THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Phase II Study of the Hyper-CVAD Regimen in Sequential Combination with Inotuzumab Ozogamicin as Frontline Therapy for Adults with B-Cell Lineage Acute Lymphocytic Leukemia
2015-0922

Core Protocol Information

Short Title	Phase II Hyper-CVAD with INO in ALL
Study Chair:	Elias Jabbour
Additional Contact:	Lori L. Smith Vicky H. Zoeller Leukemia Protocol Review Group
Additional Memo Recipients:	**Recipients List** **OPR Recipients** (for OPR use only) None **Study Staff Recipients** None
Department:	Leukemia
Phone:	713-792-4764
Unit:	428
Study Manager:	Chiamaka C. Nwachukwu
Full Title:	Phase II Study of the Hyper-CVAD Regimen in Sequential Combination with Inotuzumab Ozogamicin as Frontline Therapy for Adults with B-Cell Lineage Acute Lymphocytic Leukemia
Public Description:	na
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Activated -- Closed to new patient entry as of 01/24/2019
Version:	05
Document Status:	Saved as "Final"
Submitted by:	Lori L. Smith--12/19/2018 11:54:31 AM
OPR Action:	Accepted by: Elizabeth Orozco -- 1/2/2019 12:12:48 PM

Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

2015-0922 Protocol CLEAN 8-10-18.docx

Phase II Study of the Hyper-CVAD Regimen in Sequential Combination with Inotuzumab Ozogamicin as Frontline Therapy for Adults with B-Cell Lineage Acute Lymphocytic Leukemia

Principal Investigator: Elias Jabbour, MD

Table of Contents

Phase II Study of the Hyper-CVAD Regimen in Sequential Combination with Inotuzumab Ozogamicin as Frontline Therapy for Adults with B-Cell Lineage Acute Lymphocytic Leukemia

1.0 Objectives

1.1 Primary Objectives: To evaluate the clinical efficacy of the sequential combination of hyper-CVAD + inotuzumab ozogamicin in patients with newly diagnosed B-cell acute lymphocytic leukemia (ALL) in terms of event-free survival (EFS)

1.2 Secondary Objectives: To evaluate other efficacy endpoints such as overall survival, overall response rate, MRD negativity rate as well as the safety of this combination

2.0 Background

2.1 Acute lymphocytic 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, lymphocytic 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 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 and ofatumumab. 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]. Similarly, the addition of ofatumumab to the hyper-CVAD regimen CVAD induced a CR rate of 94% with MRD negativity rate of 67% after induction. The 1-year CRD and overall survival rates were 100% and 95% respectively.[9]

2.3 Inotuzumab ozogamicin

2.3.1 Description

Inotuzumab ozogamycin consists of a semisynthetic derivative of N-acetyl ɣ-calicheamicin 1, 2-dimethyl hydrazine dichloride (NAc ɣ-calicheamicin DMH), a potent DNA-binding cytotoxic antibiotic, attached to a humanized monoclonal IgG4 antibody, G544, directed against the CD22 antigen present on B cells in all patients with mature B-ALL and most patients (>90%) with precursor B-ALL[10]. Anti-CD22 monoclonal antibody without conjugated cytotoxic drug has shown to have no anti-tumor activity in preclinical models; instead conjugation with cytotoxic agent provides potent dose-depending cellular damage[11]. This is likely because IgG4 antibodies poorly fix complement, therefore cannot cause apoptosis via complement-mediated and antibody-dependent cytotoxicity[12]. Calicheamicin is natural product of Micromonospora echinospora species, and considered to be intolerantly toxic when not bound to the antibody[13]. Calicheamicin is linked to the antibody through 4-(4-acetylphenoxy) butanoic acid (acetyl butyrate) which provides stability in physiologic pH and successful calicheamicin release inside the acidic environment of the lysosomes[14]. INO binds to CD22 receptor on the surface of B-cell, and the CD22 receptor-INO complex is internalized forming an endosome. Subsequently, CD22 receptor-INO complex containing endosome fuses with lysosomes. This is followed by

intracellular release of calicheamicin. Calicheamicin binds to the minor groove of DNA in a sequence specific manner, and breaks double-stranded DNA, resulting in cell death.

2.3.2 Pharmacodynamics

Treatment with INO has been shown to provide greater therapeutic benefit, as single agent, compared to CVP or CHOP in B-cell NHL xenografts[15]. INO also showed anti-tumor activity in CVP- and CHOP-refractory tumors; however duration of the INO effect was not as sustained as it was in treatment naïve B-cell NHL xenografts. This observation shows that INO treatment may regress tumor growth in chemotherapy refractory cases, but eventually, some malignant B-cells can escape the anti-tumor activity and re-grow. Gemtuzumab Ozogamicin (GO), another antibody-drug conjugate of NAc γ-calicheamicin DMH, is directed against CD33 antigen, and has been used in treatment acute myeloid leukemia (AML)[16]. However, drug resistance had negative impact on clinical outcome of patients treated with GO[17]. It is proposed that the drug resistance was associated with P-glycoprotein (P-gp) expression. P-gp is a membrane glycoprotein that actively pumps cytotoxic agents out of the cells and decreases intracellular concentration the drug[18] [Takeshita et al., 2005]. As with GO, INO was also found to be effected with the same resistance mechanism. In a study, INO had no effect on CD22-positive malignant cell lines with P-gp expression compared to parental cells[18]. In clinical samples, the toxic effect of the INO was inversely related to the amount of P-gp ($p=0.003$). In contrast, the cytotoxicity of INO positively correlated with the amount of CD22 ($p=0.010$).

INO is a CD22-targated cytotoxic chemotherapy agent without any effector capabilities; in contrast rituximab is a CD20-targated immunotherapeutic agent with the capability of complement-mediated and antibody-dependent cellular toxicity. Combination of INO and rituximab has been tested in vitro setting, and showed increased cytotoxicity[19]. Anti-tumor efficacy of INO and rituximab combination has also been tested in B-cell NHL preclinical models, and demonstrated superior activity with the combination[20]. In a phase 2 clinical trial evaluating the efficacy of INO in relapsed and refractory ALL patients, rituximab was added to the patients with stable or progressive disease after two courses of INO. Addition of rituximab in nine patients with CD20 positive ALL did not provide any additional benefit[13]. Nevertheless, it was a single-arm study with a small number of patients. Efficacy of this combination in ALL patients needs to be evaluated in larger clinical trials.

2.3.3 Pharmacokinetics

Maximum tolerated dose (MTD) was determined as 1.8 mg/m^2 by a first-in-human clinical trial evaluating the safety of INO in 79 relapsed and refractory NHL patients[12]. Most patients had follicular lymphoma (FL) (44%) and diffuse large B-cell lymphoma (DLBCL) (44%), and 61% of the patients had received ≥ 4

prior chemotherapies. Following dose escalation schedules were evaluated: 0.4, 0.8, 1.34, 1.8 and 2.4 mg/m^2 intravenously (as a 1-hour infusion) once every 3 weeks in MTD lead-in cohort (36 patients). Escalation stop criteria were met as 2 of 6 cohort patients had dose limiting toxicities (one grade 4 neutropenia, one grade 4 thrombocytopenia) at 2.4 mg/m^2. Thus, 1.8 mg/m^2 was established as MTD. Reversible thrombocytopenia is one of the main (90%) side effects of INO, and it led to a number of treatment delays. Therefore, declared MTD was evaluated in once every 4 weeks schedule to allow platelet recovery. Dose limiting toxicity was not observed in the six-patient cohort of 1.8 mg/m2 once every 4 weeks. As a result, this regimen was used in extended MTD cohort (43 patients). At the end of treatment, objective response rate was 39% among 79 enrolled patients. Administration of INO with a weekly dosing schedule (same total dose of 1.8 mg/m2 per cycle) compared to single-dose schedule allowed similar response rates and less toxicity in multiply relapsed B-ALL patients[21].

The data showed that inotuzumab ozogamycin disposition was non-linear with number of dose or increasing dose. Non-linearity is seen commonly with other antibodies as well[22]. Non-linear pharmacokinetics of monoclonal antibodies is due to target-mediated drug disposition, in which elimination and distribution are affected by the antibody and target cell interaction[23]. Anti-CD22 antibody and total calicheamicin followed similar elimination trend, and the free calicheamicin concentration remained less than 1ng/ml overtime, suggesting that the acetyl butyrate linker is noticeably stable in plasma[12]

2.4 Inotuzumab ozogamicin in R/R ALL

2.4.1 Single agent inotuzumab ozogamicin

Initial studies in patients with lymphoma established an MTD of 1.8 mg/m2 IV given every 3 to 4 weeks, with reversible thrombocytopenia emerging as a frequent adverse effect.[12] This led to a single institution phase II study in patients with relapsed-refractory ALL[13]. The starting dose was 1.3 mg/m2 IV every 3 to 4 weeks for the first three patients; later patients received 1.8 mg/m2. Acetaminophen, diphenhydramine, and hydrocortisone were administered to prevent infusion reactions. Forty-nine patients were treated, 73% of whom received inotuzumab for Salvage 2 or later. The ORR was 57%, and the median survival was 5.1 months (Table 1). Nearly half of the patients treated with inotuzumab were able to proceed to ASCT (n = 22), including four patients who were receiving their second ASCT. Survival was similar whether patients underwent subsequent ASCT or not.

To optimize the benefit:risk of inotuzumab, a weekly dosing regimen was evaluated based on preclinical studies indicating that toxicity might be minimized while maintaining efficacy (Table 1).[21] Inotuzumab was given at 0.8 mg/m2 on Day 1, and 0.5 mg/m2 on Days 8 and 15, every 3-4 weeks. This is the same cumulative dose per course compared with single infusion inotuzumab every

three to four weeks. With the weekly regimen, ORR was similar to the single-dose schedule (59% versus 57%). The median survival was 9.5 months. The weekly regimen was less toxic. Additionally, 37 patients with relapsed/refractory ALL received weekly inotuzumab in a multicenter phase I/II study[24]. Seventeen (46%) patients were in Salvage 1, 9 (24%) in Salvage 2, and 11 (30%) in Salvage 3 or later. The CR and CR without count recovery rates were 79% (19/24) and 46% (6/13) in the dose expansion and dose escalation cohorts, respectively. Eighteen of the nineteen patients in the dose escalation cohort and four of the six in the dose expansion cohort achieved MRD negativity. These encouraging results led to an international study comparing weekly inotuzumab to standard ALL chemotherapy (FLAG at MD Anderson) in ALL salvage 1-2. The objective response rates were 81% and 33%, respectively. Among responders, the MRD-negativity rates were 78% and 28%, respectively. The median response duration was 4.6 versus 3.1 months (p=0.017), respectively.

Table 1. Activity of inotuzumab ozogamicin in patients with relapsed/refractory ALL

	N (%)		
Parameter	Single-Dose, n=49	Weekly, n=40	Overall, n=89
Response			
CR	9 (18)	8 (20)	17 (19)
CRp	16 (33)	13 (33)	29 (33)
CRi, bone marrow CR	3 (6)	3 (8)	6 (7)
PR	0	0	0
Resistant	18 (37)	14 (35)	32 (36)
Death < 4 weeks	3 (6)	2 (5)	5 (6)
Salvage			
Salvage 1	13 (27)	16 (40)	29 (33)
Salvage 2+	36 (73)	24 (60)	60 (67)
Median survival (months)	5.0	9.5	6.2

2.4.2 Combination of inotuzumab ozogamicin with chemotherapy

Given the promising results in the salvage studies, inotuzumab was evaluated in combination with chemotherapy. A group of patients with ALL who may particularly benefit from a more targeted regimen is elderly patients (age greater than 60 years). This group is predisposed to severe toxicity from conventional chemotherapy, which is associated with high mortality rate (30-35%) during consolidation-maintenance in CR. Thirty-four older patients (median age of 69 years; range, 60 to 79) with newly diagnosed ALL were treated in a phase II study combining inotuzumab and low-intensity hyperCVAD therapy.[25] The regimen eliminated doxorubicin in induction, used cyclophosphamide and steroids at 50% of the dose of previous regimens, and reduced methotrexate to 250 mg/m^2 on Day 1 and cytarabine to 0.5 mg/m^2 x4 (Days 2 and 3) of even courses. Inotuzumab 1.3-1.8 mg/m^2 was given once with each of the first 4 courses. The ORR was 97% (CR 83%). All patients with cytogenetic

abnormalities achieved complete cytogenetic response. All patients achieving response also had a negative MRD status, 75% of them after one cycle. The 2-year progression-free and overall survival rates were 87% and 70%, respectively. The 2-year survival rate was superior to previous results obtained with HCVAD +/- rituximab in similar patient populations (2-year survival rates 70% and 38%, respectively).

This combination was also assessed as a salvage therapy in 48 patients. The ORR was 74% (CR 52%) The 12-month progression-free and overall survival rates were 88% and 81%, respectively.[26]

2.5 Inotuzumab ozogamicin toxicity profile

Transient fever and hypotension were the 2 most frequent non-hematologic adverse events, and typically occurred shortly after the inotuzumab infusion. Liver function abnormalities were also observed, but tended to be reversible. Serious toxicity in the transplant group included the development of veno-occlusive disease (VOD) in five patients (23%). Four of the 5 patients had received multiple alkylating agents in the transplant preparative regimen, including clofarabine which may have predisposed them to VOD. Two of the 4 patients undergoing second ASCT developed VOD, suggesting this group of patients to be also at higher risk for VOD. In elderly ALL and in combination with low intensity chemotherapy, 4 patients (11%) developed a veno occlusive disease, one of them post allogeneic stem cell transplantation. All but one patient had mild VOD that resolved subsequently. One patient developed a Grade 5 VOD after 2 cycles, was switched to miniHCVD and ofatumumab, received 2 more additional courses, developed anasarca and multiple organ failure and expired thereafter. The safety profile of inotuzumab ozogamicin vs standard of care (SOC) was consistent with the initial studies. For inotuzumab vs SOC, Gr≥3 hepatobiliary AEs occurred in 9% vs 3% patients; any grade VOD occurred in 15 (14%) vs 1 (0.9%) patients (Gr≥3, 13 vs 1 patients). More patients proceeded to ASCT with inotuzumab (n=48) vs SOC (n=20); in the inotuzumab arm, 5 VOD cases (2 in patients with prior ASCT) occurred during treatment and 10 after subsequent SCT (2 fatal).

2.6 Rationale for the combination of hyper-CVAD and inotuzumab ozogamicin

Multi-agent combination chemotherapy regimens for the treatment of ALL are considered a cancer success story in the pediatric setting.[27] For adults, the same magnitude of success has not been realized using similar strategies. These regimens produce high CR rates of 80-90% but the cure rates are 40-50% .[28,29] The incorporation of targeted agents (tyrosine kinase inhibitors in Philadelphia chromosome [Ph]-positive ALL; rituximab in Burkitt leukemia and CD20-positive preB-ALL) has improved survival and cure rates in adult ALL subsets.[29-31]

Persistence or reappearance of MRD after induction chemotherapy is the most important adverse prognostic factor in patients with B-lineage ALL and identifies chemorefractory disease.[32-37] More than 90% of patients who fail to clear MRD after chemotherapy experience a clinical relapse despite continued chemotherapy. The median time to relapse of patients with MRD positive disease is 4-5 months.[38] The only option to cure these patients is allogeneic hematopoietic stem cell transplantation (HSCT), but the outcome is suboptimal .[39]

We have explored lower dose chemotherapy with inotuzumab ozogamicin in the frontline setting in elderly patients and in the relapse setting as well. The combination was found to be safe and extremely effective with an ORR of 97% in the frontline setting with all them becoming negative MRD (75% after one cycle) and 75% in the relapse setting with 2-year survival rate of 54% in Salvage 1 setting. Therefore, sequential combination of hyper-CVAD with inotuzumab ozogamicin in adults All may optimize the rate of MRD negativity and subsequently improve the cure rates of adults patients with B-cell ALL. For this patient population, tolerance to chemotherapy is better than that for elderly with significantly less toxicities and less treatment related morbidities. Inotuzumab dosing was reduced to 0.9mg/m2 in induction and 0.6mg/m2 in consolidation in the hyper-CVD + inotuzumab protocol to ameliorate risk of VOD. In this study we want to further reduce the toxicities and improved outcome by inducing higher rates of negative MRD and less relapses. Patients will receive 4 cycles of intensive chemotherapy instead of 8 (50% less). That will be followed by 4 cycles of inotuzumab and one year of maintenance therapy (instead of 3 years). We will assess this treatment regimen after 10 patient enrolled then after a total of 30 patients then at the end of the 60 patient enrolled.

3.0 Background Drug Information

3.1 Drug information for the following agents is attached as an appendix to the back of this protocol (Appendices C, D, and E).

- Cyclophosphamide
- Doxorubicin
- Vincristine
- MESNA
- Methotrexate
- Cytarabine (Ara-C)
- 6-mercaptopurine
- Filgrastim product (G-CSF)
- Dexamethasone
- Prednisone
- Ofatumumab
- Rituximab

3.4 Inotuzumab ozogamicin

3.4.1 Formulation and packaging

Inotuzumab ozogamicin is a white to off-white powder or cake, lyophilized, unpreserved 1- mg or 4-mg protein equivalent powder for intravenous injection in an amber vial.

3.4.2 Preparation and dispensing

Specific preparation and dispensing instructions for inotuzumab ozogamicin are provided in the Dosage and Administration Instructions. Once inotuzumab ozogamicin has been prepared following the Dosage and Administration Instructions, the site pharmacist will label the study medication in accordance with local requirements. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

3.4.3 Administration

All patients must be weighed within 72 hours prior to every cycle day 1 dosing to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of inotuzumab ozogamicin required for dose preparation. Decision to recalculate the dose of inotuzumab ozogamicin based on the weight obtained at each cycle can be in accordance with institutional practice; however, if the patient experienced either a weight loss or gain >10%, the required amount of inotuzumab ozogamicin needed for study drug preparation and administration must be recalculated using this most recent weight/BSA obtained. If the dose administered is 10% greater or lower than the one prescribed, it will be reported as a dosing medication error.

Inotuzumab ozogamicin is administered intravenously. Subjects will receive 2 weekly doses of inotuzumab ozogamicin over a 21- to 28-day cycle for a maximum of 4 cycles.

Pretreatment: Prior to inotuzumab ozogamicin treatment, subjects should receive pretreatment medications to reduce the incidence and severity of an anticipated infusion syndrome characterized by fever and chills, and less commonly hypotension. Premedication before inotuzumab ozogamicin may also include antiemetics. Antiemetics that do not predispose patients to Torsades de Pointes, such as granisetron (Kytril), are recommended. Subjects should be pretreated with either methylprednisolone (or other corticosteroid), or acetaminophen/paracetamol and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each inotuzumab ozogamicin administration.

Modifications to this premedication are also allowed. In cases of infusion reactions, discontinue infusion and institute appropriate medical treatment as needed (eg, glucocorticosteroids, epinephrine, bronchodilators, or oxygen). Depending on the severity of the infusion reaction and interventions required, the investigator could consider restarting the infusion at a reduced rate.

All patients will be given Ursodiol 300mg PO TID. Ursodiol should be started one week before the start of the first cycle of inotuzumab ozogamicin treatment and administered continuously through all 4 cycles of inotuzumab.

Reconstituted inotuzumab ozogamicin will be administered over 1 hour ± 10 minutes by intravenous infusion unless the subject requires temporary interruption of the administration.

3.4.4 Recommended dose modifications

In the event of significant toxicity, dosing may be delayed as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.
Dose modifications may occur as follows:

- Within a cycle: dose interruption until adequate recovery or omission of a dose during a given treatment cycle.
- Between cycles: next cycle administration may be postponed due to toxicity in the previous cycle.
- In the next cycle: dose reduction based on worst toxicity or to 0.6 mg/m2/cycle if hematologic remission is achieved in the previous cycle.

3.4.5 Dose delays

If patients do not meet the criteria below on the day of the scheduled treatment, the administration of the dose will be delayed.

1. Recovery to grade 1 or baseline non-hematologic test article-related toxicity (including liver function test abnormalities, not including alopecia).
2. Serum bilirubin ≤1.5 x ULN, and AST, ALT and alkaline phosphatase ≤2.5 x ULN. (Or if elevated due to tumor, bilirubin ≤2 x ULN). Isolated AST or alkaline phosphatase elevations need not result in dose delays if not related to hepatobiliary organs (eg, alkaline phosphatase elevations due to bone involvement). Inotuzumab ozogamicin dosing should be permanently discontinued for any patients with possible, probable or confirmed VOD or other severe liver toxicity.
3. Any serum creatinine level associated with a measured or calculated creatinine clearance ≥ 15 mL/min using the method standard for the institution.
4. Prior to the start of each cycle, for subjects with pre-treatment ANC ≥1 x 10^9/L: ANC ≥1 x 10^9/L.

5. Prior to the start of each cycle, for subjects with pre-treatment platelets ≥50 x 10^9/L: platelets ≥50 x 10^9/L.
6. Subjects with pre-treatment ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: ANC and platelets must recover to baseline values obtained for the prior cycle, or ANC ≥1 x 10^9/L and platelets ≥ 50 x 10^9/L, or the most recent bone marrow must demonstrate stable or improved disease, and the ANC and platelets are believed to be low due to disease.

There are no ANC or platelet count requirements for Cycle 1 day 1, as dosing criteria are relative to pre-treatment values. While doses given within a treatment cycle (ie, day 8) need not be delayed due to neutropenia or thrombocytopenia, dose delays within a cycle are recommended for non-hematologic toxicity.

Dose delays due to drug toxicity ≤7 days or other logistical delays (such as travel, inclement weather, scheduling issues, etc.) during a treatment cycle are permitted. Dose delays of >7 days within a cycle will result in omission of the subsequent dose; the subject remains eligible to receive the subsequent planned doses. If a treatment interruption continues beyond day 14 of the current cycle, then the day when treatment is restarted will be considered day 1 of the next cycle. Dose delays due drug toxicity >28 days at the end of a treatment cycle (ie, delay of day 1 dosing) will result in permanent discontinuation of study treatment. All toxicity grades are according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4).

3.4.6 Dose reductions

Patients with inotuzumab ozogamycin associated complications (prolonged thrombocytopenia, grade 3-4 liver toxicity) will receive subsequent doses of inotuzumab ozogamycin at a 33% dose reduction. Patients experiencing treatment interruption due drug toxicity ≥14 days may resume dosing with 33% dose reduction (-1 dose level is defined by inotuzumab dose at D1 of 0.4 mg/m2 and 0.2 mg/m2 at D8) for the subsequent cycle once adequate recovery is achieved. Once a patient has a dose reduction for a drug-related toxicity, the dose will not be re-escalated. Patient requiring more than one dose reduction will be withdrawn from treatment study.

Dose Level	**Day 1 Dose (mg/m^2)**	**Day 8 Dose (mg/m^2)**	**Total dose Per Cycle (mg/m^2)**
0 (Starting dose)	0.6	0.3	0.9
-1	0.4	0.2	0.6
-2	0.3	0.1	0.4

3.4.7 Drug storage and drug accountability

The amber vials of inotuzumab ozogamicin are to be stored at 2°C to 8°C (36°F to 46°F). Inotuzumab ozogamicin is light sensitive and should be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. Preparation of inotuzumab ozogamicin should occur in full compliance with institutional or local regulations for reconstitution of IV medications under aseptic conditions. Refer to the Dosage and Administration Instructions in the Study Manual for more information on stability, time frame of administration once reconstituted, and administration. Inotuzumab ozogamicin must be stored as indicated. Deviations from the storage requirements for any products supplied (shipped) by Pfizer, including any actions taken, must be documented and reported to Pfizer. Once a deviation is identified, the product must be quarantined and not used until Pfizer provides documentation of permission to use the investigational product. Inotuzumab ozogamicin will be labeled according to regulations. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.

The investigator must maintain a complete and current accountability record. Investigational product accountability applies to such products when they are required by the protocol and supplied (shipped) by Pfizer. All unused investigational product must be returned in the original containers to Pfizer with the appropriate form, or transferred to another site as applicable for this study. The site and the site monitor are to contact Pfizer for detailed information before the transfer of investigational product to another site, or return to Pfizer is to take place. Investigational product return must be documented on the accountability record. The site may destroy unused investigational product in an open container (ie, investigational product left after the vial was opened and/or reconstituted) and empty investigational product containers after accountability has been performed. Investigational product destruction must be documented on the accountability record. Investigational product is destroyed at the site only with Pfizer's permission. For this protocol, undispensed investigational product is destroyed at the site only with the Pfizer's permission and after accountability has been performed by Pfizer. The process of return, destruction, and accountability and reconciliation for controlled (eg, narcotics), hazardous (eg, investigational product used in oncology) and/or isotopically labeled substances, is performed in accordance with local laws and regulations. Shipment of an investigational product that is a hazardous substance or whose shipment may expose humans to risk will be done according to local laws and regulations.

3.4.8 Recommendations to reduce the risk of VOD for patients proceeding to ASCT

- For patients planning to receive an allogeneic ASCT, it is recommended that treatment with inotuzumab ozogamicin be limited to 2-3 cycles.
- The risk of relapse must be balanced against the potential risk of toxicity associated with beginning ASCT soon after the last dose of inotuzumab ozogamicin; however, approximately 5-6 weeks between inotuzumab and ASCT may be reasonable for most patients.

- Healthcare providers should use their clinical judgment to determine the most appropriate course of therapy for prophylactic treatment before the start of conditioning therapy according to standard of care (eg, prophylactic ursodeoxycholic acid at 12-15 mg/kg/day, beginning 2 weeks before the start of conditioning therapy.
- Use the least hepatotoxic conditioning regimen and, specifically, avoid using regimens that contain 2 alkylating agents and or that combine an alkylating agent with higher dose TBI (defined as >12 Gy).
- If using a busulfan-containing conditioning regimen, please consider using pharmacokinetically-dosed busulfan.
- When possible, avoid the concomitant use of hepatotoxic drugs peri-transplant.
- If significant liver toxicity occurs, consult a gastroenterology and/or hepatology service.
- When evaluating liver toxicity, inform the radiologist of the potential for hepatic vascular disease. When VOD is in the differential diagnosis, a right upper quadrant ultrasound with colorflow doppler (including resistive indices to hepatic artery flow and evaluation of hepatic venous outflow) should be performed. In addition, the radiology report should describe the degree of gall bladder wall thickening in millimeters and the volume of ascites should be estimated as closely as possible (i.e., small and localized, moderate and generalized, or large and generalized).
- Defibrotide may be used in the setting of severe VOD
- If a patient will proceed to ASCT under the care of different physicians, these recommendation should be reviewed with the new treating physicians.

3.5 Antibiotic prophylaxis

Prophylactic antibiotics, antifungals, and antiviral agents are recommended; however, the use of these or other drugs will be left to the treating physician's discretion. Antifungal prophylaxis with azoles should be held 24 hours before inotuzumab infusion and not start until 24 hours after completion of the inotuzumab ozogamycin infusion. Antibacterial antibiotic may consist of ciprofloxacin, levofloxacin, cefpodoxime, or others. Antifungal prophylaxis will be fluconazole, voriconazole, or other antifungals.

3.6 CNS leukemia

Patients who develop CNS leukemia while on study will be receive CNS-directed therapy, and may continue on the protocol after discussion with the Principal Investigator.

3.7 Concomitant medications

Necessary supportive measures for optimal medical care will be given throughout the study as determined by the treating physician and the patient's medical need. No concomitant chemotherapy (with the exception of prophylactic or therapeutic intrathecal chemotherapy for active CNS disease or CNS disease in remission), will be allowed during the study. Investigational agents that are not used for the treatment of the leukemia per se (e.g. anti-infective prophylaxis or therapy) will be allowed. Use of any hematopoietic growth factor (e.g. G-CSF, GM-CSF, or erythropoietin) is at the discretion of the treating physician and is permitted if judged in the patient's best medical interest. Concomitant medication data will not be entered into the case report form (CRF); however, the subject's medication record will contain a list of concomitant medications.

4.0 Patient Eligibility

Inclusion Criteria:

1. Patients at least 16 years of age with newly diagnosed, previously untreated B-lineage ALL, or having achieved CR with one course of induction chemotherapy.
2. Patients with extramedullary disease only are eligible
3. Failure to one induction course of chemotherapy (these patients will be analyzed separately).
4. Performance status of 0-3.
5. Adequate organ function with creatinine less than or equal to 2.0 mg/dL (unless considered tumor related), bilirubin less than or equal to 2.0 mg/dL (unless considered tumor related).
6. Adequate cardiac function as assessed by history and physical examination.
7. No active or co-existing malignancy with life expectancy less than 12 months.
8. Women of childbearing potential (WOCBP) or male subjects with a partner who is WOCBP must agree to use contraception during the study, if sexually active.

Exclusion Criteria:

1. Pregnant or nursing women.
2. Known to be HIV-positive
3. Ph-positive 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 involvement or stable chronic liver disease per investigator assessment)
7. Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal

infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis C.

5.0 Treatment Plan

5.1 General

All patients are registered through CORe. Sixty patients will be enrolled.
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.

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. Treatment delays due to unavoidable social or logistical situations such as travel, inclement weather, scheduling issues, etc. will not be considered deviations.
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. Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule. All dose adjustments will be made according to the protocol unless otherwise specified.

5.2 Doses and Schedule

<u>General:</u>

1. Hyper-CVAD (Cycles 1, and 3) will alternate with high-dose methotrexate/cytarabine (Cycles 2 and 4) 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 after completion of chemotherapy until neutrophil recovery to at least 1 x 10^9/l or higher. GFilgrastim product may be stopped earlier for bone pain or other related toxicity.
4. 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). See section 3.4.4 “Recommended Dose Modifications”, 3.4.5 “Dose Delays”, and 3.4.6 “Dose Reductions” for further clarification.
5. 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.
6. 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.
7. CNS prophylaxis: total number of prophylactic intrathecal treatments for previously untreated patients will be 8, two with each course, until total number reached. Intrathecal route preferred.
8. Ofatumumab will be administered: Days 1, 2 and 11 of Cycle 1, Days 1 and 11 of Cycle 3, and Days 1 and 8 of Cycles 2 and 4. Rituximab 375 mg/m^2 IV days 1 and 11 of Cycles 1 and 3 and days 1 and 8 of Cycles 2 and 4 replaces ofatumumab if insurance does not approve ofatumumab.
9. XRT to the chest for patients with bulky mediastinal disease when indicated.
10. Inotuzumab ozogamicin will be IV over one hour at the dose of 0.6 mg/m2 on Day 1 and 0.3 mg/m2 on Day 8 of every cycle for 4 additional cycles as a single agent after completion of 4 cycles in combination with Hyper-CVAD alternating with methotrexate/cytarabine.
11. Maintenance therapy with POMP (6-MP, vincristine, methotrexate, prednisone) for approximately 12 months after completing induction/ consolidation therapy.

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.

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

<u>Hyper-CVAD (Cycles 1 and 3):</u>

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 300 mg IV on Day 1, 2000 mg on Days 2 (+/- 2 days) and 11 (+/- 2 days) of Cycle 1, and 2000 mg IV on Days 1 (+/- 2 days) and 11 (+/- 2 days) of Cycle 3 .
7. Rituximab 375 mg/m^2 IV Days 1 (+/- 2 days) and 11 (+/- 2 days) of Cycles 1 and 3 replaces ofatumumab if insurance does not approve ofatumumab.
8. 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) starting after completion of chemotherapy until post-nadir granulocytes > 1.0 x 10^9/L.
9. 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).
10. Tumor lysis prophylaxis with allopurinol, intravenous alkalinization, oral bicarbonate for course 1 and if indicated. Urate oxidase (Rasburicase) may be substituted for allopurinol.

<u>Suggested Dose Modifications:</u>

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%

<u>High-Dose Methotrexate and Cytarabine (Cycles 2 and 4):</u>

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:
   - Neurotoxicity (Grade 2 reversible cerebellar toxicity or other ara-C related CNS toxicity) with previous cycles.
   - Age 60 years or greater.
   - Creatinine greater than or equal to 1.5 mg/dL.
   - MTX > 20 mcM at time "0" (see below), confirmed on repeat sample.
3. Citrovorum 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.
4. Check MTX around time 0h, 24h, and 48h post completion of MTX unless cleared (e.g. 0.15 mcM or less).
   - 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.
   - if > 1 mcM at 24 hrs or > 0.1 mcM at 48 hrs, increase citrovorum 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.
5. Consider oral acetazolamide 250 mg PO twice daily to promote MTX excretion if the urine pH is <7.0.
6. Ofatumumab 2000 mg IV on Days 1 (+/- 2 days) and 8 (+/- 2 days) for Cycles 2 and 4.
7. Rituximab 375 mg/m^2 IV on Days 1 (+/- 2 days) and 8 (+/- 2 days) of Cycles 2 and 4 replaces ofatumumab if insurance does not approve ofatumumab.
8. 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) after completion of chemotherapy until post-nadir granulocytes greater than or equal to 1.0 x 10^9/L.
9. CNS prophylaxis: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) Day 8 (+/- 2 days). Cytarabine 100 mg intrathecally Day 5 (+/- 2 days).

Suggested Dose Modifications:

1. Cytarabine:
    a. 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.
    b. 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:
    a. 25% to 50% reduction:
        - Grade 3 or worse mucositis with previous methotrexate course.
    b. 25% to 75% reduction:
        - delayed excretion and/or nephrotoxicity with previous methotrexate course.
    c. 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 1-4 and maintenance intensifications. Suggested dose adjustments as below:

	Age < 60	Age 60 – 74 PS 0–2	Age >74 Age > 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)	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

Inotuzumab ozogamicin Consolidation (Cycles 5 – 8)

1. Inotuzumab ozogamicin will be IV over one hour at the dose of 0.6 mg/m2 on Day 1 and 0.3 mg/m2 on Day 8 (+/- 2 days) of every cycle (approximately 21 Days) for 4 additional cycles as a single agent
2. See section 3.4 for information on administration, dose delays and suggested dose adjustments.
3. Ursodiol 300 mg PO TID should be started one week before starting the first cycle of inotuzumab ozogamicin treatment and administered continuously through all 4 cycles of inotuzumab ozogamicin.

Maintenance Therapy:

1. Patients may be moved from the intensive chemotherapy to the maintenance phase prior to completion of 4 cycles of chemotherapy and/or 4 cycles of inotuzumab ozogamicin if significantly intolerant of the intensive chemotherapy or inotuzumab ozogamicin after discussion with the Principal Investigator.

2. Maintenance chemotherapy with 6-mercaptopurine (6-MP), methotrexate (MTX), vincristine, and prednisone (POMP) for approximately 12 months:
    - 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 be 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.

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.
2. Total number of prophylactic intrathecal treatments = 8, 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.
3. 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.
4. 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).

5.4 Mediastinal disease

Patients with mediastinal lymphocytic 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 inotuzumab ozogamicin phase of therapy.

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), full physical exam and ECOG performance status.	Within 14 days of therapy
Concomitant Medications	Document concomitant medications in the medical record	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, alkaline phosphatase	Within 14 days of therapy
Bone marrow	Aspirate and/or biopsy with flow cytometry for confirmation of diagnosis	Within 21 days of therapy
Lumbar puncture	To assess for CNS disease	Within 21 days of therapy
Serology	HIV titers and hepatitis B and C titers	Within 21 days of therapy
Pregnancy test	Serum or urine, if female *and* of child-bearing potential only	Within 14 days of therapy
Imaging studies	Chest X-ray and/or PET/CT as clinically indicated	Within 14 days of therapy
Liver Ultrasound/ Elastography		Within 30 days of start of therapy

7.0 Evaluation During Study

Procedure	Comments	Schedule
Hematology	CBC with differential and platelet count	Weekly during courses 1 to 4 of intensive chemotherapy and courses 1 to 4 of inotuzumab ozogamicin and at least monthly during maintenance
Biochemistry	at least creatinine, total bilirubin, SGPT or SGOT, alkaline phosphatase	At least once every 2 weeks during course 1, then at least every 4 weeks during courses 2 - 4 of chemotherapy and courses 1-4 of inotuzumab ozogamicin, and at least every 4 weeks during maintenance therapy
Physical Examination	Focused physical examination	Prior to each treatment course
Weight		Within 72 hours prior to each cycle of inotuzumab ozogamicin (Cycle 5-8)
Bone marrow	Aspirate and/or biopsy (MRD by flow multicolor cytometry.	On day 14 +/- 3 days 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 after 3 additional courses of chemotherapy and/or before the start of

Procedure	Comments	Schedule
		inotuzumab ozogamicin, then on Day 21 +/- 7 days of the first course of inotuzumab ozogamicin, then after every cycle if MRD positive at the start of inotuzumab ozogamicin, and every 4 months (+/- 1 month), thereafter. In patients with negative MRD at the start of inotuzumab ozogamicin, bone marrow assessment will be performed every 4 months (+/- 1 month) after finishing intensive chemotherapy administration. No marrow is necessary at anytime if non-response is obvious based on peripheral blood counts
Imaging studies	Chest X-ray and or PET/CT	At the time of maximum response and/or when clinically determined to be necessary.

7.1 Follow-up

Thirty days after last dose of the inotuzumab ozogamicin concomitant medication and AE assessment will be performed. This may be done over the phone with a member of the study staff. The phone call should last about 10 minutes.

7.2 Long-term Follow-up

Patients will be followed periodically every 6 months (±3 months) for survival via brief phone call, even after being taken off treatment.

7.3 Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record. Standard laboratory examinations listed in Section 7.0 may be performed locally.
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix **H**.).
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
6. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
7. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

8. Patients will return to MDACC after every 3 courses of chemotherapy, prior to the start of inotuzumab ozogamicin (if MRD positive), and then every 4 months after achieving Complete Remission for evaluation.

8.0 Criteria for Response

8.1 Acute lymphocytic leukemia:

- Complete remission (CR):
  - Normalization of the peripheral blood and bone marrow with 5% or less blasts in a normocellular or hypercellular marrow with a granulocyte count of 1 x 10^9/L or above and 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.

- MRD negativity:
  - MRD levels will be continuously assessed during induction and consolidation therapy by 6-color multiparameter flow. MRD negativity will be defined by a value of at least 10^{-4} and confirmed on a second bone marrow aspiration/biopsy performed after a subsequent cycle. In addition, patients should have normalization of the peripheral blood and bone marrow with 5% or less blasts in a normocellular or hypercellular marrow with a granulocyte count of 1 x 10^9/L or above and a platelet count of 100 x 10^9/L or above.

8.2 Lymphocytic lymphoma (with extramedullary disease):

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

8.2.2 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 and Reporting Requirements

Adverse event (AE) reporting and recording in the CRF (Prometheus) will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines (Appendix G).

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

AEs will be recorded in the subject's source documents from the first protocol-specific intervention through 30 days after the last dose of study treatment. Serious Adverse Events (SAEs) will be captured and reported in accordance with Section 9.2 requirements. The Principal Investigator will sign and date the Adverse Event Record (AE log) for each patient at the completion of each course. Following signature, the AE logs will be used as source documentation for the adverse events for attribution to inotuzumab ozogamicin.

9.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the investigational agent(s) (unrelated, unlikely, possible, probably or definite)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Inotuzumab Ozogamicin Investigators' Brochure – See Appendix F. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

9.2 Serious Adverse Events

Serious Adverse Event Reporting (SAE) Language for MD 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 Serious 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 inotuzomab, 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.

9.3 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.

9.4 Investigator Communications with Pfizer

Reporting to the Pfizer:

Reporting of Serious Adverse Events. Within twenty-four (24) hours of first awareness of the event (immediately if the event is fatal or life-threatening), from after the first dose of inotuzumab ozogamicin until twenty-eight (28) calendar days after the last dose of inotuzumab ozogamicin. Principal Investigator will report to Pfizer by facsimile any Serious Adverse Event (SAE) for which reporting is required. Principal Investigator should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available using a reporting form approved by the local regulatory authority (eSAE). Forms should be faxed to Pfizer at 1-866-997-8322.

10.0 Criteria for Removal from the Study

Criteria for removal from study include, but are not restricted to, the following:

- Progressive disease.
- Non-compliance by the patient with protocol requirements.
- Patient's request to be removed from the study.
- If patient begins a new treatment for the disease, including stem cell transplant.

11.0 Statistical Considerations

This is a single-arm phase II study of the sequential combination of hyper-CVAD + inotuzumab ozogamicin in patients with newly diagnosed B-cell ALL. The primary objective is to evaluate the clinical efficacy of this combination. The primary efficacy endpoint is event-free survival, which is defined as the time interval from date of treatment start until the date of death, disease progression or relapse. Patients who are alive and relapse-free at the last follow-up date will be censored at that time. In addition, patients who drop off the study due to receiving allogeneic stem cell transplantation will be censored at the time off study.

The study will be continuously monitored for the primary endpoint, EFS, using the method of Thall, Wooten, and Tannir (2005). Our goal is to improve the median EFS from 27 months (based on historical treatment) by at least 9 months using the combination of hyper-CVAD and inotuzumab ozogamicin. It is assumed that the EFS time is exponentially distributed with a median of λ_E among patients who receive hyper-CVAD plus inotuzumab ozogamicin, and a median of λ_H is assumed for the historical treatment. Furthermore, we assume that λ_H follows

an inverse gamma distribution, i.e., $\lambda_H \sim IG(74.9, 1995.3)$, which has a mean of 27 months and variance of 10. To reflect the little prior knowledge of λ_E we assume an inverse gamma prior distribution with the same mean of 27 months and a much larger variance of 100, i.e., $\lambda_E \sim IG(9.29, 223.83)$. The trial will be stopped early if $Pr(\lambda_E > \lambda_H + \delta|data) < pL$, where δ = 9 months and pL=0.05 and this futility monitoring rule will be first applied when 10 patients have been enrolled. A maximum of 60 patients will be enrolled into this study at an expected accrual rate of 2 patients per month. Patients will be followed up for an additional 24 months after all patients have been enrolled. The trial will be conducted using the Clinical Trial Conduct (CTC) website maintained by the Department of Biostatistics at MDACC.

The operating characteristics of the design, based on an overall assumed accrual rate of 2 patients per month with 1000 simulated trials per scenario, are given in the following table. OneArmTTE (version 2.2) was used for the design and simulation.

Scenario	True Median EFS (months)	Pr(Stopped Early)	Mean No. patients	Average Trial Duration (months)
1	18	0.906	33.1	40.6
2	21	0.754	39.4	43.7
3	27	0.373	51.0	49.6
4	36	0.113	56.8	52.3
5	42	0.045	58.5	53.2
6	48	0.018	59.4	53.9

In addition, we will continuously monitor treatment-related toxicities using the Bayesian approach of Thall, Simon, Estey (1995). Specifically, the trial will be stopped if $Prob(\pi T>0.30 \mid data)>0.93$, where πT is the toxicity rate and we assume a beta (0.6, 1.4) prior for πT. That is, if at any given time, there is more than 93% probability that the toxicity rate of the maintenance therapy with inotuzumab ozogamicin is greater than 30%, the trial will be stopped. For the purpose of toxicity monitoring, toxicities are defined as any treatment –related grade 3 or 4 non-hematologic AEs occurred any time during the trial. We will apply this stopping rule starting from the 5^{th} patient and in cohort size of 5. An Efficacy/Toxicity Summary will be submitted to the IND Office Medical Affairs and Safety Group, after the first 5 evaluable subjects complete Cycle 5 f the study therapy, and every 5 evaluable patients thereafter. The first summary is to include treatment related toxicity during Cycle 5. On every upcoming summary submission, the Efficacy/Toxicity information from previous reported patients will be updated, until the end of their participation. The stopping boundaries corresponding to this toxicity monitoring rule are described in the following table:

Stopping boundaries for treatment-related grade 3, 4 non-hematologic toxicities

The number of patients evaluated for toxicities (in cohort size of 5)	Stop the trial if this many of patients with toxicities
5	4-5
10	6-10
15	8-15
20	10-20
25	12-25
30	14-30
35	15-35
40	17-40
45	19-45
50	21-50
55	22-55
60	Always stop with this many of patients

The operating characteristics for toxicity monitoring are described in the following table. MultcLean Desktop 2.1.0 was used for the design and simulations for toxicity monitoring.

Operating characteristics for Toxicity Monitoring

True Toxicity Rate	Early Stopping Probability	Sample Size		
		25^{th} percentile	Median	75^{th} percentile
0.10	0.0006	60	60	60
0.20	0.016	60	60	60
0.30	0.174	60	60	60
0.40	0.663	15	35	60
0.50	0.966	10	15	30

Analysis Plan

The probabilities of EFS and OS will be estimated using the method of Kaplan and Meier. For the primary analysis of the efficacy endpoint, we will compute the Bayesian posterior probability of $Pr(\lambda_E > \lambda_H + \delta|data)$, where δ = 9 months. As a secondary analysis, we will perform a competing risk analysis treating stem cell transplant as a competing event for EFS. The MRD negativity rate and overall response rate will be estimated along with the exact 95% confidence intervals. All treated patients will be included in the safety analysis set. The AEs will be summarized by organ type, grade and attribution to study treatment.

12.0 References

1. Pui CH, Evans WE. Acute lymphoblastic leukemia. N Engl J Med 1998;339:605-15.
2. Faderl S, Jeha S, Kantarjian HM. The biology and therapy of adult acute lymphoblastic leukemia. Cancer 2003;98:1337-54.
3. Bassan R, Gatta G, Tondini C, Willemze R. Adult acute lymphoblastic leukaemia. Crit Rev Oncol Hematol 2004;50:223-61.
4. Murphy SB, Bowman WP, Abromowitch M, et al. Results of treatment of advanced-stage Burkitt's lymphoma and B cell (SIg+) acute lymphoblastic leukemia with high-dose fractionated cyclophosphamide and coordinated high-dose methotrexate and cytarabine. J Clin Oncol 1986;4:1732-9.
5. Iversen OH, Iversen U, Ziegler JL, Bluming AZ. Cell kinetics in Burkitt lymphoma. Eur J Cancer 1974;10:155-63.
6. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000;18:547-61.
7. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 2004;101:2788-801.
8. Thomas DA, O'Brien S, Jorgensen JL, et al. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. Blood 2009;113:6330-7.
9. Jabbour E KH, Thomas DA, et al. Phase II Study of The Hyper-CVAD Regimen in Combination with Ofatumumab As Frontline Therapy for Adults with CD-20 Positive Acute Lymphoblastic Leukemia (ALL). Blood 2013;122:2664.
10. Piccaluga PP, Arpinati M, Candoni A, et al. Surface antigens analysis reveals significant expression of candidate targets for immunotherapy in adult acute lymphoid leukemia. Leuk Lymphoma 2011;52:325-7.
11. DiJoseph JF, Goad ME, Dougher MM, et al. Potent and specific antitumor efficacy of CMC-544, a CD22-targeted immunoconjugate of calicheamicin, against systemically disseminated B-cell lymphoma. Clin Cancer Res 2004;10:8620-9.
12. Advani A, Coiffier B, Czuczman MS, et al. Safety, pharmacokinetics, and preliminary clinical activity of inotuzumab ozogamicin, a novel immunoconjugate for the treatment of B-cell non-Hodgkin's lymphoma: results of a phase I study. J Clin Oncol 2010;28:2085-93.
13. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol 2012;13:403-11.
14. Hamann PR, Hinman LM, Beyer CF, et al. An anti-CD33 antibody-calicheamicin conjugate for treatment of acute myeloid leukemia. Choice of linker. Bioconjug Chem 2002;13:40-6.

15. DiJoseph JF, Dougher MM, Evans DY, Zhou BB, Damle NK. Preclinical anti-tumor activity of antibody-targeted chemotherapy with CMC-544 (inotuzumab ozogamicin), a CD22-specific immunoconjugate of calicheamicin, compared with non-targeted combination chemotherapy with CVP or CHOP. Cancer Chemother Pharmacol 2011;67:741-9.
16. Larson RA, Sievers EL, Stadtmauer EA, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer 2005;104:1442-52.
17. Matsui H, Takeshita A, Naito K, et al. Reduced effect of gemtuzumab ozogamicin (CMA-676) on P-glycoprotein and/or CD34-positive leukemia cells and its restoration by multidrug resistance modifiers. Leukemia 2002;16:813-9.
18. Takeshita A, Shinjo K, Yamakage N, et al. CMC-544 (inotuzumab ozogamicin) shows less effect on multidrug resistant cells: analyses in cell lines and cells from patients with B-cell chronic lymphocytic leukaemia and lymphoma. Br J Haematol 2009;146:34-43.
19. DiJoseph JF, Dougher MM, Kalyandrug LB, et al. Antitumor efficacy of a combination of CMC-544 (inotuzumab ozogamicin), a CD22-targeted cytotoxic immunoconjugate of calicheamicin, and rituximab against non-Hodgkin's B-cell lymphoma. Clin Cancer Res 2006;12:242-9.
20. DiJoseph JF, Armellino DC, Boghaert ER, et al. Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies. Blood 2004;103:1807-14.
21. Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. Cancer 2013;119:2728-36.
22. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci 2004;93:2645-68.
23. Cao Y, Jusko WJ. Incorporating target-mediated drug disposition in a minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J Pharmacokinet Pharmacodyn 2014;41:375-87.
24. Deangelo Aea. Weekly Inotuzumab ozogamicin (InO) in adult patients with relapsed or refractory CD22-positive acute lymphoblastic leukemia (ALL). Abst 3906. Blood 2013;122.
25. Jabbour E. Abstract S114 EHA 2015. Haematologica 2015;100.
26. Jabbour E. Abstract 7019 ASCO 2014. Journal of Clinical Oncology 2014;32.
27. Pui CH, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood 2012;120:1165-74.
28. Sive JI, Buck G, Fielding A, et al. Outcomes in older adults with acute lymphoblastic leukaemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial. Br J Haematol 2012;157:463-71.
29. O'Brien S, Jabbour E, Thomas DA, et al. . Phase II Study of combination of HyperCVAD with Ponatinib in Frontline Therapy of Patients with Philadelphia

Chromosome Positive Acute Lymphoblastic Leukemia. J Clin Oncol 2014:Abstract #7064.
30. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol 2010;28:3880-9.
31. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-80.
32. Bruggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. Blood 2006;107:1116-23.
33. Raff T, Gokbuget N, Luschen S, et al. Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment: data from the GMALL 06/99 and 07/03 trials. Blood 2007;109:910-5.
34. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood 2008;111:5477-85.
35. Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). Blood 2009;113:4153-62.
36. Van der Velden VH, Corral L, Valsecchi MG, et al. Prognostic significance of minimal residual disease in infants with acute lymphoblastic leukemia treated within the Interfant-99 protocol. Leukemia 2009;23:1073-9.
37. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010;115:3206-14.
38. Gokbuget N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood 2012;120:1868-76.
39. Bader P, Kreyenberg H, Henze GH, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. J Clin Oncol 2009;27:377-84.