.

Table 7. Stop accrual if the number of toxicities is greater than or equal to indicated (i.e., # patients with toxicities) among the number of patients evaluated

# patients evaluated	5	10	15	20	25
# patients with toxicities	3-5	5-10	7-15	9-20	11-25

The operating characteristics by simulations for futility and toxicity monitoring are presented in table 8. There is 68% probability to stop the trial early when the CR rate is 73% and the toxicity rate is 30%. There is only 7.9% chance to stop the trail early when CR rate is 87% and toxicity rate is 10%, however there will be 89% probability to stop the trial early when CR rate is 87% and toxicity rate is 50%.

Table 8: Operating characteristics for futility and toxicity monitoring for the newly diagnosed patient cohort

CR Rate	Toxicity rate	Probability of early stop	Avg. Num. of patients treated
0.4	0.1	0.9995	6.875
0.4	0.3	0.9996	6.562
0.4	0.4	0.9998	6.246
0.4	0.5	0.9999	5.884
0.73	0.1	0.5577	20.186
0.73	0.3	0.6826	16.794
0.73	0.4	0.8291	13.109
0.73	0.5	0.947	9.543
0.87	0.1	0.079	28.519
0.87	0.3	0.339	23.012
0.87	0.4	0.644	16.957
0.87	0.5	0.89	11.266
0.97	0.1	0.0099	29.76
0.97	0.3	0.2894	23.94
0.97	0.4	0.6175	17.534
0.97	0.5	0.8814	11.527

Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the OC table (Table 8).

Relapsed/refractory cohort

10-15 relapsed/refractory patients will be enrolled over three years to receive the study treatment. Burkitt leukemia is a rare disease, a high proportion of patients treated achieved CR and the CR usually lasts a relatively long duration. However once disease relapses, patients will die quickly. No treatment has been established for this relapse/refractory disease. The objective is to see if there is any anti-disease activity among these 10 patients. Therefore, no interim futility monitoring is designed. We will stop the enrollment in this cohort if $Pr(T_E > 0.30 \mid data) > 0.85$. The corresponding stopping boundaries are: stop the enrollment if the Num. of patients with toxicity observed / number of patients evaluated ≥ 3/5, 4/6-7, 5/8-9.

Table 9: OCs for toxicity monitoring

Toxicity rate	Probability of early stop	Avg. Num. of patients treated
0.1	0.0095	9.955
0.2	0.069	9.683
0.3	0.205	9.087
0.4	0.406	8.214
0.5	0.627	7.212

Analysis method

Safety data will be summarized using frequency and percentage. Complete response rates will be estimated along with the 95% credible intervals. Overall survival time, event-free survival (EFS) and complete response duration (CRD) will be estimated using the Kaplan-Meier method.

13.0 REPORTING REQUIREMENTS

13.1 Adverse Events Requiring Expedited Reporting: Serious unexpected adverse events (SAEs) considered associated with therapy should be reported as per institutional IRB policy.

13.2 Expected Therapy Related Events

Expected therapy-related events include those known toxicities or side effects related to the components of the chemotherapy. These grade 4 or less events will not be reported as individual SAEs, but will be summarized in the annual report to the IRB.

Examples include:

Hyperglycemia
Electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hyponatremia, hypocalcemia).
Renal failure related to tumor lysis syndrome, methotrexate or antibiotic therapy (e.g., AmBisome).
Cytarabine related central nervous system toxicity.
Catheter-related deep venous thrombosis.
Coagulation abnormalities related to induction therapy (e.g., chemical DIC or hypofibrinogenemia).
Ileus related to vincristine.
Hepatotoxicity related to 6-MP or methotrexate.
Post lumbar puncture headaches.
Avascular necrosis related to corticosteroids.

13.3 Events not considered to be serious events are hospitalizations for the routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

13.3.1Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.

13.3.2 Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

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