THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Augmented Berlin-Frankfurt-Munster therapy plus ofatumumab for young adults with acute lymphoblastic leukemia or lymphoblastic lymphoma 2014-0396

Core Protocol Information

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Phone:	713-792-4855
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Full Title:	Augmented Berlin-Frankfurt-Munster therapy plus ofatumumab for young adults with acute lymphoblastic leukemia or lymphoblastic lymphoma
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Abstract

Objectives:

Primary Objective: To assess the effectiveness and toxicity of pediatric based chemotherapy (augmented BFM) with ofatumumab or rituximab in patients 12 to 30 with untreated precursor-B acute lymphoblastic leukemia (ALL) or precursor-B lymphoblastic lymphoma (LL). Effectiveness will be assessed by 3 year event free survival (EFS).

Secondary: 1. To prospectively analyze the significance of minimal residual disease(MRD) in bone marrow samples obtained at the end of approximately 4 weeks and at the end of approximately 12 weeks of therapy.

2. To assess asparaginase antibody levels and asparagine levels in patients treated with ABFM plus ofatumumab or rituximab and overall survival (OS) and event free survival (EFS).

3. To evaluate the strategy of changing asparaginase preparations in patient with low asparaginase activity to improve OS/EFS.

4. To assess asparaginase levels and corresponding toxicity in patients treated on ABFM therapy.

5. To evaluate the safety and toxicity of adding ofatumumab or rituximab to ABFM therapy.

Rationale: (Be as concise as possible)

Multiple groups have reported that patients aged 16 to 21 with ALL have improved outcomes when treated with pediatric based therapy rather than traditional adult regimens, with five year EFS for this age group approaching 80% on pediatric-based therapy. Pediatric LL therapy has had similar excellent results in this age group, whereas adult regimens have had lesser survival rates. At M.D.Anderson, a trial of ABFM in adults with ALL/LL (2006-0375) is nearing completion. An analysis ABFM therapy indicates that toxicities are acceptable and that the treatment is effective (survival curves attached). In adult patients with ALL, the M.D.Anderson leukemia section added rituximab to traditional chemotherapy (R-Hyper CVAD) for patients with ALL where the leukemic blasts express CD20, and this resulted in improved survival for young adults with CD20 positive ALL (Thomas, et al. JCO).

Ofatumumab an anti-CD20 antibody with more potent binding capacity than rituximab, has now been added to Hyper CVAD, and early results appear promising. Ofatumumab (Humax-CD20) is a monoclonal antibody that targets a small loop epitope of CD20 and elicits potent complement dependent cytotoxicity even against cells with low CD20 expression.Toxicity from the addition of ofatumumab to the very intensive Hyper CVAD regimen (O-Hyper CVAD) has been acceptable.This study proposes to evaluate the addition of ofatumumab to ABFM therapy, with 8 doses of ofatumumab given (the same number of doses of ofatumumab that are given in O-Hyper CVAD). In the event that ofatumumab is not available for an individual patient, rituximab will be the second choice for immunotherapy added to the ABFM backbone.

Flow cytometry for MRD at two time points will be assessed for prognostic significance.

In addition, the significance of asparaginase activity will be systematically assessed in these patients. Prior pediatric studies that included adolescent patients indicate that asparaginase levels of at least 0.1 IU/ml are likely to be therapeutic. Patients that form antibodies to asparaginase have very low levels of asparaginase, and they suffer more events than patients with higher levels. Changing the asparaginase preparation to erwinia restores asparaginase levels, and may improve outcomes. Asparaginase levels will also be correlated with possible toxicities.

Eligibility: (List All Criteria)

Inclusion:

1) Patients must have precursor-B lymphoblastic leukemia or lymphoma.

2) Patients must be untreated or have had only one prior chemotherapy regimen for ALL or LL . Previously treated patients will be analyzed separately.

3) Age between 12 to 30 years old

4) Patients with CNS disease or testicular disease are eligible.

5) Intrathecal therapy with cytarabine is allowed prior to registration for patient convenience. This is

usually done at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. Systemic chemotherapy must begin within 72 hours of the first intrathecal treatment.

6) Signed informed consent prior to the start of systemic therapy. In the event of enrollment of a minor patient, an attempt to obtain assent from the patient must be documented, and parental consent must be signed.

7) Echocardiogram should be done within 7 days of starting therapy if there are cardiac risk factors (e.g., history of hypertension or of myocardial infarction)

8) Creatinine should be < 3 mg/dL bilirubin < 3 mg/dl unless due to disease

9) Zubrod Performance status of <3

10) Patients who received steroids more than 72 hours prior to study enrollment are eligible but will be analyzed separately.

11) Lymphoblasts may have any positive expression of CD20 for ofatumumab administration.

Exclusion:

1) Age less than twelve years of age or greater than 30 years.

2) More than one prior treatment regimen for ALL or LL.

3) The patient is pregnant or unwilling to practice appropriate birth control.

4) Presence of the Philadelphia chromosome t(9;22)

5) Laboratory or clinical evidence of active infectious hepatitis.

Are patients <18 years of age eligible to participate in this study? ● **Yes** ○ **No**

Studies that include children must meet the criteria for inclusion.
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc
http://www.hhs.gov/ohrp/policy/populations/children.html

Additional Comment: Separate treatment regimens are open for patients under 12 and over 30 years of age.

Are participants >65 years of age eligible to participate in this study? ○ **Yes** ● **No**

Are pregnant women eligible to participate in this study? ○ **Yes** ● **No**

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?
○ **Yes** ● **No**

Disease Group:

Leukemia

Treatment Agents/Devices/Interventions:

6-MP, 6-Thioguanine, Cyclophosphamide, Cytarabine, Daunorubicin, Dexamethasone, Doxorubicin, Methotrexate, Ofatumumab, Pegasparagase, Prednisone, Rituximab, Vincristine

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ Yes ● No

Is this a blinded or double-blinded study? ○ Yes ● No

Induction (4 weeks)
- Daunorubicin 25 mg/m2 weekly x 4 doses
- Vincristine 1.5 mg/m2 (max. dose 2 mg) weekly x 4 doses
- Prednisone 60 mg/m2/day by mouth for 28 days
- PEG-asparaginase 2000 IU/m2 (max. dose 3750 IU) on day 4 of induction +/-2 days
- Ofatumumab 300 mg on day 2 +/-2 days and Ofatumumab 2000 mg day 15 +/-2 days
- If ofatumumab not available, give Rituximab 375 mg/m2 on day 1 +/-2 days and Rituximab 375 mg/m2 on day 15 +/-2 days
- Intrathecal cytarabine day 1
- Intrathecal methotrexate 12 mg on day 8 and day 29

Consolidation 1 (8 weeks)
- Cyclophosphamide 1 gram/m2 week 1 and week 5
- Ofatumumab 2000 mg week 1 and week 5
- If ofatumumab not available, give Rituximab 375 mg/m2 week 1 and week 5
- Cytarabine 75 mg/m2 SQ days 1-4 and 8-11
- Mercaptopurine 60 mg/m2/day by mouth days 1-14
- Vincristine 1.5 mg/m2 (max. dose 2 mg) week 3 and week 4
- PEG-asparaginase 2000 IU/m2 (max. dose 3750 IU) week 3 and week 7
- Intrathecal methotrexate 12 mg weekly, weeks 1-4

Consolidation 2
- Vincristine 1.5 mg/m2 (max. dose 2 mg) every 10 days for 5 doses
- Methotrexate IV every 10 days starting at 100 mg/m2 and increasing by 50 mg/m2 as tolerated
- PEG-asparaginase 2000 IU/m2 (max. dose 3750 IU) weeks 1 and 4
- Ofatumumab 2000 mg week 1 and week 5
- If ofatumumab not available, give Rituximab 375 mg/m2 week 1 and week 5
- Intrathecal methotrexate 12 mg week 1

Consolidation 3A
- Doxorubicin 25 mg/m2 weekly x 3 doses
- Dexamethasone 10 mg/m2 by mouth on days 1-7 and days 15-21
- Vincristine 1.5 mg/m2 (max. dose 2 mg) IV weekly x 3 doses
- Ofatumumab 2000 mg week 1 and week 3
- If ofatumumab not available, give Rituximab 375 mg/m2 week 1 and week 3
- PEG-asparaginase 2000 IU/m2 (max. dose 3750 IU) in week 1
- Intrathecal methotrexate 12 mg in week 1

Consolidation 3B
- Cyclophosphamide 1 gram/m2 week 1
- Cytarabine 75 mg/m2 SQ days 1-4 and days 8-11

Thioguanine 60 mg/m2/day for 14 days
Intrathecal methotrexate 12 mg week 1 and 2
Vincristine 1.5 mg/m2 (max. dose 2 mg) weeks 3 and 4
PEG-asparaginase 2000 IU/m2 (max. dose 3750 IU) week 3

Maintenance (24 months)
Mercaptopurine 75 mg/m2 PO nightly
Methotrexate 20 mg/m2 PO weekly, hold on days of intrathecal methotrexate
Dexamethasone 6 mg/m2/day by mouth days 1- 5 every 28 days
Vincristine 1.5 mg/m2 (max. dose 2 mg) every 28 days
Intrathecal methotrexate 12 mg every 3 months for 4 doses

During the study, patients receiving PEG-asparaginase with asparaginase levels of <0.1 IU/milliliter as assayed at Al Biotech using a CLIA certified test of asparaginase will have their asparaginase preparation changed to Erwinia asparaginase dosed as per the package insert. This dose is 25,000 IU given three times weekly for two consecutive weeks (6 doses) for each planned PEG-asparaginase dose.

Slow responders repeat Consolidation 2 and Consolidation 3A/3B prior to maintenance

Testicular disease at diagnosis: if resolution by end of induction, then treatment continues as scheduled above. If abnormality persists, then a biopsy is required and radiation administered at the end of induction if the biopsy is positive.

CNS disease at diagnosis: Intrathecal therapy given twice weekly until cleared, then weekly x 6 doses, then resume intrathecal treatments as per protocol. Radiation is recommended for overt CNS disease but is per investigator choice.

For analysis of PEG-asparaginase activity and anti-asparaginase antibodies, samples will be drawn prior to the dose planned dose of PEG- asparaginase and then 1, 2 and 4 weeks after administration of asparaginase for doses in approximately weeks 1, 9 and 26 of protocol therapy treatment. Samples are sent to Al Biotech and to pharmacy lab as below.

For testing: 5 milliliters of non-heparinized blood in a red-top tube will be placed at room temperature and allowed to clot. The clotted blood will then be centrifuged and the serum will be placed in a tube marked with the patient's initials and the date/time of the phlebotomy and the date/time of the last asparaginase dose. The samples will be frozen at -40 to -80 Celsius and sent othe Pharmacy Research Laboratory at UTMDACC for storage and analysis.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: 100
Estimated monthly accrual at MDACC: 2-3

Accrual Comments:
Accrual only at MDACC.

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

General Description

This is a single-arm, open-label, phase II trial. The primary objective of this trial is to assess the efficacy and feasibility of the augmented Berlin-Frankfurt-Munich (BFM) chemotherapy plus Ofatumumab in untreated, or previously treated with only one prior chemotherapy regimen, acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL) in patients age 12 through 30. Previously treated patients will be analyzed separately. Efficacy will be assessed by EFS at 3 years of treatment. Ofatumumab is FDA approved for other lymphoid tumors. The primary end point is 3-year event-free survival (EFS) rate. The event free survival is defined as the time from treatment to relapse of leukemia or death for any reason or lost to follow-up. Current ABFM therapy without Ofatumumab yields a 3-year EFS rate of approximately 65% with response (defined as CR after four weeks of treatment) rate of 90% in this population. The toxicity rate of standard induction is less than 33% when one looks at grade 3-4 infection. The study regimen will be considered successful if it exhibits a 3-year EFS rate greater than 65% and response rate no less than 90% with Grade III-IV infectious toxicity rate in induction no more than 33%. A maximum of 100 patients will be enrolled with accrual rate of 2-3/month.

In the event that ofatumumab is not available for an individual patient, rituximab will be the second choice for immunotherapy added to the ABFM backbone.

Sample Size and End Point Monitoring:

A null hypothesis of 3-year EFS being 0.65 will be assumed. The goal is to test the alternative hypothesis that the treatment provides an improvement in 3-year EFS to be 0.75. We assume a two-sided significance level of 0.05 and an accrual rate of 2-3 patients per month (i.e., about 33 patients per year) and the follow-up time of 3 year since the last patient has been accrued, 100 patients will be yield a power of 69%. If we compare the 3-year EFS of 0.65 versus 3-year EFS to be 0.8, 100 patients will yield a power of 93% under the assumption of a two-sided significance level of 0.05, an accrual rate of 2-3 patients per month, and the follow-up time of 3 year since the last patient has been accrued.

However, it is impractical to carry out interim analysis based on the 3-year EFS rate.

The futility monitoring rule will be based on the CR rate at 4 weeks using the Bayesian approach of Thall, Simon, Estey (1995, 1996) and the extension by Thall and Sung (1998). The CR rate, and toxicity (grade 3-4 infection), denoted as TOX, will be monitored simultaneously by Bayesian stopping boundaries calculated based on beta-binomial distribution. Independence is assumed between CR and TOX. There are no historical data available. The current regimen will be considered promising if the CR rate is at least 90% and the TOX rate is below 33%. The prior probabilities of CR and TOX for the regimen are modeled by beta distributions (*Beta*(1.8, 0.2) and *Beta*(0.66, 1.34), respectively). Denoting the probabilities of the CR rate and TOX by {θCR, θ TOX}, the following decision criteria will be applied:

1) stop if Prob{ θCR < 0.9 | data} > 0.95, and
2) stop if Prob{ θTOX > 0.33 | data} > 0.95

Patients will be monitored by a cohort size of 5 according to the following stopping boundaries for CR and toxicity. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the futility/toxicity stopping boundaries and the OC table.

Table 1. Stopping boundaries for Complete Response (CR) and toxicity

Number of patients evaluated	Stop the trial if there are this many response	Stop the trial if there are this many toxicities
5	0-2	4-5
10	0-6	7-10
15	0-10	9-15
20	0-15	11-20
25	0-19	13-25
30	0-23	15-30
35	0-27	17-35
40	0-32	19-40
45	0-36	21-45
50	0-40	23-50
55	0-45	25-55
60	0-49	27-60
65	0-53	28-65
70	0-58	30-70
75	0-62	32-75
80	0-66	34-80
85	0-71	36-85
90	0-75	38-90
95	0-80	40-95

The operating characteristics are summarized in the following table.

Table 2. Operating characteristics of efficacy and safety monitoring

True Toxicity Rate	True CR Rate	Prob (stop the trial early)	Average sample size
0.25	0.8	0.92	40.4
	0.85	0.58	66.4
	0.9	0.15	90.3
	0.95	0.03	97.4
0.33	0.8	0.93	37.7
	0.85	0.65	60.8
	0.9	0.28	81.8
	0.95	0.17	88.1
0.35	0.8	0.94	36.3
	0.85	0.68	57.8
	0.9	0.35	77.2
	0.95	0.26	83.0
0.4	0.8	0.96	31.5
	0.85	0.82	47.0
	0.9	0.63	60.6
	0.95	0.58	64.7

Analysis Plan

Continuous variables (e.g., age, hematology values) will be summarized using the mean (s.d.) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of patient characteristics (e.g., low/high LDH) on the response rate. The distribution of time-to-event endpoints (e.g., EFS, overall survival) will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups of patients will be made using the log-rank test. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well being of the patient requires immediate intervention, based on the judgment of the investigator or his/her designee. In the event of a significant deviation from the protocol, the investigator will notify the MDACC surveillance committee following the institutional guidelines.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
This study is not randomized or blinded. In addition, the study is likely to be low risk. Current data an adding immunotherapy to chemotherapy for ALL has been positive, not negative. It is unlikely that

outcomes on this trial will be significantly worse than chemotherapy alone.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? No

Provide a rationale for no interim analysis.

The protocol body contains stopping rules for toxicity or lack of response as well as operating characteristics for safety monitoring.

Protocol Monitoring Plan:

Please see tables in protocol body.

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? No

☒ **Please confirm that the protocol meets all criteria for exemption according to 21CFR 312.2(b) noted below:**

(b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

Rationale for Exemption:
Please include a detailed rationale as to why this drug should be considered exempt from FDA IND regulations, including any available references to the prior use of the regimen or drug combination in human subjects.

Ofatumumab and rituximab are both FDA approved drugs for lymphoid malignancies where the malignant cells express CD20.

If this protocol includes an FDA Approved Therapy, please list the disease, dose and route of administration:

	Approved Use	Proposed in this Protocol
Disease:	Daunorubicin: Remission Induction in Adult and Pediatric Acute Nonlymphocytic Leukemia Vincristine: adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) Prednisone: for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation; for the treatment of certain endocrine conditions; for palliation of certain neoplastic conditions PEG-asparginase: First line acute ALL Ofatumumab: treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab Rituximab: Non-Hodgkin's Lymphoma (NHL); Chronic Lymphocytic Leukemia (CLL); Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies; Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids Cytarabine: in combination with other approved anticancer drugs is indicated for remission induction in	Young adults with acute lymphoblastic leukemia or lymphoblastic lymphoma

acute non-lymphocytic leukemia of adults and children. It has also been found useful in the treatment of acute lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration of cytarabine is indicated in the prophylaxis and treatment of meningeal leukemia.

Methotrexate: In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia.

Cyclophosphamide-Malignant Diseases: malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma

Mercaptopurine is indicated for maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen.

Dexamethasone: Control of severe or incapacitating allergic conditions; Hematologic disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond-Blackfan anemia), idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, and selected cases of secondary thrombocytopenia.

Doxorubicin: for the treatment of: acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, Non-Hodgkin lymphoma, metastatic breast cancer, metastatic Wilms' tumor, metastatic neuroblastoma,

	metastatic soft tissue sarcoma, metastatic bone sarcomas, metastatic ovarian carcinoma, metastatic transitional cell bladder carcinoma, metastatic thyroid carcinoma, metastatic gastric carcinoma, metastatic bronchogenic carcinoma Thioguanine: Acute Nonlymphocytic Leukemias	
Dose:	Daunorubicin hydrochloride 25 mg/m IV Day 1 weekly, in combination with vincristine 1.5 mg/m IV on day 1 every week and prednisone 40 mg/m PO daily x 4 courses; Vincristine 2.25 mg/m2 IV over 1 hour once every 7 days Prednisone: The initial dosage of Prednisone Tablets may vary from 5 mg to 60 mg per day, depending on the specific disease entity being treated PEG-asparaginase: 2,500 IU/m2 intramuscularly (IM) or intravenously (IV) no more frequently than every 14 days. (IV over 1 to 2 hours) Ofatumumab: 12 doses as follows: 300 mg initial dose, followed 1 week later by 2,000 mg weekly for 7 doses, followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses. Rituximab: NHL 375 mg/m2. CLL: 375 mg/m2 in cycle 1 and 500 mg/m2 in cycles 2-6, in combination with FC, every 28 days Cytarabine: May be given by IV infusion or injection, SQ, or intrathecally; schedule and method of administration varies. Intrathecal Cytarabine: Induction: 50 mg, every 14 days for 2 doses. Consolidation: 50 mg, every 14 days for 3 doses followed by 1 additional dose at week 13. Maintenance: 50 mg, every 28 days for 4 doses.	Daunorubicin: Induction-25 mg/m2 weekly x 4 doses Vincristine: Induction-1.5 mg/m2 (max 2 mg) weekly x 4 doses; Consolidation 1-1.5 mg/m2 (max 2 mg) week 3 and week 4; Consolidation 2-1.5 mg/m2 (max 2 mg) every 10 days x 5 doses; Consolidation 3A-1.5 mg/m2 (max 2 mg) IV weekly x 3 doses; Consolidation 3B-1.5 mg/m2 (max 2) mg weeks 3 and 4 Prednisone: Induction-60 mg/m2/day orally for 28 days PEG-asparaginase: Induction- 2000 IU/m2 day 4; Consolidation 1-2000 IU/m2 week 3 and week 4; Consolidation 2-2000 IU/m2 weeks 1 and 4; Consolidation 3A-2000 IU/m2 in week 1; Consolidation 3B-2000 IU/m2 week 3 Ofatumumab: Induction-300 mg day 1 and 2000 mg day 15; Consolidation 1-2000 mg week 1 and week 5; Consolidation 2-2000 mg week 1 and week 4; Consolidation 3A-2000 mg week 1 and week 3; Rituximab (If ofatumumab not available): Induction-375 mg/m2 day 1 and 375 mg/m2 day 15; Consolidation 1-375 mg/m2 week 1 and week 5; Consolidation 2-375 mg/m2 week 1 and week 4; Consolidation 3A-375 mg/m2 week 1 and week 3 Cytarabine: Induction-day 1 intrathercal; Consolidation 1-75 mg/m2 SQ days 1-4 and 8-11;

	Methotrexate: Intrathecal methotrexate 12 mg/m2 (maximum 15 mg). Induction, 3.3 mg/m2 in combination with 60 mg/m2 of prednisone, daily. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. Cyclophosphomide: Malignant Diseases: Adult and Pediatric Patients - Oral: Usually 1 mg per kg per day to 5 mg per kg per day Mercaptopurine: 1.5 to 2.5 mg/kg/day as a single dose-maintenance Dexamethasone: varies from 0.75 to 9 mg a day Doxorubicin: Single agent: 60 to 75 mg/m2 given intravenously every 21 days. In combination therapy: 40 to 75 mg/m2 given intravenously every 21 to 28 days. Thioguanine:The dosage which will be tolerated and effective varies according to the stage and type of neoplastic process being treated	Consolidation 3A-75 mg/m2 SQ days 1-4 and days 8-11; Methotrexate: Induction-12 mg intrathecally day 8 and day 29; Consolidation 1-12 mg intrathecally weekly, weeks 1-4; Consolidation 2-Methotrexate IV every 10 days 100 mg/m2 increasing by 50 mg/m2 as tolerated and 12 mg intrathecally week 1; Consolidation 3A-methotrexate 12 mg intrathecally week 1; Consolidation 3B-12 mg intrathecally week 1 and 2; Maintenance-20 mg/m2 PO weekly, hold on days of intrathecal methotrexate Cyclophosphamide: Consolidation 1-1 gram/m2 IV week 1 and week 5; Consolidation 3B-1 gram/m2 IV week 1 Mercaptopurine: Consolidation 1-60 mg/m2/day by mouth days 1-14; Maintenance: 75 mg/m2 PO nightly Dexamethasone: Consolidation 3A-10 mg/m2 by mouth days 1-7 and days 15-21; Maintenance-6 mg/m2/day by mouth days 1- 5 every 28 days Doxorubicin: Consolidation 3A-25 mg/m2 weekly x 3 doses Thioguanine: Consolidation 3B-60 mg/m2/day for 14 days
Route of Administration:	Daunorubicin: IV Vincristine: IV Prednisone: Oral PEG-Asparaginase: IM or IV Ofatumumab: IV Rituximab: IV Cytarabine: Intrathecally and SQ Methotrexate: Oral, IV and Intrathecal Cyclophosphomide: Oral Mercaptopurine: Oral Dexamethasone: Oral Doxorubicin: IV Thioguanine: Oral	Daunorubicin: IV Vincristine: IV Prednisone: Oral PEG-Asparaginase: IM or IV Ofatumumab: IV Rituximab: IV Cytarabine: Intrathecally and SQ Methotrexate: Oral, IV and Intrathecal Cyclophosphomide: Oral Mercaptopurine: Oral Dexamethasone: Oral Doxorubicin: IV Thioguanine: Oral

Investigational Device (IDE):

Does this study utilize an Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? No

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? No

Click here for help

Biosafety:

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve human/animal tissue other than blood derived hematopoietic stem cells? No

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

- (●) Yes
- ( ) No
- ( ) Not Applicable For This Protocol

Please provide the name of the test(s), the purpose of the test, the performing laboratory identification and contact information, and confirm that the testing lab is CLIA certified (may attach a certificate or provide a certificate number).

AIBiotech CLIA Lab document.pdf

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree? No