METHODS OF TREATING ACUTE MYELOID LEUKEMIA (AML) WITH COMBINATIONS OF ANTI-CD200 ANTIBODIES, CYTARABINE, AND DAUNORUBICIN

The present disclosure provides methods for treating hematological malignancies (e.g., AML) using an effective amount of an anti-CD200 antibody, or antigen-binding fragment thereof, an anti-metabolic agent (e.g., cytarabine), and a topoisomerase inhibitor (e.g., daunorubicin).
METHODS OF TREATING ACUTE MYELOID LEUKEMIA (AML) WITH
COMBINATIONS OF ANTI-CD200 ANTIBODIES,
CYTARABINE, AND DAUNORUBICIN

RELATED APPLICATIONS

This application claims the benefit of the priority date of U.S. Provisional Application No. 62/409,134, which was filed on October 17, 2016. The contents of this provisional application is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 11, 2017, is named AXJ-229PC_SL.txt and is 17,430 bytes in size.

BACKGROUND

Acute myeloid leukemia (AML) is a biologically heterogeneous disease of the hematopoietic system characterized by the accumulation and expansion of immature myeloid cells in the bone marrow. The standard treatment for AML for 30 years has involved a combination of anthracycline-based chemotherapy combined with continuous infusion of cytarabine, but is associated with significant toxicities. Though a respectable portion of younger patients can have long-term Disease-Free Survival (DFS) with this therapy, this benefit in elderly patients has not been seen with the exception of core-binding factor (CBF) AML.

Advances in cytogenetics and molecular studies have allowed better classification of AML in regards to prediction of response to therapy and overall prognosis. The European LeukemiaNet (ELN) has utilized these advances to define and group subsets of AML in regards to prognostic risk. However, age remains a major risk factor in regards to outcomes in AML, where elderly patients (> 60 years) fare worse than younger patients with similar cytogenetics and molecular risk. Specifically, the five-year survival rate for patient over the age of 60 is
below 20%. This is thought to be due to increased co-morbidities, increased toxicity with conventional chemotherapy, and increased disease resistance to chemotherapeutic agents.

A potential target for immunomodulation is CD200, an Ig superfamily type I transmembrane glycoprotein, expressed on a variety of cells both of hematopoietic origin (myeloid and lymphoid) as well as of non-hematopoietic origin. CD200 is a regulator of the immune checkpoint and is widely distributed on a variety of tissues, including B-cells, active T-cells, as well as certain vascular endothelia, kidney, and placenta cells. The CD200 receptor, CD200R, is mainly expressed on myeloid cells, T- and B-cells, and polarized Th2 cells. Interaction of CD200 and CD200R causes an immunosuppressive signal leading to inhibition of macrophages, induction of regulatory T cell, and switching of cytokine profiles.

CD200 is overexpressed in multiple tumor types, including AML, and this increased expression is associated with worse outcomes. Damiani and colleagues showed CD200+ AML patients have a two-fold lower probability to attain a complete response (CR); overall survival (OS) was also decreased in this subset and correlated with intensity of CD200 expression. Patients with otherwise favorable molecular markers (e.g., mutated NPM1 or wildtype FLT3) were found to have worsening of OS with CD200 expression. An additive effect of CD200 on the negative impact of OS in patients with unfavorable cytogenetics was also observed (Damiani et al., 2015) Oncotarget. Published data has found that CBF patient samples have high expression of CD200 (Tonks et al., 2007) Leukemia, 21(3):566-8).

Appropriate dosing of medications, such as antibody preparations, is a critical factor in their administration to patients and in the efficacy of medications. Accordingly, it is the object of the present disclosure to provide improved methods for treating AML patients with anti-CD200 antibodies.

SUMMARY

Provided herein are methods for treating at least one hematological malignancy (e.g., AML) in a human subject comprising administering a therapeutically effective amount of an anti-CD200 antibody, or antigen binding fragment thereof, a anti-metabolic agent, and a
topoisomerase inhibitor, according to a particular clinical dosage regimen (i.e., at a particular dose amount and according to a specific dosing schedule).

An exemplary anti-CD200 antibody is samalizumab. An exemplary anti-metabolic agent is cytarabine. An exemplary topoisomerase inhibitor is daunorubicin.

In one embodiment, the anti-CD200 antibody antigen-binding fragment thereof, comprises a heavy chain variable region CDR1 having the sequence set forth in SEQ ID NO: 7, a heavy chain variable region CDR2 having the sequence set forth in SEQ ID NO: 8, a heavy chain variable region CDR3 having the sequence set forth in SEQ ID NO: 9, a light chain variable region CDR1 having the sequence set forth in SEQ ID NO: 4, a light chain variable region CDR2 having the sequence set forth in SEQ ID NO: 5, and a light chain variable region CDR3 having the sequence set forth in SEQ ID NO: 6.

In another embodiment, the anti-CD200 antibody comprises heavy and light chain variable regions having the sequences set forth in SEQ ID NOs: 13 and 12, respectively.

In another embodiment, the anti-CD200 antibody comprises heavy and light chains having the sequences as set forth in SEQ ID NOs: 11 and 10, respectively.

In another embodiment, the anti-CD200 antibody, or antigen binding fragment thereof, comprises the CDR1, CDR2 and CDR3 domains of a heavy chain variable region having the sequence set forth in SEQ ID NO: 13, and the CDR1, CDR2 and CDR3 domains of a light chain variable region having the sequence set forth in SEQ ID NO: 12.

In another embodiment, the anti-CD200 antibody, or antigen binding fragment thereof, comprising the CDR1, CDR2 and CDR3 domains of a heavy chain region having the sequence set forth in SEQ ID NO: 11, and the CDR1, CDR2 and CDR3 domains of a light chain region having the sequence set forth in SEQ ID NO: 10.

In another embodiment, the anti-CD200 antibody is a human antibody. In another embodiment, a composition of anti-CD200 antibodies, or fragments thereof, is provided, wherein the composition (e.g., a sterile composition) comprises a pharmaceutically acceptable carrier.

In one aspect, methods of treating acute myeloid leukemia (AML) by administering an anti-CD200 antibody (e.g., samalizumab), or antigen-binding fragment thereof, in combination with a topoisomerase inhibitor (e.g., daunorubicin) and anti-metabolic agent (e.g., cytarabine) are provided herein. In one embodiment, the AML is a Core-binding factor (CBF) positive AML.
In a particular embodiment, the CBF AML is a t(8;21)(q22;q22) abnormality, pericentric inversion of chromosome 16 [inv(16)(pl3.1q22)], or balanced translocation t(16;16)(pl3.1;q22).

In one embodiment, the anti-CD200 antibody is administered at a dose of about 300 mg/m² to about 600 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 300 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 400 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 500 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 600 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 700 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 800 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 900 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 1000 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 1100 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 1200 mg/m².

In one embodiment, cytarabine is administered at a dose of about 50 to about 200 mg/m². In another embodiment, cytarabine is administered at a dose of about 100 mg/m² to about 1000 mg/m². In another embodiment, cytarabine is administered at a dose of about 100 mg/m², 200 mg/m², 300 mg/m², 400 mg/m², 500 mg/m², 600 mg/m², 700 mg/m², 800 mg/m², 900 mg/m², 1000 mg/m², 1100 mg/m², or 1200 mg/m². In a particular embodiment, cytarabine is administered at a dose of about 100 mg/m². In another particular embodiment, cytarabine is administered at a dose of about 1000 mg/m².

In one embodiment, daunorubicin is administered at a dose of about 10 mg/m² to about 100 mg/m². In another embodiment, daunorubicin is administered at a dose of about 10 mg/m², 20 mg/m², 30 mg/m², 40 mg/m², 50 mg/m², 60 mg/m², 70 mg/m², 80 mg/m², 90 mg/m², 100 mg/m², 110 mg/m², 120 mg/m², 130 mg/m², 140 mg/m², or 150 mg/m². In a particular embodiment, daunorubicin is administered at a dose of about 60 mg/m².

In another aspect, methods of treating a patient with AML are provided, wherein the method comprises administering an anti-CD200 antibody, or antigen-binding fragment thereof, cytarabine, and daunorubicin, wherein the method comprises an induction phase followed by a consolidation phase, wherein:
(a) 300 mg/m² or 600 mg/m² of the anti-CD200 antibody, or antigen-binding fragment thereof, 60 mg/m² of daunorubicin, and 100 mg/m² of cytarabine are administered during the induction phase,
(b) 300 mg/m² or 600 mg/m² of the anti-CD200 antibody, or antigen-binding fragment thereof, is administered on Day 1 of Cycle 1 of the consolidation phase and every 21 days thereafter, and 1000 mg/m² of cytarabine is administered on Days 2, 4, and 6 of Cycle 1 of the consolidation phase; and
(c) 1000 mg/m² of cytarabine is administered twice on Days 1, 3, and 5 of Cycles 2-4 of the consolidation phase.

In one embodiment, the induction phase is at least 24 days.

In another embodiment, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at least three times, daunorubicin is administered at least three times, and cytarabine is administered at least seven times in the induction phase.

In another embodiment, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at 125 mL/hr on Days 1, 3, and 24 of the induction phase. In another embodiment, daunorubicin is administered intravenously over 15 minutes on Days 4-6 of the induction phase. In another embodiment, cytarabine is administered intravenously over 24 hours daily on Days 4-10 of the induction phase.

In one embodiment, the consolidation phase comprises administering the anti-CD200 antibody, or antigen-binding fragment thereof, and cytarabine. In another embodiment, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at least 1 time, and cytarabine is administered at least 3 times in the consolidation phase. In another embodiment, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered intravenously at a dose of 300 mg/m² or 600 mg/m², and cytarabine is administered at a dose of 1000 mg/m² during the consolidation phase.

In another embodiment, the consolidation phase comprises at least 4 cycles. In another embodiment, the consolidation phase cycles are at least 21 days. In another embodiment, each cycle of the consolidation phase is about 4-6 weeks.

In another embodiment, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered on Day 1 of Cycle 1 of the consolidation phase and every 21 days thereafter. In another embodiment, cytarabine is administered intravenously during the consolidation phase.
over three hours every 12 hours on Days 2, 4, and 6 of Cycle 1 and on Days 1, 3, and 5 of Cycles 2-4. In another embodiment, subsequent cycles of the consolidation phase begin within two weeks of hematological recovery (e.g., ANC ≥ 1000/µL and platelets ≥ 100,000/µL), but no sooner than four weeks from the start of the previous Cycle. In another embodiment, a corticosteroid ophthalmic solution is administered to the patient each day prior to administering cytarabine during the consolidation phase and for at least 24 hours thereafter. In another embodiment, the ophthalmic solution is dexamethasone 0.1%.

In another embodiment, the methods further comprise a reinduction phase (e.g., after the induction phase and before the consolidation phase), wherein the anti-CD200 antibody, or antigen-binding fragment thereof, daunorubicin, and cytarabine are administered. In another embodiment, the reinduction phase comprises administering the anti-CD200 antibody, or antigen-binding fragment thereof, at least one time, daunorubicin is administered at least two times, and cytarabine is administered at least five times. In another embodiment, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at 125 mL/hr 21 days after the Day 24 induction dose. In another embodiment daunorubicin is administered intravenously on Days 1-2 of the reinduction phase. In another embodiment, cytarabine is administered intravenously over 24 hours daily on Days 1-5 of the reinduction phase.

In one embodiment, cytarabine and daunorubicin are administered simultaneously or consecutively. In another embodiment, cytarabine is administered before daunorubicin. In another embodiment, cytarabine is administered after daunorubicin. In another embodiment, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered every 21 days for 2 years after the consolidation phase. In another embodiment, the anti-CD200 antibody or antigen-binding fragment thereof is administered about every 3 weeks.

In another embodiment, the treatment produces at least one therapeutic effect, for example, morphologic complete remission, cytogenetic complete remission, morphologic CR with incomplete blood count recovery, partial remission, and/or stable disease.

In another embodiment, the anti-CD200 antibody or antigen-binding fragment thereof inhibits the interaction between CD200 and CD200R. In another embodiment, the method of treatment results in a CD200 saturation of at least 60%, 65%, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%.

In another embodiment, the patient is ≥ 60 years old.
Also provided are kits for treating a human patient with Acute Myeloid Leukemia (AML) is provided, the kit comprising:

(a) a dose of an anti-CD200 antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region CDR1 having the sequence set forth in SEQ ID NO: 7, a heavy chain variable region CDR2 having the sequence set forth in SEQ ID NO: 8, a heavy chain variable region CDR3 having the sequence set forth in SEQ ID NO: 9, a light chain variable region CDR1 having the sequence set forth in SEQ ID NO: 4, a light chain variable region CDR2 having the sequence set forth in SEQ ID NO: 5, and a light chain variable region CDR3 having the sequence set forth in SEQ ID NO: 6;

(b) a dose of cytarabine;

(c) a dose of daunorubicin; and

(d) instructions for using the anti-CD200 antibody, cytarabine, and daunorubicin in any of the methods described herein.

Other features and advantages of the methods of treatment will be apparent from the following description, the examples, and from the claims. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

**BRIEF DESCRIPTION OF THE DRAWINGS**

**Figure 1** is a graph depicting total, linear, and nonlinear clearance of samalizumab from serum.

**Figure 2** is a graphic depiction of medians of conditional predictions for final samalizumab concentrations using dosing regimen 1 (i.e., 300, 600, and 900 mg/m² Q3W with loading dose).

**Figures 3A-3F** are graphs showing median and 80% prediction intervals for percent change from baseline of B-CLL CD200⁺ [MFI] and CD200⁺CD2⁺T cells using dosing regimen 1 (i.e., 300, 600, and 900 mg/m² Q3W with loading dose).

**Figure 4** is a bar graph depicting percent change from baseline in bulky adenopathy burden for each patient with CLL (sum of the bi-dimensional products of all target lesions).
Figures 5A-5B are graphs depicting individual serum samalizumab concentration over time with Q3W (Day 1, 3) intravenous dosing (300 mg/m²) in three patients. Figure 5A is a linear plot of the data. Figure 5B is a semi-log plot of the data.

Figures 6A-6B are graphs depicting the mean serum samalizumab concentration over time with Q3W (Day 1, 3) intravenous dosing (300 mg/m²). Figure 6A is a linear plot of the data. Figure 6B is a semi-log plot of the data.

Figure 7A-7B are graphs depicting individual serum samalizumab concentration over time with Q3W (Day 1, 3) intravenous dosing (300 mg/m²) in six patients. Figure 7A is a linear plot of the data. Figure 7B is a semi-log plot of the data. The graphs include both induction and consolidation phase data points.

Figures 8A-8B are graphs depicting the mean serum samalizumab concentration over time with Q3W (Day 1, 3) intravenous dosing (300 mg/m²). Figure 8A is a linear plot of the data. Figure 8B is a semi-log plot of the data. The graphs include both induction and consolidation phase data points.

DETAILED DESCRIPTION

The present disclosure provides methods for the treatment of at least one hematological malignancy in a subject (e.g., AML) which comprises administering to a subject (e.g., a human) an effective amount an anti-CD200 antibody in combination with cytarabine and daunorubicin.

I. Definitions

In order that the present description may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, and conventional methods of immunology, protein chemistry, biochemistry, recombinant DNA techniques, and pharmacology are employed.

As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. The use of "or" or "and" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes", and "included", is not limiting.
The term "about" as used herein when referring to a measurable value such as an amount, a temporal duration and the like, is encompasses variations of up to ± 10% from the specified value. Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, etc., used herein are to be understood as being modified by the term "about".

As used herein, acute myeloid leukemia (AML) refers to a biologically heterogeneous disease of the hematopoietic system characterized by the accumulation and expansion of immature myeloid cells in the bone marrow. AML includes acute myeloid leukemia, acute myeloblasts leukemia, acute granulocytic leukemia, acute nonlymphocytic leukemia, and Core-binding factor (CBF) positive AML.

In AML, immune modulation via upregulation of cytotoxic T cells, memory T cell function, or improvement in NK cell function is an attractive approach as leukemic cells are readily accessible to normal immunological cells, and also can express a variety of normal cell surface differentiation antigens, adhesion molecules, and costimulatory molecules. In certain subtypes, leukemic cells can present unique antigens, resulting from characteristic chromosomal changes, translocations with resultant antigenic fusion proteins and certain gene mutations that would be potential immune recognition targets. However, a functional immune system is needed for tumor cell destruction and long-term immune memory to prevent relapse of disease.

Despite the importance of immune surveillance in preventing cancer, there have been few studies examining T cell and NK cell function at baseline in elderly AML patients and also during treatment. Kanakry and colleagues quite elegantly described T cell recovery after aggressive timed sequential therapy in AML among 20 patients of different ages (Kanakery et al., 2011 Blood, 117(2):608-17). They demonstrated primary thymic regeneration of T cells by the presence of a peak of T cells containing cell receptor excision circles (TREC) suggestive of newly emigrating T cells from the thymus. The proportion spike of TREC+ T cells observed was inversely proportionate to age, a finding expected given thymic involution which is typically observed with aging. However, the majority of T cells were peripherally derived. In addition to this finding, the authors demonstrated a large peak of activated CD4, C25, FOXP3+ T regulatory cells that was significantly higher than that observed in normal subjects (8.8% versus 1.4% of total). These CD4+ T regulatory cells were immunosuppressive, oligoclonally skewed,
suggesting antigenic expansion, and virtually all peripherally derived as measured by lack of TREC expression.

NK cell immune suppression has also been described in AML at baseline and is associated with poor outcome. Stringaris and colleagues demonstrated that NK cells from AML patients at diagnosis were impaired, with down-regulation of the activating receptor Nkp46 and upregulation of the inhibitory receptor NKG2A (P = 0.04) observed (Stringaris et al., 2014) *Haematologica*. 99(5); 836-47). NK cells from AML patients had impaired effector function against autologous blasts and K562 targets, with significantly reduced CD107a degranulation, TNF-α and IFN-γ production. In patients attaining CR, partial recovery of NK cell function was noted. Studies by this group demonstrated that the immunosuppressive effect was predominately mediated by interleukin 10, a cytokine produced by T regulatory cells, B regulatory cells, M2 macrophages, and tumor cells. Strategies to target the prevention and expansion of T regulatory cells and other immune suppressive molecules are therefore desirable.

CBF positive AML includes patients with the cytogenetic abnormalities of t(8;21)(q22;q22), pericentric inversion of chromosome 16 [inv(16)(p13.1q22)], or the less frequent balanced translocation t(16;16)(p13.1;q22). In patients with *de novo* AML, t(8;21) is found in 7% and inv(16) in 5-8% of patients. The frequency decreases as patients age, with approximately 7% of patients older than 60 having one of the abnormalities. These patients are considered to have ELN favorable genetic risk; however, in CBF AML this is relative as approximately 50% of this subgroup are not cured with current available therapies. Although approximately 70% of elderly patients are able to obtain complete remission (CR) with 7+3 Induction therapy (anthracycline daily on Days 1-3 and cytarabine continuously Days 1-7), this response is not durable. Among all patients with t(8;21) and inv(16) AML, repetitive courses of high dose cytarabine consolidation have shown superiority over other regimens for promoting long-term remission and Overall Survival (OS). Elderly patients (age >60) fare worse, as predicted 5-year DFS and OS decrease from approximately 55% and 65% in younger patients, respectively, to rates of 25% and 30%. This shows that the elderly CBF AML population should not be considered to have "favorable risk" disease and calls for improvement upon our current standard of care, which is 7+3 Induction therapy followed by cytarabine consolidation.
The terms "CD200", "OX-2" and "OX-2/CD200" are used interchangeably herein and refers to the highly conserved type I transmembrane glycoprotein having an amino acid sequence of the full-length precursor human CD200 isoform A (SEQ ID NO:1; Genbank Accession No. NP005935.2), the full-length human CD200 isoform B (SEQ ID NO: 2; Genbank Accession No. NP001004196.2), or the full-length human CD200 of SEQ ID NO: 3 (Genbank Accession No. CAA28943.1; FIG. 3 of McCaughan et al. (1987) Immunogenetics 25:329-335).

CD200 is overexpressed in AML, and this increased expression is associated with worse outcomes. Damiani and colleagues showed CD200+ AML patients have a two-fold lower probability to attain a CR; OS was also decreased in this subset and correlated with intensity of CD200 expression. Patients with otherwise favorable molecular markers (e.g., mutated NPM1 or wildtype FLT3) were found to have worsening of OS with CD200 expression. An additive effect of CD200 on the negative impact of OS in patients with unfavorable cytogenetics was also observed (Damiani et al., (2015) Oncotarget). Published data has found that CBF patient samples have high expression of CD200 (Tonks et al., (2007) Leukemia, 21(3):566-8). CD200 is a unique checkpoint molecule and its downstream signaling is distinct from PD-1 and CTLA-4. As a result, there is reason to believe that an anti-CD200 mAb could have effect in patients who have not responded to either PD-1/PD-L1 or CTLA-4.

CD200 interacts with the CD200 receptor (CD200R), which induces immune suppression by skewing the immune response from a Th1 -cytokine producing response, to a response characterized by an increased frequency of immunosuppressive regulatory T cells and suppression of memory T cell function. Increased expression of CD200 on AML cells diminishes NK cell directed AML tumor cytotoxicity and gamma interferon production. NK cells isolated from AML patients whose leukemic blasts expressed increased CD200 were less active toward autologous blasts. However, the NK activity could be recovered with CD200 blockade through anti-human CD200 antibody therapy. Targeting CD200 on AML blasts has also been shown to recover cytotoxic memory T cells along with Th1 memory T cell quality and function. FoxP3+ T regulatory cells that suppress the anti-leukemia cell response have also been found to be upregulated concurrently with increased CD200 expression on AML blasts.

The term "CD200 antagonist" as used herein includes any agent that is capable of inhibiting the activity, function and/or the expression of CD200 or its receptor. In certain
embodiments, the antagonist disrupts the interaction of CD200 and CD200R. In other embodiments, the CD200 antagonist is capable of decreasing the immunosuppressive effects of CD200 or are capable of targeting CD200-expressing cells for depletion or elimination.

The term "antibody" as used herein refers to polypeptides comprising at least one antibody derived antigen binding site (e.g., VH/VL region or Fv, or CDR), and includes whole antibodies and any antigen binding fragments (i.e., "antigen-binding portions") or single chains thereof. Antibodies include known forms of antibodies. For example, the antibody can be a human antibody, a humanized antibody, a bispecific antibody, or a chimeric antibody. A whole "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, in which each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region; and each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

The exact boundaries of CDRs can be defined differently according to different methods. In some embodiments, the positions of the CDRs or framework regions within a light or heavy chain variable domain can be as defined by Kabat et al. [(1991) "Sequences of Proteins of Immunological Interest." NIH Publication No. 91-3242, U.S. Department of Health and Human Services, Bethesda, MD]. In such cases, the CDRs can be referred to as "Kabat CDRs" (e.g., "Kabat LCDR2" or "Kabat HCDR1"). In other embodiments, the positions of the CDRs of a light or heavy chain variable region can be as defined by Chothia et al. (1989) Nature 342:877-883. Accordingly, these regions can be referred to as "Chothia CDRs" (e.g., "Chothia LCDR2" or "Chothia HCDR3"). In other embodiments, the positions of the CDRs of the light and heavy
chain variable regions can be as defined by a Kabat-Chothia combined definition. In such embodiments, these regions can be referred to as "combined Kabat-Chothia CDRs". Thomas et al. [(1996) Mol Immunol 33(17/18):1389-14011] exemplifies the identification of CDR boundaries according to Kabat and Chothia definitions. In other embodiments, the positions of the CDRs or framework regions within a light or heavy chain variable domain can be as defined by the international ImMunoGeneTics database (IMGT) standard. Marie-Paule Lefranc et al. [(2003) Developmental & Comparative Immunology 27(l):55-77] exemplifies the identification of and CDR boundaries according to IMGT standard. Accordingly, these regions can be referred to as "IMGT CDRs" (e.g., "IMGT-LCDR2" or "IMGT-HCDR3").

The antibody also can be of any of the following isotypes: IgGl, IgG2, IgG3, IgG4, IgM, IgAl, IgA2, IgAsec, IgD, and IgE. The antibody may be a naturally occurring antibody or may be an antibody that has been altered by a protein engineering technique (e.g., by mutation, deletion, substitution, and/or conjugation to a non-antibody moiety). For example, an antibody may include one or more variant amino acids (compared to a naturally occurring antibody) which change a property (e.g., a functional property) of the antibody. For example, numerous such alterations are known in the art which affect, e.g., half-life, effector function, and/or immune responses to the antibody in a patient. The term antibody also includes artificial or engineered polypeptide constructs which comprise at least one antibody-derived antigen binding site.

The term "human antibody," as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences as described, for example, by Kabat et al. (See Kabat, et al. (1991) Sequences of proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242).

The term "antigen-binding portion" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., CD200, e.g., a Fab, Fab’2, ScFv, SMIP, AFFIBODY® antibody mimic (Affibody AB AKTIEBOLAG, Sweden), nanobody, or a domain antibody. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL,
VH, CL and CHI domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CHI domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., 1989* Nature* 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) *Science* 242:423-426; and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. Other forms of single chain antibodies, such as diabodies are also encompassed. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger, P., et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Poljak, R. J., et al. (1994) *Structure* 2:1121-1123). In one embodiment, the composition contains an antigen-binding portions described in U.S. Pat. Nos. 6,090,382 and 6,258,562, each incorporated by reference herein.

The term "monoclonal antibody," as used herein, includes an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Monoclonal antibodies are advantageous in that they may be synthesized by a hybridoma culture, essentially uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being amongst a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. The monoclonal antibodies to be used in accordance with the formulations disclosed herein may be made by the hybridoma method first described by Kohler, et al., (1975) *Nature* 256: 495 or other methods known in the art. A "polyclonal antibody" is an antibody which was produced among or in the presence of one or more other, non-identical...
antibodies. In general, polyclonal antibodies are produced from a B-lymphocyte in the presence of several other B-lymphocytes which produced non-identical antibodies. Usually, polyclonal antibodies are obtained directly from an immunized animal.

An "isolated" antibody or antigen binding fragment is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with research, diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In some embodiments, an antibody is purified to greater than 95% by weight of antibody, and in some embodiments, to greater than 99% by weight of antibody.

The term "pharmaceutical formulation" or "pharmaceutical composition" refers to preparations which are in such form as to permit the biological activity of the active ingredients to be unequivocally effective, and which contain no additional components which are significantly toxic to the subjects to which the formulation would be administered.

As used herein, an "aqueous" pharmaceutical composition is a composition suitable for pharmaceutical use, wherein the aqueous carrier is water. A composition suitable for pharmaceutical use may be sterile, homogeneous and/or isotonic. Aqueous pharmaceutical compositions may be prepared directly in an aqueous form and/or may be reconstituted from a lyophilisate.

A "sterile" composition is aseptic or free or essentially free from all living microorganisms and their spores.

As used herein, the terms "specific binding," "selective binding," "selectively binds," and "specifically binds," refer to antibody binding to an epitope on a predetermined antigen but not to other antigens. Typically, the antibody (i) binds with an equilibrium dissociation constant (K_D) of approximately less than 10^{-7} M, such as approximately less than 10^{-8} M, 10^{-9} M or 10^{-10} M or even lower when determined by, e.g., surface plasmon resonance (SPR) technology in a BIACORE® 2000 surface plasmon resonance instrument using the predetermined antigen, e.g., recombinant human CD200, as the analyte and the antibody as the ligand, or Scatchard analysis of binding of the antibody to antigen positive cells, and (ii) binds to the predetermined antigen
with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely-related antigen. Accordingly, unless otherwise indicated, an antibody that "specifically binds to human CD200" refers to an antibody that binds to soluble or cell bound human CD200 with a KD of $10^{-7}$ M or less, such as approximately less than $10^{-8}$ M, $10^{-9}$ M or $10^{-10}$ M or even lower.

An "epitope" refers to the site on a protein (e.g., a human CD200 protein) that is bound by an antibody. "Overlapping epitopes" include at least one (e.g., two, three, four, five, or six) common amino acid residue(s). In some embodiments, an anti-CD200 antibody described herein binds to an epitope within the extracellular portion of 65 a CD200 protein. For example, in some embodiments, the anti-CD200 antibody can bind to CD200 protein at an epitope within or overlapping with: (i) amino acids 1 to 233 of the amino acid sequence depicted in SEQ ID NO: 1; (ii) amino acids 1 to 258 of the amino acid sequence depicted in SEQ ID NO:2; or amino acids 1 to 229 of the amino acid sequence depicted in SEQ ID NO:3.

In some embodiments, the anti-CD200 antibody binds to an epitope in the human CD200 protein lacking the leader sequence. For example, an anti-CD200 antibody described herein can bind to a CD200 protein at an epitope within or overlapping with amino acids 31 to 233 of the amino acid sequence depicted in SEQ ID NO: 1, which corresponds to the extracellular portion of the mature form of human CD200 isoform A less the amino terminal leader sequence. In some embodiments, an anti-CD200 antibody described herein can bind to a CD200 protein at an epitope within or overlapping with amino acids 56 to 258 of the amino acid sequence depicted in SEQ ID NO: 2, which corresponds to the extracellular portion of the mature form of human CD200 isoform B less the amino terminal leader sequence. In some embodiments, an anti-CD200 antibody described herein can bind to a CD200 protein at an epitope within or overlapping with amino acids 27 to 229 of the amino acid sequence depicted in SEQ ID NO: 3, which corresponds to the extracellular portion of the mature form of human CD200 less the amino terminal leader sequence.

In some embodiments, the anti-CD200 antibody specifically binds to a human CD200 protein (e.g., the human CD200 protein having the amino acid sequence depicted in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or the extracellular domains of the mature forms of the
CD200 proteins). Methods for identifying the epitope to which a particular antibody binds are also known in the art.


The term "Kd̂", as used herein, is intended to refer to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

The term "Kd" as used herein, is intended to refer to the dissociation constant of a particular antibody-antigen interaction.

The terms "treat," "treating," and "treatment," as used herein, refer to therapeutic measures described herein. The methods of treatment employ administration to a subject (such as a human) the combination disclosed herein in order to cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disease or disorder or recurring disease or disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

The term "subject" or "patient" are used interchangeably herein and refer to a mammal such as a human, mouse, rat, hamster, guinea pig, rabbit, cat, dog, monkey, cow, horse, pig and the like.

The terms "effective amount" or "therapeutically effective amount" are used interchangeably and refer to an amount of formulation or antibody effective to alleviate or ameliorate one or more symptom(s) of disease (such as AML) or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Therapeutically effective dosages may be determined by using in vitro and in vivo methods.
The term "prophylaxis" refers to decreasing the likelihood of, or prevention of, a disease or condition (e.g., cancer, AML, autoimmune disease, allograft rejection).

As used herein, the term "chronically" (e.g., to chronically administer a compound), or similar terms, refers to a method of administration in which an agent (e.g., an anti-CD200 antibody) is administered to a subject in an amount and with a frequency sufficient to maintain an effective amount of the agent in the subject for at least seven (e.g., at least eight, nine, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24) days. In some embodiments, an agent can be chronically administered to a subject for at least one (e.g., at least two, three, four, five, or six) month(s). In some embodiments, an agent can be chronically administered to a subject for a year or more.

An "immune response" refers to a biological response within a vertebrate against foreign agents, which response protects the organism against these agents and diseases caused by them. An immune response is mediated by the action of a cell of the immune system (for example, a T lymphocyte, B lymphocyte, natural killer (NK) cell, macrophage, eosinophil, mast cell, dendritic cell or neutrophil) and soluble macromolecules produced by any of these cells or the liver (including antibodies, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from the vertebrate's body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues. An immune response or reaction includes, e.g., activation or inhibition of a T cell, e.g., an effector T cell or a Th cell, such as a CD4+ or CD8+ T cell, or the inhibition of a Treg cell.

"Immunotherapy" refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response. "Immuno-stimulating therapy" or "immuno-stimulatory therapy" refers to a therapy that results in increasing (inducing or enhancing) an immune response in a subject for, e.g., treating cancer. "Potentiating an endogenous immune response" means increasing the effectiveness or potency of an existing immune response in a subject. This increase in effectiveness and potency may be achieved, for example, by overcoming mechanisms that suppress the endogenous host immune response or by stimulating mechanisms that enhance the endogenous host immune response.
As used herein, the term "T cell-mediated response" refers to a response mediated by T cells, including effector T cells (e.g., CD8+ cells) and helper T cells (e.g., CD4+ cells). T cell mediated responses include, for example, T cell cytotoxicity and proliferation. As used herein, the term "cytotoxic T lymphocyte (CTL) response" refers to an immune response induced by cytotoxic T cells. CTL responses are mediated primarily by CD8+ T cells.

As used herein, the terms "inhibits" or "blocks" (e.g., referring to inhibition/blocking of CD73 binding or activity) are used interchangeably and encompass both partial and complete inhibition/blocking.

As used herein, "cancer" refers a broad group of diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division may result in the formation of malignant tumors or cells that invade neighboring tissues and may metastasize to distant parts of the body through the lymphatic system or bloodstream. As used herein, the term includes pre-malignant as well as malignant cancers.

As used herein, the term "hematological malignancy" includes a lymphoma, leukemia, myeloma or a lymphoid malignancy, as well as a cancer of the spleen and the lymph nodes. Exemplary lymphomas include both B cell lymphomas and T cell lymphomas.

As used herein, the terms "induction" and "induction phase" are used interchangeably and refer to the first phase of treatment in the clinical trial. As used herein, the terms "consolidation" and "consolidation phase" are used interchangeably and refer to the second phase of treatment in the clinical trial.

As used herein, the terms "reinduction" and "reinduction phase" are used interchangeably and refer to an optional intermediary phase of treatment between the induction phase and the consolidation phase.

As used herein, the terms "maintenance" and "maintenance phase" are used interchangeably and refer to the last phase of treatment in the clinical trial. In certain embodiments, treatment is continued as long as clinical benefit is observed or until unmanageable toxicity or disease progression occurs. In other embodiments, the treatment is continued for 2 years after the consolidation phase.
An "ECOG performance status" is an attempt to quantify cancer patients' general well-being and activities of daily life. This measure is used to determine whether they can receive chemotherapy, whether dose adjustment is necessary, and as a measure for the required intensity of palliative care. It is also used in oncological randomized controlled trials as a measure of quality of life. A score of zero equals Fully active, able to carry on all pre-disease performance without restriction. A score of 1 equals Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work or office work. A score of 2 equals Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours. A score of 3 equals Capable of only limited selfcare and confined to bed or chair more than 50% of waking hours. A score of 4 equals Completely disabled; cannot carry on any selfcare; totally confined to bed or chair. A score of 5 equals Dead.

As used herein, the terms "Beat AML" and "Master Trial" are used interchangeably and refer to an "umbrella" study organized by the Leukemia & Lymphoma Society (LLS) designed to match specific AML mutations in newly diagnosed patients over the age of 60 with an investigational drug or drugs best suited to attack the specific genetic mutations causing the cancer. In the Master Trial, newly diagnosed patients have their genomic data analyzed so they can be entered into the appropriate treatment arm.

Various aspects described herein are described in further detail in the following subsections.

II. Anti-CD200 Antibodies

Anti-CD200 antibodies for use in the methods provided herein are CD200 antagonists and include whole antibodies, or antibody fragments capable of binding to CD200, particularly anti-CD200 antibodies which disrupt the interaction between CD200 and CD200R. Exemplary anti-CD200 antibodies, or antigen binding fragments thereof, which can be used in the methods described herein include, but are not limited to, those disclosed in U.S. Patent No. 7,408,041; US Patent No. 8,075,884; and WO 2012/106634 (the contents of each of which are herein incorporated by reference in their entirety).

In one embodiment, the anti-CD200 antibody, or antigen binding fragment thereof, comprises the CDR1, CDR2, and CDR3 domains of a heavy chain variable region having the
sequence set forth in SEQ ID NO: 13, and the CDR1, CDR2, and CDR3 domains of a light chain variable region having the sequence set forth in SEQ ID NO: 12.

In another embodiment, the anti-CD200 antibody, or antigen binding fragment thereof, comprising the CDR1, CDR2 and CDR3 domains of a heavy chain region having the sequence set forth in SEQ ID NO: 11, and the CDR1, CDR2 and CDR3 domains of a light chain region having the sequence set forth in SEQ ID NO: 10.

In another embodiment, the anti-CD200 antibody, or antigen binding fragment thereof, comprises: (a) a light chain variable domain that comprises (i) a light chain CDR1 comprising the sequence set forth in SEQ ID NO: 4, (ii) a light chain CDR2 comprising the sequence set forth in SEQ ID NO: 5, and (iii) a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 6; and (b) a heavy chain variable domain comprising (i) a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 7, (ii) a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 8 and (iii) a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 9.

In another embodiment, the antibody comprises a light chain region sequence as set forth in SEQ ID NO: 10 and/or a heavy chain variable region sequence as set forth in SEQ ID NO: 11. In one embodiment, the antibody comprises a light chain sequence as set forth in SEQ ID NO: 12 and/or a heavy chain sequence as set forth in SEQ ID NO: 13. In one embodiment, the anti-CD200 antibody is samalizumab (also known as ALXN6000; Alexion Pharmaceuticals, Inc., New Haven, CT).

Antibodies and antigen binding fragments thereof may be obtained according to established hybridoma and recombinant procedures. Suitable methods for producing an antibody (e.g., an anti-CD200 antibody) or antigen-binding fragments thereof may be obtained according to established hybridoma and recombinant procedures as previously disclosed (see, e.g., U.S. Pat. Nos. 7,427,665; 7,435,412; and 7,408,041). For example, a process for the production of an antibody disclosed herein includes culturing a host (e.g., E. coli or a mammalian cell), which has been transformed with a hybrid vector. The vector includes one or more expression cassettes containing a promoter operably linked to a first DNA sequence encoding a signal peptide linked in the proper reading frame to a second DNA sequence encoding the antibody protein. The antibody protein is then collected and isolated. Optionally, the expression cassette may include a
 promoter operably linked to polycistronic, for example bicistronic, DNA sequences encoding antibody proteins each individually operably linked to a signal peptide in the proper reading frame.

**Multiplication of hybridoma cells or mammalian host cells in vitro** is carried out in suitable culture media, which include the customary standard culture media (such as, for example Dulbecco's Modified Eagle Medium (DMEM) or RPMI 1640 medium), optionally replenished by a mammalian serum (e.g. fetal calf serum), or trace elements and growth sustaining supplements (e.g. feeder cells such as normal mouse peritoneal exudate cells, spleen cells, bone marrow macrophages, 2-aminoethanol, insulin, transferrin, low density lipoprotein, oleic acid, or the like). Multiplication of host cells which are bacterial cells or yeast cells is likewise carried out in suitable culture media known in the art. For example, for bacteria suitable culture media include medium LE, NZCYM, NZYM, NZM, Terrific Broth, SOB, SOC, 2xYT, or M9 Minimal Medium. For yeast, suitable culture media include medium YPD, YEPD, Minimal Medium, or Complete Minimal Dropout Medium.

**In vitro** production provides relatively pure antibody preparations and allows scale-up to give large amounts of the desired antibodies. Techniques for bacterial cell, yeast, plant, or mammalian cell cultivation are known in the art and include homogeneous suspension culture (e.g. in an airlift reactor or in a continuous stirrer reactor), and immobilized or entrapped cell culture (e.g. in hollow fibers, microcapsules, on agarose microbeads or ceramic cartridges).

Large quantities of the desired antibodies can also be obtained by multiplying mammalian cells in vivo. For this purpose, cells producing the desired antibodies are injected into histocompatible mammals to cause growth of antibody-producing tumors. Optionally, the animals are primed with a hydrocarbon, especially mineral oils such as pristane (tetramethylpentadecane), prior to the injection. After one to three weeks, the antibodies are isolated from the body fluids of those mammals. For example, hybridoma cells obtained by fusion of suitable myeloma cells with antibody-producing spleen cells from Balb/c mice, or transfected cells derived from hybridoma cell line Sp2/0 that produce the desired antibodies are injected intraperitoneally into Balb/c mice optionally pre-treated with pristane. After one to two weeks, ascitic fluid is taken from the animals.
The antibody which is formulated is preferably essentially pure and desirably essentially homogeneous (e.g., free from contaminating proteins, etc). "Essentially pure" antibody means a composition comprising at least about 90% by weight of the antibody, based on total weight of the composition, preferably at least about 95% by weight of the antibody. "Essentially homogeneous" antibody means a composition comprising at least about 99% by weight of antibody, based on total weight of the composition.

Techniques for purification of therapeutic antibodies to pharmaceutical grade are well known in the art. For example, the immunoglobulins in the culture supematants or in the ascitic fluid may be concentrated, e.g., by precipitation with ammonium sulfate, dialysis against hygroscopic material such as polyethylene glycol, filtration through selective membranes, or the like. If necessary and/or desired, the antibodies are purified by the customary chromatography methods, for example gel filtration, ion-exchange chromatography, chromatography over DEAE-cellulose and/or (immuno-) affinity chromatography, e.g. affinity chromatography with a one or more surface polypeptides derived from a CLL cell line according to this disclosure, or with Protein-A or G.

III. Cytarabine

Cytosine arabinoside or cytarabine (4-amino-l-P-D arabinofurasonyl-2(IH)-pyrimidione) is a DNA synthesis inhibitor. Specifically, cytarabine is a pyrimidine antimetabolite and competitive inhibitor of DNA polymerase. The molecular formula of cytarabine is $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_5$. Other names for cytarabine include cytosine arabinoside, Cytosar-U, 1-B-Arabinino-furanosyl-cytosine, arabinosylcytosine, cytarabine sterile, and ARA-C. Cytarabine arabinoside (or ARA-C) is a nucleoside that differs from the endogenous counterpart for the presence of an arabinoside rather than a ribose sugar. The compound is carried into the cells by a nucleoside transporter, which becomes saturated at concentrations greater than 20 $\mu$M, above which the transport is by passive diffusion. To become an active compound, ARA-C is converted to ARA-C triphosphate (ARA-CPT) by 3 sequential enzymes, deoxycytidine kinase, deoxycytidine monophosphate kinase, and nucleotide-disphosphate kinase. Competing with these enzymes, there are 2 other enzymes, cytidine deaminase and dCMP deaminase that inactivate ARA-C and ARA-CMP, respectively, to the corresponding uridine compounds. The activated ARA-CTP competes with the natural deoxycytidine triphosphate for incorporation in DNA by DNA polymerase. Once incorporated in the DNA, ARA-CTP inhibits the DNA polymerases, resulting in termination of the strand elongation important for DNA synthesis or repair. A relationship between intracellular levels of ARA-CTP and antileukemic effect has been identified, and strategies to increase these levels such as administration of high-dose ARA-C or fludarabine prior to ARA-C are being studied. Side effects of this compound include myelosuppression, nausea, vomiting, mucositis, diarrhea, and neurotoxicity in particular with high doses. High-dose cytarabine is commonly administered as part of initial (most commonly consolidation) or salvage treatment for AML.

IV. Daunorubicin

Daunorubicin ((8S, 10S)-8-acetyl-10-[2S,4S,5S,6S]-4-amino-5-hydroxy-6-methyl-oxan-2-yl]oxy-6, 8,ll-trihydroxy-l-methoxy-9, 10-dihydro-7 $H$-tetracene-5,12-dione) is a topoisomerase inhibitor. Specifically, daunorubicin is a sterile, semi-synthetic antineoplastic anthracycline. The molecular formula of duanorubicin is $\text{C}_{27}\text{H}_{29}\text{NO}_{10}$. Daunorubicin hydrochloride is hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of $\text{Streptomyces coeruleorubidus}$. Daunorubicin has both antimitotic and cytotoxic activity.
through a number of proposed mechanisms of action. Daunorubicin forms complexes with DNA by intercalating between base pairs. It inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, preventing the relegation portion of the ligation-relegation reaction that topoisomerase II catalyzes. This results in single- and double-strand DNA breaks.

Daunorubicin is rapidly and widely distributed in tissues, where it binds to many cellular components, particularly nucleic acids. Daunorubicin is extensively metabolized in the liver, and its primary metabolite, daunorubicinol, also has antineoplastic activity. Daunorubicin is also a backbone of AML therapy, commonly delivered by IV bolus for three days during the cytarabine infusion.

V. Compositions

In one aspect, the present disclosure provides a composition comprising an anti-CD200 antibody. In one embodiment, the anti-CD200 antibody is samalizumab (also known as ALXN6000). In another embodiment, the composition comprises a anti-CD200 antibody, wherein the anti-CD200 antibody comprises the CDR1, CDR2, and CDR3 domains in a heavy chain variable region having the sequence set forth in SEQ ID NO: 11 and the CDR1, CDR2, and CDR3 domains in a light chain variable region having the sequence set forth in SEQ ID NO: 10.

Pharmaceutical compositions suitable for administration to human patients are typically formulated for parenteral administration, e.g., in a liquid carrier, or suitable for reconstitution into liquid solution or suspension for intravenous administration.


In general, such compositions typically comprise a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable" means approved by a government...
regulatory agency or listed in the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, glycerol polyethylene glycol ricinoleate, and the like. Water or aqueous solution saline and aqueous dextrose and glycerol solutions may be employed as carriers, particularly for injectable solutions. Liquid compositions for parenteral administration can be formulated for administration by injection or continuous infusion. Routes of administration by injection or infusion include intravenous, intraperitoneal, intramuscular, intrathecal and subcutaneous.

For oral use, the pharmaceutical compositions of the present disclosure, may be administered, for example, in the form of tablets or capsules, powders, dispersible granules, or cachets, or as aqueous solutions or suspensions. In the case of tablets for oral use, carriers which are commonly used include lactose, corn starch, magnesium carbonate, talc, and sugar, and lubricating agents such as magnesium stearate are commonly added. For oral administration in capsule form, useful carriers include lactose, corn starch, magnesium carbonate, talc, and sugar. When aqueous suspensions are used for oral administration, emulsifying and/or suspending agents are commonly added.

In addition, sweetening and/or flavoring agents may be added to the oral compositions.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient(s) are usually employed, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of the solute(s) should be controlled in order to render the preparation isotonic.

For preparing suppositories according to the disclosure, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously in the wax, for example by stirring. The molten homogeneous mixture is then poured into conveniently sized molds and allowed to cool and thereby solidify.

Liquid preparations include solutions, suspensions and emulsions. Such preparations are exemplified by water or water/propylene glycol solutions for parenteral injection. Liquid preparations may also include solutions for intranasal administration.
Also included are solid preparations which are intended for conversion, shortly before use, to liquid preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

VI. **Patient Populations**

Provided herein are effective methods for treating a in a patient, e.g., using an anti-CD200 antibody. Cancers for which the disclosed methods may be used include but are not limited to hematological malignancies, such as, for example, a lymphoma, leukemia, myeloma or a lymphoid malignancy, as well as a cancer of the spleen and the lymph nodes. Exemplary lymphomas include both B cell lymphomas and T cell lymphomas. B-cell lymphomas include both Hodgkin's lymphomas and most non-Hodgkin's lymphomas. Non-limiting examples of B cell lymphomas include diffuse large B-cell lymphoma, follicular lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma (overlaps with chronic lymphocytic leukemia), mantle cell lymphoma (MCL), Burkitt's lymphoma, mediastinal large B cell lymphoma, Waldenstrom macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis. Non-limiting examples of T cell lymphomas include extranodal T cell lymphoma, cutaneous T cell lymphomas, anaplastic large cell lymphoma, and angioimmunoblastic T cell lymphoma. Hematological cancers also include leukemia, such as, but not limited to, secondary leukemia, chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and acute lymphoblastic leukemia (ALL). Hematological cancers further include myelomas, such as, but not limited to, multiple myeloma and smoldering multiple myeloma. Other hematological and/or B cell- or T-cell-associated cancers are encompassed by the term hematological cancer.

In one embodiment, the subject treated according to the methods provided herein has a hematological malignancy comprising cancer cells which over-express CD200 relative to normal cells of the same histological type as the cells from which the cancer cells are derived. Methods of determining the expression of CD200 are known and described, for example, in U.S. Patent No. 7,435,412; U.S. Patent No. 8,709,415; and U.S. Patent No. 9,085,623.

In another embodiment, provided herein are methods of treating acute myeloid leukemia (AML) by administering an anti-CD200 antibody (e.g., samalizumab), or antigen binding
fragment thereof, as disclosed herein in combination with cytarabine and daunorubicin. In one
embodiment, the AML is acute myeloblasts leukemia. In another embodiment, the AML is
acute granulocytic leukemia. In another embodiment, the AML is acute nonlymphocytic
leukemia. In another embodiment, the AML is a core-binding factor (CBF) positive AML. In
another embodiment, the CBF positive AML comprises an abnormality selected from the group
consisting of a cytogenetic abnormality of t(8;21)(q22;q22), a pericentric inversion of
chromosome 16 [inv(16)(pl3.1.q22)] and a balanced translocation t(16;16)(pl3.1;q22).

In certain embodiments, a patient can have a cancer that is suspected of being resistant or
is likely to become resistant to an anti-CD20 therapy. One biomarker useful in assessing
whether a cancer is likely to become resistant to an anti-CD20 therapeutic agent such as
rituximab is the presence or concentration of CD5+ cancer cells in the population (see, U.S.
Patent No. 9,085,623). In some embodiments, the anti-CD20 therapeutic agent is an anti-CD20
antibody such as, but not limited to, rituximab, ofatumumab, TRU-015, veltuzumab,
ocrelizumab, or AME-133v. In some embodiments, the methods comprise treating a subset of
CLL patients that are refractory to treatment with anti-CD20 therapy (e.g., rituximab-resistant).

For instance, the compositions described herein can be administered as a therapeutic to
cancer patients or autoimmune disease patients, especially, but not limited to AML patients.

The anti-CD200 antibodies provided herein can also be administered in combination with
other immunomodulatory compounds, vaccines, or chemotherapy. As used herein, adjunctive or
combined administration (coadministration) includes simultaneous administration of the
compositions with the immunomodulatory compound, vaccine or chemotherapy, in the same or
different dosage form, or separate administration of the compounds (e.g., sequential
administration). Thus, the anti-CD200 composition and immunomodulatory compounds,
vaccines or chemotherapy, can be simultaneously administered in a single formulation.
Alternatively, the anti-CD200 composition and immunomodulatory compounds, vaccines or
chemotherapy, can be formulated for separate administration and are administered concurrently
or sequentially.

Illustrative examples of suitable immunomodulatory therapies include the administration
of agents that block negative regulation of T cells or antigen presenting cells (e.g., anti-CTLA4
antibodies, anti-PD-L1 antibodies, anti-PDL-2 antibodies, anti-PD-1 antibodies and the like) or
the administration of agents that enhance positive co-stimulation of T cells (e.g., anti-CD40 antibodies or anti 4-IBB antibodies). Furthermore, immunomodulatory therapy could be cancer vaccines such as dendritic cells loaded with tumor cells, tumor RNA or tumor DNA, tumor protein or tumor peptides, patient derived heat-shocked proteins (hsp's) or general adjuvants stimulating the immune system at various levels such as CpG, Luivac, Biostim, Ribominyl, Imudon, Bronchovaxom or any other compound activating receptors of the innate immune system (e.g., toll like receptors). Also, immunomodulatory therapy could include treatment with cytokines such as IL-2, GM-CSF and IFN-gamma.

Accordingly in some embodiments, the methods of treatment provided herein enhance the immune response to cancer cells by the administration of the anti-CD200 compositions provided herein, alone or in combination with one of the previously mentioned immunomodulatory therapies. For example, in certain embodiments, the compositions provided herein may be used in combination with a monoclonal antibody (e.g., rituximab, trastuzumab, alemtuzumab, cetuximab, or bevacizumab), including a conjugated monoclonal antibody (e.g., gemtuzumab ozogamicin, ibrutinomab tiuxetan, or tositumomab).

In other embodiments, existing regulatory T cells are eliminated with reagents such as anti-CD25 or cyclophosphamide before starting anti-CD200 treatment. Also, therapeutic efficacy of myeloablative therapies followed by bone marrow transplantation or adoptive transfer of T cells reactive with AML cells is enhanced by treatment with the anti-CD200 compositions described herein. Furthermore, treatment with the anti-CD200 compositions can substantially enhance efficacy of cancer vaccines such as dendritic cells loaded with AML cells or proteins, peptides or RNA derived from such cells, patient-derived heat-shocked proteins, tumor peptides or protein. In other embodiments, the anti-CD200 compositions is used in combination with an immuno-stimulatory compound, such as CpG, toll-like receptor agonists or any other adjuvant, anti-CTLA-4 antibodies, and the like. In other embodiments, efficacy of the anti-CD200 compositions is improved by blocking of immunosuppressive mechanisms with, e.g., anti-PDL1 and/or 2 antibodies, anti-PDL antibodies, anti-IL-10 antibodies, or anti-IL-6 antibodies. In yet other embodiments, efficacy of an anti-CD200 compositions is improved by administration of agents that increase NK cell number or T-cell, e.g., the small molecule inhibitor EVIIDs, thalidomide, or thalidomide analogs. In certain embodiments, the methods described herein
further comprise administering one or more additional therapeutics with the anti-CD200 antibody.

VII. Additional Agents/Therapies

The anti-CD200 antibodies of the present disclosure (e.g., samalizumab) may also be used in conjunction with other well known therapies that are selected for their particular usefulness against the cancer that is being treated. Combinations of the present disclosure may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when inappropriate.

For example, the anti-CD200 antibodies described herein can further be used in combination (e.g., simultaneously or separately) with an additional treatment, such as irradiation, chemotherapy (e.g., using cytarabine, daunorubicin, camptothecin (CPT-11), 5-fluorouracil (5-FU), cisplatin, doxorubicin, irinotecan, paclitaxel, gemcitabine, cisplatin, paclitaxel, doxorubicin, 5-fu, or camptothecin + apo21/TRAIL (a 6X combo)), one or more proteasome inhibitors (e.g., bortezomib or MG132), one or more Bcl-2 inhibitors (e.g., BH3I-2’ (bcl-xl inhibitor), AT-101 (R(-)-gossypol derivative), ABT-263 (small molecule), GX-15-070 (obatoclax), or MCL-1 (myeloid leukemia cell differentiation protein- 1) antagonists), iAP (inhibitor of apoptosis protein) antagonists (e.g., smac7, smac4, small molecule smac mimicetic, synthetic smac peptides (see Fulda et al, Nat Med 2002;8:808-15), ISIS23722 (LY2181308), or AEG-35156 (GEM-640)), HDAC (histone deacetylase) inhibitors, anti-CD20 antibodies (e.g., rituximab), angiogenesis inhibitors (e.g., bevacizumab), anti-angiogenic agents targeting VEGF and VEGFR, synthetic triterpenoids (see Hyer et al, Cancer Research 2005;65:4799-808), c-FLIP (cellular FLICE-inhibitory protein) modulators (e.g., natural and synthetic ligands of PPARγ (peroxisome proliferator-activated receptor γ), 5809354 or 5569100), kinase inhibitors (e.g., Sorafenib), and/or genotoxic drugs.

The anti-CD200 antibodies described herein can further be used in combination with one or more anti-proliferative cytotoxic agents. Classes of compounds that may be used as anti-proliferative cytotoxic agents include, but are not limited to, the following:

Alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chlormethine,
Cyclophosphamide (CYTOXAN®), fosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenelamline, Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): methotrexate, 5-Fluorouracil, fluoruridine, ditarabine, 6-Mercaptopurine, 6-Thioguanine, fludarabine phosphate, pentostatine, and gemcitabine.

Suitable anti-proliferative agents for use in the methods of disclosed herein, include, without limitation, taxanes, paclitaxel (paclitaxel is commercially available as TAXOL®)(tamoxifen), docetaxel, discodermolide (DDM), dictyostatin (DCT), Peloruside A, epothilones, epothilone A, epothilone B, epothilone C, epothilone D, epothilone E, epothilone F, furanepothilone D, desoxyepothilone Bl, [17]-dehydrodesoxyepothilone B, [18]dehydrodesoxyepothilones B, C12,13-cyclopropyl-epothilone A, C6-C8 bridged epothilone A, trans-9,10-dehydroepothilone D, cis-9,10-dehydroepothilone D, 16-desmethylepoptilone B, epothilone BIO, discoderomolide, patupilone (EPO-906), KOS-862, KOS-1584, ZK-EPO, ABJ-789, XAA296A (Discodermolide), TZT-1027 (soblidotin), ILX-651 (tasidotin hydrochloride), Halichondrin B, Eribulin mesylate (E-7389), Hemiasterlin (HTI-286), E-7974, Cyptophycins, LY-355703, Maytansinoid immunoconjugates (DM-1), MKC-1, ABT-751, TI-38067, T-900607, SB-715992 (ispinesib), SB-743921, MK-0731, STA-5312, eleutherobin, 17beta-acetoxy-2-ethoxy-6-oxo-B-homo-stra-l3,5(10)-trien-3-ol, cyclostreptin, isolaulimalide, laulimalide, 4-epi-7-dehydroxy-14,16-didemethyl-(+)-discodermolides, and cryptothilone 1, in addition to other microtubulin stabilizing agents known in the art.

In cases where it is desirable to render aberrantly proliferative cells quiescent in conjunction with or prior to treatment with the chemotherapeutic methods of the disclosure, hormones and steroids (including synthetic analogs), such as 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyl-testosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, ZOLADEX® (goserelin acetate), can also be administered to the patient. When employing the methods or compositions
of the present disclosure, other agents used in the modulation of tumor growth or metastasis in a clinical setting, such as antimimetics, can also be administered as desired.

Methods for the safe and effective administration of chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the Physicians' Desk Reference (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, N.J. 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

The chemotherapeutic agent(s) and/or radiation therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent(s) and/or radiation therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent(s) and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

VIII. Treatment Protocols

Suitable treatment protocols for treating a hematological cancer in a patient include, for example, administering to the patient an effective amount of an anti-CD200 antibody, or antigen-binding fragment thereof, an anti-metabolic agent (e.g., cytarabine), and a topoisomerase inhibitor (e.g., daunorubicin), to a patient with cancer (e.g., AML).

As used herein, adjunctive or combined administration (co-administration) includes simultaneous administration of the agents in the same or different dosage form, or separate administration of the two antagonist (e.g., sequential administration).

In one embodiment, a subject is administered a single dose of an anti-CD200 antibody. In certain embodiments, multiple (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) doses of an anti-CD200 antibody are administered to a subject in need of treatment. Administration of an anti-CD200 antibody and a second anti-cancer, and/or third anti-cancer agent may be on the same day, or alternatively, the anti-CD200 antibody may be administered one or more days before or after the second or third anti-cancer agents.
In one embodiment, administration of an anti-CD200 antibody may be done weekly or monthly. In another embodiment, the anti-CD200 antibody is administered every two days. In another embodiment, the anti-CD200 antibody is administered every three weeks.

In one embodiment, the dose of the anti-CD200 antibody is varied over time. For example, the anti-CD200 antibody is initially administered at a low dose and increased over time. In another embodiment, the anti-CD200 antibody may be initially administered at a high dose and may be lowered over time.

In one embodiment, a method of treating a human patient with Acute Myeloid Leukemia is provided, the method comprising administering to the patient daunorubicin, cytarabine, and an anti-CD200 antibody, or antigen-binding fragment thereof. In other embodiments, the method comprises an induction phase followed by a consolidation phase. In other embodiments, the method further comprises a reinduction phase.

In certain embodiments, the method comprises administering the anti-CD200 antibody, or antigen-binding fragment thereof, three times during the induction phase. In other embodiments the daunorubicin is administered three times during the induction phase. In other embodiments the cytarabine is administered seven times during the induction phase.

In certain embodiments, the induction phase is at least 24 days. In other embodiments, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at 125 mL/hr on Days 1, 3, and 24 of the induction phase. In other embodiments, the daunorubicin is administered intravenously over 15 minutes on Days 4-6 of the induction phase. In other embodiments, the cytarabine is administered intravenously over 24 hours daily on Days 4-10 of the induction phase.

In certain embodiments, the consolidation phase comprises at least 4 cycles. In other embodiments, the consolidation phase cycles are at least 21 days. In other embodiments, each cycle of the consolidation phase is about 4-6 weeks. In other embodiments, the consolidation phase comprises administering the anti-CD200 antibody, or antigen-binding fragment thereof, and cytarabine. In other embodiments, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered intravenously at a dose of 300 mg/m² or 600 mg/m², and the cytarabine is administered at a dose of 1000 mg/m². In other embodiments the anti-CD200 antibody, or
antigen-binding fragment thereof, is administered on Day 1 of Cycle 1 of the consolidation phase and every 21 days thereafter, and the cytarabine is administered on Days 2, 4, and 6 of Cycle 1 of the consolidation phase. In other embodiments, cytarabine is administered intravenously during the consolidation phase over three hours every 12 hours on Days 2, 4, and 6 of Cycle 1; and Days 1, 3, and 5 of Cycles 2-4. In other embodiments, subsequent cycle of the consolidation phase begins within two weeks of hematological recovery (e.g., ANC ≥ 1000/µL and platelets ≥ 100,000/µL), but no sooner than four weeks from the start of the previous Cycle. In another embodiment, a corticosteroid ophthalmic solution is administered to the patient each day prior to administering cytarabine during the consolidation phase and for at least 24 hours thereafter. In certain embodiments, the ophthalmic solution is dexamethasone 0.1%.

In certain embodiments, the reinduction phase is after the induction phase and before the consolidation phase. In other embodiments, the reinduction phase comprises administering the anti-CD200 antibody, or antigen-binding fragment thereof, at least one time, the daunorubicin is administered at least two times; and the cytarabine is administered at least five times. In another embodiment, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at 125 mL/hr 21 days after the Day 24 induction dose. In another embodiment, the daunorubicin is administered intravenously on Days 1-2 of the reinduction phase. In another embodiment, the cytarabine is administered intravenously over 24 hours daily on Days 1-5 of the reinduction phase.

In certain embodiments, the cytarabine and daunorubicin are administered simultaneously or consecutively. In other embodiments, the anti-CD200 antibody, or antigen-binding fragment thereof, is administered every 21 days for two years after the consolidation phase. In other embodiments, the anti-CD200 antibody or antigen-binding fragment thereof is administered about every 3 weeks.

In certain embodiments, the treatment produces at least one therapeutic effect, including but not limited to morphologic complete remission, cytogenetic complete remission, morphologic CR with incomplete blood count recovery, partial remission, and/or stable disease.

In certain embodiments, the anti-CD200 antibody comprises heavy and light chain variable regions having the sequences set forth in SEQ ID NOs: 13 and 12, respectively. In other embodiments, the anti-CD200 antibody comprises heavy and light chains having the sequences
as set forth in SEQ ID NO: 11 and SEQ ID NO: 10, respectively. In other embodiments, the anti-CD200 antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region CDR1 having the sequence set forth in SEQ ID NO: 7, a heavy chain variable region CDR2 having the sequence set forth in SEQ ID NO: 8, a heavy chain variable region CDR3 having the sequence set forth in SEQ ID NO: 9, a light chain variable region CDR1 having the sequence set forth in SEQ ID NO: 4, a light chain variable region CDR2 having the sequence set forth in SEQ ID NO: 5, and a light chain variable region CDR3 having the sequence set forth in SEQ ID NO: 6. In other embodiments, the anti-CD200 antibody, or antigen binding fragment thereof, comprising the CDR1, CDR2 and CDR3 domains in a light chain variable region having the sequence set forth in SEQ ID NO: 12, and the CDR1, CDR2 and CDR3 domains in a heavy chain variable region having the sequence set forth in SEQ ID NO: 13.

In another embodiment, the amount of the anti-CD200 antibody administered is constant for each dose. In another embodiment, the amount of the anti-CD200 antibody varies with each dose. For example, the maintenance (or follow-on) dose of the antibody can be higher or the same as the loading dose which is first administered. In another embodiment, the maintenance dose of the antagonist can be lower or the same as the loading dose. A clinician may utilize preferred dosages as warranted by the condition of the patient being treated. The dose of may depend upon a number of factors, including stage of disease, DLTs, AEs, etc. The specific dose that should be administered based upon the presence of one or more of such factors is within the skill of the artisan. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired. Intermittent therapy (e.g., one week out of three weeks or three out of four weeks) may also be used.

In one aspect of the disclosure, the anti-CD200 antibody (e.g., samalizumab) is administered at a dose of about 300 mg/m², about 350 mg/m², about 400 mg/m², about 450 mg/m², about 500 mg/m², about 550 mg/m², about 600 mg/m², about 650 mg/m², about 700 mg/m², about 750 mg/m², about 800 mg/m², about 850 mg/m², or about 900 mg/m². In one embodiment, the anti-CD200 antibody is administered at a dose of about 300 mg/m² to about 900 mg/m². In another embodiment, the anti-CD200 antibody is administered at a dose of about 300
mg/m² to about 600 mg/m². In certain embodiments, the anti-CD200 antibody is administered at a dose of about 300 mg/m² or 600 mg/m². In another embodiment, the anti-CD200 antibody is administered with or without a loading dose. In another embodiment, the administration of the anti-CD200 antibody is on Day 0, Day 2, and every 21 days thereafter.

In another aspect, cytarabine is administered to the patient. In one embodiment, the cytarabine is administered at a dose of about 50 to about 200 mg/m². In another embodiment the cytarabine is administered at a dose of about 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 mg/m². In certain embodiments, cytarabine is administered at a dose of about 100 mg/m².

In one embodiment, cytarabine is administered at a dose of about 1000 mg/m². In another embodiment, cytarabine is administered at a dose of about 100 mg/m² to about 1000 mg/m². In another embodiment, cytarabine is administered at a dose of about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 mg/m².

In another aspect, daunorubicin is administered to the patient. In one embodiment, the daunorubicin is administered at a dose of about 10 mg/m² to about 100 mg/m². In one embodiment, the daunorubicin is administered at a dose of about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg/m². In certain embodiments, the daunorubicin is administered at a dose of about 60 mg/m².

In certain aspects, treatment results in a CD200 saturation of ≥ 90%. In another embodiment the CD200 is saturated from about 80% to about 100%. In other embodiments, the CD200 is saturated from about 80% to about 90%. In other embodiments, the CD200 is about 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% saturated.

In another aspect, treatment produces a median change from baseline for CD200⁺CD4⁺ T cells of about 80% to about 90%. In another embodiment, the treatment produces a change from baseline for CD200⁺CD4⁺ T cells of about 80% to about 100%. In other embodiments, the change from baseline is at least about 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%.

In some embodiments, determining whether an anti-CD200 antibody (e.g., a variant anti-CD200 antibody having reduced or no effector function) has produced a desired
immunomodulatory effect in a human can be performed by querying whether the post-treatment CD200+ leukocyte or CD200+ bone marrow cell concentration falls within a predetermined range indicative of the occurrence of a desired immunomodulatory effect by an anti-CD200 antibody in a human. In some embodiments, determining whether an anti-CD200 antibody has produced a desired immunomodulatory effect in a human can include querying if the post-treatment CD200+ leukocyte or CD200+ bone marrow cell concentration for a given histological type of CD200+ leukocytes or CD200+ bone marrow cells falls above or below a predetermined cut-off value. A cut-off value is typically the concentration of CD200+ leukocytes or CD200+ bone marrow cells of a given histological type above or below which is considered indicative of a certain phenotype—namely the occurrence of a desired immunomodulatory effect in a human produced by an anti-CD200 antibody.

In some embodiments, the methods described herein can include the step of determining whether one or more cancer cells of a human's cancer express CD200. In some embodiments, the methods can include determining whether one or more cancer cells of the human's cancer overexpress CD200, relative to a control sample. In some embodiments, the control sample is obtained from the same human and comprises normal cells of the same tissue type as the human's cancer. In some embodiments, the control sample can be the expression level (or average expression level) of cells obtained from one or more humans who do not have cancer. In some embodiments, the cancer comprises cells (e.g., a plurality or even a majority of cells) that express or overexpress CD200 (e.g., CD200 protein and/or CD200 mRNA). In some embodiments, at least (or greater than) 10 (e.g., 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95) % of the cancer cells of the human's cancer overexpress CD200. In some embodiments, all assayed cancer cells overexpress CD200 relative to normal cells. In some embodiments, a cancer cell (e.g., a plurality of cancer cells, at least 10% of cancer cells, or all assayed cancer cells) can express CD200 protein at levels at least about 1.4 (e.g., at least about 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.2, 2.5, 3.0, 3.5, 4.0, 4.5, or 5 or more)-fold higher than the expression levels found on normal cells of the same histological type or higher than the average expression of normal cells from one or more patients who do not have cancer.

In some embodiments, an anti-CD200 antibody blocks immune suppression in cancer by targeting cancer cells that express CD200. Eradication, or inhibition, of these cancer cells can
stimulate the immune system and allow further eradication of cancer cells. In some embodiments, the combination of direct cancer cell killing and driving the immune response towards a Th1 profile provides enhanced efficacy in cancer treatment. Thus, in one embodiment, a cancer treatment is provided wherein a CD200 antibody or antigen-binding fragment thereof, both a) blocks the interaction between CD200 and its receptor and b) directly kills the cancer cells expressing CD200, is administered to a cancer patient. The mechanism by which the cancer cells are killed can include, but are not limited to, ADCC or CDC; fusion with a toxin; fusion with a toxic radioactive agent; fusion with a toxic polypeptide such as granzyme B or perforin; fusion with a cytotoxic virus (e.g., cytotoxic reovirus such as Reolysin®); or fusion with a cytokine such as TNF-a or IFN-a. In an alternative embodiment, a cancer treatment involves administering an antibody that both a) blocks the interaction between CD200 and its receptor and b) enhances cytotoxic T cell or NK cell activity against the tumor. Such enhancement of the cytotoxic T cell or NK cell activity may, for example, be combined by fusing the antibody with cytokines such as, e.g., IL-2, IL-12, IL-18, IL-13, and IL-5. In addition, such enhancement may be achieved by administration of an anti-CD200 antibody in combination with inhibitors such as IMiDs, thalidomide, or thalidomide analogs.

IX. Outcomes

Patients, e.g., humans, treated according to the methods disclosed herein preferably experience improvement in at least one sign of cancer. In one embodiment, improvement is measured by a reduction in the quantity and/or size of measurable tumor lesions. In another embodiment, lesions can be measured on chest x-rays or CT or MRI films. In another embodiment, cytology or histology can be used to evaluate responsiveness to a therapy.

In one embodiment, the patient treated exhibits a complete response, partial response, and/or stable disease. In another embodiment, the patient treated experiences tumor shrinkage and/or decrease in growth rate, i.e., suppression of tumor growth. In another embodiment, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: the number of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be
prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent.

In another embodiment, the methods of treatment produce a clinical benefit (e.g., Morphologic Complete Remission (Morphologic CR), cytogenetic complete remission (CRc), morphologic CR with incomplete blood count recovery (CRi), or partial remission (PR)).

Morphologic CR requires < 5% blasts in bone marrow aspirate, neutrophils ≥ 1,000/µL, platelets ≥ 100,000/µL, no extramedullar disease, no blasts with Auer rods detected, and No circulating blasts (rare may be permitted)/ No evidence of pre-treatment blast phenotype by flow cytometry (i.e. CD34, CD7 co-expression).

CRc requires < 5% blasts in bone marrow aspirate, neutrophils ≥ 1,000/µL, platelets ≥ 100,000/µL, no extramedullar disease, no blasts with Auer rods detected, and no circulating blasts (rare may be permitted)/ no evidence of pre-treatment blast phenotype by flow cytometry (i.e. CD34, CD7 co-expression), and reversion to a normal karyotype.

CRi requires < 5% blasts in bone marrow aspirate, neutrophils < 1,000/µL or Platelets < 100,000/µL, no extramedullar disease, no blasts with Auer rods detected, and no circulating blasts (rare may be permitted)/ no evidence of pre-treatment blast phenotype by flow cytometry (i.e. CD34, CD7 co-expression).

PR requires all criteria for CR except for bone marrow blasts, must have greater than 50% decrease in blasts in bone marrow aspirate to a range of 5-25%, neutrophils ≥ 1,000/µL, platelets ≥ 100,000/µL, no extramedullar disease, and if Auer rods are detected the blast count in the bone marrow must be ≤ 5%.

In certain aspects of the disclosure, the treatment produces a loss of bone marrow cellularity. In other embodiments, the bone marrow cellularity is ≤ 20% compared to control, as determined by bone marrow aspirate and biopsy. In other embodiments, the bone marrow cellularity is less than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1%.

In another aspect, the treatment produces a loss of leukemic blasts. In other embodiments, the leukemic blast are ≤ 20% compared to control, as determined by bone marrow aspirate and biopsy. In other embodiments, the leukemic blasts are ≤ 5%.
embodiments, the leukemic blasts are less than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1%, as determined by bone marrow aspirate and biopsy.

In another aspect, the treatment produces a desired immunomodulatory effect in a human (e.g., an AML patient). The immunomodulatory effect can be characterized by a change (e.g., an increase or a decrease) in at least one biomarker, e.g., an anti-CD200 antibody-associated immunomodulatory biomarker described herein, the change selected from the group consisting of: (i) a reduced concentration of regulatory T cells, relative to the concentration of regulatory T cells of the same histological type in the human prior to the first administration of the antibody; (ii) an increased concentration of CD8+ T cells, relative to the concentration of CD8+ T cells of the same histological type in the human prior to the first administration of the antibody; (iii) an increased concentration of activated T cells, relative to the concentration of activated T cells of the same histological type in the human prior to the first administration of the antibody; (iv) a reduced concentration of CD200+ leukocytes (e.g., CD200+ T cells), relative to the concentration of CD200+ leukocytes of the same histological type in the human prior to the first administration of the antibody; (v) an increase in the concentration of CD200R+ leukocytes (e.g., CD200R+ T cells), relative to the concentration of CD200R+ leukocytes of the same histological type in the human prior to the first administration of the antibody; (vi) a ratio of percent activated T cells to percent regulatory T cells (T regs) of at least 2:1 (e.g., at least 3:1, at least 4:1, at least 5:1, at least 6:1, or at least 7:1), relative to the ratio of activated T cells to T regs in the human prior to the first administration of the antibody; (vii) a decreased level of CD200 expression by a plurality of leukocytes in a biological sample obtained from a patient prior to administration to the patient of an anti-CD200 antibody, relative to the level of CD200 expression by a plurality of leukocytes of the same histological type in a biological sample from the patient prior to administration of the antibody; and (viii) an increased level of CD200R expression by a plurality of leukocytes in a biological sample from a patient administered an anti-CD200 antibody, relative to the level of CD200R expression by a plurality of leukocytes in a biological sample from the patient prior to administration of the anti-CD200 antibody.

In some embodiments, a reduction in CD200 expression by a plurality of leukocytes (e.g., bone marrow cells or splenocytes) in a biological sample obtained from the patient after administration of the anti-CD200 antibody, as compared to a control expression level (e.g., the
level of CD200 expression in a plurality of leukocytes of the same histological type in a biological sample obtained from the patient prior to administration of the anti-CD200 antibody) indicates that the anti-CD200 antibody has produced a desired immunomodulatory effect in the human. It is understood that any of the methods described herein can involve determining whether there has been a change (e.g., an increase or a decrease) in two or more (e.g., three, four, five, six, seven, eight, nine, or 10 or more) of the anti-CD200 antibody-associated biomarkers described herein. Where interrogation of more than one of the biomarkers is practiced, any combination of two or more (e.g., three, four, five, six, seven, eight, nine, or 10 or more) of the biomarkers can be analyzed.

In embodiments in which at least two (e.g., at least three, four, five, six, seven, eight, nine, 10, 11, 12, 13, or 14 or more) doses of the anti-CD200 antibody are administered to the human prior to detecting a change (e.g., an increase or a decrease) in the at least one biomarker, the detecting can occur, e.g., within (or less than) two months (e.g., less than eight weeks, seven weeks, six weeks, five weeks, one month, four weeks, three weeks, two weeks or 13 days, 12 days, 11 days, 10 days, nine days, eight days, seven days, six days, five days, or less than 5 days), and/or not until at least 1 day (e.g., at least two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, or three weeks, four weeks, a month, five weeks, six weeks, seven weeks, or eight weeks or more) after, the last dose of the multiple dose anti-CD200 antibody regimen is administered to the human. In some embodiments, the detecting can occur between dosing (e.g., between the first and second dose, between the second and third dose, between the third and fourth dose, between the fifth and six dose, and/or between the seventh and eighth dose). Such detection can be useful for determining a dosing schedule for the human that is effective to maintain the immunomodulatory effect (e.g., the peak or maximum level of the immunomodulatory effect) in the human over the course of treatment.

In some embodiments of any of the methods described herein, the regulatory T cells can be FoxP3+, e.g., CD3+CD4+CD25+FoxP3+ T cells or CD3+CD4+FoxP3+ T cells. In some embodiments of any of the methods described herein, the activated T cells can be, e.g., CD3+CD4+CD25+FoxP3neg T cells or CD3+CD4+FoxP3neg T cells.
Methods for measuring the concentration of CD200+ cells (e.g., CD200+ T cells) are well known in the art and include, among other methods, flow cytometry. See, e.g., Chen et al. (2009) *Mol Immunol* 46(10): 1951-1963. In some embodiments, a practitioner can interrogate a biological sample obtained from a post-treatment patient (a patient to which an anti-CD200 antibody has already been administered) for the concentration of cells of a particular subset of CD200+ leukocytes (e.g., T cells). For example, a practitioner can determine the concentration of CD200+ T cells and/or the concentration of activated CD200+ T cells present in a biological sample from a post-treatment patient. In some embodiments, a practitioner can determine the concentration of CD200+/CD8+ cells. In each case, a reduction in the concentration of CD200+ T cells of a given subset, as compared to control concentration of CD200+ T cells of the same histological type, indicates that the anti-CD200 antibody has produced in the human a desired immunomodulatory effect.


In some embodiments, a practitioner can interrogate a biological sample (e.g., a blood sample) obtained from a post-treatment patient (a patient to which an anti-CD200 antibody has been administered) for the CD200 and/or CD200R expression level (e.g., the average expression level) by a plurality of leukocytes of a given histological type. For example, a practitioner can determine the expression level or average expression level of CD200R by a plurality of CD4+ T cells, CD8+ T cells, activated CD4+ T cells, NK T cells, or CD217CD257Fox3P + T cells. In one instance, an increase in CD200R expression by a given subset of leukocytes, as compared to control expression level (e.g., the average level of expression of leukocytes of the same histological type in a biological sample obtained from the patient prior to administration of the
antibody), indicates that the anti-CD200 antibody has produced in the human a desired immunomodulatory effect.

In some embodiments, immune competence can be determined by quantifying the absolute number of certain lymphocyte populations in a biological sample (e.g., a blood sample) obtained from a patient as measured by, e.g., flow cytometry. See, e.g., Shearer et al. (2003) *J Allergy Clin Immunol* 112(5):973-980 and Paglieroni and Holland (1994) *Transfusion* 34:512-516. For example, in some embodiments, immune competence is indicated by a CD45+ lymphocyte count, by flow cytometry, of: 0.66-4.60x10^3 cells/µL (for patients 0 to 17 years of age); 0.99-3.15x10^3 cells/µL (for patients aged 18 to 55 years); or 1.00-3.33x10^3 cells/µL (for patients older than 55 years).

In some embodiments, immune competence can be determined by quantifying the absolute number of CD3+ Τ cells, by flow cytometry, in a biological sample obtained from a patient. For example, in some embodiments, immune competence is indicated by a CD3+ lymphocyte count, by, e.g., flow cytometry, of: 2,500-5,500 cells/µL (for patients 0 to 2 months of age); 2,500-5,600 cells/µL (for patients aged 3 to 5 months); 1,900-5,900 cells/µL (for patients aged 6 to 11 months); 2,100-6,200 cells/µL (for patients aged 12 to 23 months); 1,400-3,700 cells/µL (for patients aged 2 to 5 years); 1,200-2,600 cells/µL (for patients aged 6 to 11 years); 1,000-2,200 cells/µL (for patients aged 12 to 17 years); 677-2,383 cells/µL (for patients aged 18 to 55 years); or 617-2,254 cells/µL (for patients older than 55 years of age).

In some embodiments, immune competence can be determined by quantifying the absolute number of CD19+B cells, by, e.g., flow cytometry, in a biological sample obtained from a patient. For example, in some embodiments, immune competence is indicated by a CD19+B cell count, by flow cytometry, of: 300-2,000 cells/µL (for patients 0 to 2 months of age); 430-3,000 cells/µL (for patients aged 3 to 5 months); 610-2,600 cells/µL (for patients aged 6 to 11 months); 720-2,600 cells/µL (for patients aged 12 to 23 months); 390-1,400 cells/µL (for patients aged 2 to 5 years); 270-860 cells/µL (for patients aged 6 to 11 years); 110-570 cells/µL (for patients aged 12 to 17 years); 99-527 cells/pt (for patients aged 18 to 55 years); or 31-409 cells/µL (for patients older than 55 years of age).

In some embodiments, immune competence can be determined by quantifying the absolute number of CD16+CD56+ Natural Killer (NK) cells, by, e.g., flow cytometry, in a
biological sample obtained from a patient. For example, in some embodiments, immune competence is indicated by a CD16+/CD56+ NK cell count, by flow cytometry, of: 170-1,100 (for patients 0 to 2 months of age); 170-830 cells/µL (for patients aged 3 to 5 months); 160-950 cells/µL (for patients aged 6 to 11 months); 180-920 cells/µL (for patients aged 12 to 23 months); 130-720 cells/µL (for patients aged 2 to 5 years); 100-480 cells/µL (for patients aged 6 to 11 years); 110-570 cells/µL (for patients aged 12 to 17 years); 101-678 cells/µL (for patients aged 18 to 55 years); or 110-657 cells/µL (for patients older than 55 years of age).

In some embodiments, immune competence can be determined by quantifying the absolute number of CD4+ Helper T cells, by, e.g., flow cytometry, in a biological sample obtained from a patient. For example, in some embodiments, immune competence is indicated by a CD4+ Helper T cell count, by flow cytometry, of: 1,600-4,000 (for patients 0 to 2 months of age); 1,800-4,000 cells/µL (for patients aged 3 to months); 1,400-4,300 cells/µL (for patients aged 6 to 11 months); 1,300-3,400 cells/µL (for patients aged 12 to 23 months); 700-2,200 cells/µL (for patients aged 2 to 5 years); 650-1,500 cells/µL (for patients aged 6 to 11 years); 530-1,300 cells/µL (for patients aged 12 to 17 years); 424-1,509 cells/µL (for patients aged 18 to 55 years); or 430-1,513 cells/µL (for patients older than 55 years of age).

In some embodiments, immune competence can be determined by quantifying the absolute number of CD8+ T cells, by, e.g., flow cytometry, in a biological sample obtained from a patient. For example, in some embodiments, immune competence is indicated by a CD8+ T cell count, by flow cytometry, of: 560-1,700 (for patients 0 to 2 months of age); 590-1,600 cells/µL (for patients aged 3 to 5 months); 500-1,700 cells/µL (for patients aged 6 to 11 months); 620-2,000 cells/µL (for patients aged 12 to 23 months); 490-1,300 cells/µL (for patients aged 2 to 5 years); 370-1,100 cells/µL (for patients aged 6 to 11 years); 330-920 cells/µL (for patients aged 12 to 17 years); 169-955 cells/µL (for patients aged 18 to 55 years); or 101-839 cells/µL (for patients older than 55 years of age).

Methods for determining immune response following treatment with an ani-CD200 antibody, or antigen-binding fragment thereof, are elaborated on in, e.g., U.S. Pat. No. 9,180,186.
X. Kits and Unit Dosage Forms

Also provided herein are kits which include a pharmaceutical composition containing an anti-CD200 antibody, anti-metabolic agent (e.g., cytarabine), and a topoisomerase inhibitor (e.g., daunorubicin), in a therapeutically effective amount adapted for use in methods described herein. In one embodiment, the anti-CD200 antibody is, e.g., samalizumab (ALXN6000). In one embodiment, the anti-metabolic agent is cytarabine. In one embodiment, the topoisomerase inhibitor is daunorubicin. The kits optionally also can include instructions, e.g., comprising administration schedules, to allow a practitioner (e.g., a physician, nurse, or patient) to administer the composition contained therein to a patient having cancer. The kit also can include a syringe.

Optionally, the kits include multiple packages of the single-dose pharmaceutical compositions each containing an effective amount of the anti-CD200 antibody, or antigen-binding fragment thereof, anti-metabolic agent (e.g., cytarabine), and a topoisomerase inhibitor (e.g., daunorubicin) for administration in accordance with the methods provided herewith. Instruments or devices necessary for administering the pharmaceutical composition(s) also may be included in the kits. For instance, a kit may provide one or more pre-filled syringes containing an amount of the anti-CD200 antibody, cytarabine, and daunorubicin.

In one embodiment, the anti-CD200 antibody comprises the CDR1, CDR2, and CDR3 domains in a heavy chain variable region having the sequence set forth in SEQ ID NO: 11, and the CDR1, CDR2, and CDR3 domains in a light chain variable region having the sequence set forth in SEQ ID NO: 10.

Kits comprising the anti-CD200 antibody, daunorubicin, and/or cytarabine may have doses for each drug as outlined above. Additionally, each kit may also include instructions for administration of each drug according to the schedules described herein.

The following examples are merely illustrative and should not be construed as limiting the scope of this disclosure in any way as many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

The contents of all references, Genbank entries, patents and published patent applications cited throughout this application are expressly incorporated herein by reference.
EXAMPLES

Example 1: Dosing regimens and PK/PD analysis

Based on extensive pharmacokinetic (PK) and pharmacodynamic (PD) studies the following dosing regimen was identified as sufficient to achieve an adequate PK concentration range and to saturate CD200 receptors.

Dose Regimen 1 (Q3W with loading dose, mg/m^2 dosing):

• 300 mg/m^2, 600 mg/m^2, or 900 mg/m^2 of the drug administered by IV on Day 0, Day 2, and every 21 days thereafter.

Estimated PK values are shown in Table 1. Estimated PD parameters for B-CLL CD200^[MFI] and CD200^CD4+T cells are shown in Tables 2 and 3. Additionally, Figure 1 demonstrates the dependence of total, linear, and nonlinear clearance (CL) on samalizumab serum concentration. Figure 1 further shows that samalizumab receptor mediated clearance is saturated at > 100 μg/ml serum concentration.

Analysis of the dosing regimen was conducted to determine (1) estimated mean exposure, (2) median drug concentration predictions over time, and (3) percent change in B-CLL CD200^[MFI] and CD200^CD4+T cells over time. For example, Table 4 shows the Mean (SD) exposure estimates for the dosing regimen.

Table 1: Samalizumab PK parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>%RSE</th>
<th>Variability</th>
<th>Shrinkage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/day)</td>
<td>θ₁</td>
<td>0.216</td>
<td>48.5</td>
<td></td>
</tr>
<tr>
<td>V₁ (L)</td>
<td>θ₂</td>
<td>5.09</td>
<td>7.01</td>
<td></td>
</tr>
<tr>
<td>Q (L/day)</td>
<td>θ₃</td>
<td>1.29</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>V₂ (L)</td>
<td>θ₄</td>
<td>4.59</td>
<td>4.83</td>
<td></td>
</tr>
<tr>
<td>K_{ss} (μg/mL)</td>
<td>θ₅</td>
<td>5.54</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Estimate</td>
<td>% RSE</td>
<td>Variability</td>
<td>Shrinkage (%)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------</td>
<td>---------</td>
<td>--------------</td>
<td>---------------</td>
</tr>
<tr>
<td>$V_{max}$ (mg/day)</td>
<td>$\theta_6$</td>
<td>1.58</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>$CL_{WT}$</td>
<td>$\theta_7$</td>
<td>1.65</td>
<td>35.3</td>
<td></td>
</tr>
<tr>
<td>$\omega_{CL}$</td>
<td>$\Omega(1,1)$</td>
<td>1.11</td>
<td>38.9</td>
<td>CV=105%</td>
</tr>
<tr>
<td>$\omega_{v1}$</td>
<td>$\Omega(2,2)$</td>
<td>0.0868</td>
<td>49.7</td>
<td>CV=29.5%</td>
</tr>
<tr>
<td>$\omega_{vmax}$</td>
<td>$\Omega(6,6)$</td>
<td>1.02</td>
<td>46.8</td>
<td>CV=101%</td>
</tr>
<tr>
<td>$\sigma^2_{Prop}$</td>
<td>$\Sigma(1,1)$</td>
<td>0.0312</td>
<td>6.93</td>
<td>CV=17.7%</td>
</tr>
</tbody>
</table>

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100*SE/PE; CV: coefficient of variation, CV=100*$\omega$%.

Table 2: PD Parameter Estimates (B-CLL CD200+[MFI])
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>%RSE</th>
<th>Variability</th>
<th>Shrinkage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASE&lt;sub&gt;v3&lt;/sub&gt;</td>
<td>θ&lt;sub&gt;8&lt;/sub&gt;</td>
<td>7.78</td>
<td>38.4</td>
<td></td>
</tr>
<tr>
<td>K&lt;sub&gt;DEGv3&lt;/sub&gt; (day&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>θ&lt;sub&gt;9&lt;/sub&gt;</td>
<td>0.191</td>
<td>32.8</td>
<td></td>
</tr>
<tr>
<td>EC&lt;sub&gt;50v3&lt;/sub&gt; (µg/mL)</td>
<td>θ&lt;sub&gt;10&lt;/sub&gt;</td>
<td>2.59</td>
<td>83.4</td>
<td></td>
</tr>
<tr>
<td>EMAX&lt;sub&gt;v3&lt;/sub&gt;</td>
<td>θ&lt;sub&gt;11&lt;/sub&gt;</td>
<td>4.67</td>
<td>32.2</td>
<td></td>
</tr>
<tr>
<td>γ&lt;sub&gt;v3&lt;/sub&gt;</td>
<td>θ&lt;sub&gt;12&lt;/sub&gt;</td>
<td>1.99</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>ω&lt;sup&gt;2&lt;/sup&gt; Eco5v3</td>
<td>Ω(1,1)</td>
<td>3.19</td>
<td>78.4</td>
<td>CV=179%</td>
</tr>
<tr>
<td>ω&lt;sup&gt;2&lt;/sup&gt; Emaxv3</td>
<td>Ω(2,2)</td>
<td>0.75</td>
<td>44.1</td>
<td>CV=86.6%</td>
</tr>
<tr>
<td>ω&lt;sup&gt;2&lt;/sup&gt; BASEv3</td>
<td>Ω(3,3)</td>
<td>0.0231</td>
<td>121</td>
<td>CV=15.2%</td>
</tr>
<tr>
<td>σ&lt;sup&gt;2&lt;/sup&gt; Propv3</td>
<td>Σ(1,1)</td>
<td>0.237</td>
<td>12.3</td>
<td>CV=48.7%</td>
</tr>
<tr>
<td>σ&lt;sup&gt;2&lt;/sup&gt; Addv3</td>
<td>Σ(2,2)</td>
<td>1.99</td>
<td>22.6</td>
<td>SD=1.41</td>
</tr>
</tbody>
</table>

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100*SE/PE. CV: coefficient of variation, CV=100*σ%. 

Table 3: PD Parameter Estimates (CD200+CD4+ T cells %)

Table 4: Mean (SD) Exposure Estimates for the Dosing Regimen

<table>
<thead>
<tr>
<th>Exposure Parameter</th>
<th>DOSE (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>117 (30.3)</td>
</tr>
<tr>
<td>$C_{max2}$</td>
<td>180 (42.6)</td>
</tr>
<tr>
<td>$C_{min}$</td>
<td>45.8 (28.2)</td>
</tr>
<tr>
<td>AUC$_1$</td>
<td>1750 (622)</td>
</tr>
<tr>
<td>$C_{maxSS}$</td>
<td>185 (83.8)</td>
</tr>
<tr>
<td>$C_{minSS}$</td>
<td>70 (74.2)</td>
</tr>
<tr>
<td>AUC$_{SS}$</td>
<td>2040 (1640)</td>
</tr>
<tr>
<td>$R_{Cmax}$</td>
<td>1.01 (0.341)</td>
</tr>
<tr>
<td>$R_{Cmin}$</td>
<td>1.15 (0.747)</td>
</tr>
<tr>
<td>RAUC</td>
<td>1.03 (0.576)</td>
</tr>
</tbody>
</table>

Figure 2 demonstrates a model prediction for drug concentrations using the dosing regimen (i.e., 300 mg/m², 600 mg/m², or 900 mg/m² by IV on Day 0, Day 2, and every 21 days thereafter). Specifically, Figure 2 demonstrates that a loading dose on Day 1 increased PK exposure for Cycle 1 to be comparable to the PK exposure at steady state. PK exposures appear comparable for all cycles. Additionally, samalizumab concentrations are > 100 µg/mL for 600 mg/m² and 900 mg/m² for all dosing cycles. Moreover, for the 300 mg/m² dosing regimen, concentration was < 100 µg/mL for $C_{min}$ and $C_{min,ss}$.

Figures 3A-3F demonstrate median and 80% prediction intervals for percent change from baseline of B-CLL CD200+[MFI] and CD200+CD4+ T cells for the dosing regimen. Specifically, Figures 3A-3F show that maximum change from baseline was reached after the 2nd dose. Median change from baseline for B-CLL CD200+ (MFI) was ~ 40 to 90% for 3 dose regimens. A dose dependent effect was evident, as well as more fluctuations at the lower dose of 300 mg/m² during a dosing interval. Median change from baseline for CD200+CD4+ T cells was about 80 to about 90%, and maximum change was reached for all 3 doses.

In summary, the PK simulation indicates that the above dosing regimens would provide PK exposures in the adequate PK concentration range to saturate receptors. With a loading dose, steady state PK exposure is reached after the 2nd dose in cycle 1. The dose reached maximum reduction of CD200+CD4+ T cells (~ 80%) after the 2nd dose and maintained reduction during a
21-day dosing interval. A dose-dependent reduction of B-CLL CD200+(MFI) cells was also shown. The PK-Tumor response relationship indicates that an increase of doses above 400 and 500 mg/m² is projected to have improved clinical benefit.

Example 2: Clinical trial of samalizumab

The first-in-human trial of samalizumab was conducted in patients with CLL under protocol C07-003 (ClinicalTrials.gov: NCT00648739). This was a Phase I/II open-label, dose-escalation study in patients with refractory, relapsing, or previously untreated advanced CLL evaluating safety, PK, pharmacodynamics (PD), and preliminary observations of efficacy. Twenty-three CLL patients were enrolled in 6 cohorts at doses ranging from 50-500 mg/m². Three extremely advanced patients with Multiple Myeloma were enrolled toward the end of the trial: 2 at 500 mg/m² and 1 at 600 mg/m². Patients received a single initial intravenous (IV) dose of samalizumab and could receive additional doses at 28-day cycles (1 dose/cycle) if the first dose was well tolerated (over 6 weeks) and if the patient exhibited at least stable disease (SD).

The trial was originally designed to allow a maximum of 4 cycles of therapy, and later amended to allow ongoing every 4-week cycles as long as the therapy continued to be well tolerated and the patients maintained SD or better. SD was defined as <50% increase in the sum of the products of at least 2 lymph nodes, no new lesions, <50% increase in absolute blood lymphocyte count, and no transition to aggressive histology. Assessments performed throughout cycle 1 and then every 2 weeks, included standard safety measures, anti-drug antibody (ADA), PK, PD, complete blood count (CBC), and follow up computerized tomography (CT) scans (at end of cycle 1, cycle 4 and every other cycle thereafter). No maximum tolerated dose (MTD) was identified during this trial.

Of the 26 patients treated with samalizumab, 25 (96%) patients experienced at least 1 adverse event (AE), 5 (19%) patients reported AEs that led to drug discontinuation, and 6 (23%) patients reported serious adverse events (SAE). A total of 6 (23%) patients reported AEs not related to study drug. Fifteen (58%) patients reported AEs that were possibly related to the study drug, and 4 (15%) patients reported AEs that were probably or definitely study drug-related. Samalizumab dosing was not associated with potent cytokine adverse reactions at any time point. Generally, AEs were mild and moderate in severity (>50% of patients) and manageable; 7 (27%)
patients reported severe AEs and 3 (12%) patients experienced life-threatening or disabling AEs. There was 1 (4%) death in this clinical study, which was judged unrelated to the study medication.

A total of 256 treatment-related adverse events were reported by 25 (96%) patients enrolled in the study. The most frequent event was fatigue reported by 12 patients (46%), followed by headache, pyrexia, and rash, each reported by 5 patients (19%). One event (dose group 200 mg/m²) was judged to be definitely related. This event was an allergic reaction associated with a pre-dose positive anti-drug antibody level.

Evidence for anti-tumor effect was observed in 77% (17/22) of evaluable CLL patients following samalizumab dosing (16 patients with SD and 1 with confirmed partial response [PR]). Disease progression was observed in 5 patients. The 16 patients who achieved SD were found across all dosing cohorts after 29-525 days of dosing. Most of these patients (13/16, 81%) had 4 or fewer dosing cycles; only 3 SD patients received 6 or more cycles; 2 received 6 cycles and one received 18 cycles.

Twenty-two of the 23 CLL patients in the trial had bulky disease evaluable by CT scan. Of the 22 patients whose target lesions were measured at baseline, 14 (64%) showed a decrease in measureable lesions at any time following treatment with samalizumab. Of these 14 patients, 11 (79%) did so after Cycle 1, between Days 28-42. Three did not have any reduction in lesion size after the initial dose, but did have reduction at a later cycle of dosing: Patient 102-303 (200 mg/m²) at Cycle 3, Patient 102-401 (300 mg/m²) at Cycle 14, and Patient 101-606 (500 mg/m²) at Cycle 4. Nine patients (41%) had a sustained cumulative maximal decrease in tumor burden (World Health Organization [WHO] criteria) of >10%. The maximum percent change from baseline in bulky adenopathy burden (sum of the bi-dimensional products of all target lesions) for each patient is shown in Figure 4.

A >30% decrease in tumor burden was observed in two of 22 (9%) evaluable CLL (two of 7 at the highest doses) patients. Patient 102-601 (500 mg/m²) had a maximum decrease of 40.5%, and Patient 102-502 (400 mg/m²) had a maximum decrease of 63.4%. These responses correlated with comparatively robust CD200 target down-regulation on tumor cells and T cells. In evaluable patients, biomarker and PD marker findings included:
Deerased CD200 on peripheral B-cell chronic lymphocytic leukemia (B-CLL) cells in 86% (18/21 patients) (sustained at higher doses).

Decreased CD200 expression on CD4+ T cells in 95% (19/20 patients) (sustained at higher doses) and concomitant increase in CD200R+ T cells in 42% (8/19 patients).

A reduction in peripheral Tregs in 36% (9/25 patients).

A modest first-dose Th1 cytokine response in 40% (10/25 patients); 88% (22/25 patients) with detectable Th1 cytokines at one or more time points during the study.

Example 3: Phase Ib/2 Trial in AML Patients

The open-label Phase Ib/2 clinical study is samalizumab administration given in addition to standard induction chemotherapy/consolidation, followed by samalizumab maintenance, in newly-diagnosed AML. The target population is assigned by Beat AML, a division of the Leukemia and Lymphoma Society (LLS), Master Protocol (the "umbrella" study) and targets patients age 60+ years with newly diagnosed, previously untreated, CBF-positive AML and marker negative (as defined by Beat AML) AML patients.

A. Objectives

The primary objective for the Phase 1b trial is to determine a well-tolerated and biologically active dose (BAD) of samalizumab in combination with standard induction/consolidation therapy for newly diagnosed marker-negative and core-binding factor (CBF)-positive acute myeloid leukemia (AML) patients ≥ 60 years old.

The primary objective for Phase 2 is to determine the complete remission (CR) rate with samalizumab in combination with induction therapy in newly diagnosed CBF-positive AML patients ≥ 60 years old.

The secondary objectives are to determine the 2-year progression-free survival (PFS) with samalizumab in combination with induction/consolidation followed by maintenance therapy in newly diagnosed CBF-positive AML patients ≥ 60 years old. Additionally, the study characterizes samalizumab pharmacokinetics (PK) following administration of samalizumab in combination with induction/consolidation followed by maintenance therapy in newly diagnosed marker-negative and CBF-positive AML patients ≥ 60 years old. Finally, the study is designed...
to determine if samalizumab treatment promotes development of anti-drug (samalizumab) antibody (ADA) in newly diagnosed marker-negative and CBF positive AML patients ≥ 60 years old.

Exploratory objectives of the study are to explore the relationships between samalizumab PK exposure and clinical response and to assess changes in immune cell responses (pharmacodynamic [PD] effects) with the addition of samalizumab to induction/consolidation therapy followed by samalizumab maintenance. Additionally, the study is designed to assess the relationship between minimal residual disease (MRD) and long-term PFS, as well as the prevalence and trajectories of patient-reported symptoms during the course of induction, consolidation, maintenance and follow-up.

B. Trial Design Summary

Samalizumab is given Days 1 and 3, followed by 7+3 induction chemotherapy starting on Day 4. Samalizumab is given again on Day 24. The therapeutic goal of adding samalizumab is to attain saturation of CD200 antigen expression on tumor and/or immune cells prior to starting chemotherapy that persists to the Day 24 time point in the study and to enhance anti-tumor immunity with long-term treatment while not increasing the toxicity of standard induction or consolidation chemotherapy. The Phase 1b part of the study is designed to establish a tolerable and biologically active dose for the combination regimen that will include both CBF and marker negative patients. The Phase 2 part of the study is designed to establish efficacy in the CBF AML population, including the complete remission (CR) rate and progression free survival (PFS) in the CBF patients relative to a historical control population.

CD200 saturation levels are assessed by the expression of CD200 on peripheral (and if feasible, bone marrow) immune effector T cells and monocytes (or residual AML cells if present) on Day 24 (prior to Day 24 samalizumab dosing). If 90% or higher of CD200 saturation is present in 5 of 6 patients at Day 24 of induction chemotherapy, and overall treatment toxicity is acceptable, the dose of anti-CD200 antibody is escalated one level above saturation to assure acceptable toxicity. The reasoning for further dose escalation is that the majority of patients enrolled in Phase 1b are marker negative (due to known rates of marker negative versus CBF in the general AML population) and CBF patients have higher expression of CD200 therefore are
likely to require higher dosing for CD200 saturation. If toxicity is acceptable at the higher dose, treatment moves forward with this dose for Phase 2 in CBF patients only.

If 90% of CD200 saturation is present and toxicity is unacceptable - defined as 2 of 6 patients with dose limiting toxicities (DLTs) - dosage of samalizumab treatment is continued using the same schedule and dosing of the conventional chemotherapy. If 90% or higher of CD200 saturation is not seen in 5 of 6 patients, and the treatment regimen is tolerated in either dose level 1 or 2, further dose escalation occurs. If neither saturation nor acceptable toxicity are able to be obtained, the treatment is stopped.

Patients who achieve complete remission (CR) after 1 or 2 cycles of induction (see treatment plan for details regarding Reinduction guidelines) undergo 4 cycles of consolidative chemotherapy with high-dose cytarabine/samalizumab (dose level the same as induction therapy). Irrespective of the ability to complete 4 cycles of cytarabine, samalizumab is administered every 21 days for 2 years in the absence of toxicity or disease progression. Safety assessment for Phase 1b is completed after 1st cycle of cytarabine/samalizumab consolidation.

Once a well-tolerated and biologically active dose has been determined in Phase 1b, the Phase 2 portion is initiated in the CBF patient population only. The Phase 2 treatment is a Simon's two stage design to assess efficacy with CR rates followed by an Expansion Phase to assess efficacy in terms of 2-year PFS. All patients receiving the recommended Phase 2 dose are included in the efficacy analysis. If 6 or fewer of 9 patients achieve CR, the treatment is terminated. If CR is seen in at least 7 of 9 patients, an additional 19 patients are enrolled. If ≥ 23 of 28 patients achieve CR, a Phase 2 expansion occurs with an additional 27 patients. All patients are followed for two years to assess PFS. PFS of >70% is considered efficacious and worthy of future study in this patient population.

C. Patient Inclusion Criteria

Patients must meet all of the following criteria to be enrolled in this study:

1. Adults, age 60 years or older at the time of diagnosis.

2. Subjects or their legal representative must be able to understand and provide written informed consent.

3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
4. Aspartate aminotransferase (AST) < 5x upper limit of normal (ULN), alanine aminotransferase (ALT) < 5x ULN, and total bilirubin < 2x ULN (except for patients with known Gilbert's syndrome) for the local laboratory.

5. Adequate renal function as defined by calculated creatinine clearance (according to the Cockcroft-Gault equation) > 40 mL/min OR serum creatinine < 1.5 x the ULN for the local laboratory.

6. Female patients of child-bearing potential must agree to use adequate contraception (two forms of contraception or abstinence) from the screening visit until 30 days following the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Male patients of childbearing potential having intercourse with females of childbearing potential must agree to abstain from heterosexual intercourse or have their partner use two forms of contraception from the screening visit until 90 days until the last dose of study treatment. They must also refrain from sperm donation from the screening visit until 90 days following the last dose of study treatment.

7. No prior chemotherapy, targeted therapy or immunotherapy for leukemia or myelodysplastic syndrome (MDS), except hydroxyurea to control leukocytosis which is permitted.

Patients must meet all of the following criteria to be enrolled in the Phase 1b portion of the study.

1. AML with marker negative status defined based on the Beat AML assignment
2. AML with CBF karyotype/interphase cytogenetics/molecular testing defined by presence of t(8;21)(q22;q22) or the molecular equivalent RUNX1/RUNX1T1 fusion transcript or inv(16)(pl3q22) or t(16;16)(pl3;q22) or the molecular equivalent CBFB/MYH11 fusion transcript based on the Beat AML assignment.

Patients must meet all of the following criteria to be enrolled in the Phase 2 portion of the study.

1. AML with CBF karyotype/interphase cytogenetics/molecular testing defined by presence of t(8;21)(q22;q22) or the molecular equivalent RUNX1/RUNX1T1 fusion
transcript or inv(16)(p13q22) or t(16;16)(p13;q22) or the molecular equivalent
CBFB/MYH11 fusion transcript based on the Beat AML assignment.

2. Candidate for intensive induction chemotherapy.
3. If the patient has co-morbid illness, life expectancy attributed to this must be greater than 2 years.
4. Left ventricular ejection fraction at or above the lower limit of institutional normal by echocardiogram or multigated acquisition (MUGA) scan.

D. Patient Exclusion Criteria

Patients meeting any of the following criteria are excluded from the study:

1. Isolated myeloid sarcoma (meaning, patients must have blood or marrow involvement with AML to enter the study).
3. Symptomatic central nervous system (CNS) involvement by AML.
4. Signs of leukostasis requiring urgent therapy.
5. Disseminated intravascular coagulopathy with active bleeding or signs of thrombosis.
6. Patients with psychological, familial, social, or geographic factors that otherwise preclude them from giving informed consent, following the protocol, or potentially hamper compliance with study treatment and follow-up.
7. Any other significant medical condition, including psychiatric illness or laboratory abnormality, that would preclude the patient participating in the trial or would confound the interpretation of the results of the trial.
8. Known active Human Immunodeficiency Virus (HIV), active hepatitis B or active hepatitis C infection.
9. Patients who require full-dose anticoagulation; anti-coagulants administered for the purpose of maintaining the patency of a central venous access device is permitted.
10. History of grade IV anaphylactic reaction to monoclonal antibody therapy.
11. Active or prior history of symptomatic autoimmune pneumonitis.
12. Patients with the following will be excluded: uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmia, myocardial infarction within 6 months prior to enrollment, New York Heart Association (NYHA) Class III or IV heart failure, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Patients with medical comorbidities that will preclude safety evaluation of the combination should not be enrolled.

13. Patients with active advanced malignant solid tumors are excluded. Patients with active additional hematologic malignancies that require treatment are excluded.

E. Criteria for Discontinuation

The treatment protocol is discontinued if any one of the follow events occur:

1. Treatment failure
2. Death
3. Withdrawal of consent
4. An AE or intercurrent illness that precludes further administration of protocol therapy or participation in the study.
5. Need for, or use of, a prohibited concomitant medication
6. Loss to follow-up
7. The trial is discontinued due to undue safety issues or at the request of the Food and Drug Administration (FDA)

F. Study Drug Preparation and Administration

Samalizumab is provided in 20 mL vials containing 20 mL of formulated active agent at a concentration of 5 mg/mL, for a total of 100 mg per vial. Each patient's dosage is calculated based on body surface area and the dosage cohort the patient is enrolled in.

The drug is diluted with an equal volume of 0.45% Sodium Chloride Injection, USP provided by the investigational site using aseptic technique by withdrawing the required amount of samalizumab from the vial(s) and the transferring the dosage to an infusion bag and diluted with an equal volume of 0.45% Sodium Chloride Injection, USP by addition to the infusion container. After dilution, the infusion bag containing the diluted samalizumab solution is gently
agitated to ensure thorough mixing of the product and diluent. The remaining unused portion of
samalizumab is discarded (after drug accountability is performed by the monitor), as the product
contains no preservatives. The partial and empty vials are destroyed prior to monitoring if
required by the site's operating procedures. The diluted solution may remain unprotected from
light for up to 24 hrs before administration begins.

The drug is not administered as an IV push or bolus injection. Samalizumab is
administered intravenously at 125 mL/hour. The diluted solution is infused via any approved
infusion pump and include an IV filter of 0.20-0.22 microns between the infusion container and
the patient.

Patients are closely monitored for at least 60 minutes after the infusion for safety
purposes. Parenteral drug products are inspected visually for particulate matter and discoloration
prior to administration. It is not necessary to protect the diluted solution of samalizumab from
light during administration to the patient.

G. Infusion Reactions and Management

Samalizumab is an antibody that has been designed to be compatible with the human
immune system; however, the possibility of infusion reactions exists. Infusion reactions are
defined according to the NCI-CTCAE version 4.03. Management is determined according to
grade of toxicity.

If toxicity of Grades 1 or 2 occur, the infusion is discontinued and acetaminophen (650
mg), diphenhydramine (25 mg intravenous) and dexamethasone (20 mg intravenous) are
administered to treat signs and symptoms if clinically indicated. Once symptoms have resolved,
the infusion is restarted at 50% of the baseline rate. If the patient's symptoms do not return and
vital signs are stable after one hour of the reduced rate, the infusion rate is increased every 30
minutes as tolerated. Vital signs are measured every 15 minutes or less as clinically indicated.
For patients who are able to tolerate an increase in the infusion rate back to baseline and
maintain normal blood pressure for 30 minutes after the rate increase then, the frequency of vital
sign assessment is reduced to every 30 minutes during the infusion.

The patient is monitored for worsening of the condition. If severity increases to a higher
Grade (Grade 3 or 4), the infusion is stopped. Patients with maximum Grade 2 infusion reactions
who continue treatment will receive prophylactic pre-medication until all infusion events resolve. These medications include acetaminophen 650mg PO, diphenhydramine 50 mg IV (which may be dose reduced or discontinued, if it is not tolerated due to side effects), and dexamethasone 20mg IV, all of which are given 30-60 minutes prior to the dose of samalizumab.

If Grade 3 toxicities are observed, the infusion is stopped and the infusion tubing is disconnected from the patient. Diphenhydramine hydrochloride 50 mg IV, dexamethasone 20 mg IV (or equivalent), and other medications/treatment are administered as medically indicated. Additionally, epinephrine or bronchodilators are administered as indicated.

Patients with Grade 3 infusion reactions resume treatment if all infusion-related toxicities resolve within 24 hours. Premedications are given as listed for Grade 1 and 2 infusion reactions. If a Grade 3 infusion reaction occurs with the same severity, treatment is permanently discontinued.

If Grade 4 toxicities are observed, the infusion is stopped and the infusion tubing is disconnected from the patient. Diphenhydramine hydrochloride 50 mg IV, dexamethasone 20 mg IV (or equivalent), and other medications/treatment are administered as medically indicated. Epinephrine or bronchodilators are administered as indicated. Patients with Grade 4 infusion reaction will not receive further samalizumab treatment and will be withdrawn from the protocol.

**H. Treatment Plan and Procedures**

**Phase 1b Treatment plan:**

**Induction**

An overview of the induction phase protocol is set forth in Table 5 (Phase 1b) and Table 9 (Phase 2). During the induction phase samalizumab is administered at a dose level 1 of 300 mg/m\(^2\) (or a Dose level 2 - 600 mg/m\(^2\)) at 125 mL/hr on Days 1, 3, and 24. Daunorubicin is administered at a dose of 60 mg/m\(^2\)/day IV over 15 minute on Days 4-6 and cytarabine is administered at a dose of 100 mg/m\(^2\) IV over 24 hours daily on Days 4-10.

Bone marrow aspirate and biopsy will be obtained, and necessity for second remission induction will be determined in a Day 24 bone marrow examination. A second induction course is given if bone marrow examination reveals >20% bone marrow cellularity and >5% leukemic blasts.
A second bone marrow aspirate and biopsy is performed at time of hematological recovery when absolute neutrophil count (ANC) is \( \geq 1000/\mu L \) and platelet count is \( \geq 100,000/\mu L \). This is the Day 24 bone marrow biopsy if count recovery has occurred. If counts have not recovered at this time, then a subsequent biopsy is performed. If no evidence of hematological recovery by Day 45, a bone marrow biopsy is performed at this time to assess disease status/hematologic toxicity. CD200 saturation and MRD detection for residual molecular mutation (e.g., CBF fusions and other markers) are also assessed.

If CD200 saturation assessment on Day 24 is not \( >90\% \) in at least 5/6 patients in a dose cohort, then the dose is escalated (Dose level 2 - 600 mg/m\(^2\)) until \( \geq 90\% \) saturation is seen in 5/6 patients as long as the dose is not too toxic. If CD200 saturation is \( \geq 90\% \) in 5 of 6 patients at Dose level 1 and the dose is not too toxic, the dose level is increased to provide reassurance CD200 saturation will be reached in CBF patients in the Phase 2 study and assess safety at this dose level. If acceptable CD200 saturation is not reached until Dose level 2 - 600 mg/m\(^2\), Phase 2 portion of the study continues based on the current dose, provided there is no unacceptable toxicity. Patients continue at their assigned dose level for Reinduction therapy (if needed), consolidation, and maintenance therapy. The timing of dose administration for samalizumab, cytarabine, and daunorubicin and circulating blasts and biopsy assessments remain the same through all dose levels. For an overview of the dose escalation schedule, see Table 13 below.

**Reinduction (if indicated by Day 24 Induction bone marrow examination):**

Reinduction treatment begins as soon as possible after bone marrow biopsy results return and no later than Day 28 from Induction therapy. MUGA or transthoracic echocardiogram is repeated prior to treatment to assure no decline in left ventricular ejection fraction to below institutional standard for further anthracycline chemotherapy.

An overview of the Reinduction phase protocol is depicted in Table 6 (Phase 1b) and Table 10 (Phase 2). During the reinduction phase samalizumab is administered at a dose level 1 of 300 mg/m\(^2\) (or a Dose level 2 - 600 mg/m\(^2\)) at 125 mL/hr and is continued 21 days from Day 24 Induction dose. Daunorubicin is administered at a dose of 60 mg/m\(^2\)/day IV over 15 minute on Days 1-2 and cytarabine is administered at a dose of 100 mg/m\(^2\) IV over 24 hours daily on Days 1-5.
Bone marrow aspirate and biopsy is performed within one week after recovery of ANC ≥ 1000/µL and platelets ≥ 100,000/µL to assess response. This exam must be performed no later than Day 45 after second remission Induction. Patients who have residual AML at this time after a second remission Induction attempt are removed from protocol therapy. Patients with complete response proceed to consolidation therapy.

Consolidation/Maintenance (for patients who achieve a CR after Induction therapy):

Patients who achieve a CR after remission induction receive four cycles of consolidation therapy. An overview of the consolidation phase protocol is depicted in Tables 7-8 (Phase 1b) and Tables 11-12 (Phase 2). Each consolidation cycle (high-dose cytarabine) is approximately 4-6 weeks in duration (based on count recovery), and subsequent cycles begin within two weeks following hematological recovery (ANC ≥ 1000/µL and platelets ≥ 100,000/µL) but not sooner than four weeks from the beginning of the previous cycle. If remission consolidation cycle is delayed > 8 weeks from the start of the previous course due to slow resolution of toxicity or slow recovery of CBC, the lead investigator is contacted. Patients continue to receive samalizumab during delay.

Cycle 1 of consolidation: samalizumab (Dose level per Induction assigned cohort) rV at 125 mL/hr starting on Day 1 of Consolidation and continue every 3 weeks until 2 years from Day 1 of Induction therapy. Cytarabine 1000 mg/m² IV is given by IV infusion over 3 hours every 12 hours on Days 2, 4, and 6 (total dose 6000 mg/m²) of cycle 1.

Cycles 2-4 of consolidation (cycles begin after count recovery from previous consolidation cycle): samalizumab (Dose level per Induction assigned cohort) dose timing varies due to 21 day cycle and cytarabine is given on Days 1, 3, and 5. Cytarabine 1000 mg/m² II is given by IV infusion over 3 hours every 12 hours on Days 1, 3, and 5 (total dose 6000 mg/m²)

All Consolidation cycles: Prior to the initiation of the cytarabine infusion dexamethasone 0.1% or other corticosteroid ophthalmic solution is administered to the patient (e.g., 2 drops to each eye four times a day) and continue for at least 24 hours after the last cytarabine dose. Serial neurologic evaluation is performed before and following the infusion of high-dose cytarabine.
Patients undergo bone marrow biopsy at count recovery after final consolidative course to assess disease status, and correlative studies are performed to assess CD200 saturation and MRD assessment for residual molecular mutation (CBF).

**Maintenance/Follow-up:**

Patients continue with samalizumab at assigned dose level every three weeks from last dose during consolidation until two years from Cycle 1 Day 1 of Induction.

Patients undergo bone marrow biopsy at relapse, with correlative studies performed to assess CD200 saturation, recurrence of molecular mutation (CBF), and clonal evolution for evidence of additional markers.

**Phase 2:**

Once a BAD is determined and tolerability criteria are met in Phase 1b (after at least 6 patients complete induction and 1 cycle of consolidation therapy at the recommended Phase 2 dose), the Phase 2 portion of the study begins with CBF patients only. For an overview of the Phase 2 dosing schedules see Tables 9-12. CR rates in the first 9 patients are checked for obvious futility. If 7 or more CRs are observed out of 9 patients, an additional 19 patients (for a total of 28 patients) are enrolled. If less than 7 patients obtain CR, the combination therapy is not considered efficacious, and enrollment to the study is halted. After completion of second stage, the drug is declared efficacious in regards to CR rate if 23 or more responses have been observed out of 28 patients. If CR efficacy endpoint is met, enrollment continues in a Phase 2 expansion cohort with an additional 27 patients to assess for 2-year PFS in all CBF patients treated at the Phase 2 dose in the Phase 1b/2 arms. An event is defined by induction treatment failure, relapse from CR or CR with incomplete blood count recovery (CRi), or death from any cause.
<table>
<thead>
<tr>
<th></th>
<th>Pre-Study</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 17</th>
<th>Day 24</th>
<th>Days 24-45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samalizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daunorubicin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height/BSA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medications</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signsa</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUGA/ECHO</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X1</td>
</tr>
<tr>
<td>Serum chemistryb</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X1</td>
</tr>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>evaluation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-HCGc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aspirate and biopsy</td>
<td>Xn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X1</td>
</tr>
<tr>
<td>PK Samplingd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antibody samplinge</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X1</td>
</tr>
<tr>
<td>Correlative studiesf</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Assessmentsg</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X1</td>
</tr>
</tbody>
</table>

| S: [Samalizumab]: Dose as assigned; administration schedule |
| B: [Daunorubicin]: Dose as assigned; administration schedule |
| C: [Cytarabine]: Dose as assigned; administration schedule |
| a: Vital signs include blood pressure, pulse, respiratory rate, temperature, and weight. |
| b: Serum chemistries include sodium, potassium, chloride, bicarbonate, glucose, BUN, serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, calcium, magnesium, and phosphorous. |
| c: Serum pregnancy test (women of childbearing potential). |
| d: Peripheral blood collection. On Day 1 and 3, PK samples are collected at predose, end of infusion, and 8 hours from the start of infusion. Additional PK samples are taken on Days 2, 4, 5, 6, 7, 10, 17, and 24. |
| e: Blood samples are collected for the testing of anti-samalizumab antibody (ADA) on Day 1 (predose), Day 7 and Day 24 (predose) |
| f: All should be drawn prior to Samalizumab if on concurrent days |
| g: Please perform PRO assessments prior to bone marrow biopsies when on concurrent days. |
| h: Bone marrow aspirate are drawn after patients assigned to LLS study cohort to assess baseline CD200 levels |
| i: Bone marrow sample for determination of CD200 saturation and for residual leukemia; patients with persistent disease receive Reinduction. Perform prior to Samalizumab dosing. |
| j: To occur weekly until count recovery and is documented at time of remission bone marrow biopsy. |
| k: Bone marrow biopsy to document complete remission is performed on Day 24-45 based on count recovery. Patients with documented CR would go on to receive Consolidation therapy. |
| l: Correlative studies are performed at time of remission bone marrow biopsy. Does not have to be repeated if Day 24 bone marrow biopsy also is considered remission marrow. |
Table 6: Phase 1b reinduction (if necessary): Dose levels 1-2

<table>
<thead>
<tr>
<th></th>
<th>Pre-Maintenance</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Days 23-26</th>
<th>Days 23-45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samalizumab Administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daunorubicin Administration</td>
<td>D</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine Administration</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height/BSA*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam/Vital signs b</td>
<td>X---------------</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUGA/ECHO*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Serum chemistry*</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>X---------------</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow aspirate and biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Correlative studies*</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Assessments*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S: [Samalizumab]: Dose as assigned; administration schedule
B: [Daunorubicin]: Dose as assigned; administration schedule
C: [Cytarabine]: Dose as assigned; administration schedule
a: BSA is calculated prior to re-dosing of chemotherapy
b: Vital signs include blood pressure, pulse, respiratory rate, temperature, and weight.
c: MUGA/ECHO occurs prior to re-dosing of chemotherapy to assure no decline in EF has occurred.
d: Serum chemistries include sodium, potassium, chloride, bicarbonate, glucose, BUN, serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, calcium, magnesium, and phosphorourous
e: All are drawn prior to samalizumab if on concurrent days.
f: Please perform PRO assessments prior to bone marrow biopsies when on concurrent days
g: Samalizumab dosing occurs between Days 23-26 based on timing from last dose of samalizumab during Induction Day 24. Occurs 21 days after Day 24 dosing.
h: Occurs weekly until count recovery and is documented at time of remission bone marrow biopsy
i: Bone marrow biopsy to document complete remission is performed on Day 23-45 based on count recovery. Patients with documented CR go on to receive Consolidation therapy
j: Correlative studies are performed at time of remission bone marrow biopsy.
Table 7: Phase 1b consolidation (cycle 1)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 6</th>
<th>Day 15</th>
<th>Day 22</th>
<th>Weekly until count recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samalizumab Administrationa</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine Administration</td>
<td></td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height/BSA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam/Vital signsb</td>
<td>X-----</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Cerebellar Toxicity Evaluationc</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Serum chemistryd</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>X-----</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>PK samplinge</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-drug antibody samplingf</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlative studiesg</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Assessmentsh</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S: [Samalizumab]: Dose as assigned; administration schedule  
C: [Cytarabine]: Dose as assigned; administration schedule  
a: Samalizumab occurs every 21 days after Day 1 of cycle 1 of Consolidation regardless of count recovery and timing with subsequent cytarabine administration.  
b: Vital signs include blood pressure, pulse, respiratory rate, temperature, and weight.  
c: Cerebellar toxicity is assessed prior each dose of cytarabine  
d: Serum chemistries include sodium, potassium, chloride, bicarbonate, glucose, BUN, serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin  
e: Peripheral blood collection. On Day 1 and 22, PK samples are collected at predose and end of infusion.  
f: Blood samples are collected for the testing of anti-samalizumab antibody (ADA) on Day 1 (predose) and Day 22 (predose)  
g: All are drawn prior to samalizumab if on concurrent days.  
h: Please perform PRO assessments prior to bone marrow biopsies when on concurrent days.
Table 8: Phase 1b consolidation (cycles 2-4)/maintenance: Dose levels 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Cycles 2-4 Phase</th>
<th>Cycles 2-4 Phase</th>
<th>Cycles 2-4 Phase</th>
<th>Every 21 Days</th>
<th>Every 21 Days</th>
<th>Every 3 Months</th>
<th>Relapse/End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 5</td>
<td>Day 5</td>
<td>Consolidation</td>
<td>Maintenance</td>
<td>Maintenance</td>
<td>Treatment</td>
</tr>
<tr>
<td>Samalizumab Administration²</td>
<td></td>
<td></td>
<td></td>
<td>S²</td>
<td>S²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine Administration²</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Height/BSA⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical exam/Vital signs⁴</td>
<td>X---------------</td>
<td>X---------------</td>
<td>X---------------</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cerebellar Toxicity Evaluation⁵</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Serum chemistry⁶</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>X---------------</td>
<td>X---------------</td>
<td>X---------------</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bone marrow aspirate and biopsy</td>
<td></td>
<td>X⁶</td>
<td></td>
<td>X³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK sampling⁸</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Anti-drug antibody sampling⁸</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Correlative studies⁴</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PRO Assessment⁷</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

S: [Samalizumab]: Dose as assigned; administration schedule  
C: [Cytarabine]: Dose as assigned; administration schedule

a: Samalizumab occurs every 21 days after Day 1 of cycle 1 of Consolidation regardless of timing with subsequent cytarabine administration. This continues for 2 years of maintenance after Dose 1 of samalizumab during Induction.
b: Cytarabine is administered on Days 1, 3, and 5 for cycle 2-4 of Consolidation.
c: BSA is calculated prior to each cycle of chemotherapy.
d: Vital signs include blood pressure, pulse, respiratory rate, temperature, and weight.
e: Cerebellar toxicity is assessed prior each dose of cytarabine.
f: Serum chemistries include sodium, potassium, chloride, bicarbonate, glucose, BUN, serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin.
g: Peripheral blood collection. On Day 1 and every 21 days during cycles 2-4 of consolidation, PK samples are collected at predose and end of infusion. PK samples are collected every 3 months during maintenance for the first 6 cycles.
h: Blood samples are collected for the testing of anti-samalizumab antibody (ADA) on Day 1 (predose) every 21 days during cycles 2-4 of consolidation. Blood samples are collected every 3 months during maintenance for the first 6 cycles.
i: All are drawn prior to samalizumab if on concurrent days.
j: Please perform PRO assessments prior to bone marrow biopsies when on concurrent days.
k: Bone marrow biopsy to document continued complete remission to be performed at count recovery only after last cycle of cytarabine Consolidation. Patients with documented continued CR go on to receive maintenance therapy. No further bone marrow biopsies required unless concern for relapse.
l: Bone marrow biopsy occurs at end of treatment and/or relapse.
Table 9: Phase 2 Induction

<table>
<thead>
<tr>
<th></th>
<th>Pre-Study</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 17</th>
<th>Day 24</th>
<th>Days 24-45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samalizumab Administration</td>
<td></td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daunorubicin Administration</td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>D</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine Administration</td>
<td></td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height/BSA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam/Vital signs</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUGA/ECHO</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum chemistryb</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-HCGc</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow aspirate and biopsy</td>
<td>Xh</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK sampling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-drug antibody samplinge</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlative studies</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Assessmentse</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S: [Samalizumab]: Dose as assigned; administration schedule
B: [Daunorubicin]: Dose as assigned; administration schedule
C: [Cytarabine]: Dose as assigned; administration schedule
a: Vital signs include blood pressure, pulse, respiratory rate, temperature, and weight.
b: Serum chemistries include sodium, potassium, chloride, bicarbonate, glucose, BUN, serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, calcium, magnesium, and phosphorous
c: Serum pregnancy test (women of childbearing potential)
d: Peripheral blood collection. On Day 1 and 3, PK samples are collected at predose, end of infusion, and 8 hours from the start of infusion. Additional PK samples are taken on Days 2, 4, 5, 6, 7, 10, 17, and 24 (pre-dose).
e: Blood samples are collected for the testing of anti-samalizumab antibody (ADA) on Day 1 (predose), Day 7 and Day 24
f: All are drawn prior to samalizumab if on concurrent days.
g: Please perform PRO assessments prior to bone marrow biopsies when on concurrent days
h: Bone marrow aspirate are drawn after patients assigned to LLS study cohort to assess baseline CD200 levels
i: Bone marrow sample for determination of residual leukemia; patients with persistent disease receive Reinduction.
j: Occur weekly until count recovery and is documented at time of remission bone marrow biopsy.
k: Bone marrow biopsy to document complete remission is performed on Day 24–45 based on count recovery. Patients with documented CR receive Consolidation therapy. Perform prior to samalizumab dosing.
Correlative studies are performed at time of remission

Table 10: Phase 2 reinduction (if necessary)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Days 23-26</th>
<th>Days 23-45</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Samalizumab Administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Daunorubicin Administration</strong></td>
<td>D</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytarabine Administration</strong></td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ECOG Performance Status</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Height/BSA</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical exam/Vital signs</strong></td>
<td>X--------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Concurrent medications</strong></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MUGA/ECHO</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CBC</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Serum chemistry</strong></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse event evaluation</strong></td>
<td>X--------------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>--------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Bone marrow aspirate and biopsy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Correlative studies</strong></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>PRO Assessments</strong></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

S: [Samalizumab]: Dose as assigned; administration schedule
B: [Daunorubicin]: Dose as assigned; administration schedule
A: [Cytarabine]: Dose as assigned; administration schedule
a: BSA is calculated prior to re-dosing of chemotherapy.
b: Vital signs include blood pressure, pulse, respiratory rate, temperature, and weight.
c: MUGA/ECHO occurs prior to re-dosing of chemotherapy to assure no decline in EF has occurred.
d: Serum chemistries include sodium, potassium, chloride, bicarbonate, glucose, BUN, serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, calcium, magnesium, and phosphorous.
e: All are drawn prior to samalizumab if on concurrent days.
f: Please perform PRO assessments prior to bone marrow biopsies when on concurrent days
g: Samalizumab dosing occurs between Days 23-26 based on timing from last dose of samalizumab during Induction Day 24. Occurs 21 days after Day 24 dosing.
h: Occurs weekly until count recovery and is documented at time of remission bone marrow biopsy
i: Bone marrow biopsy to document complete remission is performed on Day 23-45 based on count recovery. Patients with documented CR receive Consolidation therapy. Correlative studies are collected at time of remission marrow.
### Table 11: Phase 2 consolidation (cycles 1)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 6</th>
<th>Day 15</th>
<th>Day 22</th>
<th>Weekly until count recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samalizumab Administration</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine Administration</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Height/BSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Physical exam/Vital signs</td>
<td>X-----</td>
<td></td>
<td></td>
<td></td>
<td>X------</td>
<td>X------</td>
<td></td>
</tr>
<tr>
<td>Cerebellar Toxicity Evaluation</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Concurrent medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum chemistry</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>X-----</td>
<td></td>
<td></td>
<td></td>
<td>X------</td>
<td>X------</td>
<td></td>
</tr>
<tr>
<td>PK sampling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Anti-drug antibody sampling</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Correlative studies</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PRO Assessments</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

S: [Samalizumab]: Dose as assigned; administration schedule  
C: [Cytarabine]: Dose as assigned; administration schedule  
a: Samalizumab occurs every 21 days after Day 1 of cycle 1 of Consolidation regardless of count recovery and timing with subsequent cytarabine administration.  
b: Vital signs include blood pressure, pulse, respiratory rate, temperature, and weight.  
c: Cerebellar toxicity is assessed prior each dose of cytarabine  
d: Serum chemistries include sodium, potassium, chloride, bicarbonate, glucose, BUN, serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin.  
e: Peripheral blood collection. On Day 1 and 22, PK samples are collected at predose and end of infusion.  
f: Blood samples are collected for the testing of anti-samalizumab antibody (ADA) on Day 1 (predose) and Day 22 (predose)  
g: All are drawn prior to samalizumab if on concurrent days.  
h: Please perform PRO assessments prior to bone marrow biopsies when on concurrent days.
Table 12: Phase 2 consolidation (cycles 2-4)/maintenance: Dose levels 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Cycles 2-4 Day 1</th>
<th>Cycles 2-4 Day 3</th>
<th>Cycles 2-4 Day 5</th>
<th>Every 21 Days During Consolidation</th>
<th>Every 21 Days During Maintenance</th>
<th>Every 3 Months During Maintenance</th>
<th>Relapse/End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samalizumab Administration*</td>
<td></td>
<td></td>
<td></td>
<td>S(^a)</td>
<td>S(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine Administration(^b)</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height/BSA(^c)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam/Vital signs(^d)</td>
<td>X------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>X---------------------------------</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cerebellar Toxicity Evaluation(^e)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum chemistry(^f)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>X------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>X---------------------------------</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow aspirate and biopsy</td>
<td></td>
<td></td>
<td></td>
<td>X(^k)</td>
<td></td>
<td></td>
<td>X(^k)</td>
</tr>
<tr>
<td>PK sampling(^g)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-drug antibody sampling(^h)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlative studies(^i)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Assessments(^j)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5 S: [Samalizumab]: Dose as assigned; administration schedule
C: [Cytarabine]: Dose as assigned; administration schedule
a: Samalizumab occurs every 21 days after Day 1 of cycle 1 of Consolidation regardless of timing with subsequent cytarabine administration. This continues for 2 years of maintenance after Dose 1 of samalizumab during Induction.
b: Cytarabine is administered on Days 1, 3, and 5 for cycle 2-4 of Consolidation.
c: BSA is calculated prior to each cycle of chemotherapy.
d: Vital signs include blood pressure, pulse, respiratory rate, temperature, and weight.
e: Cerebellar toxicity is assessed prior each dose of cytarabine.
f: Serum chemistries includes sodium, potassium, chloride, bicarbonate, glucose, BUN, serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, and albumin.
g: Peripheral blood collection. On Day 1 and every 21 days of cycles 2-4 of consolidation, PK samples are collected at predose and end of infusion. PK samples are collected every 3 months during maintenance.
h: Blood samples are collected for the testing of anti-samalizumab antibody (ADA) on Day 1 (predose) and every 21 days during cycles 2-4 of consolidation. Blood samples are collected every 3 months during maintenance.
i: All are drawn prior to samalizumab if on concurrent days.
j: Please perform PRO assessments prior to bone marrow biopsies when on concurrent days.
k: Bone marrow biopsy to document continued complete remission is performed at count recovery only after last cycle of cytarabine Consolidation. Patients with documented continued CR receive maintenance therapy. No further bone marrow biopsies required unless concern for relapse.

Table 13: BAD and MTD Dose Escalation Schedule

<table>
<thead>
<tr>
<th>Phase 1b BAD and MTD Dose Escalation Schedule</th>
<th>Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level</td>
<td>Samalizumab (mg/m²)</td>
</tr>
<tr>
<td>Level 1</td>
<td>300</td>
</tr>
<tr>
<td>Level 2</td>
<td>600</td>
</tr>
</tbody>
</table>

*Doses are stated as exact dose in units (e.g., mg/m²) rather than as a percentage.

Definition of Dose-Limiting Toxicity:

Patients who experience dose-limiting toxicities (DLT) may continue on trial provided that the toxicity has resolved to at least Grade 2.

It is recognized that drug-related toxicity in this population may be difficult to ascertain, given the aggressive hematologic disease and intensive chemotherapy that is standard. It is attempted to assign attribution of toxicities to each drug if possible. Toxicity attributed to any of the three agents is considered dose limiting. Any AE that is possibly, probably, or definitely related to therapy is considered a DLT. Events that result directly from active leukemia are not considered a DLT. DLT is assigned, separately, to induction therapy and cycle 1 of consolidation therapy for Phase 1b portion of the protocol. If < 1/6 patients experience DLTs in the induction portion of treatment, subsequent patients are allowed to enroll in induction while assessments for DLTs are occurring for cycle 1 of consolidation.
Non-hematologic Toxicity:

Non-hematologic toxicity of ≥ grade 3 with the exception of grade 3 alopecia, grade 3 nausea and vomiting that resolves < grade 3 within 72 hours, and infection (infection-related toxicities such as fever/sepsis, see below) are considered a DLT. The grade 3/4 toxicity, designated to be DLT, is drug-related. Patients with transient grade ≥ 3 electrolyte abnormalities that are not clinically significant and are correctable within 24 hours are not considered a DLT. Patients with ≥ grade 3 transient liver function test abnormalities (AST, ALT, or alkaline phosphatase) that resolve to < grade 2 within 5 days are not considered DLT.

Grade 3 or 4 infection does not constitute as a DLT unless it is felt that the infection resulted from unexpectedly complicated myelosuppression (degree or duration).

Patients who do not receive all 3 planned induction doses of samalizumab due to an adverse event, are considered to have a DLT. These patients are considered to be evaluable for toxicity/DLT and are not replaced during the dose escalation phase of the trial unless the it is determined that further additional patients at that dose level are required for safety purposes.

However, if early withdrawal is due to an issue other than toxicity or tolerability of the treatment, the patient is replaced in order to evaluate MTD.

Hematologic Toxicity:

Hematologic toxicity is defined as: failure to recover ANC > 500/µl, or platelet count > 100,000/µl by Day 45 (of first or second induction if applicable, or after first Consolidation) in patients with < 5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of evidence of disease by flow cytometry in the bone marrow. This is considered a DLT. For patients with > 5% blasts, myelodysplastic changes, or evidence of disease by flow cytometry/cytogenetics, failure to recover neutrophil or platelet count are not considered a DLT as this could be the result of persistent disease.

Dose Escalation/Expansion Decisions:

The trial proceeds according to the following scheme based on BAD findings and DLT. Intrapatient dose escalation of samalizumab is allowed for Phase 1b patients who have achieved CR treated at dose levels below the determined Phase 2 dose starting with the second cycle of consolidation (have completed DLT assessments) to increase samalizumab to the recommended
Phase 2 dose. If a patient meets the definition of DLT, the patient continues on with the therapy provided that the toxicity can be managed according to the dose modification guidelines. The DLT is still included in the assessment of MTD. If \( \leq 1 \) out of 6 patients suffers DLT at Dose level 1 and optimal CD200 saturation is found, dose escalation proceeds to reassure saturation for the CBF patients will occur with acceptable toxicity. If \( \geq 2 \) out of 6 patients suffers DLT at Dose level 1, the treatment is stopped. If \( \leq 1 \) out of 6 patients suffers DLT at Dose level 2 and optimal CD200 saturation is found, the Phase 2 treatment begins at this dose level. If toxicity is found to be too high and BAD dosing has not been met, the protocol is stopped and discussion occurs to determine if dose or schedule will be adjusted versus discontinuing the protocol if combination is felt to not to be safe to continue.

**Duration of therapy:**

Treatment consists of an induction therapy (two cycles if applicable) plus four cycles of consolidation therapy, followed by single-agent maintenance therapy to complete 2 years after initial dose of samalizumab. Patients continue treatment per protocol guidelines during the induction and consolidation unless one of the below occurs:

- Intercurrent illness or toxicity that prevents further administration of treatment
- Unacceptable AEs as described above.
- Suspected pregnancy or positive pregnancy
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Diagnosis of new or secondary malignancies after initiating treatment

Patients removed from protocol during the Induction phase for reasons other than toxicity attributed to drug are replaced if the patient is not evaluable for consideration of tolerability.

**Duration of Follow-up:**

 Patients are followed for at least 30 days past the last dose of study drug. Patients removed from study for unacceptable AEs are followed until resolution or stabilization of the AE.
Dosing Delays/Dose Modifications:

Induction and First Consolidation

There are no dose modifications during induction or first consolidation therapy unless the patient experiences a DLT, in which case the patient may continue therapy as described below.

Dose Modification of Samalizumab

Patients who experience a non-hematologic toxicity assessed as samalizumab related that is grade 3 or higher hold dosing of samalizumab until the toxicity resolves to \( \leq \) grade 1, and then restart at the next lower dose. This does not include samalizumab-related infusion reactions.

Missed doses are defined to be greater than 7 days from planned treatment and are not made up.

Dose Modifications for Non-Hematologic Toxicity for daunorubicin and cytarabine in subsequent cycles (after DLT assessment for Induction and for first Consolidation, respectively) is permitted following guidelines provided below.

Given the disease and chemotherapy treatment, there are no routine indications to dose modify unless clinically significant heart failure or cerebellar toxicity occurs, or if other serious organ toxicity occurs affecting the metabolism of these agents, in which case chemotherapy reductions follow institutional/standard clinical practice.

There are no dose modifications for hematologic toxicity for daunorubicin or cytarabine.

I. Safety Reporting

The following list of AEs and the characteristics of an observed AE determine whether the event requires expedited reporting in addition to routine reporting.

Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.
Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of Investigational New Drug (IND) application safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Inherent in this definition is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the AE.

Adverse Reaction

An adverse reaction is any AE caused by a drug and where there is reason to conclude that the drug caused the event.

Unexpected Adverse Event

An AE or adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. As an example, under this definition, hepatic necrosis would be unexpected (by virtue of a greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents.

Serious Adverse Event

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that do not result in the above are considered serious when, based upon appropriate medical judgment, they 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, or convulsions that do not result in patient hospitalization.

An AE is considered life threatening if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalizations for elective or planned purposes, for the administration of protocol therapy, for the administration of blood products or ancillary therapies, for procedures such as endoscopy or bone marrow biopsy, or for purposes of disposition or respite care or that are less than 24 hours in duration would not fulfill the above definition of serious. Complications arising from elective or planned hospitalizations that result in prolonged hospitalization are considered SAEs.

**Adverse Event List for Samalizumab**

Detailed information about the risks and expected AEs of samalizumab may be found in the current edition of the samalizumab Investigator's Brochure. In brief, the most frequent adverse reactions were fatigue (46%), headache, pyrexia, and rash (all 19%). Immunogenicity was observed in 3 of 26 patients treated, consistent with literature reports for other therapeutic monoclonal antibodies. Two of these patients also had infusion reactions in proximity to the elevated anti-drug antibody levels.

**Adverse Event List for Cytarabine**

Bone marrow suppression, of all cell lines, is the most serious toxic effect. This effect can lead to an increased risk of infection, shortness of breath, or risk of bruising and bleeding and the need for treatment with antibiotics, transfusions, or other treatments. Gastrointestinal symptoms such as nausea or vomiting, diarrhea, and abdominal cramps have been seen in patients. Patients have also experienced alopecia.

Patients have been seen to develop skin rashes and edema. Tumor lysis has been seen causing abnormal blood levels of potassium, calcium, uric acid, and lactate dehydrogenase.
Adverse Event List for Daunorubicin

Bone marrow suppression, of all cell lines, is the most serious toxic effect for daunorubicin. This effect can lead to an increased risk of infection, shortness of breath, or risk of bruising and bleeding and the need for treatment with antibiotics, transfusions, or other treatments. Urine may appear red because of the color of the drug. Urination may be painful or difficult. Gastrointestinal symptoms such as mild nausea or vomiting occurring within 1-2 hours of treatment, diarrhea, and abdominal cramps have been seen in patients. Patients have also experienced mouth sores, alopecia and pain along the injection site.

Adverse Event Severity

All AEs are graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. For example, each Grade can be classified as follows:

- Grade 1 (mild AE; transient or mild discomfort; no limitation in activity; no medical intervention or therapy required)
- Grade 2 (moderate AE; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required)
- Grade 3 (disabling or severe AE; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization may be required)
- Grade 4 (life-threatening AE; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required; hospitalization or hospice likely)
- Grade 5 (death related to AE)

Relation to Study Drug

During the study, it is attempted to determine if an AE is in some way related to the use of the study drug. This relationship is described as follows:

Unrelated: The event has no temporal relationship to study drug administration (too early or late or study drug not taken), or there is a reasonable causal relationship between the AE and another drug, concurrent disease, or circumstance.
Unlikely: The event has a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possible: The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug, BUT the event could have been produced by an intercurrent medical condition which based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication.

Probable: The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication.

Definite: The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

Unknown: There is inadequate information to make a determination of causality.

AEs are attributed to the investigational agent or standard chemotherapy if feasible. Changes in the severity of an AE are documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The specific malignancy that qualified the patient for participation in the study is not reported as an AE. Worsening of that malignancy which is severe enough to warrant discontinuation from the study is not reported as an AE. However, if the condition is severe enough to require the patient’s hospitalization or prolongation of hospitalization, the event is reported as an SAE.
J. Study Assessments

Biomarker and Correlatives

Blood samples are collected according to the schedule of events (see Table 5 through Table 12) for analysis of PD and exploratory biomarkers. PD analyses assess the binding of samalizumab to CD200 on tumor and/or blood cells and the relationship between CD200 expression on tumor and/or blood cells and PK of samalizumab. Exploratory biomarker analyses seek to characterize the effect of samalizumab on immune cell function and tumor cell survival. Exploratory biomarker analyses also seek to evaluate the relationship between antigen binding with T cell activation and global immune response, as well as to assess the correlation between CD200 expression, activation of the CD200 signaling axis, the persistence of MRD, and the therapeutic efficacy of samalizumab. These exploratory analyses include but are not limited to profiling of residual tumor cells, immune cells (e.g. T cells, NK cells, and B regulatory cells), immune cell activation state, and gene expression analysis. Among patients who relapse following therapy, blood and bone marrow samples are collected to assess clonal evolution and other markers of disease resistance.

Pharmacokinetics Analysis

In both the Phase 1b and Phase 2 portions of the study, PK samples are collected during the induction period to assess PK following infusion of samalizumab on Day 1 and Day 3 at all dose levels, and samples are also collected at other designated time points. In the Phase 1b and 2 consolidation/maintenance portions of the study, sparse PK samples are taken.

In Phase 2 of the study, PK samples are collected at induction period (Table 5) to assess PK following infusion of samalizumab on Day 1 and Day 3 at 2 dose levels. In the Phase 2 consolidation/maintenance part of the study, sparse PK samples are taken for the first 4 cycles.

Detailed procedures for the sample collection, processing, and shipment are in a separate lab manual. Serum samples are analyzed using a validated assay. PK samples are drawn from the central line from a separate lumen from the one designated for samalizumab infusion. Samples are drawn from the lumen after saline flush has occurred. The first 2 mL of blood is discarded prior to sample collection.
Non-compartmental analysis is performed to compute PK parameters in the induction period of the study. Nonlinear mixed-effect modeling is used to analyze intensive PK concentration data and sparse PK concentration data from both induction and maintenance parts of the study. The primary PK parameters are clearance of volume of distribution. Systemic exposures, defined as area under the serum concentration-time profile (AUC) are estimated for all patients who have provided samples. The PK parameters are listed and summarized for this study population.

Relationships between samalizumab PK exposure and efficacy and safety parameters is explored. Depending on the relevance of those relationships, they are further explored by using population PK-PD modeling methods.

Response Criteria

Assessment of clinical response is made according to International Working Group criteria. The major criteria for judging response includes physical examination and examination of blood and bone marrow. All laboratory studies that are abnormal prior to study are repeated to document the degree of maximal response.

Morphologic Complete Remission (Morphologic CR)

Morphologic CR requires all of the following:

• < 5% blasts in bone marrow aspirate.
• Neutrophils ≥ 1,000/µL.
• Platelets ≥ 100,000/µL.
• No extramedullar disease.
• No blasts with Auer rods detected.
• No circulating blasts (rare may be permitted)/ No evidence of pre-treatment blast phenotype by flow cytometry (i.e. CD34, CD7 co-expression)

Cytogenetic Complete Remission (CRc)

CRc requires all of the following:

• < 5% blasts in bone marrow aspirate.
• Neutrophils ≥ 1,000/µL.
• Platelets ≥ 100,000/µL.
• No extramedullary disease.
• No blasts with Auer rods detected.
• No circulating blasts (rare may be permitted)/ No evidence of pre-treatment blast phenotype by flow cytometry (i.e. CD34, CD7 co-expression)
• Reversion to a normal karyotype.

**Morphologic CR with incomplete blood count recovery (CRi)**

CRi requires all of the following:

• < 5% blasts in bone marrow aspirate.
• Neutrophils < 1,000/µL or Platelets < 100,000/µL.
• No extramedullary disease.
• No blasts with Auer rods detected.
• No circulating blasts (rare may be permitted)/ No evidence of pre-treatment blast phenotype by flow cytometry (i.e. CD34, CD7 co-expression)

**Partial Remission (PR)**

PR requires all of the following:

• Meets all criteria for CR except for BM blasts
• Must have greater than 50% decrease in blasts in bone marrow aspirate to a range of 5-25%.
• Neutrophils ≥ 1,000/µL.
• Platelets ≥ 100,000/µL.
• No extramedullary disease.
• If Auer rods are detected, the blast count in the bone marrow must be ≤ 5%.

**Treatment Failure**

Treatment failure is classified as one of the following:
• Resistant disease: Failure to achieve a CR (morphologic CR, CRc, or CRi) or partial remission.

**Recurrence**

Recurrence is defined as any of the following:

- Evidence of morphologic relapse with the reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow not attributable to any other cause. In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5-20% blasts, a bone marrow biopsy is repeated within 1 week to distinguish relapse from bone marrow regeneration.
- The reappearance of cytologically proven extramedullary disease also indicates relapse. Reappearance of a cytogenetic abnormality is considered a cytogenetic relapse.
- New CNS disease or other new sites of extramedullary involvement.
- Aplasia: Patient survives ≥7 days after chemotherapy, but dies while cytopenic, with an aplastic marrow.
- Indeterminate cause: Patients who die <7 days after chemotherapy; patients who die ≥7 days after chemotherapy with no peripheral blood blasts, but no bone marrow examination; patients who fail to complete the first cycle of therapy.

**K. Statistical Methods and Study Design/Endpoints**

**Phase 1b**

The biologically active Phase 1b dose is the dose at which at least 5 of 6 patients achieve CD200 optimal saturation (>90%) at Day 24. This design has good properties both if the true optimal saturation rate is as high as expected (based on historical data with this agent) and if the true optimal saturation rate is low. For example, if the true proportion of patients who would achieve optimal saturation is 90%, the probability of observing 5 or more responses out of 6 patients and declaring the dose biologically active is 89%. If the true optimal saturation rate is only 50%, the probability of observing 5 of 6 responses and proceeding with a substandard dose is only 11%.
Toxicity is assessed using the standard approach that a dose is too toxic if 2 of 6 patients at any dose level experience a DLT thought to be possibly related to administration of samalizumab in combination of chemotherapy. DLT is defined as any non-hematologic toxicity. Hematological DLT is considered as failure to recover neutrophil count (ANC > 500) by Day 45 in patients with < 5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of evidence of disease by flow cytometry in the bone marrow.

Starting at dose level 1, a cohort of 6 patients are assessed for both biological activity and toxicity. For dose level 1, if toxicity is acceptable, but biological activity has not been met, the next dose level is escalated. If dose level 1 is both safe and biologically active, safety at dose level 2 is assessed during Phase 2 in order to ensure appropriate saturation in the CBF group if the toxicity is acceptable (fewer than 2 in 6 experience a DLT). If the higher dose is unacceptably toxic, Phase 2 begins with the biologically active, safe dose at dose level 1. If the BAD is dose level 2 and it has acceptable toxicity, Phase 2 proceeds with dose level 2. If toxicity if found to be too high and BAD dosing has not been met, the protocol is stopped and discussion will occur to determine if dose or schedule is adjusted versus discontinuing the protocol if combination is felt to not to be safe to continue.

Phase 2

Simon's two-stage design is used to test the hypothesis that the CR rate is > 70%. Assuming that the true CR rate among those treated is 90% and setting the type I and type II error rates to 10% (alpha = beta = 0.1), 9 patients are enrolled in the first stage. If 6 or fewer CRs are observed out of the first 9 patients, the study is terminated early. If 7 or more CRs are observed, the study enrolls an additional 19 patients for a total of 28. At the completion of the second stage, the drug is declared efficacious (and the probability of an unacceptable CR rate < 70% ruled out) if at least 23 responses have been observed out of the 28 patients enrolled.

This design has 90% power to correctly rule out a CR rate < 70% if the true rate is 90%.

Phase 2 expansion: If efficacy is demonstrated in the Phase 2 study by ruling out a CR rate < 70%, up to an additional 27 patients are enrolled in a single-arm study to further evaluate the efficacy of the treatment in regards to PFS. CBF patients who have been treated at the recommended Phase 2 dose in the Phase 1b portion of the study are included in the PFS assessment. With 27 patients and assuming a true 2-year PFS rate of 70%, this expansion has
90% power to rule out a PFS rate of 40% or lower with 97.5% confidence (one-sided alpha = 0.025). Additionally, the tolerability data from all Phase 2 patients provides additional information about the acceptable tolerability profile of this therapy.

**Sample Size/Accrual Rate**

Based on up to 12 patients in Phase 1b, a planned Phase 2 portion enrolling 28 patients and 21-27 at Phase 2 expansion, it is estimated that total accrual is between 6-67 patients at the end of the study. It is anticipated that 3-6 patients are enrolled each month during the Phase 1b portion and 1-3 patients are enrolled each month during the Phase 2 portion.

**Analysis of Correlative Studies**

For all biomarkers, descriptive statistics (means, medians, standard deviations, interquartile range) and graphical displays are used to characterize central tendency and variability over time. Values are log transformed as appropriate to reflect biologic plausibility. Statistical trends over time are evaluated using mixed-effects models with multiple measurements per person. Estimates of the change in value from baseline at each measurement time are provided along with 95% confidence intervals. Correlational analyses evaluating the relationships between biomarkers also utilize mixed models; here the strength of the association between one (or several) markers and one outcome are assessed.

Further exploratory analyses compare trends over time between patients who relapse following therapy and those with longer event-free survival.

**Example 3: Preliminary PK results for ALXN6000 Beat AML study**

Initial PK results were obtained from AML cancer patients taking samalizumab (Q3W repeated (Day 1, 3) intravenous dosing at 300 mg/m²). Figures 5A-5B are graphs showing serum samalizumab concentration over time from three individual AML patients. No anti-drug antibodies (ADA) were detected. Figures 6A-6B are graphs showing the mean serum samalizumab concentration over time.

Additional PK results were obtained from AML cancer patients taking samalizumab (Q3W repeated (Day 1, 3) intravenous dosing at 300 mg/m²). Figures 7A-7B are graphs
showing serum samalizumab concentration over time from six individual AML patients. Figures 8A-8B are graphs showing the mean serum samalizumab concentration over time. Figures 7A-7B and 8A-8B include both induction and consolidation phase data points.
<table>
<thead>
<tr>
<th>DESIGNATION</th>
<th>SEQUENCE</th>
<th>SEQ ID NO:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor human CD200 isoform A</td>
<td>MERLVIRMPFSHLSTYSLVWVMAAVVLCTAQVQVVTQDEREQLYTPASLKCSLQNAQEALIVTWQKKKAVSPENMOVTFSENHGVIQPAKYDKINITQLGLQNSTITFWNI</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human CD200 isoform B</td>
<td>MERLTLRTTIGGPLLTATLLGTINDYQVIRMPFSHLSTYSLVWVMAAVVLCTAQVQVVTQDEREQLYTPASL</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>KCSLQNAQEALIVTWQKKKAVSPENMOVTFSENHGVIQPAKYDKINITQLGLQNSTITFWNITEDEGCYCMCLFNTFGFKISGTACLTVYQVIPSLHYKFS</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>EDHNLITCSATARPAMPVFWKVPRSQGIESTVTLHSPNGTTSVTSILHIKDPKNQVGEICQVVLHGTVDFTKQTVNKGYWSVPLLISIVLVLVLILSILLYWKRHRQDREP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-length, mature human CD200</td>
<td>VIRMPFSHLSTYSLVWVMAAVVLCTAQVQVVTQDEREQLYTASSLQCSLQNAQEALIVTWQKKKAVSPENMOVTFSENHGVIQPAKYDKINITQLGLQNSTITFWNITEDEGCYCMCLFNTFGFKISGTACLTVYQVIPSLHYKFS</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>EDHNLITCSATARPAMPVFWKVPRSQGIESTVTLHSPNGTTSVTSILHIKDPKNQVGEICQVVLHGTVDFTKQTVNKGYWSVPLLISIVLVLVLILSILLYWKRHRQDREPSQGQVMDSCQ</td>
<td>5</td>
</tr>
<tr>
<td>ALXN6000 Light Chain CDR1</td>
<td>KASQDINSYLS</td>
<td>6</td>
</tr>
<tr>
<td>ALXN6000 Light Chain CDR2</td>
<td>RANRLVD</td>
<td>7</td>
</tr>
<tr>
<td>ALXN6000 Light Chain CDR3</td>
<td>LQYDEFPYT</td>
<td>8</td>
</tr>
<tr>
<td>ALXN6000 Heavy Chain CDR1</td>
<td>GYSFTDIYIL</td>
<td>9</td>
</tr>
<tr>
<td>ALXN6000 Heavy Chain CDR2</td>
<td>HIDPYYGSSNYNLKFKG</td>
<td></td>
</tr>
<tr>
<td>ALXN6000 Heavy Chain CDR3</td>
<td>SKRDFYFDY</td>
<td></td>
</tr>
<tr>
<td>ALXN6000 Light Chain</td>
<td>DIQMTQSPSS LSASIGDRVT ITCKASQDIN SYLSWFQQKP GAKPKLLIYR ANRLVDGVPSS RFSGSGSGETD YTLTISSLQF EDFAVYCLQ YDEPYFQGG GTKLEIKRTV AAPSVFIFPPP SDEQLKSGTASVVCLENNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSDK STYLSLSTLT LSKADYFEKHVYACEVTHQ GLSSPVTKSF NRGEC</td>
<td>SEQ ID NO: 10</td>
</tr>
<tr>
<td>ALXN6000 Heavy Chain</td>
<td>QVQLQQSGSE LKKPGASVKI SCKASGYFPT DIYILWVRQPN PGKGEWHIGH IDPYYGSSNY NLKFKGRVTI TADQSTTAY MELSSLRSED TAVYYYYCGRSK RYFDYWQGQ TTILTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SNFGTQTYTC NVDHKPSNTK VDKTVERKCC VECPPCPAPP VAGPSVFLFP PKPKDTRLMIS RTPEVTCVVV DVSSQEDPEVQ FNWVGDGEVEV HNAAKTPREE QFNSTRYRVS VLTVLHQQDL NGKEYKCKVS NKGLPSSEIK TISGAKGQPR EPQYTLPPS QEEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPEENYKTT PPVLSDSDF SFYSLRRTVDK SRWQEGNVSF CSVMHEALHN HYTQKSLSL S LGK</td>
<td>SEQ ID NO: 11</td>
</tr>
<tr>
<td>ALXN6000 Variable Light Chain</td>
<td>DIQMTQSP SSLSASIGDR VTITCKASQD INSYLSWFQQ KPGKAPKLLI YRANRLVDGV FSRSFGSGSG TDYITLTISSL QPEDFAVYYC LQYDEFYTF GGKTLEIKR</td>
<td>SEQ ID NO: 12</td>
</tr>
<tr>
<td>ALXN6000 Variable Heavy Chain</td>
<td>QVQLQQSGS ELKKGASVKT SCKASGYSF TDYIILWVRQ NPDKGLEWIG HIDPYYGSSN YNLKFKGRVT ITADQSTTTA YMELESSLRSE DTAVYYYCRS KRYDFYDWQ GTTLTVSS</td>
<td>SEQ ID NO: 13</td>
</tr>
</tbody>
</table>
What is claimed is:

1. A method of treating a human patient with Acute Myeloid Leukemia (AML), the method comprising administering to the patient daunorubicin, cytarabine, and an anti-CD200 antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region CDR1 having the sequence set forth in SEQ ID NO: 7, a heavy chain variable region CDR2 having the sequence set forth in SEQ ID NO: 8, a heavy chain variable region CDR3 having the sequence set forth in SEQ ID NO: 9, a light chain variable region CDR1 having the sequence set forth in SEQ ID NO: 4, a light chain variable region CDR2 having the sequence set forth in SEQ ID NO: 5, and a light chain variable region CDR3 having the sequence set forth in SEQ ID NO: 6, wherein the method comprises an induction phase followed by a consolidation phase, wherein:
   (a) 300 mg/m², 600 mg/m², or 900 mg/m² of the anti-CD200 antibody, or antigen-binding fragment thereof, 60 mg/m² of daunorubicin, and 100 mg/m² of cytarabine are administered during the induction phase,
   (b) 300 mg/m², 600 mg/m², or 900 mg/m² of the anti-CD200 antibody, or antigen-binding fragment thereof, is administered on Day 1 of Cycle 1 of the consolidation phase and every 21 days thereafter, and 1000 mg/m² of cytarabine is administered on Days 2, 4, and 6 of Cycle 1 of the consolidation phase; and
   (c) 1000 mg/m² of cytarabine is administered twice on Days 1, 3, and 5 of Cycles 2-4 of the consolidation phase.

2. The method of claim 1, wherein the induction phase is 24 days.

3. The method of claim 1 or 2, wherein during the induction phase:
   (a) the anti-CD200 antibody, or antigen-binding fragment thereof, is administered three times;
   (b) daunorubicin is administered three times; and
   (c) cytarabine is administered seven times.
4. The method any one of the preceding claims, wherein the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at 125 mL/hr on Days 1, 3, and 24 of the induction phase.

5. The method of any one of the preceding claims, wherein daunorubicin is administered intravenously over 15 minutes on Days 4-6 of the induction phase.

6. The method of any one of the preceding claims, wherein cytarabine is administered intravenously over 24 hours daily on Days 4-10 of the induction phase.

7. The method of any one of the preceding claims, wherein the consolidation phase comprises four 21 day cycles.

8. The method of any one of the preceding claims, wherein cytarabine is administered intravenously during the consolidation phase over three hours every 12 hours on:
   (a) Days 2, 4, and 6 of Cycle 1; and
   (b) Days 1, 3, and 5 of Cycles 2-4.

9. The method of any one of the preceding claims, wherein each cycle of the consolidation phase is about 4-6 weeks.

10. The method of any one of the preceding claims, wherein each subsequent cycle of the consolidation phase begins within two weeks of hematological recovery (ANC ≥ 1000/µL and platelets ≥ 100,000/µL), but no sooner than four weeks from the start of the previous Cycle.

11. The method of any one of the preceding claims, further comprising a reinduction phase after the induction phase and before the consolidation phase, wherein during the reinduction phase:
   (a) the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at least one time;
   (b) daunorubicin is administered two times; and
(c) cytarabine is administered five times.

12. The method of claim 11, wherein the anti-CD200 antibody, or antigen-binding fragment thereof, is administered at 125 mL/hr 21 days after the Day 24 induction dose.

13. The method of claim 11 or 12, wherein daunorubicin is administered intravenously on Days 1-2 of the reinduction phase.

14. The method of any one of claims 11-13 wherein cytarabine is administered intravenously over 24 hours daily on Days 1-5 of the reinduction phase.

15. The method of any one of claims 1-6, wherein cytarabine and daunorubicin are administered simultaneously or consecutively.

16. The method of any one of the preceding claims, further comprising administering a corticosteroid ophthalmic solution to the patient each day prior to administering cytarabine during the consolidation phase and for at least 24 hours thereafter.

17. The method of claim 16, wherein the ophthalmic solution is dexamethasone 0.1%.

18. The method of any of the preceding claims, wherein the anti-CD200 antibody, or antigen-binding fragment thereof, is administered every 21 days for 2 years after the consolidation phase.

19. The method of any one of the preceding claims, wherein the anti-CD200 antibody comprises heavy and light chain variable regions having the sequences set forth in SEQ ID NOs: 13 and 12, respectively.

20. The method of any one of the preceding claims, wherein the anti-CD200 antibody comprises heavy and light chains having the sequences as set forth in SEQ ID NOs: 11 and 10, respectively.

21. The method of any one of the preceding claims, wherein the anti-CD200 antibody is Samalizumab or an antigen-binding fragment thereof.
22. The method of any one of the preceding claims, wherein the anti-CD200 antibody or antigen-binding fragment thereof inhibits the interaction between CD200 and CD200R.

23. The method of any one of the preceding claims wherein the treatment results in a CD200 saturation of at least about 70, 75, 80, 85, 90, or 95%.

24. The method of any one of the preceding claims, wherein the treatment produces at least one therapeutic effect chosen from the group consisting of morphologic complete remission, cytogenetic complete remission, morphologic CR with incomplete blood count recovery, partial remission, and stable disease.

25. The method any one of the preceding claims, wherein the AML is a core-binding factor (CBF) positive AML.

26. The method of claim 25, wherein the CBF positive AML comprises an abnormality selected from the group consisting of a:
   a) cytogenetic abnormality of t(8;21)(q22;q22);
   b) pericentric inversion of chromosome 16 [inv(16)(p13.1;q22)]; and
   c) balanced translocation t(16;16)(p13.1;q22).

27. The method of any one of the preceding claims, wherein the human patient is \( \geq 60 \) years old.

28. The method of any one of the preceding claims, wherein the anti-CD200 antibody or antigen-binding fragment thereof is administered about every 3 weeks.

29. A kit for treating a human patient with Acute Myeloid Leukemia (AML), the kit comprising:
   a) a dose of an anti-CD200 antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region CDR1 having the sequence set forth in SEQ ID NO: 7, a heavy chain variable region CDR2 having the sequence
set forth in SEQ ID NO: 8, a heavy chain variable region CDR3 having the sequence set forth in SEQ ID NO: 9, a light chain variable region CDR1 having the sequence set forth in SEQ ID NO: 4, a light chain variable region CDR2 having the sequence set forth in SEQ ID NO: 5, and a light chain variable region CDR3 having the sequence set forth in SEQ ID NO: 6, particularly samalizumab;

(b) a dose of cytarabine;

(c) a dose of daunorubicin; and

(d) instructions for using the anti-CD200 antibody, cytarabine, and daunorubicin in the method of any one of the previous claims.
FIG. 1
LINES ARE MEDIANS OF CONDITIONAL PREDICTIONS FROM THE FINAL MODELS FOR 25 SUBJECTS OF THE ANALYSIS DATA SET. DOSES DENOTED BY VERTICAL DASHED LINES WERE ADMINISTERED ON DAY 0, DAY 2, AND THEN EVERY 21 DAYS. TOP: 900 mg/m² REGIMEN; MIDDLE: 600 mg/m² REGIMEN; BOTTOM: 300 mg/m² REGIMEN

FIG. 2
INDIVIDUAL PK - 300 mg/m² IV Q3W (DAY 1, 3)
LINEAR PLOT

FIG. 5A
INDIVIDUAL PK - 300 mg/m² IV Q3W (DAY 1, 3)
SEMI-LOG PLOT

Serum Samalizumab Concentration (µg/mL)

Time after First Dose (day)

FIG. 5B
MEAN PK - 300 mg/m² IV Q3W (DAY 1, 3)
LINEAR PLOT

Serum Ramucirumab Concentration (µg/mL)

Time after First Dose (day)

FIG. 6A
MEAN PK - 300 mg/m² IV Q3W (DAY 1, 3)

SEMI-LOG PLOT

Serum Samalizumab Concentration (µg/mL)

Time after First Dose (day)

FIG. 6B
INDIVIDUAL PK - 300 mg/m² IV Q3W (DAY 1, 3)
INDUCTION + CONSOLIDATION PHASES
LINEAR PLOT

FIG. 7A
INDIVIDUAL PK - 300 mg/m² IV Q3W (DAY 1, 3)
INDUCTION + CONSOLIDATION PHASES

SEMI-LOG PLOT

Serum Samalizumab Concentration (µg/mL)

Time after First Dose (day)

FIG. 7B
MEAN PK (MEAN ± SD) - 300 mg/m$^2$ IV Q3W (DAYS 1, 3) INDUCTION + CONSOLIDATION PHASES (N = 1 - 6)

LINEAR PLOT

Serum Salmizumab Concentration (µg/mL)

Time after First Dose (day)

FIG. 8A
MEAN PK (MEAN ± SD) - 300 mg/m² IV Q3W (DAYS 1, 3)
INDUCTION + CONSOLIDATION PHASES (N = 1 - 6)

SEMI-LOG PLOT

FIG. 8B
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION No.**

PCT/US2017/056806

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K39/395 C07K16/28

**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

**X** Further documents are listed in the continuation of Box C. **X** See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

**Date of the actual completion of the international search**

27 November 2017

**Date of mailing of the international search report**

06/12/2017

**Name and mailing address of the ISA/**

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

**Authorized officer**

Bumb, Peter
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>COLES S J ET AL: &quot;Increased CD200 expression in acute myeloid leukemia is linked with an increased frequency of FoxP3+ regulatory T cells.&quot; , LEUKEMIA SEP 2012, vol . 26, no. 9, September 2012 (2012-09), pages 2146-2148, XP002776042, ISSN : 1476-5551 page 2149, right-hand column</td>
<td>1-29</td>
</tr>
<tr>
<td>Y</td>
<td>ALESSANDR0 ISID0RI ET AL: &quot;Renewing the immunological approach to AML treatment: from novel pathways to innovative therapies&quot; , CANCER RESEARCH FRONTIERS, vol . 2, no. 2, 16 May 2016 (2016-05-16) , pages 226-251, XP002776045, table 1</td>
<td>1-29</td>
</tr>
<tr>
<td>Y</td>
<td>wo 2011/085343 AI (ALEXION PHARMA INC [US]; FAAS MCKNIGHT SUSAN [US]; COFI ELL R0XANNE [US]) 14 July 2011 (2011-07-14) examples 1-3</td>
<td>1-29</td>
</tr>
<tr>
<td>Category</td>
<td>Citation of document, with indication, where appropriate, of the relevant passages</td>
<td>Relevant to claim No.</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>WO 2011085343 AI</td>
<td>14-07-2011</td>
<td>AU 2011203879 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2786692 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102906115 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2523976 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2013516494 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2015155465 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20130005264 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 601111 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2012134369 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SG 182408 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013202602 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2016033514 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2011085343 AI</td>
</tr>
</tbody>
</table>