THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Phase II Study of the Hyper - CVAD Regimen in Combination with Ofatumumab as Frontline Therapy for patients with CD-20 positive Acute Lymphoblastic Leukemia 2010-0708

Core Protocol Information

Short Title	Phase II Study of HCVAD – Ofatumumab in CD-20 + ALL
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Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

2010-0708 - HCVAD Ofatumumab Protocol - November 5 2018 CLEAN.docx

Phase II Study of the Hyper-CVAD Regimen in Combination with Ofatumumab as Frontline Therapy for patients with CD-20 positive Acute Lymphoblastic Leukemia

1.0 Objectives

1.1 Primary Objectives: To evaluate the clinical efficacy of the combination of hyper-CVAD + ofatumumab in patients with newly diagnosed acute lymphoblastic leukemia with any level of CD20 expression:

- Event-free survival
- Overall response rate
- Overall survival

1.2 Secondary Objectives: To evaluate the safety of this combination.

2.0 Background

2.1 Acute Lymphoblastic Leukemia (ALL)

Adult ALL encompasses a heterogeneous group of lymphoid malignancies. Prognosis is related to age, karyotype, molecular profile, immunophenotype, and other disease features. Prognosis for pediatric ALL has improved significantly over the last several decades to current long-term survival rates of greater than 80% [1]. However, long-term survival in adults is currently only 35% to 45% [2,3]. The predominant reason for failure is disease recurrence.

Recent advances in treatment have been based on the pediatrics regimens. 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) [6,7]. 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.

2.2 Rationale for the Combination of hyper-CVAD and immunotherapy

Expression of CD20 was associated with a higher incidence of relapse, lower 3-year complete remission duration (CRD) and lower 3-year overall survival (OS) rate. The independent adverse influence of CD20 expression on event-free survival (EFS) was observed in a multivariate analysis, particularly among the youngest group of patients [8].
In order to improve the outcome of these patients, several modifications were incorporated. Among them the addition of anti CD20 monoclonal antibody, rituximab. 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 [8].

The improvement in the CRD and OS rates with the use of rituximab in the CD20 positive patients (CD20 expression defined by a threshold ≥20%) means that currently, the outcome for these patients is identical to that of patients with CD20 negative disease: 3-year EFS rates of 52% and 53%, respectively. Therefore, patients with lower expression of CD20 may benefit from monoclonal antibodies with higher and more potent binding capacity.

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 [9]. 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 [10]. 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 [11]. A phase II study of ofatumumab combined with cyclophosphamide and fludarabine in previously untreated patients recently completed accrual.

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 E).

- Cyclophosphamide
- Doxorubicin
- Vincristine
- MESNA
- Methotrexate
- Cytarabine (Ara-C)
- 6-mercaptopurine
- Filgrastim Product (G-CSF)
- Pegaspargase
- Dexamethasone
- Prednisone

3.2 Ofatumumab [12]

The investigational (non-commercial) medicinal product (IMP) is a clear colorless liquid concentrate intended for intravenous infusion after dilution in sterile, pyrogen free 0.9% sodium chloride. During infusion the IMP 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.

3.21 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

3.22 Packaging and Labeling of Ofatumumab IMP

The Ofatumumab IMP will be supplied to the site/pharmacy in cartons., Labeling will be according to local legal requirements.

3.23 Storage of Ofatumumab IMP

The IMP will be stored refrigerated (2-8°C) in a safe and secure place. The IMP will not be frozen. A temperature log with daily readings will be kept. Exact time of dilution will be written on the infusion bag label. The IMP will not be utilized after the expiry date printed on the label. Drug supplies will be kept in an appropriate restricted area, accessible only to the investigator, pharmacist or duly designated person. Returned, unused or expired ofatumumab will be destroyed according to MDACC guidelines.

3.24 Ofatumumab Drug Accountability and Compliance Check.

The investigator will ensure that a designated person receives IMP deliveries from Novartis

3.25 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

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 (not for commercial product) has been established:

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 (supplied by NOVARTIS)
- Needles and syringes (50 mL sterile syringe) not supplied by NOVARTIS
- Intravenous (IV) cannula (not required if subject has central venous access) [not supplied by NOVARTIS]
- Infusion pump and infusion tubing set (not supplied by NOVARTIS)
- In-line low protein binding, polyether sulfone filter 0.2 μm (please make sure a spare filter is available in case the filter needs to be changed) [not supplied by NOVARTIS]. Please note that the commercial filters are sterilizing-grade (0.22 μm) hydrophilic Durapore by Millipore.

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.

3.26 Ofatumumab administration:

During Ofatumumab infusion the patient should be monitored closely and appropriate measurements should be performed according to institutional standards and whenever judged necessary. There are no proposed or planned ofatumumab dose reductions for toxicities. Toxicities will be addressed by escalating premedication, slowing the infusion rate, or delaying planned dose as determined by institutional standards and the treating physician.

3.27 Safety Advisory of Ofatumumab: Subjects who are HBsAg negative, anti-HBc positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring. Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive. Initiate anti-viral therapy if required. If a subject's HBV DNA becomes positive during the study, notify the NOVARTIS medical monitor. For subjects who have not completed planned ofatumumab therapy, discuss with the medical monitor the risks and benefits of continuing or discontinuing ofatumumab before appropriate treatment decisions are made for that individual subject

4.0 Patient Eligibility

Inclusion Criteria:

4.1 Patients of all ages with newly diagnosed, previously untreated CD-20+ ALL, or lymphoblastic lymphoma, Burkitt Leukemia/Lymphoma or having achieved CR with one course of induction chemotherapy.

4.2 Failure to one induction course of chemotherapy (these patients will be analyzed separately).

4.3 Performance status of 0, 1, or 2.

4.4 Adequate organ function with creatinine less than or equal to 3.0 mg/dL (unless considered tumor related), bilirubin less than or equal to 3.0 mg/dL (unless considered tumor related).

4.5 Adequate cardiac function defined as no clinically significant history of arrhythmia as determined by the PI and/or the treating physician, history of MI or clinically significant abnormal EKG, as determined by the PI and/or the treating physician, within 3 months prior to study enrollment. Cardiac function will be assessed by history and physical examination.

4.6 No active or co-existing malignancy (other than ALL or lymphoblastic lymphoma) with life expectancy less than 12 months due to that malignancy.

Exclusion criteria:
1. Pregnant or nursing women.
2. Known to be HIV+
3. Ph+ ALL
4. Active and uncontrolled disease/infection as judged by the treating physician
5. Unable or unwilling to sign the consent form
6. 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)
7. Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half-lives (calculated by multiplying the reported terminal half-life by 5) or 3 weeks prior to enrollment, whichever is longer, or currently participating in any other interventional clinical study
8. History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms or sequelae
9. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded. Consult with a physician experienced in care & management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive.
10. Positive serology for hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a HC RIBA immunoblot assay on the same sample to confirm the result

- Female patients of child bearing potential will be required to use a barrier method of contraception which must be used independently or in addition to another form of contraception while on the study and for 30 days after the last dose of study medication.
- Men must agree not to father a child and agree to use a condom if his partner is of child bearing potential while on study and until 30 days after the last dose of study medication.

5.0 Treatment Plan

Monitoring Plan: (2010-0708) Phase II Study of the Hyper - CVAD Regimen in Combination with Ofatumumab as Frontline Therapy for patients with CD-20 positive Acute Lymphoblastic Leukemia

This monitoring plan will be used as a guide for monitoring the clinical study 2010-0708 that is sponsored by M D Anderson Cancer Center. The purpose of the plan is to provide guidance to ensure that the rights and wellbeing of human subjects are protected, the conduct of the trial is in accordance with the protocol, regulatory requirements, and good clinical practices (GCP) and that data reporting (including safety reporting to IRB, FDA, and MDACC) is accurate and complete.

1. Monitoring Visit Intervals

The Clinical Research Monitor (CRM) will notify the site in writing of planned visits and the purpose of the visit to ensure the availability of medical records, study personnel and regulatory documents if they are scheduled for review.

- *THE INITIAL MONITORING VISIT WILL OCCUR AFTER THE FIRST SUBJECT HAS COMPLETED THEIR FIRST COURSE OF TREATMENT.*

- *INTERIM SITE MONITORING VISITS WILL THEN BE CONDUCTED EVERY 8-12 WEEKS DURING THE ENROLLMENT PHASE OF THE STUDY.*

- *ADDITIONAL MONITORING VISITS MAY BE CONDUCTED IF: ENROLLMENT PROCEEDS MORE RAPIDLY THAN EXPECTED; DATA FORMS ARE NOT BEING COMPLETED IN A TIMELY MANNER AND/OR THE SITE IS NOT IN COMPLIANCE WITH THE PROTOCOL, FEDERAL AND STATE REGULATIONS, AND GCP.*

2. Enrollment

The research team will be responsible for screening and enrolling all subjects. During scheduled monitoring visits protocol eligibility criteria will be reviewed for each pre-selected subject in order to verify that all criteria were met, and the subject was eligible for study participation.

3. Monitoring Requirements

The following procedures will be performed during each monitoring visit unless otherwise indicated:

- The CRM will generate queries, and provide them in writing to the PI and research team. A meeting with the CRM and research team to discuss the queries will be encouraged.
- Findings will be recorded in the Monitoring Visit Report.
- A Follow-up Visit Memo will be submitted to the investigator indicating all outstanding issues and significant findings that require attention as well as any deviations/violations.

For this phase II trial, subjects 1 and 2 will be monitored; and 30% of future accruals will be reviewed. Additional subjects may be monitored as needed and determined by the sponsor.

The Monitoring Log (which will be located in the regulatory binder) will be signed/dated by the CRM and the research team.

3.1 SOURCE DOCUMENT VERIFICATION

All existing source material including, but not limited to, progress notes, laboratory results, hospital admission records, discharge summaries, consultations, diagnostic testing results, and documentation of all clinic (including study-specified) visits along with all other clinical data in support of case report form entries that comprise the study database will be compared and verified.

CRMs will review 100% of the source documentation for the subjects selected for monitoring; and compare the case report form entries with the source documents to ensure that the data is complete, accurate, and all study procedures were conducted per protocol specifications.

3.2 Informed Consent Process

CRMs will verify that the current IRB-approved informed consent form was used to obtain informed consent, that the dates of signatures precede the performance of any study-related procedures and that all required signatures are present. Comparison of signature dates will be made against the required notation in the subjects' medical record regarding the informed consent process between the subject and the individual obtaining consent.

3.3 Study Drug Accountability/Administration

Pharmacy records regarding study drug shipping, receipt, storage and return, documentation of destruction documents compared against physical inventory and dispensing records will be reviewed periodically throughout the study.

For each subject the CRM will verify the following:

- dose modification scheme was adjusted accordingly
- that the appropriate dose and volume were prepared and administered
- that dose interruption/delay guidelines as outlined in the protocol were followed

4. Subject Visits

CRMs will verify that all subject visits have occurred within protocol accepted windows. For missed visits and subjects who are lost-to-follow-up, the CRM will verify that the site recorded all attempts to contact the subject in source documents

and that protocol procedures for documentation were followed. Substantial deviations from the protocol and data management guidelines will be reported to the investigator and documented in the Monitoring Visit Report.

5. Adverse Event Reporting

CRM's will verify AEs are graded using NCI Common Toxicity Grading Criteria (CTC) as noted in the protocol and that causality is appropriately assigned by the Principal Investigator. The CRM will ensure serious adverse events are reported per sponsor and IRB guidelines.

6. Concomitant Medication

All of the enrolled subjects' concomitant medications will be collected and readily available in the MDACC electronic medical record and will not be entered into the CRF.

7. Laboratory Specimen Samples, Handling and Reporting

CRM's will verify that protocol specific laboratory tests are documented as having been obtained according to protocol. In addition, CRMs will verify the following:

- documentation indicative of review and sign-off for laboratory results by the Principal Investigator or designee with any clinically significant results denoted as such.

- lab reports will be checked against data forms and results checked against NCI Common Toxicity Grading Criteria to ensure that clinically significant results are recorded by study personnel as adverse events as outlined in the protocol

8. Response

CRMs will verify that all response assessments will be obtained, handled and documented according to protocol

9. Data Recording

PDMS, the electronic case report forms (eCRF) will be utilized for this study. The CRM will review the eCRF's in comparison to all available source data during interim monitoring visits. Queries will be generated by the CRM during the site visit and submitted to the research team for resolution.

10. Regulatory Document File Review

Periodically throughout the trial the CRM will review the site's regulatory document file for updated information, accuracy and completeness.

11. Monitoring Visit Reports

Monitoring visit reports will be completed and forwarded to the IND Medical Monitor for review.

Information will include, but not be limited to:

- enrollment updates
- inventory of informed consents and supportive source data
- status of completion of data forms and queries
- data quality issues
- new SAEs (including deaths) and updates on previously reported SAEs
- protocol compliance/protocol deviations
- compliance with all applicable regulations and GCP
- concerns/issues expressed by study site personnel
- premature terminations or subjects lost-to-follow-up

The monitor will attempt to meet with the study coordinator at each visit, document discussions and note any follow-up that is required in a follow-up letter to the investigator.

Status of previously identified issues will be addressed in subsequent visit reports, including actions taken.

12. Deviations/Violations

Deviations/violations from the protocol and applicable regulations will be documented in the Monitoring Visit Report and reported to the investigator.

13. Study Discontinuation

After the last subject has been removed from the study, a final closeout visit will be conducted to ensure all data is complete and regulatory documents are in order. The CRM will generate a close-out visit report that will outline the status of all trial documents and data.

5.1 General

All patients are registered through CORE

No dose escalations beyond those specified in the protocol are allowed. Other variations to the treatment plan outlined are allowed if felt to be in the best clinical interest of the patient. Major deviations should be discussed with the Principal Investigator.
Dexamethasone 40mg IV or PO on D1-4 of the induction course are encouraged to be completed despite any doses given as supportive care prior to start of protocol treatment, but omission of one or more of these doses in the best interest of the patient per the treating physician will not be considered a deviation and does not require discussion with the PI. Patients with Burkitt Leukemia/Lymphoma will only receive induction, consolidation and intrathecal chemotherapy as per protocol. They will not receive maintenance therapy nor will they receive late intensification.

After three major deviations, while the participants are on protocol treatment the course will be reviewed by the Principal Investigator for consideration of removal from study with monitoring for disease-free and overall survival only.

Examples of these clinical scenarios include:
1- Treatment delays (> 14 days from recovery) despite hematologic recovery for reasons of patients 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.
2- 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.
3- Other clinical scenarios after approval by the Principal Investigator.

5.2 Doses and Schedule
General:

Hyper-CVAD + ofatumumab consists of 8 cycles of dose intensive therapy with hyper-CVAD + ofatumumab (odd courses) alternating with high-dose methotrexate and cytarabine + ofatumumab (even courses) administered approximately every 21-28 days (may delay for recovery from myelosuppression or infection; or sooner if count recovery allows).

1- Hyper-CVAD (courses 1, 3, 5, and 7) will alternate with high-dose methotrexate/cytarabine (courses 2, 4, 6, and 8) administered approximately every 21 days or later to allow for recovery from myelosuppression or infection; or earlier if count recovery allows.
2- Anti-emetic therapy with each course of intensive chemotherapy as indicated.
3- Filgrastim product (G-CSF) at 10 mcg/kg/day (rounded) or pegfilgrastim 6 mg as a single dose within 72 +/- 48 hours may be given after chemotherapy until

neutrophil recovery to at least 1 x 10^9/l or higher. G-CSF may be stopped earlier for bone pain or other related toxicity.
Next course may be started when granulocytes >= 1 x 10^9/L and platelets >= 50 x 10^9/L, following discontinuation of Filgrastim product (G-CSF). Courses may be started with dose reductions prior to full platelet recovery, if the treatment is delayed (e.g., 28 days or later from the start of last course). Instances where lab results fall outside of above criteria in the time between evaluation of next course and the actual start of next course will not be considered a deviation. Start of courses in the best interest of the patient outside these parameters need to be discussed with and approved by the PI with reasons documented. The choice of filgrastim product will be determined by the institutional formulary and patient's insurance.

4- Prophylactic antibiotics (e.g. levaquin, trimethprim-sulfamethoxazole, fluconazole, valacyclovir) may be given with each course as indicated until neutrophil recovery 500/μL. Prophylactic antibiotics will vary based on the patients' tolerance and allergy status.
5- Patients with newly diagnosed, active disease who are aged 60 years or older may receive the first induction course in the protective environment unless they refuse, are unable to be confined, and/or medical illness prohibits. Protective environment is optional.
6- CNS prophylaxis: total number of prophylactic intrathecal treatments for previously untreated patients will be 8, except for patients with Burkitt's Leukemia/Lymphoma will receive 16, two with each course.Intrathecal route preferred.
7- Eight injections of ofatumumab will be administered: Day 1 and 11 +/- 2 days of cycles 1 and 3 and day 1 and 8 +/- 2 days of cycles 2 and 4 (The first dose given will be 300 mg, the subsequent doses will be 2000 mg).
8- XRT to the chest for patients with bulky mediastinal disease when indicated.
9- Maintenance therapy with POMP (6-MP, vincristine, methotrexate, prednisone) for approximately 30 months, interrupted by intensifications courses 6 and 7 and courses 18 and 19 with hyper-CVAD + ofatumumab and methotrexate + pegaspargase.

Hyper-CVAD (courses 1, 3, 5, 7):
1- Cyclophosphamide (CTX) 300 mg/m^2 IV over 3 h every 12 hrs x 6 doses days 1,2,3 (total dose 1800 mg/m^2).
2- MESNA 600 mg/m^2/d IV continuous infusion daily for 24 hrs, starting approximately 1 hour prior to CTX and completing by approximately 12 hrs after the last dose of CTX.
3- Doxorubicin 50 mg/m^2 IV over 24 hrs via central venous catheter on day 4 after last dose of CTX given (infuse over 48 hrs in patients with reduced ejection fractions < 50%). May be given by shorter infusion if difficulty with central venous access.
4- Vincristine 2 mg IV on day 4 +/- 2 days and day 11 +/- 2 days.

5- Dexamethasone 40 mg IV or p.o. daily on days 1-4 +/- 2 days and days 11-14 +/- 2 days.
6- Ofatumumab 2000 mg IV on day 1 and 11 +/- 2 days for courses 1 and 3. (Ofatumumab will be given at the dose of 300 mg on day 1 of cycle 1. Subsequent infusions will be given at the dose of 2000 mg).
7- Pegfilgrastim 6 mg as a one time dose or filgrastim product (G-CSF) 10 mcg /kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes > 1.0 x 10^9/L.
8- CNS prophylaxis: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) on day 2 +/- 2 days. Cytarabine 100 mg intrathecally on day 7 +/- 2 days.
9- Tumor lysis prophylaxis with allopurinol, intravenous alkalinization, oral bicarbonate for course 1 and if indicated. Urate oxidase (Rasburicase) may be substituted for allopurinol.

Suggested Dose Modifications:
1- Vincristine
50% reduction (1 mg):
- Bilirubin > 2 mg/dL and </= 3 mg/dL
- Grade 2 persistent neuropathy.
Eliminate vincristine:
- Grade 3-4 neuropathy
- Ileus suspected to be related to vincristine
- Bilirubin > 3 mg/dL
2- Doxorubicin
50% reduction:
- Bilirubin 2 to </= 3 mg/dL
75% reduction:
- Bilirubin 3.1 to 5 mg/dL
Eliminate doxorubicin:
- Bilirubin > 5 mg/dL
- Consider elimination in the first course in patients with small/large bowel or gastric involvement to reduce the length of myelosuppression and risk of perforation.
Administer over 48 hrs:
- LVEF (if known) < 50%

High-Dose Methotrexate and Cytarabine (courses 2, 4, 6, 8):
1- Methotrexate (MTX) 200 mg/m^2 IV over 2 hrs followed by 800 mg/m^2 over 22 hrs on day 1.
2- Cytarabine 3 g/m^2 IV over 2 hrs every 12 hrs for 4 doses on days 2,3. Reduce to 1 g/m^2 IV over 2 hrs every 12 hrs for 4 doses on days 2 and 3 for:
a- Neurotoxicity (Grade 2 reversible cerebellar toxicity or other ara-C related CNS toxicity) with previous courses.
b- Age 60 years or greater.
c- Creatinine greater than or equal to 1.5 mg/dL.

d- MTX > 20 mcM at time "0" (see below), confirmed on repeat sample.
3- Leucovorin rescue 50 mg IV followed by 15 mg IV every 6 hours for 8 doses beginning 12 hrs +/- 2 hrs post MTX. Additional rescue allowed as indicated for elevated levels or delayed methotrexate clearance.
Check MTX around time 0h, 24h, and 48h post completion of MTX unless cleared (e.g. 0.15 mcM or less).
a- if > 20 mcM at time "0", hold ara-C and repeat level; if continues to be > 20 mcM reduce ara-C to 1 g/m^2 IV over 2 hrs every 12 hrs for 4 doses on days 2, 3.
b- if > 1 mcM at 24 hrs or > 0.1 mcM at 48 hrs, increase leucovorin rescue until serum MTX level is < 0.1 mcM.
Clearance to levels 0.15 mcM or less is acceptable in patients with normal renal function.
4- Consider oral acetazolamide 250 mg PO twice daily to promote MTX excretion if the urine pH is <7.0.
5- Ofatumumab 2000 mg IV on day 1 and 8 +/- 2 days for courses 2 and 4.
6- Pegfilgrastim 6 mg as a one time dose or filgrastim product (G-CSF) 10 mcg/kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes greater than or equal to 1.0 x 10^9/L.
7- CNS prophylaxis: Ara-C 100 mg intrathecally day 5 + 3 days and Methotrexate 12 mg intrathecally (6 mg if via Ommaya reservoir) day 8 +/-3 days.

Suggested Dose Modifications:
1- Cytarabine:
- 1 g/m^2 IV over 2 hrs every 12 hrs for 4 doses on days 2, 3:
    - Creatinine >= 1.5 mg/dL.
    - Time "0" MTX level > 20 mcM (on repeat level).
    - Age >= 60 years.
    - Grade 2 reversible cerebellar toxicity related to high-dose Ara-C.
- 1 g/m^2 IV continuous infusion days 2, 3:
    - Grade 2 reversible cerebellar toxicity related to ara-C 1 g/m^2 or grade 3 reversible cerebellar toxicity related to any dose of ara-C.

2- Methotrexate:
- 25% to 50% reduction:
    - Grade 3 or worse mucositis with previous methotrexate course.
- 25% to 75% reduction:
    - delayed excretion and/or nephrotoxicity with previous methotrexate course.
- 50% reduction:
    - pleural effusion or ascites (drain effusion if possible)
    - Calculated creatinine clearance:
    - 10 to 50 ml/min: reduce by 50%
    - < 10 ml/min: hold MTX

Dosing modifications based on age and performance status will be permitted on cycles 1-8 and maintenance intensifications. Suggested dose adjustments as below:

	< 60	60 – 74 PS 0–2	>74 > 60, PS 3–4
Cyclophosphamide (mg/m^2)	300	250	200
Doxorubicin (mg/m^2)	50	37.5	25
Vincristine (mg)	2	2	1
Dexamethasone (mg)	40	20	20
Methotrexate (mg/m^2) mg/m^2	200 800	100 400	50 100
Cytarabine (g/m^2)	3	1	0.5

Note: Age 60 – 64 with PS 0-1 may be treated with full doses (except for reduction of cytarabine to 1 g/m^2 as per design) at the discretion of the treating physician

Maintenance Therapy:
1- Patients may be moved from the intensive chemotherapy to the maintenance phase prior to completion of 8 cycles of chemotherapy if significantly intolerant of the intensive chemotherapy after discussion with the Principal Investigator. A maintenance cycle will be defined as 28 days.
2- Maintenance chemotherapy with 6-mercaptopurine (6-MP), methotrexate (MTX), vincristine, and prednisone (POMP) for approximately 30 months (except for consolidations with hyper-CVAD + ofatumumab followed by MTX/pegaspargase [or vice versa] at Course 6 and 7 and MTX/pegaspargase followed by hyper-CVAD-ofatumumab [or vice versa] at course 18 and 19) beginning at level 0 (or lower dose level if previous toxicity warrants):
- 6-MP 50 mg PO three times daily (TID),
- MTX 20mg/m^2 (rounded) PO weekly
- Vincristine 2 mg IV approximately every 28 days
- Prednisone 200 mg PO daily days 1 to 5 approximately every 28 days, starting with vincristine (if given).

Suggested maintenance chemotherapy dose adjustments as below:

Level	MTX (mg/m^2) (rounded)	6-MP (mg/d)	Vincristine (mg)	Prednisone (mg)
0	20	150	2	200
-1	15	100	1	100
-2	10	50	0	50
-3	5	50	0	0

3- Dose adjustments for myelosuppression include MTX and 6-MP, but not vincristine or prednisone (the latter should remain 200 mg unless steroid myopathy or other uncontrolled significant toxicity occurs). Titrate to keep granulocytes >= 1 x 10^9/L and platelet count >= 50 x 10^9/L.
4- Methotrexate
- Decrease by one dose level for mucositis > grade 2.
- Decrease by one dose level for bilirubin > 2.5 or elevation of transaminases >= 5 x upper limit of normal.
- Hold if granulocyte count nadir < 0.5 x 10^9/L or platelets < 10 x 10^9/L, resume with decrease in one dose level or lower depending on duration of cytopenias.
5- 6-mercaptopurine
- Decrease by one dose level for bilirubin > 2.5 mg/dL or elevation of transaminases >= 5 x upper limit of normal.
- Hold if granulocyte count nadir < 0.5 x 10^9/L or platelets < 10 x 10^9/L, resume with decrease in one dose level or lower depending on duration of cytopenias.
6- Vincristine
- Decrease by one dose level for >= grade 2 peripheral neuropathy persisting for more than 2 weeks.
- Discontinue for grade 3 or greater peripheral neuropathy.
7- Note that the dose adjustments of POMP are guidelines, and the dosing needs to individualized to the patient, as differential toxicities between 6-MP and methotrexate may be difficult to discern.

Continued antiviral prophylaxis to prevent herpes zoster is strongly encouraged. Consider antifungal prophylaxis during days of prednisone. Consider PCP prophylaxis.

Early and Late Intensifications (interrupting maintenance phase as follows):
-Two courses of chemotherapy months 6 (methotrexate + pegaspargase) and 7 (hyper-CVAD + ofatumumab) of maintenance, repeated at months 18 (methotrexate + pegaspargase) and 19 (hyper-CVAD + ofatumumab) of maintenance Hyper-CVAD may precede or follow MTX + pegaspargase.

- Methotrexate 100 mg/m^2 day 1 IV over 2 hours and pegaspargase at a dose of 2000 IU/m^2 dose will be capped at 3,750 international on units day 2 by IV over 2 hours and this dose will be reduced to 1000 IU/m^2 on day 2 by IV over 2 hours on patients older than 60 years of age.Hyper- CVAD + ofatumumab
  Cyclophosphamide (CTX) 300 mg/m^2 IV over 3 h every 12 hrs x 6 doses days 1,2,3 (total dose 1800 mg/m^2).
  MESNA 600 mg/m^2/d IV continuous infusion daily for 24 hrs, starting approximately 1 hour prior to CTX and completing by approximately 12 hrs after the last dose of CTX.
  Doxorubicin 50 mg/m^2 IV over 24 hrs via central venous catheter on day 4 after last dose of CTX given (infuse over 48 hrs in patients with reduced ejection fractions < 50%). May be given by shorter infusion if difficulty with central venous access.

Vincristine 2 mg IV on day 4 +/- 2 days and day 11 +/- 2 days.
Dexamethasone 40 mg IV or p.o. daily on days 1-4 +/- 2 days and days 11-14 +/- 2 days.
Ofatumumab 2000 mg IV on day 1 +/- 2 days and day 11 +/- 2 days

- Intensification course may be started when granulocytes >= 1 x 109/L and platelets >= 50 x 109/L following discontinuation of Filgrastim product (G-CSF). Courses may be started with dose reductions prior to full platelet recovery, if the treatment is delayed (e.g., 28 days or later from the start of last course.) Instances where lab results fall outside of above criteria in the time between evaluation of next course and the actual start of next course will not be considered a deviation. Start of courses in the best interest of the patient outside these parameters need to be discussed with and approved by the PI with reasons documented
- Intensifications may be eliminated or given alternate months of the maintenance therapy, depending on patient tolerance and/or clinical situation, with reasons documented.
- Treating physician has discretion to repeat course 1 dose escalation of ofatumumab during maintenance intensification

All infusion times are approximate. Infusion time variations due to IV bag overfill/underfill and institutional policy on IV flush solutions will not result in a protocol deviation. Administration of oral medications will be documented via diary or verbally by the patient. Occasional missed doses of an oral medication will not result in a protocol violation.

5.3 Central Nervous System (CNS) Management

1. Standard CNS prophylaxis with intrathecal methotrexate and ara-C with each course if no evidence of CNS disease. Total number of prophylactic intrathecal treatments:= 8, except for patients with Burkitt's Leukemia/Lymphoma will receive 16, consisting of 2 intrathecal treatments with methotrexate and ara-C with each course until total number reached. Missed intrathecals (e.g., related to failed procedure attempts, scheduling issues, patient social situations) can be "made up" with subsequent courses of chemotherapy. All patients will receive 8 intrathecal treatments except for patients with Burkitt's Leukemia/Lymphoma will receive 16.

2. If the patient has been previously treated, and has had prior intrathecal therapy, or prior CNS disease, discuss management of CNS prophylaxis/therapy with the Principal Investigator.

3. If active CNS disease: methotrexate alternating with ara-C twice weekly until CSF clear; then once weekly for 4 weeks, then back to prophylactic schedule. Consider XRT to the base of the skull, particularly 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 palsy). Alternative methods of treating CNS disease are allowed if appropriate for the patient (e.g., intrathecal liposomal ara-C, topotecan, ifosfamide, radionucleotides or others).

4. Additional intrathecal treatments done as prophylaxis may be allowed after discussion with the PI.

5. Additional Intrathecal treatments done as clinically indicated during exploratory lumbar puncture for symptoms of suspected CNS relapse are allowed and will not be considered a deviation from the protocol.

6. LPs done outside of window will not be considered a deviation if dose is made up (if clinically indicated).

5.4 Mediastinal disease
Patients with mediastinal lymphoblastic lymphoma and bulky mediastinal disease (defined as >= 7 cm) or residual mediastinal lymphadenopathy at the end of the intensive chemotherapy portion of the treatment should be considered for consolidative mediastinal irradiation after recovery from the last course of consolidation therapy and prior to the maintenance phase of therapy.

5.5 Maintenance therapy
Maintenance therapy is planned for all patients as described in section 5.2, unless toxicity prohibits. Patients may move to the maintenance phase of therapy prior to completion of cycles 2 to 8 if they develop side effects prohibiting further intensive chemotherapy. Patients who do not complete all therapy per protocol, but remain in remission, will not be considered off-protocol, but will be monitored for disease-free survival only. An end-of-treatment date will indicate completion of therapy.

5.6 Monitoring Patients on Study
1- The hyper-CVAD regimens have been conducted since 1992, and have accrued over 500 patients on similar induction-consolidation-maintenance phases. The treatment-associated side effects, both myelosuppressive and extramedullary are well-known, and have been described and reported. Known and anticipated side effects of this regimen (see Appendix D) will not be reported as individual ADRs, according to the Code of Federal Regulations and ICH guidelines - CGP Section 4.11.1, p. 24. This also complies with the NCI CTEP-CTC guidelines which state that for expected events "grade 4 myelosuppression or other grade 4 events that do not require expedited reporting will be specified in the protocol." AEs will not be collected in the maintenance phase, only SAEs will be collected.

2- The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. Adverse events (event name, grade, start/stop date, and attribution will be documented in the medical record and entered into the case report form). PDMS/CORE will be used as the electronic case report form for this protocol

3- Recognizing there will be instances where patients cannot receive all of their care at M.D. Anderson Cancer Center, the following monitoring plan is proposed:
- All patients who are enrolled on the protocol, will receive their courses of therapy that incorporate ofatumumab.
- Subsequent courses of therapy may be given by a local physician under direction of the M.D. Anderson Cancer Center treating physician or the Principal Investigator. The referring physician will be identified, contacted and the protocol details discussed.
- It will be detailed that therapy should not be administered except at the direction of the Principal Investigator or treating physician at M.D. Anderson. A review of laboratory data, review of compliance with the program, and review of toxicities will be performed. The participants will be informed of the intended procedure, and that their physician will be asked to comply, or they may be removed from the protocol.
4- Physicians will be requested to sign a letter stipulating these items, and indicating their willingness to participate in the therapy as requested. Direction of therapy will be documented in the patient's medical record.
5- Documentation will be requested from outside physicians, including drug administration records to ensure that the orders were followed. Outside physicians will be asked to contact us for prior approval of any decisions or changes related to the chemotherapy. However, dose holds by the patient or local physician due to illness or concern for injury that are initiated prior to speaking with MDACC treating physician but are then reported to the MDACC Treating physician will not be considered a deviation. Note that occasional missed doses of medication self – administered by patient will be not be listed as a deviation.

6.0 Pretreatment evaluation

Procedure	Comments	Schedule
Informed Consent	Obtain standard informed consent approved by IRB	Within 14 days of therapy
Medical History	History of present illness, known allergies, prior cancer history as far as traceable, and past medical/ surgical history as far as relevant.	Within 14 days of therapy
Physical Examination	Vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status.	Within 14 days of therapy

Hematology	CBC with differential and platelet count	Within 14 days of therapy
Biochemistry	at least creatinine, total bilirubin, uric acid, LDH, SGPT or SGOT	Within 14 days of therapy
Bone marrow	Aspirate and/or biopsy with flow cytometry for confirmation of diagnosis and PCR testing for TCR gene rearrangements.	Within 21 days of therapy
Cardiology	12-lead ECG	Within 14 days of therapy
Serology	Hepatitis B & C	Within 14 days of therapy
Pregnancy test	▪ Serum or urine, if female *and* of child-bearing potential only. Females able to bear children that has not been postmenopausal for at least 12 consecutive months or who had not undergone surgical sterilization)	Within 14 days of therapy
Imaging studies	Chest X-ray and/or PET/CT as clinically indicated	Within 14 days of therapy

7.0 Evaluation During Study

Procedure	Comments	Schedule
Hematology	CBC with differential and platelet count	Minimum of Weekly during courses 1 to 8; preferred at least monthly during maintenance (except at least weekly during intensification courses during maintenance). Delay of labs for up to 2 weeks after 3rd week of intensive cycle and up to 6 weeks in POMP maintenance will be permitted without being considered deviation.
Biochemistry	at least creatinine, total bilirubin, SGPT or SGOT	At least once every 2 weeks during course 1, then at least every 4 weeks during courses 2 - 8 of chemotherapy, and at least every 4 weeks during maintenance therapy Delay of labs up to 6 weeks in POMP maintenance will be permitted without being considered deviation.
Physical Examination	Focused physical examination	Prior to each treatment course
Bone marrow	Aspirate and/or biopsy (immunophenotyping by flow cytometry as indicated). Will include PCR testing for MRD if applicable. Only patients with involvement of bone marrow at time of	On day 14 +/- 3 days strongly encouraged, but no later than day 21 of the first course of chemotherapy for patients with involvement of marrow at diagnosis, then weekly +/- 3 days until remission or lack of response established. Once in CR, marrows will be repeated every 4 months (+/- 1 month) including PCR testing for eventual assessment of minimal residual disease.

Commented [SM1]: Clarified wording and windows to minimize deviations without compromising safety.

	diagnosis, will require bone marrow assessments as specified	For patients with evidence of Leukemia in peripheral blood the bone marrow maybe omitted after discussion with and approval of PI.
Imaging studies	Chest X-ray and or PET/CT	At the time of maximum response and/or when clinically determined to be necessary.

Post treatment follow up - Until 30 days post last dose of Ofatumumab patient will be followed for toxicity or until another treatment is received.

Long term follow up - Every 3 months, for 1 year. After you are off treatment you will be called and asked a series of questions. 1. How are you feeling? 2. Have you had any side effects? 3. Have you taken any other drugs?

8.0 Criteria for Response

8.1 Acute lymphoblastic leukemia:

Complete remission (CR):

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

Partial response (PR):

As above, except for the presence of 6-25% marrow blasts.

8.2 Lymphoblastic lymphoma (with extramedullary disease) except for patients with Burkitt's Leukemia/Lymphoma:

8.21 Objective response of bi-dimensionally measurable and uni-dimensionally measurable parameters:

Complete response (CR):

Complete disappearance of all known disease.

Partial response (PR):

50% or more 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% or greater increase in size of exising lesions (increase 50% or greater if only one lesion is available and is 2 cm or less in size).

8.22 Objective response for non-measurable parameters.

CR, NR, and PD same as above but estimated.

PR: definite improvement estimated to be at least 75% of lesion but not quantifiable by measurement.

9.0 Evaluation of Toxicity
Toxicities will be graded according to the NCI Expanded Common Toxicity Criteria (see Appendix F).

10.0 Criteria for Removal from the Study
Criteria for removal from study include, but are not restricted to, the following:
10.1 Progressive disease.
10.2 Non-compliance by the patient with protocol requirements.
10.3 Patient's request to be removed from the study.

11.0 Statistical Considerations
This is a phase II study of Hyper-CVAD + ofatumumab in patients with CD-20 positive acute leukemia (ALL). The primary objective is to evaluate the event-free survival (EFS), where the event-free survival will be measured from the start of therapy until failure to respond, relapse or death.

Historical data suggested that the 3-year EFS rate in patients with CD-20 positive ALL was 50% with a median survival of 3 years. It will be promising if the 3-year EFS rate will increase to 65%-70% with the treatment of Hyper-CVAD + ofatumumab with a potential median survival of 4.8 to 5.8 years. Assuming the event-free survival time follows an exponential distribution, the estimated median event-free survival time was 3 years for historical standard treatment, and it is expected to improve the median event-survival time to 4.8 to 5.8 years in this study. A maximum of 80 will be recruited for the study at a rate of < 1 patient per month, leading to a maximum accrual period of 1 year and five months. Assuming the median event-free survival time is 3 years, then the 95% credible interval with 80 patients would be (2.22, 4.05), while assuming median survival time is 4.8 years, then the 95% credible interval with 80 patients would be (3.56, 6.49). The toxicity and efficacy will be monitored during the study, and all the data will be used to update the prior distributions for toxicity and efficacy parameters. The study will be stopped for toxicity and futility based on the following stopping rules.

The primary endpoint time-to-event will be monitored using the method of Thall et al.[13] Let T_E and T_S represent the event-free survival time for the experimental treatment and standard treatment respectively. We assume that both $T_E \mid m_E$ and $T_S \mid m_S$ follow exponential distributions with median m_E and m_S. We also assume that m_E and m_S have a inverse gamma distribution, with prior distributions of $m_S \sim IG(50, 1746)$ and $m_E \sim IG(3, 72)$. Throughout the trial, we will update the distribution on m_E and will stop if at any point.

$$Prob(m_E > m_S \mid data) < 0.05$$

Table 1: Operating characteristics (additional follow-up 1 year)

True median Time to event (month)	Pr(stop early)	Average Number of Patients Treated (25th, 75th percentiles)

10	1	23 (16, 28)
20	0.94	49 (30, 68)
25	0.64	61 (40, 80)
30	0.32	71 (74, 80)
36	0.14	75 (80, 80)
40	0.08	77 (80, 80)
45	0.04	79 (80, 80)
58	0.02	79 (80, 80)

In addition, toxicity will be monitored closely in all patients using the method of Thall et al.[14] The monitoring will be 7 interim looks. Denote the probability of toxicity by θ_E, where non-hematologic toxicity is defined as any Grade 3 or greater complications attributable to Ofatumumab. We assume $\theta_E \sim$ beta (0.6, 1.4). We will stop the trail if at any point $Pr(\theta_E > 0.30 \mid data) > 0.85$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 85% chance that the toxicity rate is more than 30%. Stopping boundaries corresponding to this stopping rule are listed in table 2.

Table 2: Stopping boundaries for non-hematologic toxicity monitoring

Among These Number of Patients	Recommend Stopping if Toxicity Observed in n or more patients
10	5
20	13
30	22
40	30
50	38
60	47
70	55

Table 3: The operating characteristics for non-hematologic toxicity monitoring are summarized in the following table

True toxicity probability	Probability of early stop	Sample size percentiles (10, 25, 50, 75, 90)
0.1	0.002	80 80 80 80 80
0.2	0.043	80 80 80 80 80
0.3	0.319	10 30 80 80 80
0.4	0.841	10 10 20 50 80
0.5	0.994	10 10 10 20 30
0.6	1	10 10 10 10 20

Analysis Plan:
For discrete or categorical data, descriptive statistics will include tabulations of frequencies. For continuous data, summary statistics including n, mean, standard deviation, median, minimum and maximum will be computed. The posterior median time to event and it 95% credible interval will be estimated. Kaplan-Meier method, Log rank test and Cox proportional hazards regression modeling will be utilized to analyze event free survival and overall survival.

This study will utilize the clinical conduct (CTC) website (https://biostatistics.mdanderson.org/ClinicalTrialConduct maintained by the Department of Biostatistics to monitor event-free-surv

12.0 Reporting Requirements
12.1 See Appendix D for guidelines for reporting ADR's to the IRB. Adverse events should be reported for 30 days post last dose of Ofatumumab or until another treatment is received.

12.2 Adverse Events Requiring Expedited Reporting: Serious unexpected adverse events (SUSARs) considered associated with therapy should be reported to the study nurse or the Principal Investigator [Elias Jabbour, M.D., Telephone (713) 742-4764] within 24 hours of observing or learning of the event. All AEs should be reported to the study nurse.

12.3 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 (see Appendix D):
Hyperglycemia
Electrolyte abnormalities
Renal failure related to tumor lysis syndrome, methotrexate, or antibiotic therapy (e.g. AmBisome, aminoglycosides).
Ara-C related central nervous system toxicity.
Catheter-related deep venous thrombosis.
Coagulation abnormalities during induction chemotherapy (e.g. chemical DIC or hypofibrinogenemia).
Ileus related to vincristine.
Hepatotoxicity related to methotrexate or antibioitic therapy (e.g. azole antifungals).
Post lumbar puncture headaches.

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

12.4.1 Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.
12.4.2 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.
12.4.3 Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

Death

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

  Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

- It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy

12.5 Update of Adverse Event (AE) Data Capture Required as of 12/8/2015 on all active treatment patients

Adverse events are collected in accordance with the Leukemia Specific AE Recording Guidelines under Appendix D. In accordance with these guidelines, only unexpected AEs will be recorded in the Case Report Form (CRF). An AE is considered to be unexpected if it is "not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended" (21 CFR § 312.32, 2015). Events expected during leukemia therapy are also listed within the Leukemia Specific AE Recording Guidelines.

Abnormal hematologic values will not be captured in the CRFs or on the Leukemia AE Record. Only the highest grade per course of grade 3 or 4 chemistry lab abnormalities will be captured on the AE Record as well. All Serious Adverse Events will be captured on the Leukemia AE Record as well as entered in the CRFs, regardless of expectedness.

Any “unexpected” AE will have such noted in the comments section of the AE Records moving forward. The Principal Investigator will sign and date the AE log per each patient after the completion of each course.

12.6 Novartis Adverse Events

Adverse Events:
Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Events meeting the definition of an AE include:

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

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.
Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition.

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

Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

   An overnight hospital stay due to slow infusion rates will not be considered a Serious Adverse Event.

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect

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

Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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

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

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

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

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

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

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

Time Period and Frequency of Detecting and SAEs

Once an investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to NOVARTIS within 24 hours of being notified of the event. All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product to after the last dose of investigational product (30 days post last dose of Ofatumumab or until another treatment is received). All SAEs regardless of causality will be collected for 30 days post last dose of Ofatumumab or until another treatment is received.

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

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

Pregnancy

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

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

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

1. **Fax SAEs to Novartis via the following:**

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)

2. **Novartis Coversheets must be attached to all SAE submissions**

3. **SAE Submissions must reference your Novartis Study Code COMB157DUS16T**

13.0 References

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