THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Treatment of Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL) with CMC-544 (Inotuzumab Ozogamycin), with or without Later Addition of Rituximab 2009-0872

Core Protocol Information

Short Title	CMC-544 in relapsed refractory ALL
Study Chair:	Hagop Kantarjian
Additional Contact:	Jhinelle L. Graham Vicky H. Zoeller Leukemia Protocol Review Group
Department:	Leukemia
Phone:	713-792-7026
Unit:	428
Full Title:	Treatment of Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL) with CMC-544 (Inotuzumab Ozogamycin), with or without Later Addition of Rituximab
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Terminated 04/19/2018
Version:	15
Submitted by:	Vicky H. Zoeller--7/21/2017 11:39:36 AM
OPR Action:	Accepted by: Julie Arevalo -- 7/31/2017 4:07:23 PM

Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

CMC-544 in ALL December 2011 v9 Final.doc

Treatment of Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL) with CMC-544 (Inotuzumab Ozogamycin), with or without Later Addition of Rituximab

Short Title: CMC-544 in relapsed refractory ALL

Table of Contents

Treatment of Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL) with CMC-544 (Inotuzumab Ozogamycin), with or without Later Addition of Rituximab

1.0 Objectives

- To evaluate the efficacy of treatment with CMC-544 with or without later rituximab in patients with relapsed or refractory ALL.
- To evaluate the side effects of the treatment.

2.0 Background

2.1 Acute Lymphoblastic Leukemia (ALL)

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

The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and ara-C) **(4,5)**, developed at M. D. Anderson, demonstrated significant activity, producing a complete remission (CR) rate of 90% and a cure rate of 40%-50%.

Current outcomes of salvage chemotherapy for ALL are poor, with complete response rates of 20% to 30% depending on prior therapy and duration of first remission. Median disease-free survival ranges from 2 to 7.5 months. Long-term survival after ALL salvage therapy is rare. Less than 10% of patients are eligible for allogeneic stem cell transplant. Among them the cure rate is 20% or less. No standard of care has been defined, so that salvage therapy options are generally limited to investigational agents once patients fail standard chemotherapy regimens**(6,7)**. Not many treatments are available for ALL salvage.

New agents or regimens are needed to improve outcome in ALL. ALL blasts express several surface markers including CD19, CD20, and CD22. CD22 is expressed on the surface of ALL blasts in more than 90% of patients. Several new monoclonal antibodies have been developed that target these surface markers. Monoclonal antibodies with proven efficacy against ALL could potentially, when used in combination with chemotherapy, significantly improve ALL prognosis. For example, rituximab has minimal single agent activity in ALL but, when added to hyper-CVAD, has improved significantly the outcome in Burkitt's ALL and in CD20-positive pre-B ALL.

2.2 The Treatment -- CMC-544 (Inotuzumab Ozogamycin) and Rituximab

CMC-544 (inotuzumab ozogamicin) is a CD22-targeted cytotoxic agent composed of a humanized IgG4 anti-CD22 antibody covalently linked to N-acetyl-g-calicheamicin dimethyl hydrazide (CalichDMH) via the acid-labile 4-(4V-acetylphenoxy) butanoic acid linker **(8-10)**. CD22 is a B-lymphoid lineage–specific differentiation antigen expressed

on both normal and malignant B cells. CMC-544 binds CD22 with subnanomolar affinity, and, upon binding, is rapidly internalized delivering the conjugated CalichDMH inside the cells. This preferential intracellular delivery of CalichDMH causes DNA damage resulting in B-cellular apoptosis. CalichDMH is a derivative of g-calicheamicin, a natural product produced by Micromonospora echinospora and is significantly more potent than cytotoxic chemotherapeutic agents used in cancer therapy. It binds in the minor groove of DNA and causes double strand DNA breaks in a relatively sequence-specific and thioldependent manner leading to apoptotic response in cells **(11-13)**. CMC-544 exerts potent and CD22-selective growth inhibitory activity against CD22+ B-cell lymphoma (BCL) cell lines in vitro and causes regression of developing (minimal disease), small established (palpable disease), and large BCL xenografts, with a high therapeutic index **(9)**. In addition, CMC-544 had in vitro high activity against CD22 positive ALL cell lines **(14)**. In the absence of the conjugated CalichDMH, G5/44, the targeting monoclonal antibody (mAb) in CMC-544 is ineffective in vivo as an antitumor agent in various preclinical models **(8).** Thus, CMC-544 is regarded as an antibody-targeted chemotherapy agent rather than an immunotherapeutic agent like rituximab. Largely due to its tumor-targeted, drug-delivery capability, CMC-544 is likely to have a better therapeutic index than that of conventional chemotherapeutic agents. Based on its potent antitumor activity in preclinical models, CMC-544 is currently being evaluated in patients with B-cell non-Hodgkin lymphoma (B-NHL). Early results show encouraging activity with response rates of 40% to 75% in patients with refractory relapsed BNHL**(15).** CD22 is expressed on leukemic blasts in more than 90% of adults with ALL. Thus, CMC-544 may be also an effective treatment for ALL.

Rituximab is a chimeric human IgG1 antibody targeted to another B-lymphoid lineage–specific molecule, CD20. It represents a major therapeutic advance in B-NHL therapy. Rituximab mediates its antitumor activity by multiple mechanisms that include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and direct induction of apoptosis in BCL **(16-17)**. The activity of single agent rituximab is modest in BNHL, chronic lymphocytic leukemia, and ALL. However when combined with chemotherapy it has improved outcome significantly in all 3 entities **(18-21)**.

2.3 Rationale for the Study Design

Due to its clinical safety, rituximab is widely used in combination with various cytotoxic agents. Treatments using combinations of rituximab with cytoreductive combination chemotherapy, like CHOP (a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone), hyper-CVAD, or fludarabine-cyclophosphomide are highly active. However, such combinations of chemoimmunotherapy also suffer from various systemic toxicities associated with the non-targeted nature of chemotherapy. Thus, studies of targeted therapy combinations like CMC-544 (target CD22) and rituximab (targets CD20) in pre-B ALL would be highly attractive, because of the potential of high efficacy and low toxicity. This is the purpose of this study. If successful, this combined targeted therapy may become a new standard of care for patients with refractory relapsed ALL. It may also be brought into frontline therapy of minimal residual disease to increase the

cure of patients with newly diagnosed pre-B ALL. Thus the study has major potential therapeutic implications for improving adult ALL prognosis.

The phase I-II studies of CMC-544 determined the phase II dose to be 1.8 mg/m^2 once every 3-4 weeks. The DLT was myelosuppression. Other side effects were gastrointestinal and hepatic. Only 1 case of veno occlusive disease was noted among 176 patients treated**(14).** Phase II studies combining rituximab 375 mg/m^2 on Day 1 and CMC-544 1.8 mg/m^2 on Day 2 were safe and effective in lymphomas**(15).**

2.4 Update of October 6, 2010

At present, a total of 21 patients with refractory relapse ALL have been treated. Fifteen of them were in second salvage or worse; eight of them have translocation 4;11 or Philadelphia positive ALL. Overall, 12 of 21 patients have achieved either CR (n=5) or Cri (n=7), for an overall response rate of 57%. This is even better than what is expected using standard combination intensive chemotherapy in first salvage, with which the CR rate would be expected to be about 30%. Toxicity has been minimal. There were two episodes of tumor lysis responding to standard measures. Fever on Day 2 post therapy is common. Transient grade 1-3 elevations of liver enzymes have been observed, which are expected and self-limited. Two patients died within four weeks, one of them with progressive disease. Overall the treatment appears to be extremely effective with minimal toxicity. This has allowed so far at least 4 patients to undergo allogeneic stem cell transplant. Based on the findings we propose to 1) allow treatment of patients in first salvage regardless of the duration of first CR, and 2) increase the total number of

patients to 60 to allow more accurate assessment of the overall response rate and define more precisely predictive factors for response to therapy.

2.5 Update of January 7, 2011

At the present update, 38 patients have been treated. Of 32 evaluable patients, 8 achieved CR and 10 achieved CRi or CRp for an overall response rate of 18/32 =56%. Toxicities were reasonable and included Grade 1-2 elevations of liver function tests which were transient. Two patients had Grade 3 liver function abnormalities; the attribution to the drug was questionable.

From preclinical studies, it is thought that lower dose more frequent exposure schedules to inotuzumab may offer better anti-ALL efficacy. Following discussions in the Leukemia group and with Pfizer investigators, it was decided to study a different schedule of inotuzumab given weekly times 3. The total dose per course is the same, 1.8 mg/m2. The treatment will be with inotuzumab 0.8 mg/m2 on Day 1, 0.5 mg/m2 on Day 8, and 0.5 mg/m2 on Day 15. Courses are given every 3 weeks. When rituximab is required, it will be given weekly with inotuzumab. A total of 20 patients will be treated to gain experience with efficacy and toxicity. Early stopping rules will be implemented for an overall response rate < 40%.

2.6 Update of December 2, 2011

This study has completed accrual of 20 patients on the weekly schedule. The early analysis shows encouraging results with trends for similar or better efficacy and less

toxicity. Among the first 15 evaluable patients, 2 achieved CR (12%), 5 achieved CRp (31%) and 1 achieved CRi (6%). Thus, 8 of 15 evaluable patients (53%) achieved marrow CR. Five of the 7 evaluable responders (71%) achieved MRD negativity. Three patients underwent allogeneic SCT; no VODs were noted. Transient liver enzyme elevations grade 1-2 were noted in 5 of 20 (25%), severe in 2.

In discussions with Pfizer, we emphasized the importance of these findings but the limited number of patients makes definite conclusions difficult. It was agreed to increase the number of treated patients on the weekly schedule by another 20, for a total of 40 patients, to assess more precisely the response and toxicity profile compared with the 49 patients treated with the single dose every 3-4 weeks.

3.0 Background Drug Information

3.1 Inotuzumab Ozogamicin Nonclinical Data

Inotuzumab ozogamicin is an antibody-targeted intravenous (IV) chemotherapy agent composed of an antibody, targeting CD22 antigen, which is linked to calicheamicin, a potent cytotoxic antitumor antibiotic. The targeting agent in inotuzumab ozogamicin is a humanized IgG4 antibody, G544 that specifically recognizes human CD22. Being an IgG4 isotype antibody, G544 is not expected to mediate effector functions such as complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity. CD22 is expressed on both normal and malignant cells of the mature B-lymphocyte lineage. Nonmalignant, mature lymphocytes express CD22; however, lymphocyte precursor

cells and memory B cells do not express CD22. Thus, the impact of treatment with inotuzumab ozogamicin on long-term immune function is expected to be minimal.

The concept of antibody-targeted chemotherapy has been successfully translated into a clinically validated therapeutic agent, gemtuzumab ozogamicin (Mylotarg). N-acetyl calicheamicin dimethyl hydrazide (N-acetyl calicheamicin DMH), the cytotoxic entity in both inotuzumab ozogamicin and gemtuzumab ozogamicin, is a derivative of calicheamicin methyl trisulfide.

N-acetyl calicheamicin DMH is at least 100- to 1000-fold more potent than current cytotoxic therapeutics, such as doxorubicin. Its high potency makes N-acetyl calicheamicin DMH an ideal candidate for antibody-targeted chemotherapy.

Inotuzumab ozogamicin is expected to have greater efficacy than unlabeled monoclonal antibodies and to have efficacy at least comparable to the leading chemotherapeutic or radio-immunoconjugate based therapies. Because of its targeted nature, it is expected to have a reduced incidence of side effects compared with conventional cytotoxic chemotherapy or radioimmunotherapy. This may confer important advantages in tolerability and reduced need for supportive care for subjects treated with inotuzumab ozogamicin as a single agent and offers the potential to intensify combination regimens without substantial additional toxicity.

CD22 was chosen as a target for conjugate delivery for a number of reasons. CD22 is expressed on the malignant cells of the majority of B-lymphocyte malignancies. It is not expressed on hematopoietic stem cells or any other nonlymphoid hematopoietic or nonhematopoietic cells.

Moreover, based on in vitro testing of human NHL cell lines, CD22 is one of the better internalizing molecules among several B- lymphoid lineage-specific surface antigens and is not shed into the extracellular environment. The normal function of CD22 is to regulate signal transduction of the surface immunoglobulin receptors on B cells.

Inotuzumab ozogamicin exhibits a potent dose-dependent cytotoxicity in vitro and in vivo animal tumor models. Unconjugated G544 does not fix complement, does not mediate antibody-dependent-cellular cytotoxicity, and has no antitumor activity. In addition, inotuzumab ozogamicin was effective against human B-cell lymphomas in nonclinical murine models in which rituximab, a chimeric anti-CD20 monoclonal antibody, had failed as a therapeutic agent.

This important nonclinical therapeutic advantage conferred by inotuzumab ozogamicin strongly supports its targeted clinical application in NHL. Nonclinical data also indicate a synergistic effect between inotuzumab ozogamicin and rituximab, as the combination of inotuzumab ozogamicin plus rituximab was: (a) more efficacious against established subcutaneous Ramos B lymphoma xenografts in nude mice, and (b) increased long term survival of severe immunodeficient mice with disseminated Ramos B lymphoma

than either agent alone **(22)**. See the most recent version of the investigator's brochure for all nonclinical data that potentially have a clinical significance and from clinical studies that are relevant to this study **(23)**. Also refer to the most recent version of the investigator's brochure for a summary of the known and potential risks and benefits, if any, to human subjects.

3.2 Inotuzumab Ozogamicin Clinical Data

The first in human trial (3129K1-100-WW [100-WW]) of inotuzumab ozogamicin was an open-label, dose-escalating, single-agent study in 79 subjects with CD22-positive B-cell NHL**(23)**.

The study defined the maximum-tolerated dose and showed a safety profile (and preliminary efficacy data) that supported advancement of inotuzumab ozogamicin's clinical development**(8,9,22)**.

This continued clinical development included initiation of 4 additional trials (2 global and 2 in Japan) involving the use of inotuzumab ozogamicin as either a single agent or in combination with rituximab for treatment of CD22-positive B-cell NHL. The combination strategy was evaluated since B-NHL cells consistently express both CD20 and CD22; thus, it is reasonable to combine rituximab and inotuzumab ozogamicin (anti-CD20 and CD22 targeting antibodies, respectively) in an attempt to enhance the therapeutic advantage of either agent. Nonclinical data supported this reasoning (see Inotuzumab Ozogamicin Nonclincal Data section).

The following safety and efficacy discussions focus on 2 of the 5 studies currently comprising the clinical development of inotuzumab ozogamicin (studies 100-WW and 3129K3-101-WW [101-WW]) since these are global trials that include patients with DLBCL. Furthermore, because response data are available by NHL class, efficacy discussions for studies 100-WW and 101-WW will focus on patients with diffuse large B-cell lymphoma (DLBCL).

3.2.1 Study 100-WW: Safety and Efficacy of Single-agent Inotuzumab Ozogamicin.

Study 100-WW was a phase 1, open-label, dose-escalation study of the safety, tolerability, and pharmacokinetics (PK) of inotuzumab ozogamicin administered as a single-agent to 79 subjects with CD22-positive B-cell NHL. Dose escalation was based on safety evaluations through days 21 to 28 after the first dose of inotuzumab ozogamicin. The maximum tolerated dose (MTD) was determined to be 1.8 mg/m2 given every 28 days. Of the 49 subjects in the MTD cohort, 26 subjects had DLBCL. All 79 subjects in the study had received prior chemotherapy, immunotherapy, or hormonal therapy per the inclusion criteria defined in the protocol, and most subjects (60.8%) had received at least 4 prior treatment regimens. Subjects ranged in age from 26 to 82 years (median, 60 years).

The most common treatment emergent adverse events (TEAEs, incidence ≥ 20% of subjects) were hematologic (thrombocytopenia [84.8%], neutropenia [43.0%], anemia [22.8%], and leukopenia [21.5%]); gastrointestinal (nausea [51.9%], anorexia [31.6%],

constipation [24.1%], and vomiting and diarrhea [21.5% each]); metabolic (aspartate aminotransferase [AST] increased [39.2%], alkaline phosphatase increased [26.6%], alanine aminotransferase [ALT] increased [21.5%], and bilirubinemia [20.3%]); respiratory (cough increased [21.5%]); asthenia (65.8%); fever (39.2%); abdominal pain (35.4%); and headache (21.5%). The most common grade 3/4 TEAEs (incidence ≥ 5% of subjects) were predominantly hematologic or metabolic: thrombocytopenia (59.5%), neutropenia (25.3%), leukopenia (13.9%), lymphopenia (11.4%), and anemia and hypokalemia (6.3% each). Others were: asthenia (10.1%) and gamma glutamyl transpeptidase (GGT) increased (6.3%) increased blood fibrinogen, blood lactate dehydrogenase, and venooclusive disease among adverse reactions or as adverse reactions leading to the discontinuation of the drug. Dose-limiting toxicities were all hematologic events: 3 cases of grade 4 thrombocytopenia, 1 event of bleeding (injury-related) that required a platelet transfusion because of concurrent thrombocytopenia, and 1 event of grade 4 neutropenia. Fifteen (15) subjects with DLBCL in the expanded MTD cohort were evaluable for tumor response **(24)** (received ≥ 2 doses of inotuzumab ozogamicin and had tumor assessments at both baseline and postbaseline visits). These subjects had a best overall response rate (ORR) of 47.0% (2 CR and 5 PR), a median progression-free-survival (PFS) of 105 days (95% confidence interval [CI], 55 to 343), and a median overall survival (OS) of 273 days (95% CI, 168 to 518).

3.2.2 Study 101-WW: Safety and Efficacy of Inotuzumab Ozogamicin in Combination with Rituximab.

Study 101-WW is an ongoing phase 1/2, open-label, dose-escalation study of the safety, tolerability, and PK of inotuzumab ozogamicin in

combination with rituximab in patients with relapsed DLBCL or follicular NHL. Subjects for whom curative therapies were available (ie, high-dose (HD) chemo and a stem cell transplant [SCT] for DLBCL) were not eligible for the study. Subjects who had relapsed after obtaining a response (progressed > 6 months after start of prior therapy) to first or second line rituximab-containing therapies were eligible for participation. For this ongoing study, the following results reflect data available as of September 23, 2008 (a third cohort recently opened to enroll 30 subjects with DLBCL that is refractory to treatment with rituximab in combination with chemotherapy [ie, progressed ≤ 6 months of start of prior therapy]; no safety or efficacy data is currently available for this new cohort). In total, 74 subjects have received study drug, including 66 subjects (27 with DLBCL) treated at the MTD (375 mg/m2 rituximab on day 1, and 1.8 mg/m2 inotuzumab ozogamicin on day 2). Subjects ranged in age from 29 to 85 years (median, 65.5 years) and most (54%) had received 2 prior lines of therapy.

The observed TEAEs are those characteristic of rituximab and inotuzumab ozogamicin when administered as single agents. The most common TEAEs (incidence ≥ 20% of subjects) were hematologic (thrombocytopenia [40.5%], neutropenia [23.0%]); gastrointestinal (nausea [51.4%], constipation [21.6%], and vomiting [24.3%]); metabolic (AST increased [33.8%]); fatigue (43.2%); infections (40.5%); pyrexia (29.7%); headache (20.3%); and vascular disorders (20.3%). The most common grade 3/4 TEAEs (incidence ≥ 5% of subjects) were predominantly hematologic (thrombocytopenia [21.6%], neutropenia [17.6%], and lymphopenia [5.4%]). Others

were: gastrointestinal (5.4%) or general (8.1%) disorders, infections (8.1%), and abnormal laboratory results (10.8%).

A best overall response rate (ORR) of 79% (80% CI, 64.8% to 89.5%) has been achieved for 24 DLBCL subjects treated at the MTD. Informal analyses of current data indicate that the response rate is unaffected by both the number and duration of response to prior therapies, as well as IPI score and age: best ORRs were 80% (N =15) and 78% (N = 9) for subjects with 1 and 2 prior line of therapy, respectively; 75% (N = 8) and 81% (N = 16) for subjects with prior response durations of < 12 and ≥ 12 months, respectively; 72% (N = 18) and 100% (N = 6) for subjects with IPI scores > 1 and < 2, respectively; and 87.5% (N = 8) and 75% (N = 16) for subjects < 60 and > 60 years of age, respectively. At the time of evaluation (September 23, 2008), these 24 subjects have a 6-month PFS rate of 65% (80% CI, 48% to 78%).

4.0 Patient Eligibility

4.1 Inclusion Criteria:

1. Previously treated ALL (including Burkitt's lymphoma and lymphoblastic lymphoma) in relapse or primary refractory. Patients in first relapse will be eligible regardless of the first remission duration. At least 10 patients in Salvage 1-2 will be treated to assess anti-ALL response more precisely.
2. Age 16 years or older. Pediatric patients (<16 years old) will be allowed into the study after safety is established, that is at least 10 adult patients having received 1 or more cycles each.

3. Zubrod performance status 0-3.
4. Adequate liver function (bilirubin $\leq$ 1.5 mg/dL and SGPT or SGOT $\leq$ 3 x upper limit of normal [ULN], unless considered due to tumor), and renal function (creatinine $\leq$ 2 mg/dL). Even if organ function abnormalities are considered due to tumor, the upper limit for bilirubin is $\leq$ 2.0 mg/dL and creatinine $\leq$ 3 mg/dL.
5. Male and female patients who are of childbearing potential agree to use an effective barrier method of birth control (e.g., latex condom, diaphragm, cervical cap, etc.) to avoid pregnancy. Female patients need a negative serum or urine pregnancy test within 14 days of study start (applies only if patient is of childbearing potential. Non-childbearing is defined as $\geq$ 1 year postmenopausal or surgically sterilized).

4.2 Exclusion Criteria:

1. Patient with active heart disease (NYHA class $\geq$ 3 as assessed by history and physical examination).
2. Patients with a cardiac ejection fraction (as measured by either MUGA or echocardiogram) < 45% are excluded.
3. Patients who receive other chemotherapy. Patients must have been off previous therapy for $\geq$ 2 weeks and must have recovered from acute toxicity (to grade 1 or less) of all previous therapy prior to enrollment (consent signing). (Concurrent therapy for central nervous system [CNS] prophylaxis or treatment for CNS relapse is permitted). Treatment may start earlier if

necessitated by the patient's medical condition (e.g. rapidly progressive disease) following discussion with the Principal Investigator.

4. Prior allogeneic stem cell transplant in previous 4 months.
5. Peripheral lymphoblasts > 50 x 10^9/L.
6. Pregnant and breast-feeding patients are excluded.
7. Patients with known hepatitis B are excluded.

5.0 Treatment Plan

5.1 General

This is an open label, phase II study. The design will evaluate single agent efficacy of CMC-544 as initial treatment, first in patients ≥ 16 years and then in patients less than 16 years. If stable disease or worse after 2 courses, CMC-544 will continue with the addition of rituximab, as detailed below.

CMC-544 will be provided by Wyeth Corporation. Any unused or expired drug will be destroyed per institutional policy.

5.2 Treatment Schema

5.2.1 The first 3 patients ≥ 16 years and the first 3 patients < 16 years will receive CMC-544 at a dose of 1.3 mg/m^2 IV over 1 hour (+/- 15 minutes) during Course 1, and 1.8 mg/m^2 IV over 1 hour (+/- 15 minutes) during Course 2 and subsequently. In all other patients, if there are no safety issues, CMC-544 will be given at a dose of 1.8 mg/m^2 IV over 1 hour (+/- 15 minutes) about every 4 weeks. This will constitute a course of therapy. Courses will be repeated about every 4 weeks (range 3-6 weeks).

Courses can be started earlier, every 2 weeks if evidence of rapid progression after approval by the principal investigator.

5.2.2 In a second phase (see 2.4), 20 patients will be treated with weekly CMC-544. CMC-544 will be given at 0.8 mg/m2 IV over 1 hour (± 15 minutes) on Day 1, 0.5 mg/m2 IV over 1 hour (± 15 minutes) on Day 8, and 0.5 mg/m2 IV over 1 hour (± 15 minutes) on Day 15. Weekly doses can be given at ± 1 day. Course may be repeated every 3 weeks.

Recommended premedication before CMC-544: acetaminophen 650 mg orally, diphenhydramine 10-25 mg IV, hydrocortisone 25 mg IV. Modifications to this premedication are also allowed.

Prophylaxis for tumor lysis syndrome may be administered at the discretion of the treating physician.

5.2.3 If stable disease, no improvement or progression after 2 courses of CMC-544, patients may continue on CMC-544 at the same dose every 3-4 weeks, with the addition of rituximab 375 mg/m^2 IV over 2-6 hours every 3-4 weeks. The first dose of rituximab will be given as a slow infusion over 6-8 hours depending on reactions and side effects. It will be given on Day 1 and CMC-544 on Day 2. Subsequent courses of CMC-544 and rituximab may be given on the same day; CMC-544 will be given at least 2-4 hours after completion of rituximab. Courses can be started earlier, every 2 weeks if evidence of

rapid progression after approval by the principal investigator. In the second phase of weekly CMC-544, rituximab will be given on Day 1 and CMC-544 on Day 2 of the first dose; with subsequent weekly doses, both will be given weekly, rituximab preceding CMC-544. The weekly dose of rituximab will be 375 mg/m2.

Infusion 1 of rituximab will be over 6-8 hours following infusion rate increases as per hospital standards. Infusions 2-6 of rituximab may be run at faster rates of 2-6 hours as indicated by side effects and per hospital standards.

5.2.4 Patients achieving response, defined as CR or CRi, or partial remission (PR) may continue therapy for up to 8 cycles (about 8-12 months of therapy). Patients with progression at any time or without objective response after 3 cycles will be taken off study.

5.3 Treatment Duration and Dose Adjustments

Patients will receive 2 courses of CMC-544. If CR, complete remission without platelet recovery (CRi), or PR is documented, whichever comes first, then continue CMC-544. If a patient does not achieve a CR, CRi, or PR then add rituximab as under 5.2.

Patients who achieve a CR, CRi, or PR may receive up to a total of 8 cycles of therapy depending on leukemia response and resolution of toxicities. Subjects who demonstrate a CR or CRi after 1 or 2 cycles of therapy will receive a maximum of 4 cycles of therapy. Subjects who are in a CR or CRi after 3-4 cycles may receive a maximum of 2

additional cycles of therapy after achieving a CR or CRi. After a total of 4 cycles, patients will be assessed for the need of the 4 additional cycles based on response and liver toxicities with the previous 4 cycles. Cycles are repeated about every 4 weeks (range 3-6 weeks) depending on leukemia response, resolution of toxicities, and recovery of hematopoiesis.

Patients receiving subsequent cycles (cycles 2-8) will be treated at the same dose level if grade $\leq$ 2 non-hematologic toxicity has occurred and if they have experienced a favorable response of their leukemia (decrease in peripheral blood or marrow blasts). Re-treatment will only occur upon recovery to < grade 2 non-hematologic or baseline toxicity. If they have non-hematologic toxicity of $\geq$ grade 3 and a favorable response to therapy, additional cycles of therapy at 25% dose reduction of CMC-544 may be considered after this is discussed with and approved by the Principal Investigator. No dose reductions for rituximab are needed.

Patients who develop CNS leukemia while on study will be removed from the study and receive CNS-directed therapy, except where such patients have a positive response to therapy in which case they will continue on study after discussion with the Principal Investigator.

5.4 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), immunotherapy, or therapy with monoclonal antibodies 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.

Prophylactic antibiotics, antifungals, and antiviral agents (e.g. levofloxacin, itraconazole, valacyclovir, etc.) are recommended; however, the use of these or other drugs will be left to the treating physician's discretion.

The use of hydroxyurea or steroids is permitted for temporary control of WBC elevations in patients with aggressive disease both prior and during treatment. Hydroxyurea may be given at 1-5 g daily for up to 5 days in Course 1. Dexamethasone may be given at 40 mg daily x 4 with each of the first 2 courses.

6.0 Pretreatment evaluation

Procedure	Comments	Schedule
Informed Consent	Obtain standard informed consent approved by IRB	Within 14 days of study start

Procedure	Comments	Schedule
Medical History	Includes history of present illness, prior cancer history as far as traceable, and past medical/ surgical history as far as relevant.	Within 14 days of study start
Physical Examination	Includes vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status	Within 14 days of study start
Concomitant Medications	Document concomitant medications as far as traceable.	Within 14 days of study start
Hematology	CBC with differential and platelet count	Within 14 days of study start
Biochemistry	Creatinine, bilirubin, SGPT or SGOT, uric acid	Within 14 days of study start
Pregnancy test	Serum or urine	Within 14 days of study start
Bone Marrow	Aspirate and/or biopsy. Flow cytometry if required to establish diagnosis.	Within 30 days of study start
MUGA or Echocardiogram	Assessment of QTc and cardiac ejection fraction	Within 30 days of study start
Immunophenotype	Assess ALL markers including CD22	Within 14 days of study start
Flow cytometry	CD22 expression	Within 14 days of study start
Optional: In vitro CMC-544 sensitivity studies (Pharmacokinetics)	CMC-544 saturation and survival studies	Within 14 days of study start

7.0 Evaluation during therapy

Procedure	Comments	Schedule
Physical Examination	Includes recording of vital signs, concomitant medications, adverse events, and performance status	Prior to each subsequent course.
Hematology	CBC with differential (if granulocytes > 1.0 x 10^9/L) and platelet count	1 to 3 times weekly during induction (courses 1 and/or 2) i.e. until achievement of response, then at least weekly during consolidation.

Procedure	Comments	Schedule
Biochemistry	Creatinine, bilirubin, SGPT or SGOT.	Weekly during induction (courses 1 and/or 2), then at least once every 2 weeks during consolidation.
Bone Marrow	Aspirate and/or biopsy.	Bone marrow at Day 14-21(+/- 3 days), then as indicated in course 1 to confirm response, and then every 1-2 courses to confirm response. Other marrow examinations as indicated. *No* bone marrow is necessary if non-response or progressive disease can be diagnosed from peripheral blood evaluation, or, in patients with a WBC < 0.3, if the bone marrow test is considered non-contributory by the Investigator. Cytogenetic studies *only* if abnormal prior to study and/or the additional information is considered of consequence. Cytogenetic studies may be assessed on any bone marrow at the discretion of the treating physician. Further bone marrow tests as indicated by development of peripheral blood counts.
ECGs	Assessment of QTc and cardiac ejection fraction	Patients with history of arrhythmias or angina will have ECGs performed prior to the start of the rituximab, once during the infusion, and within 2 hours post infusion. Rituximab infusion will be discontinued for any clinically significant cardiac arrhythmia. In addition, all patients should have 12-lead ECG assessments to evaluate the potential for QTc prolongation regarding CMC-544 therapy. ECGs should be collected prior to course 1 CMC-544.
Diagnostic evaluation		Patients with complaints of abdominal pain will be examined for any signs or symptoms of bowel obstruction and/or perforation. Appropriate radiologic tests and surgical consults will be performed as needed.
CD22 expression	If peripheral blast count > 5000	CD22 expression obtained pretreatment
Pharmacokinetics (CMC-544) (optional) (see the laboratory manual or processing instruction)	During Course 1	PK during course 1: Day 1 pre-dose, end of infusion, 3 hrs post, Day 8 pre-dose, end of infusion, 3 hrs post, and Day 15 pre-dose, end of infusion, 3 hrs post.

Patients are allowed to have hematology tests performed in outside laboratory facilities. Laboratory results will be obtained by the research nurse assigned to this study.

7.1 Post Treatment Evaluation

Patients will be evaluated 30 days post receiving the last treatment of CMC-544 to collect information regarding toxicity unless the patient receives further therapy. This could be done during a regular clinic or inpatient visit or by phone call (research nurse or physician) if patient cannot be physically present at MD Anderson.

8.0 Criteria for Response

8.1 Complete remission (CR): Disappearance of all clinical and/or radiologic evidence of disease. Neutrophil count $\geq$ 1.0 x10^9/L, platelet count $\geq$100x10^9/L, and normal marrow differential ($\leq$ 5% blasts).

8.2 Complete remission without recovery of counts (CRi): Peripheral blood and marrow results as for CR, but with incomplete recover of counts (platelets < 100 x 10^9/L; neutrophils < 1 x 10^9/L).

8.3 Partial remission (PR): Peripheral blood count recovery as for CR, but with decrease in marrow blasts of $\geq$ 50% and not more than 25% abnormal cells in the marrow.

8.4 Other: All other responses will be considered as failures.

9.0 Criteria for Removal from the Study

The Investigator may remove patients from the study for any of the following reasons:

9.1 Progressive disease. This is defined as a doubling of the peripheral blasts and an absolute increase of > 5 x 10^9/L.

9.2 Unacceptable adverse events/toxicities (any >/= grade 3 non-hematologic toxicity that does not at least resolve to < grade 2 or baseline).

9.3 Investigator thinks a change of therapy would be in the best interest of the patient.

9.4 If the patient has intercurrent, non-leukemia-related illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree and require discontinuation of protocol therapy.

9.5 Patient request.

9.6 Patient is non-compliant with protocol requirements.

The Principal Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to:

9.7 If the incidence or severity of adverse events indicates a potential health hazard to patients.

9.8 If the patient enrollment is unsatisfactory.

10.0 Reporting Requirements

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 **(Appendix A)** will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

Refer to **Appendix E** for Leukemia-Specific Adverse Event Recording and Reporting Guidelines. Only unexpected AEs will be recorded in the Case Report Form (CRF). The Principal Investigator will sign and date the PDMS Case Report Form toxicity pages per each patient at the completion of each course. Following signature, the Case Report Form will be used as source documentation for the adverse events for attribution.

Serious Adverse Event Reporting (SAE)
A serious adverse event is – any adverse drug experience occurring at any dose that 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 disability/incapacity – a substantial disruption of a person's 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, Office of Research Education and Regulatory Management (ORERM).

- 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 “University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to ORERM, regardless of attribution (within 5 working days of knowledge of the event). Hospitalizations for the management of any expected adverse events (previously described) will not have an expedited report but it will be included in the annual report via the SAE log.
- **All life-threatening or fatal events,** expected or unexpected, and regardless of attribution 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 ORERM.
- The MDACC “Internal SAE Report Form for Prompt Reporting” will be used for reporting to ORERM.
- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test 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 ORERM. This may include the development of a secondary malignancy.

(Please see **Appendix E** regarding data capturing of adverse events and adverse events source documentation.)

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager ORERM) 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.

11.0 Statistical Considerations

A total of up to 60 patients will be treated. The primary endpoint for efficacy is response which is defined as CR, CRi or PR.

The method of Thall [1995] will be employed to perform interim futility monitoring. The trial will be stopped early if: $Pr[\theta > 0.20 \mid data] < 0.10$. Where θ denotes the response rate. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is less than a 10% chance that the response rate is 20% or more, we will stop the trial for futility. We assume a prior distribution of θ ~beta(1,1). Stopping boundaries corresponding to this probability criterion are to terminate the trial if:

(# patients with CR, CRi, or PR) / (# patients evaluated)

$\leq$ 0/10, 1/17, 2/24, 3/31, 4/37

The operating characteristics for the futility monitoring rule are shown in the following table.

Operating Characteristics for Stopping Rule (PL=0.10)

Clinical Scenario	Early Stopping Probability	Achieved Sample Size (25th, 50th, 75th percentile)
Response rate is 0.1	0.79	10, 17, 37
Response rate is 0.2	0.24	40, 40, 40
Response rate is 0.3	0.044	40, 40, 40

Reference:

Thall, Peter F., Simon, R. and Estey, E.H. "Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes," Statistics in Medicine 14:357-379, 1995.

11.1 In an update of the data on October 6, 2010, 12 of the first 21 patients treated (57%) had achieved CR or Cri. This was achieved with minimal drug related side effects, and allowed several patients to proceed safely to allogeneic stem cell transplant. These data are very encouraging and if consistent in a larger number of patients may show that single agent CMC-544 therapy is superior to standard combination intensive chemotherapy with regard to safety and efficacy. We therefore propose to increase the total number of patients treated to 60 patients to allow a more accurate assessment of the response rate and to define more precisely predictive

factors for response and outcome with CMC-544 therapy. The analysis of predictive factors for response, durability of response, and survival will be conducted using standard statistical methods, and will be descriptive, for the purpose of guiding future large scale and pivotal trials with CMC-544 in ALL.

11.2 Following the update of January 7, 2011, it is proposed to treat 20 patients with a weekly schedule of CMC-544, to gain experience with efficacy and toxicity. This portion of the study should protect against an overall response rate < 40%. Therefore the study will stop early if the number of responses over number evaluable is: 0/7, 1/10, 2/14, and 3/17. Otherwise a total of 20 patients will be treated. The response and toxicity evaluations will be descriptive.

11.3 Following an update on December 2, 2011, the weekly schedule was assessed to demonstrate equal or better efficacy and perhaps less toxicity than the single dose every 3-4 weeks. In the first 15 evaluable patients, 8 (53%) achieved marrow CR. An additional 20 patients will be treated for a total of 40 patients to assess more precisely the response and toxicity rates with the weekly schedule.

12.0 References

1. Pui CH, Evans WE. Acute lymphoblastic leukemia. N Engl J Med 339: 605-615, 1998.

2. Faderl S, Jeha S, Kantarjian HM. The biology and therapy of adult acute lymphoblastic leukemia. Cancer 98: 1337-1354, 2003.

3. Bassan R, Gatta G, Tondini C, Willemze R. Adult acute lymphoblastic leukemia. Crit Rev Oncol/Hematol 50: 223-261, 2004.

4. 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 18: 547-561, 2000.

5. 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 101: 2788-2801, 2004.

6. Thomas DA, Kantarjian H, Smith TL, et al. Primary refractory and relapsed adult acute lymphoblastic leukemia. Cancer 86: 1216-1230.

7. Garcia-Manero G, Thomas DA. Salvage therapy for refractory or relapsed acute lymphocytic leukemia. Hematol Oncol Clin North Am 15: 163-205, 2001.

8. DiJosephJF, Armellino DC, BoghaertER, 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.

9. DiJoseph FJ, Dougher MM, Kalyandrug LB, Armellino DC, Boghaert ER, Hamann PR, Moran JK, and Damle NK. 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 12:242-249, 2006.

10. Damle NK. Tumor-targeted chemotherapy using immunoconjugates of calicheamicin. Expert Opin Biol Ther 2004;4:1445-52.
11. Lee M, DunneT, Chang C, eta l. Calicheamicins, a novel family of antibiotics. 4. Structural elucidations of calicheamicins. JAm Chem Soc1992;114:985-7.
12. Zein N, Sinha A, McGahren W, Ellestad G. Calicheamicin g1I: an antitumor antibiotic that cleaves doublestranded DNA site specifically. Science 1988;240: 1198-201.
13. Thorson J, Sievers E, AhlertJ, et al. Understanding and exploiting nature's chemical arsenal: the past, presentand future of calicheamicin research. Curr Pharm Des 2000;6:1841-79.
14. DiJoseph JF, Dougher MM, Armellino DC, Evans DY and Damle NK. Therapeutic potential of CD22-specific antibody-targeted chemotherapy using inotuzumab ozogamycin (CMC-544) for the treatment of acute lymphoblastic leukemia. Leukemia 21:2240-45, 2007.
15. Fayad L, Patel H, Verhoef G, et al. Safety and clinical activity of the anti-CD22 immunoconjugate inotuzumab ozogamycin (CMC-544) in combination with rituximab in follicular lymphoma or diffuse large b-cell lymphoma: Preliminary report of a phase 1/2 study. Blood, 112:Abst 266, 2008.

16. Czuczman MS, Grillo-Lopez AJ,White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999;17:268-76.

17. Coiffier B, HerbrechtR , Tilly H, et al. GELA study comparing CHOP and R-CHOP in elderly patients with DLCL: 3-year median follow-up with an analysis according to co-morbidity factors [abstract 2395]. Proc Am Soc Clin Oncol 2003; 22:596.

18. Wierda W, O'Brien S, Wang X et al. Characteristics associated with important clinical end points in patients with chronic lymphocytic leukemia at initial treatment. J Clin Oncol 27:1637-1643, 2009.

19. Tam C, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphomide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 112:975-980, 2008.

20. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphomide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 223:4070-4078, 2005.

21. Thomas D, 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 106:1569-80, 2006.

22. DiJoseph J, Dougher M, Kalyandrug L, 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 Can Res. 2006;12:242-249.

23. Wyeth investigator’s brochure: inotuzumab ozogamicin [WAY-207294].

24. Cheson B, Horning S, Coiffie R, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999;17:1244-1253.