COMPOSITIONS COMPRISING ANTI-CD38 ANTIBODIES AND LENALIDOMIDE

[01] CROSS-REFERENCE TO RELATED APPLICATIONS

[02] This application claims the benefit of U.S. Application No. 61/734,524, filed 7 December 2012, U.S. Application No. 61/769,247, filed 26 February 2013, and U.S. Application No. 61/808,372, filed 4 April 2013, all of which are herein incorporated by reference in their entirety.

[03] REFERENCE TO A SEQUENCE LISTING SUBMITTED VIA EFS-WEB

[04] The content of the ASCII text file of the sequence listing named "20130404_034543_001P3_seq" which is 56.7 kb in size was created on 4 April 2013 (technically modified Thursday, April 04, 2013, 11:12:48 AM, and created Friday, July 26, 2013, 12:23:47 PM) and electronically submitted via EFS-Web herewith the application is incorporated herein by reference in its entirety.

[05] BACKGROUND OF THE INVENTION

[06] 1. FIELD OF THE INVENTION

[07] The field of the present invention relates to anti-CD38 antibodies, lenalidomide, and cancer treatments.

[08] 2. DESCRIPTION OF THE RELATED ART

[09] Multiple myeloma (MM) is a B cell malignancy. In MM, abnormal plasma cells accumulate in the bone marrow where they interfere with the production of normal cells. Current therapy of MM includes administration of proteasome inhibitors such as bortezomib, immunomodulatory drugs such as lenalidomide and thalidomide, and chemotherapy such as melphalan and prednisone. While these agents have improved survival in multiple myeloma, invariably resistance becomes problematic and patients succumb from their illness. Multiple myeloma thus remains ultimately fatal, with a median survival of approximately 3 to 5 years only.

[10] CD38 is expressed on malignant plasma cells. CD38 is a 45 kD type II transmembrane glycolprotein with a long C-terminal extracellular domain and a short N-terminal cytoplasmic domain. The CD38 protein is a bifunctional ectoenzyme that can catalyze the conversion of NAD^+ into cyclic ADP-ribose (cADPR) and also hydrolyze cADPR into ADP-ribose. CD38 is up-regulated and has been implicated in many hematopoietic malignancies.

[11] Thus, some proposed MM treatments include the administration of anti-CD38 antibodies. See, for example, WO 2012/041800; de Weers et al. (2011) J Immunol 186:1840-1848; and Van der Veer et al. (2011) Haematologica 96(2):284-290. Unfortunately, like various drugs and chemotherapies, not all antibodies are the same and not all antibodies against the same antigen exhibit the same activities.

[12] There is thus a need for new and efficacious treatments for extending survival and improving outcome of treatments of multiple myeloma, and more generally of blood cancers.

[13] DESCRIPTION OF THE DRAWINGS

[14] Both the foregoing general description and the following detailed description are exemplary and explanatory only and are intended to provide further explanation of the invention as claimed. The accompanying drawings are included to provide a further understanding of the invention and are incorporated in and constitute part of this specification, illustrate several embodiments of the invention, and together with the description serve to explain the principles of the invention.

[15] This invention is further understood by reference to the drawings wherein:

[16] Figure 1A shows the growth rate of tumors in xenograft models implanted with H929 cells (H929 models).

[17] Figure 1B shows the growth rate of tumors in xenograft models implanted with RPMI8226 cells (RPMI8226 models).

[18] Figure 2A shows the tumor volume of tumors in RPMI8226 models after treatment with the indicated dose of hu38SB19 at the indicated times (arrows).

[19] Figure 2B shows the body weight of the RPMI8226 models after treatment with the indicated dose of hu38SB19 at the indicated times (arrows).

[20] Figure 3A shows the tumor volume of tumors in RPMI8226 models after treatment with the indicated dose of lenalidomide at the indicated times (arrows).

[21] Figure 3B shows the body weight of the RPMI8226 models after treatment with the indicated dose of lenalidomide at the indicated times (arrows).

[22] Figure 4A shows the tumor volume of tumors in RPMI8226 models after treatment with the indicated dose of hu38SB19 at the indicated times (top arrows) and the indicated dose of lenalidomide at the indicated times (bottom arrows).

[23] Figure 4B shows the body weight of the RPMI8226 models after treatment with the indicated dose of hu38SB19 at the indicated times (top arrows) and the indicated dose of lenalidomide at the indicated times (bottom arrows).

[24] Figure 5A shows the tumor volume of tumors in H929 models after treatment with the indicated dose of hu38SB19 at the indicated times (arrows).

[25] Figure 5B shows the body weight of the H929 models after treatment with the indicated dose of hu38SB19 at the indicated times (arrows).

[26] Figure 6A shows the tumor volume of tumors in H929 models after treatment with the indicated dose of hu38SB19 at the indicated times (arrows).

[27] Figure 6B shows the body weight of the H929 models after treatment with the indicated dose of hu38SB19 at the indicated times (arrows).

[28] Figure 7A shows the tumor volume of tumors in H929 models after treatment with the indicated dose of hu38SB19 at the indicated times (arrows).

[29] Figure 7B shows the body weight of the H929 models after treatment with the indicated dose of hu38SB19 at the indicated times (arrows).

[30] Figure 8A shows the tumor volume of tumors in H929 models after treatment with the indicated dose of lenalidomide at the indicated times (arrows).

[31] Figure 8B shows the body weight of the H929 models after treatment with the indicated dose of lenalidomide at the indicated times (arrows).

[32] Figure 9A is a graph showing the mean wet tumor weights of the RPMI8226 models after the indicated treatment with lenalidomide and/or hu38SB19 (mAb).

[33] Figure 9B is a graph showing the median wet tumor weights of the RPMI8226 models after the indicated treatment with lenalidomide and/or hu38SB19 (mAb).

[34] Figure 10A shows the tumor volume of tumors in H929 models after treatment with the indicated dose of hu38SB19 at the indicated times (top arrows) and the indicated dose of lenalidomide at the indicated times (bottom arrows).

[35] Figure 10B shows the body weight of the H929 models after treatment with the indicated dose of hu38SB19 at the indicated times (top arrows) and the indicated dose of lenalidomide at the indicated times (bottom arrows).

[36] Figure 11A is a graph showing the mean wet tumor weights of the H929 models after the indicated treatment with lenalidomide and/or hu38SB19 (mAb).

[37] Figure 11B is a graph showing the median wet tumor weights of the H929 models after the indicated treatment with lenalidomide and/or hu38SB19 (mAb).

[38] Figure 12 is a graph showing the cell surface density of CD38 in multiple myeloma cell lines.

[39] Figure 13 is a graph showing that hu38SB19 inhibits RPMI-8226 tumor growth as a single-agent, i.e., as the sole active ingredient.

[40] Figure 14 is a graph showing that treatment with both hu38SB19 and lenalidomide inhibits growth of RPMI-8226 tumors.

[41] SUMMARY OF THE INVENTION

[42] In some embodiments, the present invention relates to a method of treating a cancer in a subject which comprises administering one or more anti-CD38 antibodies and one or more lenalidomide compounds to the subject. In some embodiments, the cancer is a hematological malignancy. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is a relapsed multiple myeloma or a refractory multiple myeloma. In some embodiments, the one or more lenalidomide compounds is lenalidomide. In some embodiments, the one or more anti-CD38 antibodies are administered in an effective amount, preferably a synergistic amount. In some embodiments, the one or more anti-CD38 antibodies and/or the one or more lenalidomide compounds are administered in a therapeutically effective amount. In some embodiments, at least one of the one or more anti-CD38 antibodies is capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). In some embodiments, the antibody is hu38SB19. In some embodiments, at least one of the one or more anti-CD38 antibodies comprises one or more complementarity-determining region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 13, 14, 81, 15, 16, 17, 18, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36. In some embodiments, at least one of the one or more anti-CD38 antibodies is selected from the group consisting of: a) an antibody comprising a heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 13, 15 and either SEQ ID NO: 14 or SEQ ID NO: 81, and a light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 16, 17 and 18; b) an antibody comprising a heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 25, 26 and 27, and a light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 28, 29 and 30; c) an antibody comprising a heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 1, 2 and 3, and a light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 4, 5 and 6; d) an antibody comprising a heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 7, 8 and 9, and a light

chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 10, 11 and 12; e) an antibody comprising a heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 19, 20 and 21, and a light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 22, 23 and 24; and f) an antibody comprising a heavy chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 31, 32 and 33, and a light chain comprising three sequential CDRs having amino acid sequences consisting of SEQ ID NOs: 34, 35 and 36. In some embodiments, the antibody comprises a heavy chain having a VH variable region represented by SEQ ID NO: 66, and a light chain having a VL variable region represented by either SEQ ID NO: 62 or SEQ ID NO: 64. In some embodiments, the antibody comprises a heavy chain having a VH variable region represented by SEQ ID NO: 72, and a light chain having a VL variable region represented by either SEQ ID NO: 68 or SEQ ID NO: 70. In some embodiments, the one or more anti-CD38 antibodies are administered intravenously. In some embodiments, the one or more lenalidomide compounds are administered orally. In some embodiments, the one or more anti-CD38 antibodies and the one or more lenalidomide compounds are administered sequentially. In some embodiments, the method further comprises administering a dexamethasone compound, preferably dexamethasone, to the subject. In some embodiments, the dexamethasone compound is administered orally. In some embodiments, the dexamethasone compound is administered at a low dose. In some embodiments, the one or more anti-CD38 antibodies, the one or more lenalidomide compounds, and the dexamethasone compound are administered sequentially. In some embodiments, the method further comprises administering an anti-coagulation agent to the subject. In some embodiments, the anti-coagulation agent is selected from the group consisting of aspirin, warfarin, and low molecular weight heparin. In some embodiments, the one or more anti-CD38 antibodies, the one or more lenalidomide compounds, and the anti-coagulation agent are administered sequentially.

[43] In some embodiments, the present invention relates to a composition comprising a) at least one anti-CD38 antibody, preferably the antibody is capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC); and b) at least one lenalidomide compound, preferably lenalidomide; and, optionally c) a dexamethasone

compound, preferably dexamethasone; and, optionally d) an anti-coagulation agent. In some embodiments, the present invention relates to a composition comprising a) at least one anti-CD38 antibody; and b) at least one lenalidomide compound; and, optionally i) a dexamethasone compound; and/or ii) an anti-coagulation agent. In some embodiments, the antibody is capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). In some embodiments, the antibody is hu38SB19. In some embodiments, the lenalidomide compound is lenalidomide. In some embodiments, the dexamethasone compound is dexamethasone.

[44] In some embodiments, the present invention is directed to a kit comprising a) a first composition comprising at least one anti-CD38 antibody, preferably the antibody is capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC); and b) a second composition comprising at least one lenalidomide compound, preferably lenalidomide. In some embodiments, the compositions in the kit are packaged for sequential administration to a subject. In some embodiments, the antibody is hu38SB19. In some embodiments, the kit further includes a dexamethasone compound, preferably dexamethasone, and/or an anti-coagulation agent. In some embodiments, the dexamethasone compound and/or the anti-coagulation agent are packaged sequential administration to a subject.

[45] In some embodiments, the present invention is directed to a kit comprising at least one anti-CD38 antibody capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC), packaged together with a label having one or more messages that the at least one anti-CD38 antibody shall be administered in combination with lenalidomide, and optionally with dexamethasone and/or an anti-coagulation agent. In some embodiments, the antibody is hu38SB19. In some embodiments, the kit further includes a dexamethasone compound, preferably dexamethasone, and/or an anti-coagulation agent. In some embodiments, the dexamethasone compound and/or the anti-coagulation agent are packaged sequential administration to a subject.

[46] In some embodiments, the present invention is directed to a combination of: (i) at least one anti-CD38 antibody, preferably the antibody is capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC); and (ii) at least one lenalidomide

compound, preferably lenalidomide; and, optionally (iii) a dexamethasone compound, preferably dexamethasone; and, optionally (iv) an anti-coagulation agent. In some embodiments, the present invention relates to a combination comprising a) at least one anti-CD38 antibody; and b) at least one lenalidomide compound; and, optionally i) a dexamethasone compound; and/or ii) an anti-coagulation agent. In some embodiments, the antibody is capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). In some embodiments, the antibody is hu38SB19. In some embodiments, the lenalidomide compound is lenalidomide. In some embodiments, the dexamethasone compound is dexamethasone. In some embodiments, the combination is for sequential use in the treatment of a hematological malignancy, preferably multiple myeloma.

[47] In some embodiments, the present invention is directed to use of (i) at least one anti-CD38 antibody, preferably the antibody is capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC); and (ii) at least one lenalidomide compound, preferably lenalidomide; and, optionally (iii) a dexamethasone compound, preferably dexamethasone; and, optionally (iv) an anti-coagulation agent for the treatment of a hematological malignancy, preferably multiple myeloma. In some embodiments, the present invention relates to use of a) at least one anti-CD38 antibody; and b) at least one lenalidomide compound; and, optionally i) a dexamethasone compound; and/or ii) an anti-coagulation agent for the treatment of a hematological malignancy, preferably multiple myeloma. In some embodiments, the antibody is capable of killing a CD38+ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). In some embodiments, the antibody is hu38SB19. In some embodiments, the lenalidomide compound is lenalidomide. In some embodiments, the dexamethasone compound is dexamethasone.

[48] In some of the various embodiments of the present invention, the subject to be treated is mammalian. In some of the various embodiments of the present invention, the subject to be treated is a test animal such as a mouse. In some of the various embodiments of the present invention, the subject to be treated is human.

[49] DETAILED DESCRIPTION OF THE INVENTION

[50] The present invention relates to methods of treating a cancer in a subject which comprises administering one or more anti-CD38 antibodies and one or more

lenalidomide jurors will compounds to the subject. As used herein, "treat" or "treating" means to alleviate symptoms, eliminate the causation of the symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition. As disclosed herein, the efficacy of a lenalidomide compound is considerably improved when administered in conjunction with one or more anti-CD38 antibodies according to the present invention. In fact, the administration of one or more anti-CD38 antibodies which exhibit (a) the capability of killing a $CD38^+$ cell by apoptosis, (b) antibody-dependent cell-mediated cytotoxicity (ADCC), and (c) complement-dependent cytotoxicity (CDC) is believed to considerably improve the efficacy of lenalidomide compounds in the treatment of hematological malignancies, including MM, to a degree that is unexpectedly more than other anti-CD38 antibodies which do not exhibit all three (a)-(c) activities. Therefore, in some embodiments, the one or more anti-CD38 antibodies are capable of (a) killing a $CD38^+$ cell by apoptosis, (b) antibody-dependent cell-mediated cytotoxicity (ADCC), and (c) complement-dependent cytotoxicity (CDC). In some embodiments, the one or more anti-CD38 antibodies and/or the one or more lenalidomide compounds are administered in a therapeutically effective amount. As used herein, a "therapeutically effective amount" of a substance refers to an amount of that substance that results in the alleviation of one or more symptoms, elimination of the causation of the symptoms either on a temporary or permanent basis, and/or the prevention or reduction in the appearance of symptoms of the named disorder or condition in the majority of subjects afflicted with and similarly treated for the named disease or disorder.

[51] In some embodiments, the cancer is one in which CD38 is expressed by the malignant cells. In some embodiments, the cancer is a hematological malignancy of the blood, bone marrow, and/or lymph nodes. In some embodiments, the cancer is a blood cancer. Blood cancers include myeloma, lymphoma and leukemia. The blood cancer might, for instance, be selected from the group consisting of multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, hairy cell leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, acute myeloid leukemia, and acute lymphocytic leukemia. In some embodiments, the cancer is multiple myeloma (MM). In some embodiments, the cancer is a relapse MM or refractory MM. As used herein, relapsed MM refers to clinically active MM after a period of remission and refractory MM refers to progressive or stable disease while being

treated or progressive disease within 3 months of the last does of the prior treatment. See Dimopoulos et al. (2010) Eur J Haematology 88:1-15.

[52] In some embodiments, the subject is mammalian, preferably human. In some embodiments, the subject is an adult human, e.g., at least 18 years. In some embodiments, the subject is in need of treatment for the cancer. In some embodiments, the subject has been diagnosed as having the cancer. In some embodiments, the cancer is in partial or complete remission, however, the one or more lenalidomide compounds and the one or more anti-CD38 antibodies are administered to the subject so as to reduce the likelihood of relapse. In some embodiments, the subject has a Karnofsky performance status equal or superior to 60%. The Karnofsky status runs from 100 to 0, where 100 is "perfect" health and 0 is death (Karnofsky and Burchenal, 1949, "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press). In some embodiments, the subject has undergone at least one or two prior therapies for multiple myeloma, induction therapy being considered one prior therapy. In some embodiments, the subject exhibits evidence that either the cancer progressed while the subject underwent a prior therapy, or that the subject was refractory to the prior therapy.

[53] In some embodiments, the anti-CD38 antibodies specifically bind CD38. In some embodiments, the anti-CD38 antibodies are raised against CD38 or an epitope thereof. In some embodiments, the anti-CD38 antibodies are monoclonal antibodies. In some embodiments, one or more of the anti-CD38 antibodies according to the present invention are monoclonal antibodies as described in WO 2008/047242, which is herein incorporated by reference in its entirety. In some embodiments, one or more of the anti-CD38 antibodies are monoclonal antibodies 38SB13, 38SB18, 38SB19, 38SB30, 38SB31, and 38SB39 as described in WO 2008/047242, which is herein incorporated by reference in its entirety. In some embodiments, the one or more anti-CD38 antibodies are capable of killing $CD38^+$ cells by three different cytotoxic mechanisms, induction of apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC).

[54] The term "antibody" is used herein in the broadest sense and includes monoclonal antibodies (including full length monoclonal antibodies) of any isotype such as IgG, IgM, IgA, IgD and IgE, polyclonal antibodies, multispecific antibodies, chimeric antibodies, and antibody fragments. As used herein, the prefix “anti-” when

in conjunction with an antigen, indicates that the given antibody is reactive with the given antigen. An antibody reactive with a specific antigen can be generated by synthetic and/or recombinant methods such as selection of libraries of recombinant antibodies in phage or similar vectors, or by immunizing an animal with the antigen or an antigen-encoding nucleic acid.

[55] A typical IgG antibody is comprised of two identical heavy chains and two identical light chains that are joined by disulfide bonds. Each heavy and light chain contains a constant region and a variable region. Each variable region contains three segments called "complementarity-determining regions" ("CDRs") or "hypervariable regions", which are primarily responsible for binding an epitope of an antigen. They are usually referred to as CDR1, CDR2, and CDR3, numbered sequentially from the N-terminus. The more highly conserved portions of the variable regions outside of the CDRs are called the "framework regions". As used herein, "V_H" or "VH" refers to the variable region of an immunoglobulin heavy chain of an antibody, including the heavy chain of an Fv, scFv, dsFv, Fab, Fab' or $F(ab')_2$ fragment. Reference to "V_L" or "VL" refers to the variable region of the immunoglobulin light chain of an antibody, including the light chain of an Fv, scFv, dsFv, Fab, Fab' or $F(ab')_2$ fragment.

[56] The antibodies according to the present invention may be, e.g., murine, chimeric, and/or humanized antibodies. As used herein, a "chimeric antibody" is an antibody in which the constant region, or a portion thereof, is altered, replaced, or exchanged, so that the variable region is linked to a constant region of a different species, or belonging to another antibody class or subclass. "Chimeric antibody" also refers to an antibody in which the variable region, or a portion thereof, is altered, replaced, or exchanged, so that the constant region is linked to a variable region of a different species, or belonging to another antibody class or subclass. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, 1985, Science, 229: 1202; Oi et al., 1986, BioTechniques, 4: 214; Gillies et al., 1989, J. Immunol. Methods, 125: 191-202; U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entireties. The term "humanized antibody", as used herein, refers to a chimeric antibody which contain minimal sequence derived from non-human immunoglobulin. The goal of humanization is a reduction in the immunogenicity of a xenogenic antibody, such as a murine antibody, for introduction into a human, while maintaining the full antigen

binding affinity and specificity of the antibody. Humanized antibodies, or antibodies adapted for non-rejection by other mammals, may be produced using several technologies such as resurfacing and CDR grafting. As used herein, the resurfacing technology uses a combination of molecular modelling, statistical analysis and mutagenesis to alter the non-CDR surfaces of antibody variable regions to resemble the surfaces of known antibodies of the target host. The CDR grafting technology involves substituting the complementarity determining regions of, for example, a mouse antibody, into a human framework domain, e.g., see W0 92/22653. Humanized chimeric antibodies preferably have constant regions and variable regions other than the complementarity determining regions (CDRs) derived substantially or exclusively from the corresponding human antibody regions and CDRs derived substantially or exclusively from a mammal other than a human.

[57] Strategies and methods for the resurfacing of antibodies, and other methods for reducing immunogenicity of antibodies within a different host, are disclosed in US Pat. No. 5,639,641, which is hereby incorporated in its entirety by reference. Antibodies can be humanized using a variety of other techniques including CDR-grafting (EP 0 239 400; WO 91/09967; US Pat. Nos. 5,530,101; and 5,585,089), veneering or resurfacing (EP 0 592 106; EP 0 519 596; Padlan E. A., 1991, Molecular Immunology 28(4/5): 489-498; Studnicka G. M. et al., 1994, Protein Engineering, 7(6): 805-814; Roguska M.A. et al., 1994, PNAS, 91: 969-973), chain shuffling (US Pat. No. 5,565,332), and identification of flexible residues (PCT/US2008/074381). Human antibodies can be made by a variety of methods known in the art including phage display methods. See also US Pat. Nos. 4,444,887, 4,716,111, 5,545,806, and 5,814,318; and international patent application publication numbers WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741 (said references incorporated by reference in their entireties).

[58] In some embodiments, one or more of the anti-CD38 antibodies according to the invention are capable of killing a $CD38^+$ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). In some embodiments, one or more of the anti-CD38 antibodies according to the invention are capable of killing said $CD38^+$ cells by apoptosis even in the absence of stroma cells or stroma-derived cytokines. These activities can be assessed as described in WO 2008/047242, which is hereby incorporated by reference in its entirety.

[59] In some embodiments according to the invention, one or more anti-CD38 antibodies are selected from the group consisting of 38SB13, 38SB18, 38SB19, 38SB30, 38SB31, 38SB39, and antibodies cross-competing with 38SB13, 38SB18, 38SB19, 38SB30, 38SB31 or 38SB39. The hybridoma cell lines producing the 38SB13, 38SB18, 38SB19, 38SB30, 38SB31, and 38SB39 murine anti-CD38 antibodies have been deposited at the American Type Culture Collection (10801 University Bld, Manassas, VA, 20110-2209, USA), on 21 June 21 2006, under the deposit numbers PTA-7667, PTA-7669, PTA-7670, PTA-7666, PTA-7668, and PTA-7671, respectively (as described in WO 2008/047242, which is herein incorporated by reference in its entirety).

[60] As disclosed herein, references to SEQ ID NOs refers to the sequences set forth in the Sequence Listing submitted herewith and also as recited in WO 2008/047242, which is herein incorporated by reference in its entirety. In some embodiments, the anti-CD38 antibodies according to the present invention may, for instance, comprise a heavy chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 1, 2, and 3, and a light chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 4, 5, and 6. An example of such an antibody is the 38SB13 antibody, which comprises a heavy chain having a V_H variable region represented by SEQ ID NO: 50, and a light chain having a V_L variable region represented by SEQ ID NO: 38.

[61] In some embodiments, the anti-CD38 antibodies according to the present invention may, for instance, comprise a heavy chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 7, 8, and 9, and a light chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 10, 11, and 12. An example of such an antibody is the 38SB18 antibody, which comprises a heavy chain having a V_H variable region represented by SEQ ID NO: 52 and a light chain having a V_L variable region represented by SEQ ID NO: 40.

[62] In some embodiments, the anti-CD38 antibodies according to the present invention may, for instance, comprise a heavy chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NO: 13, SEQ ID NO: 15 and either SEQ ID NO: 14 or SEQ ID NO: 81, and a light chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 16, 17, and 18. An example of such an antibody is the 38SB19 antibody, which comprises a

heavy chain having a V_H variable region represented by SEQ ID NO: 54 and a light chain having a V_L variable region represented by SEQ ID NO: 42. Specific examples of humanized versions of 38SB19 (hu38SB19) include antibodies comprising a heavy chain having a V_H variable region represented by SEQ ID NO: 66, and a light chain having a V_L variable region represented by either SEQ ID NO: 62 or SEQ ID NO: 64. hu38SB19 is a humanized anti-CD38 antibody currently undergoing clinical evaluation in CD38-positive hematologic malignancies, including multiple myeloma. Previous and current studies demonstrate that the anti-myeloma activity associated with this agent involve mechanisms of ADCC, and CDC, as well as novel, direct apoptotic and anti-ADP-ribosyl cyclase activity. See Marie-Cécile Wetzel, Céline Nicolazzi, François Vallée, et al. hu38SB19: characterization of a potent phase I humanized anti-CD38 antibody for the treatment of multiple myeloma and other hematologic malignancies. AACR Annual Meeting 2013, Abstract #4735.

[63] In some embodiments, the anti-CD38 antibodies according to the present invention may, for instance, comprise a heavy chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 19, 20, and 21, and a light chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 22, 23, and 24. An example of such an antibody is the 38SB30 antibody, which comprises a heavy chain having a V_H variable region represented by SEQ ID NO: 56 and a light chain having a V_L variable region represented by SEQ ID NO: 44.

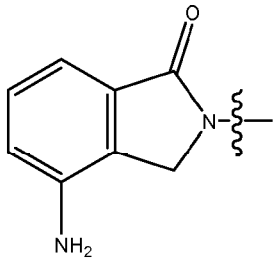
[64] In some embodiments, the anti-CD38 antibodies according to the present invention may, for instance, comprise a heavy chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 25, 26, and 27, and a light chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 28, 29, and 30. An example of such an antibody is the 38SB31 antibody, which comprises a heavy chain having a V_H variable region represented by SEQ ID NO: 58 and a light chain having a V_L variable region represented by SEQ ID NO: 46. Specific examples of humanized versions of 38SB31 (hu38SB31) include antibodies comprising a heavy chain having a V_H variable region represented by SEQ ID NO: 72, and a light chain having a V_L variable region represented by either SEQ ID NO: 68 or SEQ ID NO: 70.

[65] In some embodiments, the anti-CD38 antibodies according to the present invention may, for instance, comprise a heavy chain comprising three sequential

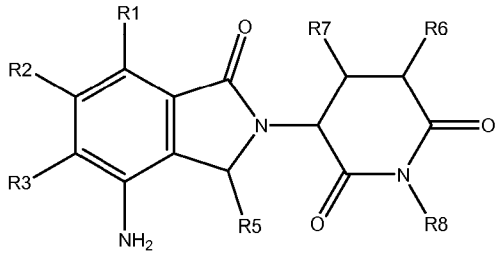
CDRs having amino acid sequences represented by SEQ ID NOs: 31, 32 and 33, and a light chain comprising three sequential CDRs having amino acid sequences represented by SEQ ID NOs: 34, 35, and 36. An example of such an antibody is the 38SB39 antibody, which comprises a heavy chain having a V_H variable region represented by SEQ ID NO: 60 and a light chain having a V_L variable region represented by SEQ ID NO: 48.

[66] In some embodiments, the anti-CD38 antibodies according to the invention are humanized antibodies consisting of two identical heavy chains and of two identical light chains, wherein each chain consists of one constant region and of one variable region.

[67] As used herein, a "lenalidomide compound" refers to lenalidomide ((*RS*)-3-(4-amino-1-oxo-3*H*-isoindol-2-yl)piperidine-2,6-dione) and lenalidomide derivatives. As used herein, "lenalidomide derivatives" refers to compounds which have 4-amino-1-oxo-3*H*-2-isoindolyl, i.e.,



which may or may not be substituted, as part of its structural formula. For example, "lenalidomide derivatives" include those having the following formula:



wherein R1-R8 are each independently H, a halogen, an alkyl, an alkoxy, amino, or an alkylamine, and wherein R5 may additionally be a double bonded oxygen. In some embodiments, R5 is H. In some embodiments, R8 is H. In some embodiments, both R5 and R8 are H.

[68] In some embodiments, the one or more anti-CD38 antibodies are administered in an effective amount. As used herein, an effective amount of the one or more anti-CD38 antibodies is an amount which results in an additive or a synergistic effect with the one or more lenalidomide compounds. As used herein, a "synergistic amount" is

one that results in a synergistic effect. As used herein, a "synergistic effect" refers to the effect of the combination of the one or more anti-CD38 antibodies and the one or more lenalidomide compounds which is more than their expected additive effect. In some embodiments, the one or more anti-CD38 antibodies are administered before, during, and/or after the administration of the one or more lenalidomide compounds. In some embodiments, the one or more anti-CD38 antibodies and the one or more lenalidomide compounds are co-administered in the form of a single composition, e.g., as a mixture.

[69] Thus, in some embodiments, the present invention is directed to compositions comprising a mixture of at least one anti-CD38 antibody and at least one lenalidomide compound. In some embodiments, the mixture comprises the at least one anti-CD38 antibody in an amount that results in an additive or a synergistic effect with the at least one lenalidomide compound in a subject when both are administered. In some embodiments, the at least one anti-CD38 antibody in the mixture is one which is capable of killing a $CD38^+$ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC); and at least one lenalidomide compound.

[70] For the purposes of the present invention, the methods and compositions of the present invention are not exclusively limited to those which are obtained by physical association of the anti-CD38 antibodies and the lenalidomide compound, but also to those which permit a separate administration, which can be simultaneous or spaced out over a period of time. Thus, in some embodiments, the present invention is directed to a first composition comprising the one or more anti-CD38 antibodies, and a second composition comprising one or more lenalidomide compounds. In some embodiments, the at least one anti-CD38 antibody is one which is capable of killing a $CD38^+$ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC); and at least one lenalidomide compound. In some embodiments, the amount of the one or more anti-CD38 antibodies provided in the first composition is one that results in an additive or a synergistic effect with the at least one lenalidomide compound in the second composition in a subject when both are administered.

[71] In some embodiments, the first and second compositions may be packaged in a kit. Thus, in some embodiments, the present invention is directed to kits which comprise a first composition comprising the one or more anti-CD38 antibodies, and a

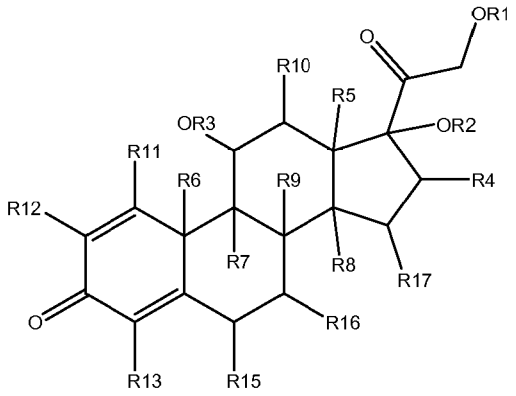
second composition comprising one or more lenalidomide compounds. In some embodiments, the first and second composition may be mixed together before administering to a subject. In some embodiments, the first and second compositions, may be administered either simultaneously or sequentially (i.e., spaced out over a period of time) so as to obtain the maximum efficacy, additivity, synergy, or a combination thereof of the combination. In some embodiments, the present invention is directed to kits comprising at least one anti-CD38 antibody packaged together with a label having one or more messages that the anti-CD38 antibody shall or might be administered in combination with lenalidomide and optionally with dexamethasone and/or an anti-coagulation agent. The kits according to the present invention may further comprise one or more messages that the antibody shall or might be administered to a subject suffering from a blood cancer such as multiple myeloma (e.g., relapsed or refractory multiple myeloma). In some embodiments, the one or more anti-CD38 antibodies in the kits of the present invention are those which are capable of killing a $CD38^+$ cell by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC).

[72] In some embodiments, the compositions of the present invention are pharmaceutical compositions. As used herein, the term "pharmaceutical composition" refers to a composition comprising at least one active principle (e.g., an anti-CD38 antibody or a lenalidomide compound) and at least one pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known to the skilled in the art, and usually depend on the chosen route of administration. Pharmaceutical compositions according to the present invention may be provided in any form or formulation that is suitable for the chosen route of administration, such as e.g., a solution in case of an intravenous route of administration, e.g., capsules, pills or tablets in case of an oral route of administration, etc.

[73] The dosage regimen of the active principles and of the pharmaceutical composition described herein can be chosen by prescribing physicians, based on their knowledge of the art, including information published by regulatory authorities. For example, lenalidomide is typically administered orally. According to the European Medicines Agency (EMA), the recommended dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. Since, however, co-administration of the one or more anti-CD38 antibodies and the one or more lenalidomide compounds results in an additive or a synergistic effect, the dosing of the

lenalidomide compound may be adjusted accordingly, e.g., the dose changed and/or the dosing schedule modified. Of course, prescribing physicians might reconsider which dose and schedule to use depending on the condition and disease status of the patient and based upon clinical and laboratory findings.

[74] As lenalidomide is approved for the treatment of MM in combination with dexamethasone, the methods and compositions of the present invention may further include dexamethasone, which is member of the glucocorticoid class of steroid drugs, and acts as an anti-inflammatory and immunosuppressant. Thus, in some embodiments, the treatment methods of the present invention further comprise administering a dexamethasone compound to the subject being treated with the one or more anti-CD38 antibodies and the one or more lenalidomide compounds. Similarly, the compositions and kits of the present invention which comprise the one or more anti-CD38 antibodies and/or the one or more lenalidomide compounds may further comprise a dexamethasone compound. As used herein, a "dexamethasone compound" refers to dexamethasone ((8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9- Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16- trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one) and dexamethasone derivatives. As used herein, a "dexamethasone derivative" refers to a compound having the following structural formula:



wherein R1-R17 are each independently H, a halogen, an alkyl, an alkoxy, amino, or an alkylamine. In some preferred embodiments, R1-R3 are H. In some preferred embodiments, R4-R6 are methyl. In some preferred embodiments, R7 is a halogen, preferably fluorine. In some preferred embodiments, R8 is H. In some preferred embodiments, R1-R3 are H, R4-R6 are methyl, R7 is a halogen, preferably fluorine, and R8 is H.

[75] In some embodiments, the dexamethasone compound may be administered orally. According to the EMA, when combined with lenalidomide, the recommended

dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Prescribing physicians might also re-evaluate which dose of dexamethasone to use upon clinical and laboratory findings.

[76] However, in some embodiments, the dexamethasone compound may be administered at a lower dose than the dose recommended for dexamethasone by the EMA. Indeed, recent studies suggest that lenalidomide plus low dose dexamethasone is associated with better short-term overall survival and with lower toxicity than lenalidomide plus high-dose dexamethasone in patients with newly diagnosed myeloma (Rajkumar *et al.* (2010) Lancet Onco. 11:29-37). Therefore, in some embodiments of the present invention, the dexamethasone compound is administered at low dose. The term "low dose" in this context refers to any dose that is at least 20, 30 or 40% lower that the dose of dexamethasone recommended by EMA at the date of first marketing approval of the lenalidomide plus dexamethasone combination. For instance, administration of 40 mg of dexamethasone on days 1, 8, 15, and 22 of a 28-day cycle is considered as a low dose of dexamethasone.

[77] In some embodiments, the methods and compositions of the present invention may further include an anti-coagulation agent, such as e.g., aspirin, warfarin, low molecular weight heparin or equivalent anti-platelet therapeutic. For example, in some embodiments, the treatment methods of the present invention further comprise administering an anti-coagulation agent to the subject being treated with the one or more anti-CD38 antibodies and the one or more lenalidomide compounds. Similarly, the compositions and kits of the present invention which comprise the one or more anti-CD38 antibodies and/or the one or more lenalidomide compounds may further comprise an anti-coagulation agent.

[78] The compositions of the present invention may be used as a medicament and/or for use in the manufacture of a medicament. In some embodiments, the compositions of the present invention may be used as a medicament and/or for use in the manufacture of a medicament for use in the treatment of a cancer such as a hematological malignancy of the blood, bone marrow, and/or lymph nodes, preferably a blood cancer.

[79] Several documents are cited throughout the text of this specification. Each of the documents herein (including any journal article or abstract, published or unpublished patent application, issued patent, manufacturer's specifications,

instructions, *etc.*) are hereby incorporated by reference. However, there is no admission that any document cited herein is indeed prior art in respect of the present invention.

[80] The following examples are intended to illustrate but not to limit the invention.

[81] EXAMPLES

[82] hu38SB19 was provided in solution at 5 mg/ml, stored at 4°C. It was diluted into sterile saline in preparation for dosing, stored at 4°C and used within 10 days of dilution.

[83] Lenolidomide was obtained from AK Scientific Inc. (Mountain View, CA) and prepared as a suspension in 1% (w/v) carboxymethyl cellulose (Sigma). Preparation was made using a mortar and pestle to generate a slurry suspension in the vehicle, diluted to the appropriate concentration, and used for dosing by oral gavage.

[84] *Example 1: Effect of the administration of both anti-CD38 antibody and lenalidomide in a mice model of MM*

[85] These studies under this Example were done under approval of the UCSF IACUC.

[86] The subcutaneous multiple myeloma (MM) xenograft mouse models were established using H929 and RPMI8226 cell lines. Specifically, 5-6 week old female Balb/c Scid mice were obtained from Jackson Lab. Mice were housed for 7-10 days prior to implantation. Mice were housed in a dedicated room in the UCSF Mt Zion Animal Barrier Facility. NCI-H929 and RPMI-8226 cells were obtained from the German Collection of Microorganisms and Cell Cultures, DSMZ, (Deutsche Sammlung von Mikroorganismen und Zellkulturen), and grown in sterile suspension culture in T225 flasks as follows: NCI-H929: RPMI1640 + 20% FBS + 4 mM L-glutamine + 1 mM sodium pyruvate + 50 μM mercaptoethanol. RPMI-8226: RPMI1640 + 10% FBS + 4 mM L-glutamine.

[87] At the time of implantation, mice were shaved on the right flank and shoulder region and anesthetized with ip avertin. MM cells suspended in serum free RPMI 1640 media diluted 1:1 with Matrigel (BD) at a concentration of $1x10^8$ cells per ml were injected sc into the right flank in 100 μL volume ($1x10^7$ cells) using a 1 ml syringe and 25 g needle. Mice were monitored twice weekly for the appearance of

tumors and once tumors were visible, measurements were collected twice weekly for body weight and tumor volume. Electronic balance and calipers were used and data was collected directly into a study management program (Study Director). When the mean tumor volume reached about 150-200 mm^3, the mice were distributed into treatment groups of 8-10 mice per groups and dosing was begun.

[88] The dosing schedule was hu38SB19 was 2x/wk x 2 wk (iv lateral tail vein) and lenalidomide was qdx7 x 3 wk (po) (orally, one dose per day, 7 days a week, for 21 days). Dose levels for use in combination studies are as follows:

Cell Type	Lenalidomide	hu38SB19
H929	1 mpk	0.5 mpk
RPMI8226	15 mpk	15 mpk
mpk = mg per kg body weight		

[89] Data were collected using electronic balance and calipers using a study management application called StudyLog (Study Director). Graphs are taken directly from the application. The experimental results are provided in Figures 1A-11B.

[90] Based on the single agent results of hu38SB19 and lenalidomide in RPMI-8226 and NCI-H929 mutiple myeloma xenograft models, NCI-H929 appears to be a more sensitive model to both agents while RPMI-8226 seems to be more resistant to the treatments even at the highest doses tested (Figures 1-3, 5-8). Therefore in the combination studies, a suboptimal dose for each agent was chosen to evaluate the activity of the combination treatment (lenalidomide + hu38SB19) in the NCI-H929 model while higher doses of lenalidomide and hu38SB19 were tested in the RPMI-8226 model.

[91] Antitumor activity was determined according to NCI standards based on the ratio of the median tumor volume change of the treated / median tumor volume change of the control x 100 (%$\Delta T/\Delta C$). Low numerical values for $\Delta T/\Delta C$ describe stronger anti-tumor activity. Anti-tumor activity is defined as $\Delta T/\Delta C \leq 40\%$ at minimum. $\Delta T/\Delta C < 10\%$ is considered high anti-tumor activity.

[92] In the RPMI-8226 model, hu38SB19 alone at 15 mg/kg/injection (twice a week for 2 weeks) was inactive with a %$\Delta T/\Delta C$ of 44% . Treatment with lenalidomide alone at 15 mg/kg/day (dosed daily for three weeks) was inactive (61%$\Delta T/\Delta C$). The combination of hu38SB19 (15 mg/kg/injection) and lenalidomide

(15 mg/kg/day) had higher activity with %T/C of 13% (Figure 4). The results are summarized in Table 1.

TABLE 1

Anti-tumor efficacy of hu38SB19 in combination with lenalidomide against RPMI-8226 multiple myeloma model

Agent	Dose in mg/kg (total dose)	Schedule of Administration IV or PO route	%ΔT/ΔC (D69)	Activity
PBS	-	2x/wk x 2 wk (IV)		
hu38SB19	15 (60)	2x/wk x 2 wk (IV)	44	Inactive
Lenalidomide	15 (315)	QD x 21 d (PO)	61	Inactive
hu38SB19 + Lenalidomide	15 (60) + 15 (315)	2x/wk x 2 wk (IV) + QD x 21 d (PO)	13	Active

%ΔT/ΔC Median tumor volume change of the treated / Median tumor volume change of the control x 100, IV=intravenous, PO=oral, d=days, wk=week, QD=once daily, PBS: phosphate buffered saline

[93] In the NCI-H929 model, hu38SB19 alone at 0.5 mg/kg/injection (twice a week for 2 weeks) was active with a %ΔT/ΔC of 10%. Treatment with lenalidomide alone at 1 mg/kg/day (dosed daily for three weeks) was active (20%ΔTΔ/C). The combination of hu38SB19 (0.5 mg/kg/injection) and lenalidomide (1 mg/kg/day) had higher activity (tumor regression) with %ΔT/ΔC of -8% (Figure 10). The results are summarized in Table 2.

TABLE 2

Anti-tumor efficacy of hu38SB19 in combination with lenalidomide against NCI-H929 multiple myeloma model

Agent	Dose in mg/kg (total dose)	Schedule of Administration IV or PO route	%ΔT/ΔC (D69)	Activity
PBS	-	2x/wk x 2 wk (IV)		
hu38SB19	0.5 (2)	2x/wk x 2 wk (IV)	10	Active
Lenalidomide	1 (21)	QD x 21 d (PO)	20	Active
hu38SB19 + Lenalidomide	0.5 (2) + 1 (21)	2x/wk x 2 wk (IV) + QD x 21 d (PO)	-8	Highly Active

%ΔT/ΔC Median tumor volume change of the treated / Median tumor volume change of the control x 100, IV=intravenous, PO=oral, d=days, wk=week, QD=once daily, PBS: phosphate buffered saline

[94] In both models, the combination treatment inhibited tumor growth to a much greater extent than a single agent alone, indicating the combination of hu38SB19 and lenalidomide blocked tumor cell growth through potential synergistic mechanisms. Although the molecular mechanisms of action of lenalidomide is still unknown, it is

generally believed that lenalidomide enhances natural killer cell activity which is important for antibody dependent cellular cytotoxicity (ADCC) and directly induces apoptosis in tumor cells. Hu38SB19 has demonstrated potent ADCC and direct apoptosis induction activity on tumor cells and these activities are further enhanced by lenalidomide as evidenced by the experiments herein.

[95] It has been reported that some CD38 antibodies such as Daratumumab is able to induce apoptosis only after cross-linking with a secondary antibody without much direct effect by itself. However, in preclinical studies, hu38SB19 demonstrated potent direct pro-apoptotic activity on tumor cells without cross-linking. Thus, this unique property of hu38SB19 may also lead to greater tumor cell killing when in combination with lenalidomide compared to other CD38 antibodies combined with lenalidomide.

[96] *Example 2: Effect of the administration of both anti-CD38 antibody and lenalidomide in humans*

[97] A Phase 1b study for evaluating the effects of a treatment with hu38SB19 combined with lenalidomide and low dose dexamethasone in patients with relapsed or refractory multiple myeloma is performed as described below.

[98] The main goals of the Phase 1b study include:

- To determine the efficacy and the maximum tolerated dose;
- To evaluate the safety, including immunogenicity, of hu38SB19 in combination with lenalidomide in relapse or refractory multiple myeloma. The severity, frequency and incidence of all toxicities is assessed;
- To evaluate the pharmacokinetics (PK) of hu38SB19 when administered in combination with lenalidomide and the PK of lenalidomide in combination with HU38SB19 and dexamethasone.
- To assess the relationship between clinical (adverse event and/or tumor response) effects and pharmacologic parameters (PK/pharmacodynamics), and/or biologic (correlative laboratory) results;
- Estimate the activity (response rate) using International Myeloma Working Group defined response criteria of hu38SB19 plus lenalidomide and dexamethasone; and
- To describe overall survival, progression free survival (PFS) and time to disease progression in patients treated with this combination.

[99] About 20 to 40 patients may be selected based on the following criteria: The patients are male or female, but must be diagnosed with multiple myeloma and be aged of at least 18 years. For each patient, there is a documentation of at least 2 prior therapies (induction therapy is considered one prior therapy). There is no maximum number of prior regimens and prior bone marrow transplant is acceptable. There is a confirmed evidence of disease progression from immediately prior MM therapy or refractory to the immediately prior therapy. Patients may have received prior immunomodulatory drugs (IMiDs) (e.g., lenalidomide or thalidomide). Patients are with measurable disease. Patients are with a Karnofsky ≥60% performance status. Females of childbearing potential are included provided they have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 to 4 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by RevAssist®) and must either commit to continued abstinence from heterosexual intercourse or begin two acceptable methods of birth control, one highly effective method and one additional effective method at the same time, at least 28 days before she starts taking lenalidomide. Females of childbearing potential must also agree to ongoing pregnancy testing. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations). The patient must be able to take aspirin daily as prophylactic anti-coagulation therapy (patients intolerant to aspirin may use warfarin, low molecular weight heparin or equivalent anti-platelet therapy).

[100] In addition, patients meeting at least one of the following criteria are excluded:

- Diagnosed or treated for another malignancy within 3 years prior to enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low risk prostate cancer after curative therapy;
- Prior anti-cancer therapy (chemotherapy, targeted agents, radiotherapy, and immunotherapy) within 21 days except for alkylating agents (e.g., melphalan) where 28 days will be required or participated in another clinical trial during the past 30 days;
- History of significant cardiovascular disease within the past 6 months, unless the disease is well-controlled. Significant cardiac diseases includes second/third degree heart block; significant ischemic heart disease (eg,

angina); QTc interval >450 msec at baseline (read by local cardiologist); poorly controlled hypertension; congestive heart failure of New York Heart Association (NYHA) Class II (slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea) or worse; left-ventricular ejection fraction (LVEF) <50%;

- Prior peripheral stem cell transplant within 12 weeks of the first dose of study treatment;
- Daily requirement for corticosteroids (>10 mg/kg prednisone qd) (except for inhalation corticosteroids);
- Evidence of mucosal or internal bleeding;
- Prior radiation therapy or major surgical procedure within 4 weeks of the first dose of study treatment;
- Known active infection requiring parenteral or oral anti-infective treatment;
- Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse follow-up evaluation;
- Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient. Examples of such conditions include any pre-existing kidney disease (acute or chronic, unless renal insufficiency is felt to be secondary to MM, hypertension, active seizure disorder or pulmonary diseases that would impose excessive risk to the patient;
- Hypersensitivity to any of the components of study therapy that is not amenable to premedication with steroids and H2 blockers;
- Known human immunodeficiency virus (HIV) or active hepatitis B or C viral infection;
- Neuropathy ≥ Grade 3 or painful neuropathy ≥ Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 4.0);
- Gastro-intestinal abnormalities, including bowel obstruction, inability to take oral medication, requirement for intravenous (IV) alimentation, active peptic ulcer or prior surgical procedures or bowel resection affecting absorption; and
- Pregnancy.

[101] The patients are treated with hu38SB19 combined with lenalidomide and dexamethasone. hu38SB19 is administered intravenously as a solution.

Lenalidomide is administered orally as capsules. Dexamethasone is administered orally as tablets. The study duration for an individual patient includes a screening period for inclusion of up to 21 days, and at least 4 weeks of treatment in the absence of severe adverse reaction, dose limiting toxicity or disease progression plus up to 60 days post-treatment follow up. The total duration of the study may be up to one year.

[102] The following parameters are measured during and/or at the end of the study:

- Number of patients with adverse events when treated with hu38SB19 in combination with Lenalidomide
- Assessment of partial response, complete response, progression free survival, and survival;
- Assessment of the following PK parameters: area under curve (AUC), maximum concentration (Cmax) and plasma half-life (T 1/2)
- Number of CD38 receptors occupied by hu38SB19; and
- Number of anti-SAR antibodies in response to hu38SB19.

[103] *Example 3: Efficacy of anti-CD38 antibody in in vivo tumor models of multiple myeloma as a single-agent or in combination with and lenalidomide in humans the standard-of-care immunomodulatory targeting agent, Lenalidomide.*

[104] A. Materials and Methods

[105] CD38 Density: CD38 density was determined using anti-CD38-PE Quantibrite (BD Biosciences; Cat.342371) per the manufacturer's recommended protocols.

[106] Reagents & Compounds: hu38SB19 was provided by Sanofi Oncology in solution at 5 mg/ml and stored at 4° C. hu38SB19 was diluted into sterile saline in preparation for dosing and used within 10 days of dilution. hu38SB19 was administered twice weekly x 2 wk IV. Lenolidomide (TC27682) was obtained from AK Scientific Inc. (Mountain View, CA) and prepared as a suspension in 1% (w/v) carboxymethyl cellulose (Sigma). Preparation was made using a mortar and pestle to generate a slurry suspension in the vehicle, diluted to the appropriate concentration, and used for dosing by oral gavage. Lenalidomide was administered qdx7 x 3 wk PO.

[107] Test Animals: 5-6 week old female Balb/c Scid mice were obtained from Jackson Lab. Mice were housed for 7-10 days prior to implantation of multiple

myeloma (MM) cell lines. Mice were housed in a dedicated room in the UCSF Mt. Zion Animal Barrier Facility.

[108] Cell culture: RPMI-8226 cells were obtained from the German Collection of Microorganisms and Cell Cultures, DSMZ, (Deutsche Sammlung von Mikroorganismen und Zellkulturen), and grown in sterile suspension culture in T225 flasks. RPMI-8226 were cultured in RPMI1640 + 10% FBS + 4 mM L-glutamine.

[109] Xenograft Model: At the time of implantation, mice were shaved on the right flank and shoulder. MM cells were suspended in serum free RPMI 1640 media diluted 1:1 with Matrigel (BD) at a concentration of $1x10^8$ cells per ml were injected sc into the right flank in 100 ul volume ($1x10^7$ cells) using a 1 ml syringe and 25 g needle. Mice were monitored twice weekly for the appearance of tumors and once tumors were visible, measurements were collected twice weekly for body weight and tumor volume. Electronic balance and calipers were used and data was collected directly into a study management program (Study Director). When the mean tumor volume reached approximately 150-200 mm^3, mice were distributed into treatment groups of 8-10 mice per group and dosing was initiated.

[110] B. Summary and Conclusions

[111] hu38SB19 is a humanized anti-CD38 antibody whose anti-myeloma effects incorporate mechanisms of ADCC, CDC, and direct apoptosis. Figure 21 shows the cell surface density of CD38 in multiple myeloma cell lines. See Kim D, Park CY, Medeiros BC, Weissman IL. CD19-CD45 low/- CD38 high/CD138+ plasma cells enrich for human tumorigenic myeloma cells. *Leukemia*. 2012 Dec, 26(12):2530-7. CD38-positive multiple myeloma plasma cells demonstrate variable CD38 cell surface densities. All cell lines, with the exception of XG-6, are reported as CD38-positive. See Bataille R, Jégo G, Robillard N, et al. The phenotype of normal, reactive and malignant plasma cells. Identification of "many and multiple myelomas" and of new targets for myeloma therapy. *Haematologica*. 2006 Sept, 91(9):1234-40. Binding of hu38SB19 to CD38 also impinges on the ADPRC enzymatic activity of CD38. *In vivo,* hu38SB19 demonstrates potent anti-tumor effects in multiple myeloma xenografts, a disease largely characterized by neoplastic plasma cells expressing CD38. Figure 13 shows that single-agent administration of hu38SB19 results in dose-dependent inhibition of tumor growth in an RPMI-8226 hind-flank model. The magnitude and significance of tumor growth inhibition at the end of the

study increased with increased doses of hu38SB19. Figure 14 shows that a combined regimen of hu38SB19 and Lenalidomide results in significant tumor growth inhibition in an RPMI-8226 xenograft model that is not robustly sensitive to single-agent therapy with Lenalidomide. These data demonstrate that single-agent hu38SB19 inhibits growth of RPMI-8226 tumors and combines with sub-efficacious doses of Lenalidomide to produce significant inhibition of tumor growth. Taken together, these data support further evaluation of hu38SB19, both as a single-agent and in combination with standard-of-care treatment regimens, as a potential therapy for the treatment of multiple myeloma.

[112] To the extent necessary to understand or complete the disclosure of the present invention, all publications, patents, and patent applications mentioned herein are expressly incorporated by reference therein to the same extent as though each were individually so incorporated.

[113] Having thus described exemplary embodiments of the present invention, it should be noted by those skilled in the art that the within disclosures are exemplary only and that various other alternatives, adaptations, and modifications may be made within the scope of the present invention. Accordingly, the present invention is not limited to the specific embodiments as illustrated herein, but is only limited by the following claims.

What is claimed is:

1. A method of treating a cancer in a subject which comprises

administering one or more anti-CD38 antibodies and one or more lenalidomide compounds to the subject.