ANTI-CD38 ANTIBODIES FOR TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA

FIELD OF THE INVENTION

The present invention relates to methods of treatment of acute lymphoblastic leukemia with anti-CD38 antibodies.

BACKGROUND OF THE INVENTION

CD38 is a multifunctional protein having function in receptor-mediated adhesion and signaling, as well as mediating calcium mobilization via its ecto-enzymatic activity catalyzing formation of cyclic ADP-ribose (cADPR) and ADPR. CD38 mediates cytokine secretion and activation and proliferation of lymphocytes (Funaro *et al.*, J Immunol 145:2390-6, 1990; Terhorst *et al.*, Cell 771-80, 1981; Guse *et al.*, Nature 398:70-3, 1999). CD38, via its NAD glycohydrolase activity, also regulates extracellular NAD^+ levels, which have been implicated in modulating the regulatory T-cell compartment (Adriouch *et al.*, 14:1284-92, 2012; Chiarugi *et al.*, Nature Reviews 12:741-52, 2012). In addition to signaling via Ca^{2+}, CD38 signaling occurs via cross-talk with antigen-receptor complexes on T and B cells or other types of receptor complexes, e.g ., MHC molecules, involving CD38 in several cellular responses, but also in switching and secretion of IgG1.

CD38 is a type II transmembrane glycoprotein expressed on hemopoietic cells such as medullary thymocytes, activated T- and B-cells, resting NK cells and monocytes, lymph node germinal center lymphoblasts, plasma B cells, intrafollicular cells and dendritic cells. A portion of normal bone marrow cells, particular precursor cells as well as umbilical cord cells are CD38-positive. In addition to lymphoid precursor cells, CD38 is expressed on erythrocytes and on platelets, and expression is also found in some solid tissues such as gut, brain, prostate, bone, and pancreas. Mature resting T- and B-cells express limited to no surface CD38.

CD38 is also expressed in a variety of malignant hematological diseases, including multiple myeloma, leukemias and lymphomas, such as B-cell chronic lymphocytic leukemia, T- and B-cell acute lymphocytic leukemia, Waldenstrom macroglobulinemia, primary systemic amyloidosis, mantle-cell lymphoma, pro-lymphocytic/myelocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, follicular lymphoma, Burkitt's lymphoma, large granular lymphocytic (LGL) leukemia, NK-cell leukemia and plasma-cell leukemia.

Expression of CD38 has been described on epithelial/endothelial cells of different origin, including glandular epithelium in prostate, islet cells in pancreas, ductal epithelium in glands, including parotid gland, bronchial epithelial cells, cells in testis and ovary and tumor epithelium in colorectal adenocarcinoma. Other diseases, where CD38 expression could be involved, include, e.g., broncho-epithelial carcinomas of the lung, breast cancer (evolving from malignant proliferation of epithelial lining in ducts and lobules of the breast), pancreatic tumors, evolving from the β-cells (insulinomas), tumors evolving from epithelium in the gut (e.g. adenocarcinoma and squamous cell carcinoma), carcinoma in the prostate gland, and seminomas in testis and ovarian cancers. In the central nervous system, neuroblastomas express CD38.

Acute lymphoblastic leukemia (ALL) is characterized by impaired early lymphoid development and is classified as either B-cell or T-cell ALL. Buriktt's lymphoma ("Mature B cell lymphoma") is also classified as ALL. Incidence of ALL is about 6000 new cases per year, or approximately 1 in 50,000. Both genetic and environmental factors contribute to ALL, with several chromosomal rearrangement and submicroscopic genetic alterations identified (Inaba *et al.,* Lancet 381:1943-55, 2013). Overall response rates to therapy in children having ALL is about 80%, and about 45%-60% in adults with ALL. Unfortunately, prognosis in relapsed ALL is poor.

Therefore, there remains a need for effective treatments for ALL.

SUMMARY OF THE INVENTION

One embodiment of the invention is a method of treating a subject having acute lymphoblastic leukemia (ALL), comprising administering to a patient in need thereof an anti-CD38 antibody that competes for binding to CD38 with an antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 4 and a light chain variable region (VL) of SEQ ID NO: 5, wherein the anti-CD38 antibody induces *in vitro* killing of ALL cells by antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC), apoptosis, or *in vitro* modulation of CD38 enzymatic activity.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the efficacy of daratumumab in ALL patient tumor model of disease (ALL 7015 model). Graph was plotted by Mean ± SEM; Mean ± SEM plotted only when there were 80% or more animals (at least 8 animals per each cohort) on the study for each time

point (initially there were 10 mice per each cohort). Y-axis shows the percentage of tumor burden measured as % of human $CD45^+$ cells divided by live cells.

Figure 2 shows the efficacy of daratumumab in ALL patient tumor model of disease (ALL 7043 model). Graph was plotted by Mean ± SEM; Mean ± SEM plotted only when there were 80% or more animals (at least 8 animals per each cohort) on the study for each time point (initially there were 10 mice per each cohort).

Figure 3 shows the efficacy of daratumumab and daratumumab in combination with vincristine in ALL cell line tumor xenograft model (NALM-6 model). Animals were divided in four treatment groups and were administered, 10 mg/kg daratumumab, 0.5 mg/kg vincristine, or daratumumab in combination with vincristine. Median survival time was plotted against days after tumor inoculation.

DETAILED DESCRIPTION OF THE INVENTION

"CD38" refers to the human CD38 protein (synonyms: ADP-ribosyl cyclase 1, cADPr hydrolase 1, cyclic ADP-ribose hydrolase 1). Human CD38 has an amino acid sequence shown in SEQ ID NO: 1

The term "antibodies" as used herein is meant in a broad sense and includes immunoglobulin molecules including polyclonal antibodies, monoclonal antibodies including murine, human, human-adapted, humanized and chimeric monoclonal antibodies, antibody fragments, bispecific or multispecific antibodies, dimeric, tetrameric or multimeric antibodies, and single chain antibodies.

Immunoglobulins can be assigned to five major classes, namely IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA_1, IgA_2, IgG_1, IgG_2, IgG_3 and IgG_4. Antibody light chains of any vertebrate species can be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

The term "antibody fragments" refers to a portion of an immunoglobulin molecule that retains the heavy chain and/or the light chain antigen binding site, such as heavy chain complementarity determining regions (HCDR) 1, 2 and 3, light chain complementarity determining regions (LCDR) 1, 2 and 3, a heavy chain variable region (VH), or a light chain variable region (VL). Antibody fragments include a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a $F(ab)_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL

and VH domains of a single arm of an antibody; a domain antibody (dAb) fragment (Ward *et al* (1989) *Nature* 341:544- 546), which consists of a VH domain. VH and VL domains can be engineered and linked together via a synthetic linker to form various types of single chain antibody designs where the VH/VL domains pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chain antibody constructs, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody; described for example in PCT Intl. Publ. Nos. WO1998/44001, WO1988/01649, WO1994/13804, and WO1992/01047. These antibody fragments are obtained using well known techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are full length antibodies.

The phrase "isolated antibody" refers to an antibody or antibody fragment that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody specifically binding CD38 is substantially free of antibodies that specifically bind antigens other than human CD38). An isolated antibody that specifically binds CD38, however, can have cross-reactivity to other antigens, such as orthologs of human CD38, such as *Macaca fascicularis* (cynomolgus) CD38. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

An antibody variable region consists of a "framework" region interrupted by three "antigen binding sites". The antigen binding sites are defined using various terms such as Complementarity Determining Regions (CDRs), three in the VH (HCDR1, HCDR2, HCDR3), and three in the VL (LCDR1, LCDR2, LCDR3), are based on sequence variability (Wu and Kabat J Exp Med 132:211-50, 1970; Kabat et al Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991) or "Hypervariable regions", "HVR", or "HV", three in the VH (H1, H2, H3) and three in the VL (L1, L2, L3), refer to the regions of an antibody variable domains which are hypervariable in structure as defined by Chothia and Lesk (Chothia and Lesk Mol Biol 196:901-17, 1987). Other terms include "IMGT-CDRs" (Lefranc *et al.*, Dev Comparat Immunol 27:55-77, 2003) and "Specificity Determining Residue Usage" (SDRU) (Almagro, Mol Recognit 17:132-43, 2004). The International ImMunoGeneTics (IMGT) database (http://www_imgt_org) provides a standardized numbering and definition of antigen-binding sites. The correspondence between CDRs, HVs and IMGT delineations is described in Lefranc *et al.*, Dev Comparat Immunol 27:55-77, 2003.

"Chothia residues" as used herein are the antibody VL and VH residues numbered according to Al-Lazikani (Al-Lazikani *et al.*, J Mol Biol 273:927-48, 1997).

"Framework" or "framework sequences" are the remaining sequences of a variable region other than those defined to be antigen binding sites. Because the antigen binding sites can be defined by various terms as described above, the exact amino acid sequence of a framework depends on how the antigen-binding site was defined.

"Humanized antibody" refers to an antibody in which the antigen binding sites are derived from non-human species and the variable region frameworks are derived from human immunoglobulin sequences. Humanized antibodies may include substitutions in the framework regions so that the framework may not be an exact copy of expressed human immunoglobulin or germline gene sequences.

"Human-adapted" antibodies or "human framework adapted (HFA)" antibodies refers to humanized antibodies adapted according to methods described in U.S. Pat. Publ. No. US2009/0118127. Human-adapted antibodies are humanized by selecting the acceptor human frameworks based on the maximum CDR and FR similarities, length compatibilities and sequence similarities of CDR1 and CDR2 loops and a portion of light chain CDR3 loops.

"Human antibody" refers to an antibody having heavy and light chain variable regions in which both the framework and the antigen binding sites are derived from sequences of human origin. If the antibody contains a constant region, the constant region also is derived from sequences of human origin.

A human antibody comprises heavy or light chain variable regions that are "derived from" sequences of human origin wherein the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such systems include human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice carrying human immunoglobulin loci as described herein. A "human antibody" may contain amino acid differences when compared to the human germline or rearranged immunoglobulin sequences due to for example naturally occurring somatic mutations or intentional introduction of substitutions in the framework or antigen binding sites. Typically, a human antibody 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% identical in amino acid sequence to an amino acid sequence encoded by a human germline or rearranged immunoglobulin gene. In some cases, "human antibody" may contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik *et al.*, J Mol Biol 296:57-86, 2000), or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example

as described in Shi *et al.*, J Mol Biol 397:385-96, 2010 and Intl. Pat. Publ. No. WO2009/085462). Antibodies in which antigen binding sites are derived from a non-human species are not included in the definition of human antibody.

Isolated humanized antibodies may be synthetic. Human antibodies, while derived from human immunoglobulin sequences, may be generated using systems such as phage display incorporating synthetic CDRs and/or synthetic frameworks, or can be subjected to *in vitro* mutagenesis to improve antibody properties, resulting in antibodies that do not naturally exist within the human antibody germline repertoire *in vivo*.

The term "recombinant antibody" as used herein, includes all antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), antibodies isolated from a host cell transformed to express the antibody, antibodies isolated from a recombinant, combinatorial antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences, or antibodies that are generated *in vitro* using Fab arm exchange such as bispecific antibodies.

The term "monoclonal antibody" as used herein refers to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope, or in a case of a bispecific monoclonal antibody, a dual binding specificity to two distinct epitopes.

The term "epitope" as used herein means a portion of an antigen to which an antibody specifically binds. Epitopes usually consist of chemically active (such as polar, non-polar or hydrophobic) surface groupings of moieties such as amino acids or polysaccharide side chains and can have specific three-dimensional structural characteristics, as well as specific charge characteristics. An epitope can be composed of contiguous and/or discontiguous amino acids that form a conformational spatial unit. For a discontiguous epitope, amino acids from differing portions of the linear sequence of the antigen come in close proximity in 3-dimensional space through the folding of the protein molecule.

"Variant" as used herein refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications for example, substitutions, insertions or deletions.

"Synergy", "synergism" or "synergistic" mean more than the expected additive effect of a combination.

The term "in combination with" as used herein means that two or more therapeutics can be administered to a subject together in a mixture, concurrently as single agents or sequentially as single agents in any order.

The terms "treat" or "treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development or spread of tumor or tumor cells. Beneficial or desired clinical results include alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if a subject was not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

"Inhibits growth" (e.g. referring to cells, such as tumor cells) refers to a measurable decrease in the cell growth *in vitro* or *in vivo* when contacted with a therapeutic or a combination of therapeutics or drugs when compared to the growth of the same cells grown in appropriate control conditions well known to the skilled in the art. Inhibition of growth of a cell *in vitro* or *in vivo* may be at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, or 100%. Inhibition of cell growth can occur by a variety of mechanisms, for example by antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC), apoptosis, necrosis, or by inhibition of cell proliferation.

A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Exemplary indicators of an effective therapeutic or combination of therapeutics include, for example, improved well-being of the patient, reduction of a tumor burden, arrested or slowed growth of a tumor, and/or absence of metastasis of cancer cells to other locations in the body.

One embodiment of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, is a method of treating a subject having acute lymphoblastic leukemia (ALL), comprising administering to a patient in need thereof an anti-CD38 antibody that competes for binding to CD38 with an

antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 4 and a light chain variable region (VL) of SEQ ID NO: 5, wherein the anti-CD38 antibody induces *in vitro* killing of ALL cells by antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC), apoptosis, or *in vitro* modulation of CD38 enzymatic activity.

Another embodiment of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, is a method of treating a subject having acute lymphoblastic leukemia (ALL), comprising administering to a patient in need thereof an anti-CD38 antibody that binds to the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and the region EKVQTLEAWVIHGG (SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1), wherein the anti-CD38 antibody induces *in vitro* killing of ALL cells by antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC), apoptosis, or *in vitro* modulation of CD38 enzymatic activity. The epitope of the antibody includes some or all of the residues having the sequences shown in SEQ ID NO: 2 or SEQ ID NO: 3. In some embodiments disclosed herein, including in the numbered embodiments listed below, the antibody epitope comprises at least one amino acid in the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and at least one amino acid in the region EKVQTLEAWVIHGG (SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1). In some embodiments disclosed herein, including in the numbered embodiments listed below, the antibody epitope comprises at least two amino acids in the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and at least two amino acids in the region EKVQTLEAWVIHGG (SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1). In some embodiments disclosed herein, including in the numbered embodiments listed below, the antibody epitope comprises at least three amino acids in the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and at least three amino acids in the region EKVQTLEAWVIHGG (SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1). In some embodiments disclosed herein, including in the numbered embodiments listed below, the anti-CD38 antibody binds to an epitope comprising at least KRN in the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and comprising at least VQLT (SEQ ID NO: 14) in the region EKVQTLEAWVIHGG (SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1).

An exemplary antibody that binds to the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and the region EKVQTLEAWVIHGG (SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1) or minimally to residues KRN and VQLT (SEQ ID NO: 14) as shown above is daratumumab (see Intl. Pat. Publ. No. WO2006/0998647). Daratumumab comprises VH

and a VL amino acid sequences shown in SEQ ID NO: 4 and 5, respectively, heavy chain CDRs HCDR1, HCDR2 and HCDR3 of SEQ ID NOs: 6, 7 and 8, and light chain CDRs LCDR1, LCDR2 and LCDR3 of SEQ ID NOs: 9, 10 and 11, respectively, and is of IgG1/κ subtype. Daratumumab heavy chain amino acid sequence is shown in SEQ ID NO: 12 and light chain amino acid sequence shown in SEQ ID NO: 13.

SEQ ID NO: 1
MANCEFSPVSGDKPCCRLSRRAQLCLGVSILVLILVVVLAVVVPRWRQQWSGPGT
TKRFPETVLARCVKYTEIHPEMRHVDCQSVWDAFKGAFISKHPCNITEEDYQPLM
KLGTQTVPCNKILLWSRIKDLAHQFTQVQRDMFTLEDTLLGYLADDLTWCGEFN
TSKINYQSCPDWRKDCSNNPVSVFWKTVSRRFAEAACDVVHVMLNGSRSKIFDK
NSTFGSVEVHNLQPEKVQTLEAWVIHGGREDSRDLCQDPTIKELESIISKRNIQFSC
KNIYRPDKFLQCVKNPEDSSCTSEI

SEQ ID NO: 2
SKRNIQFSCKNIYR

SEQ ID NO: 3
EKVQTLEAWVIHGG

SEQ ID NO: 4
EVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSA
ISGSGGGTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCAKDK
ILWFGEPVFDYWGQGTLVTVSS

SEQ ID NO: 5
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYD
ASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPTFGQ
GTKVEIK

SEQ ID NO: 6
SFAMS

SEQ ID NO: 7
AISGSGGGTYYADSVKG

SEQ ID NO: 8
DKILWFGEPVFDY

SEQ ID NO: 9
RASQSVSSYLA

SEQ ID NO: 10
DASNRAT

SEQ ID NO: 11
QQRSNWPPTF

SEQ ID NO: 12
EVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSAISGSG
GGTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYFCAKDKILWFGEPVF
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK

SEQ ID NO: 13
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRAT
GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPTFGQGTKVEIKRTVAAP
SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 14
VQLT

Antibodies can be evaluated for their competition with daratumumab having VH of SEQ ID NO: 4 and VL of SEQ ID NO: 5 for binding to CD38 using well known *in vitro*

methods. In an exemplary method, CHO cells recombinantly expressing CD38 may be incubated with unlabeled daratumumab for 15 min at 4°C, followed by incubation with an excess of fluorescently labeled test antibody for 45 min at 4°C. After washing in PBS/BSA, fluorescence may be measured by flow cytometry using standard methods. In another exemplary method, extracellular portion of human CD38 may be coated on the surface of an ELISA plate. Excess of unlabelled daratumumab may be added for about 15 minutes and subsequently biotinylated test antibodies may be added. After washes in PBS/Tween, binding of the test biotinylated antibody may be detected using horseradish peroxidase (HRP)-conjugated streptavidine and the signal detected using standard methods. It is readily apparent that in the competition assays, daratumumab may be labelled and the test antibody unlabeled. The test antibody competes with daratumumab when daratumumab inhibits binding of the test antibody, or the test antibody inhibits binding of daratumumab by 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90% , 95% or 100%. The epitope of the test antibody can further be defined for example by peptide mapping or hydrogen/deuterium protection assays using known methods, or by crystal structure determination.

Antibodies binding to the same region on CD38 as daratumumab can be generated for example by immunizing mice with peptides having the amino acid sequences shown in SEQ ID NOs: 2 and 3 using standard methods and as described herein. Antibodies can be further evaluated for example by assaying competition between daratumumab and a test antibody for binding to CD38 using well known *in vitro* methods and as described above.

The Fc portion of the antibody may mediate antibody effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) or complement dependent cytotoxicity (CDC). Such function may be mediated by binding of an Fc effector domain(s) to an Fc receptor on an immune cell with phagocytic or lytic activity or by binding of an Fc effector domain(s) to components of the complement system. Typically, the effect(s) mediated by the Fc-binding cells or complement components result in inhibition and/or depletion of target cells, for example CD38-expressing cells. Human IgG isotypes IgG1, IgG2, IgG3 and IgG4 exhibit differential capacity for effector functions. ADCC may be mediated by IgG1 and IgG3, ADCP may be mediated by IgG1, IgG2, IgG3 and IgG4, and CDC may be mediated by IgG1 and IgG3.

In the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody is of IgG1, IgG2, IgG3 or IgG4 isotype.

In the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 induces *in vitro* killing of ALL cells that express CD38 by ADCC.

In the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 induces *in vitro* killing of ALL cells that express CD38 by CDC.

In the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody induces *in vitro* killing of ALL cells that express CD38 by ADCP.

In the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody induces *in vitro* killing of ALL cells that express CD38 by apoptosis.

In the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody induces *in vitro* killing of ALL cells that express CD38 by ADCC and CDC

While not wishing to be bound to any particular theory on mechanism of action, it is expected that the anti-CD38 antibody of the invention will induce *in vivo* killing of ALL cells that express CD38 by ADCC, CDC, ADCP, apoptosis or *in vivo* modulation of CD38 enzymatic activity.

"Antibody-dependent cellular cytotoxicity", "antibody-dependent cell-mediated cytotoxicity" or "ADCC" is a mechanism for inducing cell death that depends upon the interaction of antibody-coated target cells with effector cells possessing lytic activity, such as natural killer cells, monocytes, macrophages and neutrophils via Fc gamma receptors (FcγR) expressed on effector cells. For example, NK cells express FcγRIIIa, whereas monocytes express FcγRI, FcγRII and FcvRIIIa. Death of the antibody-coated target cell, such as CD38-expressing cells, occurs as a result of effector cell activity through the secretion of membrane pore-forming proteins and proteases. To assess ADCC activity of an anti-CD38 antibody, the antibody may be added to CD38-expressing cells in combination with immune effector cells, which may be activated by the antigen antibody complexes resulting in cytolysis of the target cell. Cytolysis is generally detected by the release of label (e.g. radioactive substrates, fluorescent dyes or natural intracellular

proteins) from the lysed cells. Exemplary effector cells for such assays include peripheral blood mononuclear cells (PBMC) and NK cells. Exemplary target cells include Daudi cells (ATCC® CCL-213™) or B cell leukemia or lymphoma tumor cells expressing CD38. In an exemplary assay, target cells are labeled with 20 μCi of ^{51}Cr for 2 hours and washed extensively. Cell concentration of the target cells can be adjusted to 1×10^6 cells/ml, and anti-CD38 antibodies at various concentrations are added. Assays are started by adding Daudi cells at an effector:target cell ratio of 40:1. After incubation for 3 hr at 37°C assays are stopped by centrifugation, and ^{51}Cr release from lysed cells are measured in a scintillation counter. Percentage of cellular cytotoxicity may be calculated as % maximal lysis which may be induced by adding 3% perchloric acid to target cells. Anti-CD38 antibodies used in the methods of the invention may induce ADCC by about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of control (cell lysis induced by 3% perchloric acid).

"Antibody-dependent cellular phagocytosis" ("ADCP") refers to a mechanism of elimination of antibody-coated target cells by internalization by phagocytic cells, such as macrophages or dendritic cells. ADCP may be evaluated by using monocyte-derived macrophages as effector cells and Daudi cells (ATCC® CCL-213™) or B cell leukemia or lymphoma tumor cells expressing CD38 as target cells engineered to express GFP or other labeled molecule. Effector:target cell ratio may be for example 4:1. Effector cells may be incubated with target cells for 4 hours with or without anti-CD38 antibody. After incubation, cells may be detached using accutase. Macrophages can be identified with anti-CD11b and anti-CD14 antibodies coupled to a fluorescent label, and percent phagocytosis can be determined based on % GFP fluorescent in the $CD11^+CD14^+$ macrophages using standard methods. Anti-CD38 antibodies used in the methods of the invention may induce ADCP by about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% .

"Complement-dependent cytotoxicity", or "CDC", refers to a mechanism for inducing cell death in which an Fc effector domain of a target-bound antibody binds and activates complement component C1q which in turn activates the complement cascade leading to target cell death. Activation of complement may also result in deposition of complement components on the target cell surface that facilitate ADCC by binding complement receptors (e.g., CR3) on leukocytes. CDC of CD38-expressing cells can be measured for example by plating Daudi cells at 1×10^5 cells/well (50 μl/well) in RPMI-B (RPMI supplemented with 1% BSA), adding 50 μl anti-CD38 antibodies to the wells at final concentration between 0-100 μg/ml, incubating the reaction for 15 min at room

temperature, adding 11 μl of pooled human serum to the wells, and incubation the reaction for 45 min at 37° C. Percentage (%) lysed cells may be detected as % propidium iodide stained cells in FACS assay using standard methods. Anti-CD38 antibodies used in the methods of the invention may induce CDC by about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% .

The ability of monoclonal antibodies to induce ADCC can be enhanced by engineering their oligosaccharide component. Human IgG1 or IgG3 are N-glycosylated at Asn297 with the majority of the glycans in the well-known biantennary G0, G0F, G1, G1F, G2 or G2F forms. Antibodies produced by non-engineered CHO cells typically have a glycan fucose content of about at least 85%. The removal of the core fucose from the biantennary complex-type oligosaccharides attached to the Fc regions enhances the ADCC of antibodies via improved FcγRIIIa binding without altering antigen binding or CDC activity. Such mAbs can be achieved using different methods reported to lead to the successful expression of relatively high defucosylated antibodies bearing the biantennary complex-type of Fc oligosaccharides such as control of culture osmolality (Konno *et al.*, Cytotechnology 64:249-65, 2012), application of a variant CHO line Lec13 as the host cell line (Shields *et al.*, J Biol Chem 277:26733-26740, 2002), application of a variant CHO line EB66 as the host cell line (Olivier *et al.*, MAbs ;2(4), 2010; Epub ahead of print; PMID:20562582), application of a rat hybridoma cell line YB2/0 as the host cell line (Shinkawa *et al.*, J Biol Chem 278:3466-3473, 2003), introduction of small interfering RNA specifically against the α 1,6-fucosyltrasferase (*FUT8)* gene (Mori *et al.*, Biotechnol Bioeng88:901-908, 2004), or coexpression of β-1,4-*N*-acetylglucosaminyltransferase III and Golgi α-mannosidase II or a potent alpha-mannosidase I inhibitor, kifunensine (Ferrara *et al.*, J Biol Chem281:5032-5036, 2006, Ferrara *et al.*, Biotechnol Bioeng 93:851-861, 2006; Xhou *et al.*, Biotechnol Bioeng 99:652-65, 2008). ADCC elicited by anti-CD38 antibodies used in the methods of the invention, and in some embodiments of each and every one of the numbered embodiments listed below, may also be enhanced by certain substitutions in the antibody Fc. Exemplary substitutions are for example substitutions at amino acid positions 256, 290, 298, 312, 356, 330, 333, 334, 360, 378 or 430 (residue numbering according to the EU index) as described in U.S. Pat. No. 6,737,056.

In some methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibodies comprise a substitution in the antibody Fc.

In some methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibodies comprise a substitution in the antibody Fc at amino acid positions 256, 290, 298, 312, 356, 330, 333, 334, 360, 378 or 430 (residue numbering according to the EU index).

In some methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody has a biantennary glycan structure with fucose content of about between 0% to about 15%, for example 15%, 14%, 13%, 12%, 11% 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or 0%.

In some methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody has a biantennary glycan structure with fucose content of about 50%, 40%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 14%, 13%, 12%, 11% 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or 0%

Substitutions in the Fc and reduced fucose content may enhance the ADCC activity of the anti-CD38 antibody.

"Fucose content" means the amount of the fucose monosaccharide within the sugar chain at Asn297. The relative amount of fucose is the percentage of fucose-containing structures related to all glycostructures. These may be characterized and quantified by multiple methods, for example: 1) using MALDI-TOF of N-glycosidase F treated sample (e.g. complex, hybrid and oligo- and high-mannose structures) as described in Intl. Pat. Publ. No. WO2008/077546; 2) by enzymatic release of the Asn297 glycans with subsequent derivatization and detection/ quantitation by HPLC (UPLC) with fluorescence detection and/or HPLC-MS (UPLC-MS); 3) intact protein analysis of the native or reduced mAb, with or without treatment of the Asn297 glycans with Endo S or other enzyme that cleaves between the first and the second GlcNAc monosaccharides, leaving the fucose attached to the first GlcNAc; 4) digestion of the mAb to constituent peptides by enzymatic digestion (e.g., trypsin or endopeptidase Lys-C), and subsequent separation, detection and quantitation by HPLC-MS (UPLC-MS) or 5) separation of the mAb oligosaccharides from the mAb protein by specific enzymatic deglycosylation with PNGase F at Asn 297. The oligosaccharides released can be labeled with a fluorophore, separated and identified by various complementary techniques which allow: fine characterization of the glycan structures by matrix-assisted laser desorption ionization (MALDI) mass spectrometry by comparison of the experimental masses with the theoretical masses, determination of the degree of sialylation by ion exchange HPLC (GlycoSep C), separation and quantification of the oligosacharride forms according to hydrophilicity criteria by normal-phase HPLC (GlycoSep N), and separation and

quantification of the oligosaccharides by high performance capillary electrophoresis-laser induced fluorescence (HPCE-LIF).

"Low fucose" or "low fucose content" as used in the application refers to antibodies with fucose content of about 0% - 15%.

"Normal fucose" or 'normal fucose content" as used herein refers to antibodies with fucose content of about over 50%, typically about over 60%, 70%, 80% or over 85%.

The anti-CD38 antibodies used in the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may induce *in vitro* killing of ALL cells by apoptosis. Methods for evaluating apoptosis are well known, and include for example annexin IV staining using standard methods. The anti-CD38 antibodies used in the methods of the invention may induce apoptosis in about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of cells.

The anti-CD38 antibodies used in the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may induce *in vitro* killing of ALL cells by modulation of CD38 enzymatic activity. CD38 is a multifunctional ectoenzme with ADP-ribosyl cyclase 1 activity catalyzing the formation of cyclic ADP-ribose (cADPR) and ADPR from NAD^+, and also functions to hydrolyze NAD^+ and cADPR to ADPR. CD38 also catalyzes the exchange of the nicotinamide group of $NADP^+$ with nicotinic acid under acidic conditions, to yield $NAADP^+$ (nicotinic acid-adenine dinucleotide phosphate). Modulation of the enzymatic activity of human CD38 with anti-CD38 antibodies used in the methods of the invention may be measured in an assay described in Graeff *et al.*, J. Biol. Chem. 269, 30260-30267 (1994). For example, substrate NGD^+ may be incubated with CD38, and the modulation of the production of cyclic GDP-ribose (cGDPR) may be monitored spectrophotometrically at excitation at 340 nM and emission at 410 nM at different time points after addition of the antibody at various concentrations. Inhibition of the synthesis of cADPR can be determined according to the HPLC method described in Munshi *et al.*, J. Biol. Chem. 275, 21566-21571 (2000). The anti-CD38 antibodies used in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may inhibit CD38 enzymatic activity by at least about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% .

In some methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody

comprises the heavy chain complementarity determining regions (HCDR) 1 (HCDR1), 2 (HCDR2) and 3 (HCDR3) sequences of SEQ ID NOs: 6, 7 and 8, respectively.

In some methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody comprises the light chain complementarity determining regions (LCDR) 1 (LCDR1), 2 (LCDR2) and 3 (LCDR3) sequences of SEQ ID NOs: 9, 10 and 11, respectively.

In some methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody comprises the heavy chain variable region (VH) of SEQ ID NO: 4 and the light chain variable region (VL) of SEQ ID NO: 5.

In some methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody comprises a heavy chain of SEQ ID NO: 12 and a light chain of SEQ ID NO: 13.

In some methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody comprises a heavy chain comprising an amino acid sequence that is 95%, 96%, 97%, 98% or 99% identical to that of SEQ ID NO: 12 and a light chain comprising an amino acid sequence that is 95%, 96%, 97%, 98% or 99% identical to that of SEQ ID NO: 13.

Antibodies that are substantially identical to the antibody comprising the heavy chain of SEQ ID NO: 12 and the light chain of SEQ ID NO: 13 may be used in the methods of the invention. The term "substantially identical" as used herein means that the two antibody heavy chain or light chain amino acid sequences being compared are identical or have "insubstantial differences". Insubstantial differences are substitutions of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids in an antibody heavy chain or light chain that do not adversely affect antibody properties. Percent identity can be determined for example by pairwise alignment using the default settings of the AlignX module of Vector NTI v.9.0.0 (Invitrogen, Carlsbad, CA). The protein sequences of the present invention can be used as a query sequence to perform a search against public or patent databases to, for example, identify related sequences. Exemplary programs used to perform such searches are the XBLAST or BLASTP programs (http_//www_ncbi_nlm/nih_gov), or the GenomeQuest™ (GenomeQuest, Westborough, MA) suite using the default settings. Exemplary substitutions that can be made to the anti-CD38 antibodies used in the methods of the invention are for example conservative substitutions with an amino acid having similar charge, hydrophobic, or stereochemical characteristics. Conservative substitutions may also be made to improve antibody

properties, for example stability or affinity, or to improve antibody effector functions. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid substitutions may be made for example to the heavy or the light chain of the anti-CD38 antibody. Furthermore, any native residue in the heavy or light chain may also be substituted with alanine, as has been previously described for alanine scanning mutagenesis (MacLennan *et al.*, Acta Physiol Scand Suppl 643:55-67, 1998; Sasaki *et al.*, Adv Biophys 35:1-24, 1998). Desired amino acid substitutions may be determined by those skilled in the art at the time such substitutions are desired. Amino acid substitutions may be done for example by PCR mutagenesis (U.S. Pat. No. 4,683,195). Libraries of variants may be generated using well known methods, for example using random (NNK) or non-random codons, for example DVK codons, which encode 11 amino acids (Ala, Cys, Asp, Glu, Gly, Lys, Asn, Arg, Ser, Tyr, Trp) and screening the libraries for variants with desired properties. The generated variants may be tested for their binding to CD38, their ability to induce ADCC, ADCP or apoptosis, or modulate CD38 enzymatic activity *in vitro* using methods described herein.

In the methods described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody can bind human CD38 with a range of affinities (K_D). In one embodiment according to the invention, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody binds to CD38 with high affinity, for example, with a K_D equal to or less than about 10^{-7} M, such as but not limited to, 1-9.9 (or any range or value therein, such as 1, 2, 3, 4, 5, 6, 7, 8, or 9) X 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13}, 10^{-14}, 10^{-15} or any range or value therein, as determined by surface plasmon resonance or the Kinexa method, as practiced by those of skill in the art. One exemplary affinity is equal to or less than $1x10^{-8}$ M. Another exemplary affinity is equal to or less than $1x10^{-9}$ M.

In some embodiments, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody is a bispecific antibody. The VL and/or the VH regions of the existing anti-CD38 antibodies or the VL and VH regions identified *de novo* as described above may be engineered into bispecific full length antibodies. Such bispecific antibodies may be made by modulating the CH3 interactions between the monospecific antibody heavy chains to form bispecific antibodies using technologies such as those described in U.S. Pat. No. 7,695,936; Int. Pat. Publ. No. WO04/111233; U.S. Pat. Publ. No. US2010/0015133; U.S. Pat. Publ. No. US2007/0287170; Int. Pat. Publ. No. WO2008/119353; U.S. Pat. Publ. No. US2009/0182127; U.S. Pat. Publ. No. US2010/0286374; U.S. Pat. Publ. No. US2011/0123532; Int. Pat. Publ. No. WO2011/131746; Int. Pat. Publ. No.

WO2011/143545; or U.S. Pat. Publ. No. US2012/0149876. Additional bispecific structures into which the VL and/or the VH regions of the antibodies of the invention can be incorporated are for example Dual Variable Domain Immunoglobulins (Int. Pat. Publ. No. WO2009/134776), or structures that include various dimerization domains to connect the two antibody arms with different specificity, such as leucine zipper or collagen dimerization domains (Int. Pat. Publ. No. WO2012/022811, U.S. Pat. No. 5,932,448; U.S. Pat. No. 6,833,441).

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody is conjugated to a toxin. Conjugation methods and suitable toxins are well known.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the ALL is B-cell lineage ALL.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the ALL is T-cell lineage ALL.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the ALL is adult ALL.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the ALL is pediatric ALL.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody is administered as a remission induction or as a postinduction therapy.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the ALL is refractory or relapsed ALL.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the subject has a white blood cell count of at least about 1×10^9 /L.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the ALL cells have a Philadelphia chromosome.

"Philadelphia chromosome" or "Ph" refers to a well-known chromosomal translocation between chromosomes 9 and 22, resulting in the oncogenic BCR-ABL gene fusion with constitutively active tyrosine kinase activity. The translocation results in a portion of the BCR gene from chromosome 22q11 becoming fused with a portion of the ABL gene from chromosome 9q34, and is designated as t(9;22)(q34;q11) under the

International System for Human Cytogenetic Nomenclature (ISCN). Depending on the precise location of the fusion, the molecular weight of the resulting fusion protein can range from 185 to 210 kDa. "Philadelphia chromosome" refers to all BCR-ABL fusion proteins formed due the (9;22)(q34;q11) translocation.

The Ph chromosome is present in about 20% of adults with ALL and a small percentage of children with ALL and is associated with poor prognosis. At a time of relapse, patients with Ph+ positive ALL may be on tyrosine kinase inhibitor (TKI) regimen and may have therefore become resistant to the TKI. The anti-CD38 antibodies may thus be administered to a subject who has become resistant to selective or partially selective BCR-ABL inhibitors. Exemplary BCR-ABL inhibitors are for example imatinib, dasatinib, nilotinib, bosutinib, ponatinib, bafetinib, saracatinib, tozasertib, danusertib or ibrutinib.

Other chromosomal rearrangements identified in B-lineage ALL patients are t(v;11q23) (MLL rearranged), t(1;19)(q23;p13.3); TCF3-PBX1 (E2A-PBX1), t(12;21)(p13;q22); ETV6-RUNX1 (TEL-AML1) and t(5;14)(q31;q32); IL3-IGH.

In some embodiments, the subject has ALL with t(v;11q23) (MLL rearranged), t(1;19)(q23;p13.3); TCF3-PBX1 (E2A-PBX1), t(12;21)(p13;q22); ETV6-RUNX1 (TEL-AML1) or t(5;14)(q31;q32); IL3-IGH chromosomal rearrangement.

Chromosomal rearrangements can be identified using well known methods, for example fluorescent in situ hybridization, karyotyping, pulsed field gel electrophoresis, or sequencing.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the subject is resistant or has acquired resistance to treatment with at least one BCR-ABL kinase inhibitor.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the at least one BCR-ABL kinase inhibitor is imatinib, dasatinib, nilotinib, bosutinib, ponatinib, bafetinib, saracatinib, tozasertib, danusertib or ibrutinib.

Various qualitative and/or quantitative methods may be used to determine if a subject is resistant, has developed or is susceptible to developing a resistance to treatment with at least one BCR-ABL kinase inhibitor. Symptoms that may be associated with resistance include, for example, a decline or plateau of the well-being of the patient, an increase in the size of a tumor, increase in the number of cancer cells, arrested or slowed decline in growth of a tumor or tumor cells, and/or the spread of cancerous cells in the body from one location to other organs, tissues or cells. Re-establishment or worsening of

various symptoms associated with tumor may also be an indication that a subject has developed or is susceptible to developing resistance to at least one BCR-ABL kinase inhibitor. The symptoms associated with cancer may vary according to the type of cancer. For example, symptoms associated with ALL may include swollen lymph nodes in neck, groin or armpits, fever, night sweats, coughing, chest paint, unexplained weight loss, abdominal swelling or pain, or a feeling of fullness. Other means to determine if a subject has developed a resistance to at least one BCR-ABL kinase inhibitor include analyses of tumor burden in a patient with ALL.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibody is administered in combination with vincristine.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the subject has received or will receive radiotherapy.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the subject has received or will receive a bone marrow transplant.

In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the subject having ALL is homozygous for phenylalanine at position 158 of CD16 (FcγRIIIa-158F/F genotype) or heterozygous for valine and pheynylalanine at position 158 of CD16 (FcγRIIIa-158F/V genotype). CD16 is also known as the Fc gamma receptor IIIa (FcγRIIIa) or the low affinity immunoglobulin gamma Fc region receptor III-A isoform. Valine/phenylalanine (V/F) polymorphism at FcγRIIIa protein residue position 158 has been shown to affect FcγRIIIa affinity to human IgG. Receptor with FcγRIIIa-158F/F or FcγRIIIa-158F/V polymorphisms demonstrates reduced Fc engagement and therefore reduced ADCC when compared to the FcγRIIIa-158V/V. The lack of or low amount of fucose on human N-linked oligosaccharides improves the ability of the antibodies to induce ADCC due to improved binding of the antibodies to human FcγRIIIa (CD16) (Shields *et al.*, J Biol Chem 277:26733-40, 2002). Patients can be analyzed for their FcγRIIIa polymorphism using routine methods.

The invention also provides for the method of treating a subject having ALL, comprising administering to a patient in need thereof an anti-CD38 antibody that binds to the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and the region EKVQTLEAWVIHGG

(SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1), wherein the anti-CD38 antibody induces *in vitro* killing of CD38-expressing cells by antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC), apoptosis, or *in vitro* modulation of CD38 enzymatic activity, wherein the subject is homozygous for phenylalanine at position 158 of CD16 or heterozygous for valine and pheynylalanine at position 158 of CD16.

The invention also provides for the method of treating a subject having ALL, comprising administering to a patient in need thereof an anti-CD38 antibody that competes for binding to CD38 with an antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 4 and a light chain variable region (VL) of SEQ ID NO: 5, wherein the anti-CD38 antibody induces *in vitro* killing of ALL cells by antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC), apoptosis, or *in vitro* modulation of CD38 enzymatic activity, wherein the subject is homozygous for phenylalanine at position 158 of CD16 or heterozygous for valine and pheynylalanine at position 158 of CD16.

Administration/ Pharmaceutical Compositions

In the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-CD38 antibodies may be provided in suitable pharmaceutical compositions comprising the anti-CD38 antibody and a pharmaceutically acceptable carrier. The carrier may be diluent, adjuvant, excipient, or vehicle with which the anti-CD38 antibody is administered. Such vehicles may be 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 and the like. For example, 0.4% saline and 0.3% glycine can be used. These solutions are sterile and generally free of particulate matter. They may be sterilized by conventional, well-known sterilization techniques (*e.g.*, filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, stabilizing, thickening, lubricating and coloring agents, etc. The concentration of the molecules or antibodies of the invention in such pharmaceutical formulation may vary widely, *i.e.*, from less than about 0.5%, usually to at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on required dose, fluid volumes, viscosities, etc., according to the particular mode of administration selected. Suitable vehicles and formulations, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in e.g. Remington: The

Science and Practice of Pharmacy, 21st Edition, Troy, D.B. ed., Lipincott Williams and Wilkins, Philadelphia, PA 2006, Part 5, Pharmaceutical Manufacturing pp 691-1092, see especially pp. 958-989.

The mode of administration of the anti-CD38 antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be any suitable route such as parenteral administration, e.g., intradermal, intramuscular, intraperitoneal, intravenous or subcutaneous, pulmonary, transmucosal (oral, intranasal, intravaginal, rectal) or other means appreciated by the skilled artisan, as well known in the art.

The anti-CD38 antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be administered to a patient by any suitable route, for example parentally by intravenous *(i.v.)* infusion or bolus injection, intramuscularly or subcutaneously or intraperitoneally. *i.v.* infusion may be given over for example 15, 30, 60, 90, 120, 180, or 240 minutes, or from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 hours.

The dose given to a patient having ALL is sufficient to alleviate or at least partially arrest the disease being treated ("therapeutically effective amount") and may be sometimes 0.005 mg to about 100 mg/kg, e.g. about 0.05 mg to about 30 mg/kg or about 5 mg to about 25 mg/kg, or about 4 mg/kg, about 8 mg/kg, about 16 mg/kg or about 24 mg/kg , or for example about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mg/kg, but may even higher, for example about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40, 50, 60, 70, 80, 90 or 100 mg/kg.

A fixed unit dose may also be given, for example, 50, 100, 200, 500 or 1000 mg, or the dose may be based on the patient's surface area, e.g., 500, 400, 300, 250, 200, or 100 mg/m^2. Usually between 1 and 8 doses, (e.g., 1, 2, 3, 4, 5, 6, 7 or 8) may be administered to treat ALL, but 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more doses may be given.

The administration of the anti-CD38 antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be repeated after one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, two months, three months, four months, five months, six months or longer. Repeated courses of treatment are also possible, as is chronic administration. The repeated administration may be at the same dose or at a different dose. For example, the anti-CD38 antibody in the methods of the invention may be administered at 8 mg/kg or at 16 mg/kg at weekly interval for 8 weeks, followed by administration at 8 mg/kg or at 16 mg/kg every

two weeks for an additional 16 weeks, followed by administration at 8 mg/kg or at 16 mg/kg every four weeks by intravenous infusion.

The anti-CD38 antibodies may be administered in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, by maintenance therapy, such as, e.g ., once a week for a period of 6 months or more.

For example, anti-CD38 antibodies in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be provided as a daily dosage in an amount of about 0.1-100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 after initiation of treatment, or any combination thereof, using single or divided doses of every 24, 12, 8, 6, 4, or 2 hours, or any combination thereof.

Anti-CD38 antibodies in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may also be administered prophylactically in order to reduce the risk of developing cancer, delay the onset of the occurrence of an event in cancer progression, and/or reduce the risk of recurrence when a cancer is in remission. This may be especially useful in patients wherein it is difficult to locate a tumor that is known to be present due to other biological factors.

The anti-CD38 antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional protein preparations and well known lyophilization and reconstitution techniques can be employed.

The anti-CD38 antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be administered in combination with vincristine.

Vincristine may be administered for example at about 0.1 to 2 mg/kg single dose i.p., for example 0.1 to 0.5 mg/kg single dose i.p, for example 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9 or 2.0 mg/kg. Vincristine may be given as *i.v.* infusion.

In the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the combination of the anti-CD38 antibody and vincristine may be administered over any convenient timeframe. For example, the anti-CD38 antibody and vincristine may be administered to a patient on the same day, and even in the same intravenous infusion. However, the anti-CD38 antibody and vincristine may also be administered on alternating days or alternating weeks or months, and so on. In some methods, the anti-CD38 antibody and vincristine may be administered with sufficient proximity in time that they are simultaneously present (e.g., in the serum) at detectable levels in the patient being treated. In some methods, an entire course of treatment with the anti-CD38 antibody consisting of a number of doses over a time period is followed or preceded by a course of treatment with vincristine, consisting of a number of doses. A recovery period of 1, 2 or several days or weeks may be used between administration of the anti-CD38 antibody and vincristine.

Anti-CD38 antibody or a combination of anti-CD38 antibody and vincristine may be administered together with any form of radiation therapy including external beam radiation, intensity modulated radiation therapy (IMRT) and any form of radiosurgery including Gamma Knife, Cyberknife, Linac, and interstitial radiation (e.g. implanted radioactive seeds, GliaSite balloon), and/or with surgery.

While having described the invention in general terms, the embodiments of the invention will be further disclosed in the following examples that should not be construed as limiting the scope of the claims.

Further embodiments of the invention

Set out below are certain further embodiments of the invention according to the disclosures elsewhere herein. Features from embodiments of the invention set out above described as relating to the invention disclosed herein also relate to each and every one of these further numbered embodiments.

1. An anti-CD38 antibody for use in treating a subject having acute lymphoblastic leukemia (ALL).
2. An anti-CD38 antibody for use in treating a subject having ALL, in combination vincristine.
3. Vincristine for use in treating a subject having ALL, in combination with an anti-CD38 antibody.

4. 3. The combination of an anti-CD38 antibody and vincristine for use in treating a subject having ALL.
5. The anti-CD38 antibody for use according to embodiment 1 or 2, vincristine for use according to embodiment 3, or the combination according to embodiment 4, wherein the anti-CD38 antibody competes for binding to CD38 with an antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 4 and a light chain variable region (VL) of SEQ ID NO: 5.
6. The anti-CD38 antibody for use according to embodiment 1, 2 or 5, vincristine for use according to embodiment 3 or 5, or the combination according to embodiment 4 or 5, wherein the anti-CD38 antibody induces *in vitro* killing of ALL cells by antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC), apoptosis, or *in vitro* modulation of CD38 enzymatic activity, preferably wherein the anti-CD38 antibody induces *in vitro* killing of the ALL cells by ADCC or CDC.
7. The anti-CD38 antibody for use according to embodiment 1, 2, 5 or 6, vincristine for use according to embodiment 3, 5 or 6, or the combination according to embodiment 4-6, wherein the anti-CD38 antibody binds to the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and the region EKVQTLEAWVIHGG (SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1).
8. The anti-CD38 antibody for use according to embodiment 1, 2, 5-7, vincristine for use according to embodiment 3, 5 -7, or the combination according to embodiment 4-7, wherein the anti-CD38 antibody:
    a. is of IgG1, IgG2, IgG3 or IgG4 isotype;
    b. has a biantennary glycan structure with fucose content of about 50%, 40%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 14%, 13%, 12%, 11% 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or 0%; or
    c. comprise a substitution in the antibody Fc at amino acid positions 256, 290, 298, 312, 356, 330, 333, 334, 360, 378 or 430, when residue numbering according to the EU index.
9. The anti-CD38 antibody for use according to embodiment 1, 2, 5-8, vincristine for use according to embodiment 3, 5-8, or the combination according to embodiment 4-8, wherein the anti-CD38 antibody comprises

a. the heavy chain complementarity determining regions (HCDR) 1 (HCDR1), 2 (HCDR2) and 3 (HCDR3) sequences of SEQ ID NOs: 6, 7 and 8, respectively;
b. the light chain complementarity determining regions (LCDR) 1 (LCDR1), 2 (LCDR2) and 3 (LCDR3) sequences of SEQ ID NOs: 9, 10 and 11, respectively;
c. the heavy chain variable region (VH) of SEQ ID NO: 4 and the light chain variable region (VL) of SEQ ID NO: 5;
d. a heavy chain comprising an amino acid sequence that is 95%, 96%, 97%, 98% or 99% identical to that of SEQ ID NO: 12 and a light chain comprising an amino acid sequence that is 95%, 96%, 97%, 98% or 99% identical to that of SEQ ID NO: 13; or
e. the heavy chain of SEQ ID NO: 12 and the light chain of SEQ ID NO: 13.

10. The anti-CD38 antibody for use according to embodiment 1, 2, 5-9, vincristine for use according to embodiment 3, 5-9, or the combination according to embodiment 4-9, wherein ALL is B-cell lineage ALL, T-cell lineage ALL, adult ALL, pediatric ALL, refractory ALL or relapsed ALL.

11. The anti-CD38 antibody for use according to embodiment 1, 2, 5-10, vincristine for use according to embodiment 3, 5-10, or the combination according to embodiment 4-10, wherein the anti-CD38 antibody is administered as a remission induction or as postinduction therapy.

12. The anti-CD38 antibody for use according to embodiment 1, 2, 5-11, vincristine for use according to embodiment 3, 5-11, or the combination according to embodiment 4-11, wherein the subject

a. has a white blood cell count of at least about 1×10^9 /L; or
b. has ALL cells with a Philadelphia chromosome.

13. The anti-CD38 antibody for use according to embodiment 1, 2, 5-12, vincristine for use according to embodiment 3, 5-12, or the combination according to embodiment 4-12, wherein the BCR-ABL kinase inhibitor is imatinib, dasatinib, nilotinib, bosutinib, ponatinib, bafetinib, saracatinib, tozasertib, danusertib or ibrutinib.

14. The anti-CD38 antibody for use according to embodiment 1, 2, 5-13, vincristine for use according to embodiment 3, 5-13, or the combination according to embodiment 4-13, wherein the anti-CD38 antibody and vincristine are administered simultaneously, sequentially or separately.

15. The anti-CD38 antibody for use according to embodiment 1, 2, 5-14, vincristine for use according to embodiment 3, 5-14, or the combination according to embodiment 4-14, wherein

a. the subject is further treated or has been treated with radiotherapy; or

b. the subject has received hematopoietic stem cell transplantation.

Example 1. Efficacy of daratumumab in patient-derived ALL model

Methods

Patient tumor models ALL 7015 & ALL 7473 were used in the study.

ALL 7015 model: Tumor was resected from a 17 year old female having B cell lineage ALL. White blood cell count (WBC) was 98 x 10^9/L, hemoglobin (HB) 101g/L and platelet count (plt) 24 x 10^9/L. Philadelphia chromosome was evident in tumor cells with rearrangement BCR/ABL-P210 (t9;22)(q34;q11). Tumor cells were negative for following rearrangements: TEL/AML1, E2A/PBX1, MLL related gene, SIL/TAL1, IgH. Ratio of expression of Wilm's tumor 1 gene (WT1) to ABL gene (WT1/ABL) was 1.2%. Grade 1 hyperplasia with 95% of primitive lymphocytes was evident in bone marrow. 92.8% of abnormal bone marrow cells expressed CD38.

ALL 7473 model: Tumor was resected from a 35 year old make having T cell lineage ALL. WBC was 7.4 x 10^9/L, HB 112 g/L, and plt 73 x 10^9/L. Tumor cells were negative for following chromosomal rearrangement: BCR/ABL. SIL/TAL, MLL related gene, TCRδ. WT1/ABL was 2.0%. Grade I-II hyperplasia with 86% of primitive lymphocytes was evident in the bone marrow. 78% of abnormal cells expressed CD38.

NOD/SCID (female, 3-4 weeks old) were inoculated with 2x10^6 of ALL-7015 or ALL-7473 frozen cells. The animals were evaluated every 3-4 days for the appearance of tumor cells in the peripheral blood. Treatment was initiated when the tumor burden in the blood reached a specified level (ALL 7015: ~4.2% and ALL 7473: ~0.5%). The Tumor Burden (TB) was measured once a week by flow cytometry and measured as percentage of $CD45^+CD38^+$ cells in peripheral blood obtained from retro-orbital bleed. The animals were also monitored daily for morbidity and mortality. Death and observed clinical signs are recorded on the basis of the numbers of animals within each subset.

Statistical analyses of the potential therapeutic effects between treatments were analyzed by two-way ANOVA. All data with p values< 0.05 were considered to be statistically significant.

Figure 1 shows the efficacy of daratumumab in the ALL 7015 model and Figure 2 shows the efficacy of daratumumab in the ALL 7473 model. Table 1 shows the tumor burden at different time points in the ALL 7015 model. Treatment with daratumumab at 10 mg/kg resulted in significant tumor growth inhibition at Day 29, Day36 and Day43 when compared to mice treated with isotype control.

Table 1.

Days	ALL-7015: Tumor Burden (TB)				
	(% of human $CD45^+$ cell population)				Statistic Results
	Isotype (10mg/kg)		Daratumumab (10mg/kg)		Isotype vs. Daratumumab (10mg/kg)
	n	TB	n	TB	P Value
D22 (Grouping)	10	4.4±0.3	10	4.6±0.5	P>0.05
D29	10	33.4±1.5	10	19.7±2.5	P<0.01
D36	10	53.3±4.5	10	19.8±3.4	P<0.001
D43	10	80.7±2.5	10	53.6±3.4	P<0.001

Table 2 shows the tumor burden at different time points in the ALL 7015 model. Treatment of mice with daratumumab showed significant tumor growth inhibition compared to mice treated with a control antibody.

Table 2.

Days	ALL-7473: Tumor Burden (TB)		
	(% of human $CD45^+$ cell population)		Statistic Results
	Isotype	Daratumumab (10mg/kg)	Isotype vs. Daratumumab

					(10mg/kg)
	n	TB	n	TB	P Value
D22 (Grouping)	10	0.5±0.1	10	0.7±0.3	P>0.05
D29	10	13.7±3.9	10	4.8±0.7	P<0.05
D36	6	-	7	-	-
D43	1	-	1	-	-

Example 2. Efficacy of daratumumab in cell-line derived pre-B cell ALL model

CB17 SCID mice were inoculated intravenously via the tail vein with the cell line NALM-6 tumor cells at 1×10^5 in 100 µL PBS for tumor development. The date of tumor cell inoculation is denoted as Day 0. Animals were divided in four treatment groups and were administered daratumumab, vincristine, or daratumumab in combination with vincristine at dosages as described in Table 3. NALM-6 cell line (ACC128, DZMZ) is established from the peripheral blood of a 10-year old man with ALL in relapse. Karyotype of the cell line is 46(43-47)<2n>XY, t(5;12)(q33.2;p13.2).

Table 3.

Groups	**n[a]**	**Treatment**	**Dose (mg/kg)**	**Dosing Route[b]**	**Schedule[c] Till the end of the study**
1	12	Vehicle (IgG)	10	*i.p.*	QW
2	12	Daratumumab	10	*i.p.*	QW
3	12	Vincristine	0.5	*i.v.*	QW

4	12	Daratumumab + Vincristine	10+0.5	*i.p.* + *i.v.*	QW + QW

a: n, animal number;
i.p.: intraperitoneal injection;
i.v.: intravenous injection;
QW: once a week;

Endpoint: The major endpoint was animal survival. Each mouse was evaluated daily and mice that showed deteriorating and moribund condition (animals have lost significant body mass: body weight lost > 20%) and animals that could not get to adequate food or water were euthanized with CO_2. The survival of all animals was followed and median survival time (MST) was calculated for each group. Body weights were measured twice per week. The surviving mice after a maximum of twice the median survival of the vehicle group were sacrificed. In addition, autopsy was performed at the termination to confirm the tumor progression.

Results: Treatment of mice with daratumumab either alone (as monotherapy) or in combination with the standard of care (vincristine) showed significant prolongation of survival compared to mice treated with control or vincristine alone (Figure3).

Claims:

1. A method of treating a subject having acute lymphoblastic leukemia (ALL), comprising administering to a patient in need thereof an anti-CD38 antibody that competes for binding to CD38 with an antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 4 and a light chain variable region (VL) of SEQ ID NO: 5, wherein the anti-CD38 antibody induces *in vitro* killing of ALL cells by antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement dependent cytotoxicity (CDC), apoptosis, or *in vitro* modulation of CD38 enzymatic activity.
2. The method of claim 1, wherein the anti-CD38 antibody binds to the region SKRNIQFSCKNIYR (SEQ ID NO: 2) and the region EKVQTLEAWVIHGG (SEQ ID NO: 3) of human CD38 (SEQ ID NO: 1).
3. The method of claim 2, wherein the anti-CD38 antibody induces *in vitro* killing of the ALL cells that express CD38 by ADCC or CDC.
4. The method of claim 1, wherein the anti-CD38 antibody is of IgG1, IgG2, IgG3 or IgG4 isotype.
5. The method of claim 4, wherein the anti-CD38 antibody has a biantennary glycan structure with fucose content of about 50%, 40%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 14%, 13%, 12%, 11% 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or 0%.
6. The method of claim 4, wherein the anti-CD38 antibodies comprise a substitution in the antibody Fc at amino acid positions 256, 290, 298, 312, 356, 330, 333, 334, 360, 378 or 430, wherein residue numbering is according to the EU index.
7. The method of claim 1, wherein the anti-CD38 antibody comprises the heavy chain complementarity determining regions (HCDR) 1 (HCDR1), 2 (HCDR2) and 3 (HCDR3) sequences of SEQ ID NOs: 6, 7 and 8, respectively.
8. The method of claim 7, wherein the anti-CD38 antibody comprises the light chain complementarity determining regions (LCDR) 1 (LCDR1), 2 (LCDR2) and 3 (LCDR3) sequences of SEQ ID NOs: 9, 10 and 11, respectively.
9. The method of claim 8, wherein the anti-CD38 antibody comprises the heavy chain variable region (VH) of SEQ ID NO: 4 and the light chain variable region (VL) of SEQ ID NO: 5.
10. The method of claim 1, wherein the anti-CD38 antibody comprises a heavy chain comprising an amino acid sequence that is 95%, 96%, 97%, 98% or 99% identical

to that of SEQ ID NO: 12 and a light chain comprising an amino acid sequence that is 95%, 96%, 97%, 98% or 99% identical to that of SEQ ID NO: 13.

11. The method of claim 10, wherein the anti-CD38 antibody comprises the heavy chain of SEQ ID NO: 12 and the light chain of SEQ ID NO: 13.

12. The method of claim 1, wherein the ALL is B-cell lineage ALL, T-cell lineage ALL, adult ALL or pediatric ALL.

13. The method of claim 12, wherein the ALL is refractory or relapsed ALL.

14. The method of claim 12, wherein the anti-CD38 antibody is administered as a remission induction or as postinduction therapy.

15. The method of claim 12, wherein the subject has a white blood cell count of at least about 1 x 10^9 /L.

16. The method of claim 12, wherein the ALL cells have a Philadelphia chromosome.

17. The method of claim 12, wherein the subject is resistant or has acquired resistance to treatment with a BCR-ABL kinase inhibitor.

18. The method of claim 17, wherein the BCR-ABL kinase inhibitor is imatinib, dasatinib, nilotinib, bosutinib, ponatinib, bafetinib, saracatinib, tozasertib danusertib or ibrutinib.

19. The method of claim 1 or 12, wherein the anti-CD38 antibody is administered in combination with vincristine.

20. The method of claim 19, wherein the anti-CD38 antibody and vincristine are administered simultaneously, sequentially or separately.

21. The method of claim 1 or 12, wherein the subject is further treated or has been treated with radiotherapy.

22. The method of claim 1 or 12, wherein the subject has received hematopoietic stem cell transplantation.