Phase I/II Study of the Combination of Inotuzumab Ozogamycin (CMC-544) with Low-intensity Chemotherapy in Patients with Acute Lymphoblastic Leukemia (ALL)

Short Title: Inotuzumab Ozogamycin in ALL
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1.0 Objectives

1.1 Phase I: Determine the maximum tolerated dose (MTD) of inotuzumab ozogamycin in combination with low-intensity chemotherapy in elderly patients (age 60 or older) with ALL.

1.2 Phase II:
   a. Evaluate the efficacy of inotuzumab ozogamycin in combination with low-intensity chemotherapy in elderly patients with ALL. To evaluate the side effects of the treatment.
   b. Evaluate the regimen efficacy in refractory-relapsed ALL.

1.3 Primary Study Endpoint
   a. Phase I: Define the dose limiting toxicities (DLTs) and MTD.
   b. Phase II: Evaluate progression-free survival (PFS) in frontline elderly ALL.
   c. Evaluate response rate and survival in refractory-relapsed ALL.

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%.

A major determinant of prognosis in adult ALL is patient age. In particular, in multiple studies of adult ALL, older patients have a significantly worse outcome. This is primarily due to poor tolerance of intensity chemotherapy which results in ineffective delivery of induction-consolidation-maintenance chemotherapy, and to the high mortality during the periods of induction consolidation and maintenance.(6, 7, 8, 9). The potential addition of targeted nonmyelosuppressive therapy to effective low-intensity chemotherapy in older patients with ALL might improve their outcome. This has been the case when combining rituximab with chemotherapy in Burkitt Leukemia, and BCR-ABL tyrosine kinase inhibitors with chemotherapy in Philadelphia (Ph) chromosome positive ALL (10, 11). In particular a recent study in elderly Ph-positive ALL combining dasatinib and low-intensity chemotherapy in older patients produced very encouraging results (12).

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 (13, 14). Not many treatments are available for ALL salvage. In particular, older patients with ALL who relapse have a very poor prognosis and very limited options.

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, as mentioned earlier, 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 -- Inotuzumab Ozogamycin

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 (15-17). CD22 is a B-lymphoid lineage–specific differentiation antigen expressed on both normal and malignant B cells. Inotuzumab ozogamycin 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 (18-20). Inotuzumab ozogamycin 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 (16). In addition, inotuzumab ozogamycin had in vitro high activity against CD22 positive ALL cell lines (21). In the absence of the conjugated CalichDMH, G5/44, the targeting monoclonal antibody (mAb) in inotuzumab ozogamycin is ineffective in vivo as an antitumor agent in various preclinical models (15). Thus, inotuzumab ozogamycin is regarded as an antibody-targeted chemotherapy agent rather than an immunotherapeutic agent like rituximab. Largely due to its tumor-targeted, drug-delivery capability, inotuzumab ozogamycin is likely to have a better therapeutic index than that of conventional chemotherapeutic agents. Based on its potent antitumor activity in preclinical models, inotuzumab ozogamycin 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, inotuzumab ozogamycin 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 (23-24). 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 (25-28). In this study, rituximab may be added for patients with pre-B ALL, regardless of CD20 expression, since recent data indicates that chemotherapy can increase CD20 expression and since rituximab may have a positive effect even among patients with low expression of CD20 (< 20%).

2.3 Inotuzumab Ozogamycin in Refractory and Relapsed ALL
Since CD22 is universally and highly expressed in ALL, we proposed an investigator initiated study of inotuzumab ozogamycin in patients with refractory/relapsed ALL. Entry and exclusion criteria were standard. Pediatric patients were allowed after 10 adult patients were treated. The starting dose in adults and in pediatric was 1.3 mg/m2 IV x1. Courses could be repeated every 3-4 weeks. Subsequent doses in all patients were 1.8 mg/m2. Patients not responding after 2 cycles could be given rituximab.

A total of 34 patients have been treated so far. Their median age is 36 yrs (range 6-72). Seven patients were 60 years or older. Sixteen patients were females. Cytogenetics
were diploid in 10 patients, Ph-positive in 3 patients, translocation (4;11) in 5 patients, and other abnormalities in 16 patients. CD22 was expressed in ALL blasts in all patients tested. Four patients had extramedulary disease (bone, kidneys, testicles, CNS). The median number of courses so far is 2 (range 1-3). Patients received inotuzumab ozogamycin as salvage 1 in 9 patients, as salvage 2 in 16 patients and as salvage 3 or beyond in 8 patients. Seven patients had undergone allogeneic stem cell transplant prior to inotuzumab ozogamycin.

The percent of marrow blasts at the start of therapy ranged from 11% to 90%. Thirty-two of 34 patients had marrow blasts more than 30%.

Overall, 8 patients (24%) achieved CR and 9 patients (26%) achieved marrow CR (14 patients failed, 2 patients too early). Overall, 17 of 32 currently evaluable patients achieved CR or marrow CR = 53%. The median courses to response is 1 (range 1-2). At present, 10 patients underwent or are planned to undergo allogeneic stem cell transplant, 5 patients have actually undergone allogeneic stem cell transplant; 2 of them underwent allogeneic SCT as a second transplant post-inotuzumab ozogamycin response.

In summary, inotuzumab ozogamycin is, in our experience, the most active single-agent for the treatment of ALL.

2.4 Rationale for the Study Design
The low-intensity chemotherapy proposes to exclude anthracyclines from the chemotherapy regimen because of: 1) preclinical data suggesting that anthracyclines and inotuzumab ozogamycin may have synergistic hepatotoxicity; 2) many older patients have cardiac problems that preclude anthracyclines delivery; and 3) a benefit of adding anthracyclines in the setting of elderly ALL is not proven. 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 inotuzumab ozogamycin (targets CD22) and rituximab (targets CD20) with low-intensity chemotherapy in older patients with 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, the combined targeted therapy (rituximab and inotuzumab ozogamycin) 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 inotuzumab ozogamycin determined the phase II dose to be 1.8 mg/m² 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\(^{(21)}\). Phase II studies combining rituximab 375 mg/m\(^2\) on Day 1 and inotuzumab ozogamycin 1.8 mg/m\(^2\) on Day 2 were safe and effective in lymphomas\(^{(22)}\).

This study is a single arm study evaluating the combination of inotuzumab ozogamycin and low-intensity chemotherapy. The Phase I portion is designed to define the DLTs and MTD of the combination. The Phase II portion is designed to evaluate the efficacy of the combination as measured by PFS.

2.5 Proposal of the Study Treatment.

Patients with ALL age 60 or older will be eligible. The emphasis will be newly diagnosed patients. However, patients with relapsed-refractory ALL of any age are eligible, provided they are not eligible for regimens of higher priority. The treatment will consist of low-intensity hyper-CVAD. The hyper-CVAD cycles (cycles 1, 3, 5, and 7) will use cyclophosphomide at 50\% of the dose of standard hyper-CVAD, will eliminate anthracyclines, and will reduce dexamethasone to 50\% of the standard dexamethasone dose. To simplify the treatment delivery, vincristine will be given on Day 1 and 8 of the courses. The methotrexate ara-C cycles (cycles 2, 4, 6, and 8) will use methotrexate at 25\% of the standard hyper-CVAD dose, ara-C as 0.5 g/m\(^2\) x 4. Intrathecal chemotherapy will be for 8 doses (Days 2 and 8 of the first 4 courses). Rituximab may be given on Day 2 and 8 of the first 4 courses. Inotuzumab ozogamycin will be given on Day 3 of each of the first 4 courses. The POMP maintenance will be standard for 3
years.

In the Phase I portion an initial cohort of 6 subjects will be treated at the first dose level of inotuzumab ozogamycin: 1.3 mg/m² for cycle 1 followed by 0.8 mg/m² for subsequent cycles. Dose limiting toxicities (DLTs) will be collected for all 6 subjects. For the purpose of defining DLT, the first 28 day cycle will be used; however information on observed toxicities during subsequent cycles will be collected from all patients. No intrapatient escalation is allowed.

If there are no safety concerns and fewer than 2 of the 6 subjects have DLTs, the remaining subjects will be treated at the second dose level of inotuzumab ozogamycin: 1.8mg/m² for cycle 1, followed by 1.3 mg/m² for subsequent cycles. If there are no safety concerns and fewer than 2 out of 6 subjects have DLTs, then the remaining subjects will be treated at second dose level of inotuzumab ozogamycin.

However, if there are safety concerns or 2 or more DLTs at the second dose level, then the remaining subjects will be treated at first dose level.

Due to a recent review of patients treated via protocol 2010-0991 (section 2.8), patients were found to have a higher incidence of developing veno-occlusive disease of the liver (VOD) and recurrent thrombocytopenia. Therefore, in order to avoid these toxicities all phase II patients will receive a reduced dose of inotuzumab: 1.3mg/m² during induction and 1.0mg/m² during subsequent courses 2, 3, and 4.
2.6  **Update of status and inclusion of patients with refractory-relapsed ALL**

*(10/05/2012)*. At present 7 elderly patients with newly diagnosed pre-B ALL have been treated on study. All patients achieved CR. All patients achieved MRD-negative status at CR. There were no treatment related deaths. With a median follow-up of 4 months, no relapses have occurred. This early experience is very encouraging compared to our historical data.

In ALL salvage, we have used inotuzumab as a single agent in a single dose IV schedule (1.8 mg/m2) every 3-4 weeks, and as a weekly schedule. The experience in about 75 patients indicates a high marrow CR rate of 55%. However responses are short lasting and the median survival is only 6 months. In Philadelphia chromosome (Ph)-positive ALL, single agent tryrosine kinase inhibitors (TKIs) or chemotherapy combinations alone are associated with poor outcome. However combining chemotherapy with TKIs has resulted in a 5-year survival rate of 50% in newly diagnosed Ph-positive ALL and in durable remissions in Ph-positive ALL in salvage. Following discussions with the supporting drug company Pfizer, it was agreed to open the study in refractory-relapsed ALL. This is based on the hypothesis that if we see higher and more durable response rates and improved survival, this information may support a pivotal trial comparing the combination of chemotherapy plus inotuzumab to standard chemotherapy care.

2.7  **Update of the experience in refractory-relapsed ALL as of October 1, 2014.**
The original salvage experience was planned to treat 40 patients. At present 37 patients have been treated, 20 in first salvage and 17 in Salvage 2 and beyond. Overall, among 36 evaluable patients, 18 (50%) achieved CR, 7 (20%) had marrow CR, for an overall response rate of 25/36 = 69%. This is extremely encouraging and almost unprecedented in this setting, where the response rate with chemotherapy would be about 30-35%, and with inotuzumab about 40-50%. The estimated 1-year progression free survival is 56% and survival 45%. The historical experience suggests a median survival of 3-6 months. Among 19 patients in first salvage the estimated 15 month survival is 55%.

Considering this experience, we would like to expand the pilot salvage to 60 patients. This will allow us 1) to offer patients the best available care at present (until better options or until monoclonals become more readily available), 2) provide more precise estimates of the response rates and longer term outcome, 3) analyze factors associated with differences in outcome, and 4) provide broader information to design the potential future randomized trials of inotuzumab plus chemotherapy in ALL salvage for the purpose of FDA pivotal trials.

2.8 Update of the experience as of April 22, 2015

This protocol is a Phase I/II Study for elderly patients to receive a Combination of HyperCVD and Inotuzumab Ozogamycin. The phase I was done and was found to be safe then we moved to phase II and the drug was given at a dose of 1.8 mg/m² during the first cycle and at 1.3 mg/m² during subsequent 2 to 4. Among 33 patients enrolled in the
frontline, 2 patients developed veno-occlusive disease of the liver or VOD, and two additional patients in whom, there was a high suspicion but liver biopsies were not conclusive and unfortunately had to be taken off of the protocol. In addition, more than three quarters of the patients had recurring thrombocytopenia and that could be due to the drug per se. Therefore, in order to avoid these toxicities, minimize the myelosuppression and eliminate the VOD and in order to give the full 4 cycles to the patients where they can hopefully benefit in the long run we want to amend the protocol to reduce the dose of inotuzumab to 1.3 mg/m² during induction and 1.0 mg/m² during subsequent courses 2, 3 and 4.

2.9 Update of the experience as of October 8, 2015

We plan to amend the study and accrue 20 more patients. The results updated so far, after enrolling 52 patients are very positive with an objective response rate of 76% and a 1-year survival of 45%. Furthermore, the 2-year survival rate for patients in salvage 1 is 53%, which is better than any previous treatment. We therefore, request an amendment to the study so we can treat more patients. We are looking to enroll 20 more patients. That will give us more power to perform additional analysis including prognostic factor for outcome, multivariate analysis for response and survival, etc.

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,
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 effect or 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 (29). 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 (30). 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(30).

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(15,16,29).

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 Nonclinical 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

**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 venoocclusive 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 post baseline 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 (i.e., 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 [i.e., 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. Patients age 60 years or older with previously untreated ALL pre-B, Philadelphia chromosome (Ph-) negative ALL. Minimal prior therapy (less
than 1 week of steroids, vincristine, and/or 1 dose of anthracycline or alkylating agents) are allowed.

2. Zubrod performance status 0-3.

3. Adequate liver function (bilirubin ≤ 1.95 mg/dL and SGPT or SGOT ≤ 3 x upper limit of normal [ULN], unless considered due to tumor), and renal function (creatinine ≤ 2 mg/dL). Even if organ function abnormalities are considered due to tumor, the upper limit for bilirubin is ≤ 2.6 mg/dL and creatinine ≤ 3 mg/dL.

4. Provision of written informed consent.

5. Patients in first remission are eligible.

6. Patients with refractory-relapsed ALL of any age are eligible, provided they are not eligible for regimens of higher priority.

4.2 Exclusion Criteria:

1. Ph-positive ALL, Burkitt’s Leukemia or Lymphoma, T-cell ALL or lymphoblastic lymphoma.

2. Patient with active heart disease (NYHA class ≥ 3 as assessed by history and physical examination).

3. Patients with a cardiac ejection fraction (as measured by either MUGA or echocardiogram) < 40% are excluded.

4. Patients with active hepatitis are excluded.

5. Pregnant or breast-feeding women are excluded.
5.0 Treatment Plan

5.1 General

This is a single institution, Phase I/II study of the combination of inotuzumab ozogamycin with low-dose intensive chemotherapy in older patients (age 60 years or older) with untreated or minimally treated pre-B Ph-negative ALL. The phase I portion will determine the DLTs and MTD of the combination. The phase II portion will evaluate the efficacy of the regimen and the side effects.

Inotuzumab ozogamycin will be provided by Pfizer Corporation. Any unused or expired drug will be destroyed per institutional policy.

5.2 Treatment Schema

5.2.1 General: The treatment will consist of 8 induction – consolidation cycles of low-intensity therapy with hyper-CVAD alternating with methotrexate ara-C. Each induction – consolidation cycles is approximately 28 days. Delays in cycles are acceptable depending on recovery from cytopenias or other side-effects, socioeconomic situation, or patients or physician preference, in the best interest of the patients. These will not be considered as deviations unless delay is more than 3 months from the start of a cycle. Intrathecal prophylaxis will consist of 8 intrathecal doses given twice per cycle in the first 4 cycles. All patients may receive rituximab 375 mg/m² on Day 2 (± 2 days) and Day 8 (± 2 days) of each of the first 4 cycles. Rituximab will be administered to the patient, if the PI and/or treating physician thinks the patient will receive clinical benefit. However, if rituximab is not administered to the patient due to: lack of insurance coverage or due to
the PI and/or treating physician not ordering its administration, it will not result in a protocol deviation. If there is any change in a patient’s CD20 status or insurance coverage, the administration of rituximab, during cycles 1-4, will be at the discretion of the PI and/or treating physician. All inotuzumab ozogamycin treatment will be given at MD Anderson Cancer Center.

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.

The Phase I study will start with inotuzumab ozogamycin at dose level 1: Cycle 1: 1.3 mg/m² IV over approximately 1h on Day 3; and 0.8 mg/m² on Day 3 for subsequent cycles. Prior to advancing dose levels a cohort summary will be submitted to the Clinical Research Monitor (IND Office).

Dose limiting toxicities (DLTs) will be collected for 6 evaluable subjects. For the purpose of defining DLT, the first 28 day cycle will be used; however information on observed toxicities during subsequent cycles will be collected from all patients. No intrapatient escalation is allowed.

If there are no safety concerns and fewer than 2 of the 6 subjects have DLTs, the Phase II portion will begin and six patients will then be treated at the second dose level of inotuzumab ozogamycin: 1.3 mg/m² for cycle 1, followed by 1.0 mg/m² for subsequent
cycles. If there are no safety concerns and fewer than 2 out of 6 subjects have DLTs,
then the remaining patients will be treated at the second dose level.

However, if there are safety concerns or 2 or more DLTs at the second dose level, then
the remaining patients will be treated at first dose level.

**Definition of Dose limiting toxicities (DLT)**

Dose limiting toxicities will be according to the NCI CTEP criteria. A non-hematologic
DLT is defined as a clinically significant (as assessed by treating physician) Grade 3 or
4 adverse event or abnormal laboratory value (according to CTCAE criteria) assessed
by treating physician as related to study drug (and unrelated to disease progression,
intercurrent illness, or concomitant medications) occurring during the first 28 days on
study. A hematologic dose-limiting toxicity is defined as severe myelosuppression with
a hypoplastic marrow with less than 5% cellularity and no evidence of leukemia 42 days
from start of therapy. This will define severe and delayed myelosuppression not related
to persistent leukemia and likely related to treatment.

a. If grade 3-4 drug-related toxicities are observed in less than 2/6 at dose level 2 of
inotuzumab ozogamycin, the study will open broadly for the phase II at this
schedule.

b. If grade 3-4 drug-related toxicities are observed in 2/6 or more evaluable patients
at dose level 2 of inotuzumab ozogamycin, this dose level would exceed the
MTD, and the Phase II study will open at dose level 1 of inotuzumab ozogamycin
(please refer to above under 2.5). The Phase II portion will open broadly after
consultation with and approval of the IND Office and Medical Monitor, and in consultation with the Pfizer collaborators.

DLT will be defined as any of the following events that are judged by the investigator(s) to be at least possibly related to the study therapy.

**Non-Hematologic Dose-Limiting Toxicities:**

- Any Grade 4, or 5 non hematologic toxicity (or grade 3 toxicities lasting 7 days or more), with the exception of: nausea, vomiting, diarrhea or hypersensitivity reactions that in the opinion of the Investigator occurs in the setting of inadequate treatment with supportive care measures and lasts for less than 48 hours;
- Any unresolved drug-related toxicity that prevents (re) treatment for ≥2 weeks from the date of the next scheduled treatment

Recommended premedication before inotuzumab ozogamicin: 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.

Antibiotic prophylaxis is recommended. Antibacterial antibiotic may consist of ciprofloxacin, levaquin, vantin, or others. Antifungal prophylaxis will be fluconazole, voriconazole, or other antifungals. It is advised that -azoles antifungals be held one day...
before, on the day of vincristine, and one day after vincristine to reduce the possibility of neurotoxicity. Antiviral prophylaxis will consist of valtrex or others.

5.2.2 If given, administration of rituximab will be in accordance with the prescribing information or institutional standards. It will be given on Day 2 (± 2 days) of course 1 and inotuzumab ozogamycin on Day 3 (± 2 days) of course 1. Subsequent courses of rituximab (Day 2 ± 2 days) and inotuzumab ozogamycin (Day 3 ± 2 days) will be given separately on 2 consecutive days, but may both be given on Day 2 if felt appropriate.

5.2.3 Hyper-CVAD Cycles – Cycles 1, 3, 5, 7

Hyper-CVAD cycles will consist of the following:

a) Cyclophosphamide 150 mg/m² IV over approximately 3 hours twice a day for 3 days – Days 1, 2, and 3.

b) MESNA 300 mg/m²/d IV continuous infusion daily for approximately 24 hrs, starting approximately 1 hour prior to cyclophosphamide and completing by approximately 12 hrs after the last dose of cyclophosphamide.

c) Vincristine 2 mg IV on Day 1 (± 2 days) and 8 (± 2 days).

d) Dexamethasone 20 mg IV or PO on Days 1-4 (± 2 days) and 11-14 (± 2 days).

e) Rituximab 375 mg/m² IV on Day 2 (± 2 days) and 8 (± 2 days): this is for cycles 1 and 3, as well as cycles 2 and 4 (described later), if receiving rituximab, per PI and/or treating physician discretion.

f) The first 6 patients treated will receive inotuzumab ozogamycin at dose level one: 1.3 mg/m² IV over approximately 1 hour on Day 3 (±/− 2 days) of the first
cycle and 0.8 mg/m² for the following cycles for a total 4 inotuzumab ozogamycin doses. If DLT is not observed, six patients and all phase II patients will receive inotuzumab ozogamycin at dose level 2: 1.3 mg/m² IV on Day 3 (± 2 days) of cycle 1 and 1.0 mg/m² on Day 2 or 3 (± 2 days) of cycles 2, 3, and 4.

g) Intrathecal methotrexate 12 mg (6 mg via ommaya) on Day 2 (± 2 days) – cycles 1, 2, 3, and 4; intrathecal ara-C 100 mg on Day 8 (± 2 days); total 8 intrathecals.

h) Peg-filgrastim (neulasta) 6 mg subcutaneously on Day 4 (± 2 days). Filgrastim may substitute for peg-filgrastim at an approximate dose of 5-10 mcg/kg daily (to accommodate vial size) starting Day 4 (± 2 days) or as indicated until recovery of granulocyte count.

5.2.4 Methotrexate, Ara-C Cycles – Cycles 2, 4, 6, and 8

The methotrexate –ara-C cycles will consist of the following:

a) Methotrexate 50 mg/m² IV over approximately 2 hours followed by 200 mg/m² continuous infusion over approximately 22 hours on Day 1 total duration approximately 24 hours.

b) Ara-C 0.5 g/m² IV over approximately 3 hours twice a day x 4 doses – Days 2 and 3.

c) Rituximab 375 mg/m² IV on Day 2 (± 2 days) and 8 (± 2 days) of cycles 2 and 4, if receiving rituximab, per PI and/or treating physician discretion.

d) The first 6 patients treated will receive inotuzumab ozogamycin at a dose of
1.3 mg/m² IV over approximately 1 hour on Day 3 (+/- 2 days) of the first cycle and 0.8 mg/m² for the following cycles (total 4 inotuzumab ozogamycin doses). If DLTs not observed, six patients and all phase II patients will receive inotuzumab ozogamycin 1.3 mg/m² IV on Day 3 (+ 2 days) of cycle 1 and 1.0 mg/m² on Day 2 or 3 (+ 2 days) of cycles 2, 3, and 4.

e) Peg-filgrastim (neulasta) 6 mg subcutaneously on Day 4 (± 2 days).
Filgrastim may substitute for peg-filgrastim at an approximate dose of 5-10 mcg/kg daily (to accommodate vial size) starting Day 4 (± 2 days) or as indicated until recovery of granulocyte count.

f) Citrovorum rescue 50 mg IV or PO followed by 15 mg IV or PO every 6 hours for 8 doses beginning 12 hrs ± 2 hrs post MTX completion, i.e. approximately 36 hours from start of MTX.

g) Check MTX levels around time 0h, 24h and 48h post completion of MTX unless methotrexate cleared:

1) if > 20 µM at time 0, hold cytarabine and repeat level; if continues to be > 20 µM reduce cytarabine to 0.25 g/m² IV over 2 hours every 12 hours for 4 doses on days 2,3. Begin citrovorum rescue as described above.

2) if > 1 µM at 24hrs or > 0.1 µM at 48 hours, increase citrovorum rescue to 50 mg IV or PO every 6 hrs until serum methotrexate level is < 0.1 µM.

Clearance to levels 0.15 µM or less is acceptable in patients with normal renal function.

3) Citrovorum rescue may be increased further for elevated methotrexate levels or delayed clearance.
5.2.5 Intrathecal Prophylaxis

Patients will receive a total of 8 intrathecal prophylaxis doses with methotrexate alternating with ara-C on Days 2 (± 2 days) and 8 (± 2 days) of each of the first 4 courses – total 8 intrathecals. Other changes in intrathecal schedules are allowed as indicated by patient condition. Patients with CNS leukemia will be treated with therapeutic intrathecal therapy as per standard of care. This usually consists of twice weekly intrathecal until CSF negative for at least 4 weeks then weekly intrathecals for 2 months, then intrathecals every other week for 2 months, then intrathecals monthly to complete a total of 1 year of therapy.

5.2.6. Antibiotic Prophylaxis

Antibiotics prophylaxis is recommended. Antibacterial antibiotic may consist of ciprofloxacin, levaquin, vantin, or others. Antifungal prophylaxis will be fluconazole, voriconazole, or other antifungals. It is advised that azoles antifungals be held one day before, on the day of vincristine, and one day after vincristine to reduce the possibility of neurotoxicity. Antiviral prophylaxis will consist of valtrex or others.

5.2.7 Suggested Standard Dose Reductions/Modifications:

a) Vincristine 1 mg IV days 1 and 8 (50% reduction).
   
   • Bilirubin > 2.6 g/dl and ≤ 3.9 g/dl
   
   • Clinically significant grade 2 peripheral neuropathy persisting greater than 2 weeks.
• Eliminate vincristine for grade 3-4 peripheral neuropathy, including grade 3-4 ileus suspected to be related to vincristine, bilirubin > 3.9 g/dL.

b) Methotrexate:

• Consider reduction by 25%-50% for grade 3 or worse mucositis with previous methotrexate course.

• Reduce by 50% for calculated creatinine clearance 10-50 ml/min, if < 10 ml/min, hold methotrexate.

• Reduce by 25% to 75% for delayed excretion and/or nephrotoxicity with previous methotrexate course.

• Reduce by 50% for pleural effusion or ascites (drain effusion if possible).

All patients should have a chest radiograph prior to each course of methotrexate and cytarabine.

c) Other modifications of drug schedules may be implemented if judged to be in the best clinical interest of the patient after discussion with PI or at the discretion of the treating physician. This includes delays in chemotherapy cycles because of persistent myelosuppression, other side effects, patient request, or other reasons.

d) Inotuzumab Ozogamycin

Patients with inotuzumab ozogamycin associated complications (prolonged thrombocytopenia, grade 3-4 liver toxicity) will receive subsequent doses of inotuzumab ozogamycin at a 25% dose reduction: for patients enrolled on the Phase I portion or first dose level: -1 level will be 1 mg/m²; -2 dose level will be 0.75 mg/m². For patients enrolled on the Phase II portion or second
dose level: -1 level will be \(-0.8\) mg/m\(^2\); -2 dose level will be - 0.5 mg/m\(^2\).

5.2.8 **Maintenance Therapy with POMP.**

Maintenance therapy will be for 3 years. This will consist of:

a) 6-Mercaptopurine 50 mg orally BID
b) Methotrexate 10 mg/m\(^2\) orally weekly
c) Vincristine 2 mg IV monthly for 1 year
d) Prednisone 50 mg orally daily x 5 every month for 1 year.

5.2.9 **Suggested Maintenance Chemotherapy Dose Adjustments are as Below:**

<table>
<thead>
<tr>
<th>Level</th>
<th>VCR (mg)</th>
<th>Prednisone (mg)</th>
<th>6-Mercaptopurine</th>
<th>Methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>50</td>
<td>50 mg BID daily</td>
<td>10 mg/m(^2) weekly</td>
</tr>
<tr>
<td>-1</td>
<td>1</td>
<td>40</td>
<td>50 mg daily</td>
<td>7.5 mg/m(^2) weekly</td>
</tr>
<tr>
<td>-2</td>
<td>0</td>
<td>30</td>
<td>50 mg daily</td>
<td>5 mg/m(^2) weekly</td>
</tr>
<tr>
<td>-3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a) Prednisone
   - Dose should remain at 50 mg unless steroid myopathy or other significant toxicity occurs.
   - Prednisone not required to be dose adjusted for hyperglycemia.

b) Vincristine
   - Decrease by one dose level for grade 2 peripheral neuropathy persisting longer than 2 weeks.
• Discontinue for grade 3 or greater peripheral neuropathy persisting longer than 2 weeks.

c) Dose reductions for 6-Mercaptopurine and Methotrexate for Grade 3 myelosuppression or worse, or for Grade 3 or worse non-myelosuppression complications. May interrupt treatment and resume at -1 level when toxicity resolved to Grade 1 or better.

d) Other dose modifications may be implemented if judged to be in the best clinical interest of the patient after discussion with principal investigator or at the discretion of the treating physician. This includes delays in chemotherapy cycles because of persistent myelosuppression, other side effects, patient request, or other reasons.

5.2.10 Treatment of Minimal Residual Disease

Marrow studies will be done periodically during consolidation and maintenance using multi-parameter flow cytometry. Patients with persistent minimal residual disease (MRD; more than 0.1% after consolidations) may be offered therapy for minimal residual disease with inotuzumab ozogamycin 0.8 mg/m² every 3 to 4 weeks for up to 6 doses. In them POMP maintenance will not be given. Marrow studies will be performed every 2 cycles for MRD (multiparameter flow cytometry), and then every 3 months for a year or until relapse, whichever comes first.

Additional cycles of inotuzumab therapy may be administered, for minimal residual disease, provided that the patient meets the following criteria on Day 1 of each cycle:
- ANC count ≥ 0.75x10^9/L
- Platelets ≥ 75x10^9/L
- Non-hematologic toxicity recovered to ≤ grade 1
- Normal serum total bilirubin required for cycles 3 through 6
- No evidence of progressive disease

**Dose modifications:** If on Day 1 of a new cycle, the patient does not meet criteria for dosing for treatment of MRD, the patient may be delayed for up to 8 weeks to allow for recovery. If the patient does not meet criteria for dosing for treatment of MRD following max of 8 weeks recovery, inotuzumab ozogamycin will be discontinued, or considered at a lower dose of 0.5 mg/m² if in the patient best interest.

### 5.2.11 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.

### 5.3 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.

Prophylactic antibiotics, antifungals, and antiviral agents as discussed above are recommended; however, the use of these or other drugs will be left to the treating physician’s discretion. Antifungal prophylaxis with azoles should not start until at least 24 hours after completion of the last inotuzumab ozogamycin infusion, and should be avoided on Day -1, 0, and +1 of vincristine.

### 6.0 Pretreatment Evaluation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Comments</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>Obtain standard informed consent approved by IRB</td>
<td>Within 14 days of start of treatment</td>
</tr>
<tr>
<td>Medical History</td>
<td>Includes history of present illness, prior cancer history as far as traceable, and past medical/surgical history as far as relevant.</td>
<td>Within 14 days of start of treatment</td>
</tr>
<tr>
<td>Physical Examination</td>
<td>Includes vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status</td>
<td>Within 14 days of start of treatment</td>
</tr>
</tbody>
</table>
### Procedure | Comments | Schedule
--- | --- | ---
Concomitant Medications | Document concomitant medications as far as traceable. | Within 14 days of start of treatment
Hematology | CBC with differential and platelet count | Within 14 days of start of treatment
Biochemistry | Creatinine, bilirubin, SGPT or SGOT, uric acid | Within 14 days of start of treatment
Pregnancy test | Serum or urine | Within 14 days of start of treatment
Bone Marrow | Aspirate and/or biopsy. Flow cytometry if required to establish diagnosis. | Within 30 days of start of treatment
MUGA or Echocardiogram and ECG | Assessment of QTc and cardiac ejection fraction | Within 30 days of start of treatment
Immunophenotype | Assess ALL markers including CD22 | Within 14 days of start of treatment

### 7.0 Evaluation During Therapy

| Procedure | Comments | Schedule |
--- | --- | ---
Physical Examination | Includes vital signs (temperature, heart rate, respiratory rate, blood) | Within 1 week before **Day 1 of each study cycle** |
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Comments</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant Medications</td>
<td>Document concomitant medications</td>
<td>Within 1 week before Day 1 of each study cycle and at each study visit during maintenance.</td>
</tr>
<tr>
<td>Adverse event assessment</td>
<td></td>
<td>Within 1 week before Day 1 of each study cycle and at each study visit during maintenance.</td>
</tr>
<tr>
<td>Hematology</td>
<td>CBC with differential (if granulocytes &gt; 1.0 x 10^9/L) and platelet count</td>
<td>1 to 3 times weekly during induction (courses 1 and/or 2) i.e. until achievement of response, then at least every 1-2 weeks during consolidation, then every 2-4 weeks during maintenance.</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>Creatinine, bilirubin, SGPT or SGOT.</td>
<td>Weekly during induction (courses 1 and/or 2), then at least once every 2-4 weeks during consolidation, then every 1-2 months during maintenance.</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>Aspirate and/or biopsy.</td>
<td>Bone marrow at Day 14-21(+/− 7 days), then as indicated in course 1 to confirm response, and then every 2-4 cycles of consolidation and every 3 months during maintenance to confirm response. Bone</td>
</tr>
<tr>
<td>Procedure</td>
<td>Comments</td>
<td>Schedule</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>marrow analysis for MRD by multiparameter flow cytometry with marrow exam if indicated. Other marrow examinations as indicated. Patients with positive MRD during maintenance who will receive inotuzumab ozogamycin for MRD will have the bone marrows done every 2 cycles x 2 then every 3 months for 1 year or until relapse whichever comes first. Marrow studies by the 2(^{nd}) year in CR will be done every 3-6 months 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 &lt; 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</td>
</tr>
<tr>
<td>Procedure</td>
<td>Comments</td>
<td>Schedule</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tests as indicated by development of peripheral blood counts.</td>
</tr>
<tr>
<td>ECGs</td>
<td>Assessment of QTc</td>
<td>Patients with history of arrhythmias or angina will have ECGs performed prior to the start of therapy. <strong>Other ECGs during therapy will be done as indicated by the clinical condition.</strong></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>All patients should have a chest x-ray prior to each course of methotrexate and cytarabine</td>
<td>Within 1 week before <strong>Day 1 of Cycles 2, 4, 6, and 8</strong></td>
</tr>
</tbody>
</table>

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

Clinical constraints that preclude sampling or assessments will not be considered protocol deviations.

All protocol specific data will be entered into PDMS/CORe
7.1 Post Treatment Evaluation

Post treatment evaluation will be performed about 30 days (+/- 3 days) after the last
dose of study drug(s) as indicated by clinical condition to assess for potential relapse or
for treatment related complications. 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 ≥ $1.0 \times 10^9 /L$, platelet count ≥ $100 \times 10^9 /L$, and
normal marrow differential (< 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 < $100 \times 10^9 /L$;
neutrophils < $1 \times 10^9 /L$).

8.3 Partial remission (PR): Peripheral blood count recovery as for CR, but with
decrease in marrow blasts of ≥ 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 $> 5 \times 10^9/L$.

9.2 Unacceptable adverse events/toxicities (any $\geq$ grade 3 non-hematologic toxicity that does not at least resolve to $<\text{ grade 2 or baseline}$) within 2 months.

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 repetitively 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 4.3 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

Only unexpected AEs will be recorded in the Case Report Form (CRF). The Principal Investigator will review toxicity reports 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)**

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 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, IND Office.

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

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

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory 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 IND Office. This may include the development of a secondary malignancy.

**Reporting to FDA:**

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.
It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

11.0 Statistical Considerations

11.1 A total of up to 60 patients with newly diagnosed ALL will be treated. The primary endpoint for efficacy is event-free survival at 2 years.

Based on the MD Anderson experience in older ALL treated with hyper-CVAD the estimated 2 year event-free survival (EFS) is <30%. We would like to improve the estimated 2 year EFS by at least 50%. A target 2 year EFS rate of at least 45% or more would be favorable. We will treat a total of 60 older patients with newly diagnosed ALL and compare their outcome to previous experience.

11.3 Trial conduct:

The Department of Biostatistics will provide and maintain a website (“Clinical Trial Conduct”) for enrolling patients on this study and evaluating the monitoring rules described below. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology.
Personnel responsible for enrolling patients on trials will be trained in the use of the trial website, with emphasis on the importance of timely updating of follow-up times and recording of events. The monitoring rules described below will be automatically evaluated each time patient data are updated on the trial website. If the stopping rule is met, the study statistician, research nurse, and principal investigator will each receive an email notification that the stopping boundary has been met.

11.4 Statistical Considerations:

This is a single arm, open label, phase I/II study to assess the MTD and the efficacy of Inotuzumab Ozogamycin (CMC-544) plus low-intensity chemotherapy in older patients (age 60 or order) with ALL.

a. The phase I portion will define the DLTs and MTD of the combination. Six patients will be treated at dose level 1 of inotuzumab ozogamycin. If DLTs are observed in less than 2 out of 6 patients treated, six additional patients will be treated at dose level 2 of inotuzumab ozogamycin. If DLTs are observed in < 2/6 patients treated, the phase II portion opens at dose level 2. If DLTs are observed in 2 or more out of 6 patients treated, the Phase II portion will open at dose level 1 of inotuzumab ozogamycin.

b. Phase II portion: The primary endpoint is progression free survival (PFS). A maximum of 60 new patients will be accrued from MDACC at a rate of 2 to 4 patients per month.

c. Study portion in refractory-relapsed ALL: In this component of the protocol, we will treat up to 40 patients. The historical expectations in patients in salvage 3 or
worse, which constitute the majority of the patients, is as follows: 1) with intensive chemotherapy, the expected CR rate is < 10% and median survival < 2 months; and 2) with inotuzumab, the expected marrow CR rate is 30% and the median survival 3 months. The statistical results will be descriptive, defining the precise CR and marrow CR rate in refractory-relapsed ALL (mostly in salvage 3 or worse) and the median survival and 1 year survival rate. These results will be compared descriptively to these two historical data.

d. As of October 1, 2014, 37 patients with refractory relapsed ALL were treated in the Phase II portion of the study. Their overall response rate is 67%, 1-year PFS 56%, and 1-year survival 45%. Because of these encouraging results, we will increase the number of patients treated with refractory-relapsed ALL to 60, to allow better estimates of outcome and better designs of future pivotal trials comparing the combination of inotuzumab plus chemotherapy to either modality. This will increase the overall accrual to 126 patients.

e. As of October 8, 2015, after enrolling 52 patients with relapsed/refractory ALL, the results are very positive with an objective response rate of 76% and a 1-year survival of 45%. Furthermore, the 2-year survival rate for patients in salvage 1 is 53%, which is better than any previous treatment. We therefore, we will increase accrual for patients with relapsed-refractory ALL by 20 more patients. That will give us more power to perform additional analysis including prognostic factor for outcome, multivariate analysis for response and survival, etc. Total accrual will be increased to 146 patients.
11.4.1 Efficacy monitoring

Bayesian time-to-event model [1] will be used to monitor progression free survival.

Historical data showed that the 2-year PFS for standard treatment was less than 15% and we assume the new combination treatment can improve this rate by 10%, which corresponds to a median time to progression (TTP) of 8.76 months for standard treatment and a 3.24 months increase of the new treatment (the median TTP of the new treatment is 12 months).

Let $T_e$ and $T_s$ represent the TTP for the new treatment and the standard treatment, respectively. We assume $T_e|\mu_e$ and $T_s|\mu_s$ follow an exponential distribution with median $\mu_e$ and $\mu_s$, respectively. We further assume that the prior for $\mu_s$ follows Inverse Gamma (IG) (50, 429) to reflect our knowledge of median TTP from the historical data of standard treatment, which has a mean of 8.76 months and a variance of 1.60. The prior for $\mu_e$ is assumed to be IG (3, 17.5), which has the same mean as $\mu_s$ but with a much larger variance to reflect much greater uncertainty about the median TTP of the new combination treatment.

The interim monitoring will be first conducted after the first 10 patients have been enrolled and then be repeated every three months. The study will be stopped early if, based on the available data, we have little reason to believe that the median TTP of the new combination treatment is 3.24 months or more than that of standard treatment. Formally, we’ll stop the study early if
P(Me>M_s+3.24|data)<0.03

That is, if there is less than 3% chance the median TTP of the new combination treatment is 3.24 months more than that of standard treatment, the trial will be stopped.

The operating characteristics of this decision rule are shown in Table 1:

<table>
<thead>
<tr>
<th>True Median TTP (Months)</th>
<th>P(Stop)</th>
<th>Mean number of Pts (25%, 75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.99</td>
<td>30.89 (21, 41)</td>
</tr>
<tr>
<td>8.76</td>
<td>0.44</td>
<td>49.90 (41, 60)</td>
</tr>
<tr>
<td>12</td>
<td>0.052</td>
<td>58.77 (60, 60)</td>
</tr>
<tr>
<td>15</td>
<td>0.016</td>
<td>59.32 (60, 60)</td>
</tr>
</tbody>
</table>

11.4.2 Safety monitoring

Toxicities will be monitored using the method of Thall, Simon, and Estey [2].

Toxicity is defined as non-hematologic grade 3 or 4 toxicities during the first course. We would like to control the rate of non-hematologic grade 3/4 toxicities to be lower than 20%. Using this information a non-informative flat prior distribution of Beta (0.4, 1.6) was chosen for the new combination treatment.
The interim monitoring will be first conducted after the first 10 patients have been evaluated and then be repeated continuously. The monitoring rule for toxicity is $\Pr(\theta_{E, \text{Tox}} > 0.2 \mid \text{data}) > 0.90$, where $\theta_{E, \text{Tox}}$ is the proportion of any grade 3 or 4 non-hematologic toxicities. That is, the trial will be terminated if at any time during the study there is a more than 90% chance that the average rate of grade 3 or 4 non-hematologic adverse events is more than 20%.

The stopping boundaries, based on these assumptions and monitoring conditions are shown in Table 2. For example, accrual will be stopped if 5 or more patients experience toxicity among the first 10 patients treated or if 6 or more patients experience toxicity in the first 14 patients.

<table>
<thead>
<tr>
<th># Grade 3 or 4 toxicity</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>10</td>
<td>14</td>
<td>18</td>
<td>22</td>
<td>26</td>
<td>30</td>
<td>34</td>
<td>38</td>
<td>42</td>
<td>46</td>
<td>50</td>
<td>55</td>
<td>59</td>
</tr>
</tbody>
</table>

Table 3 shows the operating characteristics for this stopping rule based on 10000 simulations.

<table>
<thead>
<tr>
<th>True Probability</th>
<th>Stop</th>
<th>Trial Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>0.10</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>0.2</td>
<td>51</td>
<td>60</td>
</tr>
<tr>
<td>0.30</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>0.35</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

The endpoints of PFS and toxicities are highly correlated and the overall stopping probability of the trial will be higher than it is indicated in the operating characteristics (OC) tables. That is to say, the true operating characteristics will be more conservative (safer) than the current OC tables. Since the power in the table at the target (PFS=12 months) is very high (power=1-0.05=95%), even though the actual power will be decreased, it should still be acceptable.

All calculations were performed using Multc99 and onearmTTE v2.0.0.3.2.

**11.4.3 Analysis Plan**

Kaplan and Meier product limit method will be used to estimate the PFS and OS along with the 95% confidence intervals for the median PFS and median OS. Univariate and multivariate Cox proportional hazards regression models will be used to identify prognostic factors for PFS and OS. Adverse events will be summarized and toxicity rate will be estimated with a 90% credible interval.

12.0 References


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