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(54) Title: ANTI-CD37 IMMUNOCONJUGATE DOSING REGIMENS

(57) Abstract: Methods of administering immunoconjugates that bind to CD37 are provided. The methods comprise administering an anti-CD37 immunoconjugate, optionally in combination with an anti-CD20 therapy, to a person in need thereof, for example, a cancer patient, at a therapeutically effective dosing regimen that results in minimal adverse effects.



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ANTI-CD37 IMMUNOCONJUGATE DOSING REGIMENS

Field of the Invention

[0001] The field of the invention generally relates to methods of administering anti-CD37 immunoconjugates (e.g., Debio 1562), e.g., in combination with an anti-CD20 therapy (e.g., rituximab), for the treatment of diseases, such as cancer.

Background of the Invention

[0002] Cancer is one of the leading causes of death in the developed world, with over one million people diagnosed with cancer and 500,000 deaths per year in the United States alone. Overall it is estimated that more than 1 in 3 people will develop some form of cancer during their lifetime. Non-Hodgkin Lymphoma (NHL) is one of the most common cancers in the United States, where it accounts for about 4% of all cancers. The anti-CD20 antibody rituximab has had a significant effect on patient outcomes, but patients may show primary and secondary resistance.

[0003] Leukocyte antigen CD37 ("CD37"), also known as GP52-40, tetraspanin-26, or TSPAN26, is expressed on B cells during the pre-B to peripheral mature B-cell stages, but is absent on terminal differentiation to plasma cells. (Link et al., 1987, J Pathol. 152:12-21). The CD37 antigen is only weakly expressed on T-cells, myeloid cells and granulocytes (Schwartz-Albiez et al. 1988, J. Immunol., 140(3)905-914). However, CD37 is also expressed on malignant B-cells such as those found in non-Hodgkin's lymphoma (NHL) and chronic lymphoid leukemia (CLL) (Moore et al. 1986, J Immunol. 137(9):3013-8). This expression profile suggests that CD37 represents a promising therapeutic target for B-cell malignancies, and currently, there is a clear unmet medical need for more effective therapeutics for B-cell malignancies.

BRIEF SUMMARY OF THE INVENTION

[0004] Provided herein are methods for treating cancer in human patients using an anti-CD37 immunoconjugate (e.g., Debio 1562).

[0005] In certain instances, a method for treating a cancer in a human patient comprises administering to the patient a pharmaceutical composition comprising an anti-CD37 immunoconjugate once a week in a three-week cycle, wherein: a) 0.2 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week; b) 0.3 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg are administered in the second week, and 0.3 mg/kg are administered in the third week; c) 0.3 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week; d) 0.3 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week; e) 0.4 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg are administered in the second week, and 0.3 mg/kg are administered in the third week; f) 0.4 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week; g) 0.4 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week; h) 0.5 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg is administered in the second week, and 0.2 mg/kg are administered in the third week; i) 0.5 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week; or j) 0.6 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week; wherein the immunoconjugate comprises (i) an antibody or antigen-binding fragment thereof comprising a VH-CDR1 comprising the amino acid sequence of SEQ ID NO:2, a VH-CDR2 comprising the amino acid sequence of SEQ ID NO:3, a VH-CDR3 comprising the amino acid sequence of SEQ ID NO:4, a VL-CDR1 comprising the amino acid sequence of SEQ ID NO:5, a VL-CDR2 comprising the amino acid sequence of SEQ ID NO:6, and a VL-CDR3 comprising the amino acid sequence of SEQ ID NO:7 and (ii) a maytansinoid.

[0006] In certain instances, the antibody or antigen-binding fragment comprises a variable heavy chain comprising the amino acid sequence of SEQ ID NO:8. In certain instances, the antibody or antigen-binding fragment thereof comprises a variable light chain comprising the amino acid sequence of SEQ ID NO:10. In certain instances, the antibody or

antigen-binding fragment comprises a full length heavy chain comprising the amino acid sequence of SEQ ID NO:11. In certain instances, the antibody or antigen-binding fragment comprises a full length light chain comprising the amino acid sequence of SEQ ID NO:12. In certain instances, the antibody comprises a light chain comprising the same amino acid sequence as the light chain encoded by the phuCD37-3LC plasmid deposited as ATCC deposit PTA-10722 and a heavy chain comprising the same amino acid sequence as the heavy chain encoded by the phuCD37-3HCv1.0 deposited as ATCC deposit PTA-10723.

[0007] In certain instances, the maytansinoid is DM1. In certain instances, the maytansinoid is linked to the antibody or antigen-binding fragment by an SMCC linker.

[0008] In certain instances, the antibody comprises a full length heavy chain comprising the amino acid sequence of SEQ ID NO:11 and a full length light chain comprising the amino acid sequence of SEQ ID NO:12, the maytansinoid is DM1, and the DM1 is linked to the antibody by an SMCC linker.

[0009] In certain instances, the immunoconjugate comprises 1-10 maytansinoids per antibody.

[0010] In certain instances, the pharmaceutical composition comprises at least two of the immunoconjugates, and the immunoconjugates comprise an average of 3 to 4 maytansinoids per antibody. In certain instances, the pharmaceutical composition comprises at least two of the immunoconjugates, and the immunoconjugates comprise an average of 3.5 maytansinoids per antibody.

[0011] In certain instances, the immunoconjugate is administered for six three-week cycles.

[0012] In certain instances, the immunoconjugate is administered intravenously.

[0013] In certain instances, the immunoconjugate is administered in combination with an anti-CD20 therapy. In certain instances, the anti-CD20 therapy and the immunoconjugate are administered in separate pharmaceutical compositions.

[0014] In certain instances, the anti-CD20 therapy is rituximab. In certain instances, 375 mg/m² of the rituximab is administered. In certain instances, the rituximab is administered once every three weeks. In certain instances, the rituximab is administered on day one of the three-week cycle. In certain instances, the immunoconjugate and the rituximab are administered on the same day. In certain instances, the rituximab is administered after the immunoconjugate is administered. In certain instances, the rituximab is administered for six

three-week cycles. In certain instances, the rituximab is administered once every four weeks (one month), once every two months, or once every three months.

[0015] In certain instances, the pharmaceutical composition comprises at least two immunoconjugates and the immunoconjugates comprise an average of 3 to 4 maytansinoids per antibody, wherein the antibody comprises a full length heavy chain comprising the amino acid sequence of SEQ ID NO:11 and a full length light chain comprising the amino acid sequence of SEQ ID NO:12, wherein the maytansinoid is DM1, and wherein the DM1 is linked to the antibody by an SMCC linker, wherein the immunoconjugate is administered in combination with 375 mg/m² of rituximab administered once every three weeks on day one of the three-week cycle after administration of the immunoconjugate.

[0016] In certain instances, the methods further comprise administering a corticosteroid to the patient. In certain instances, the corticosteroid is administered prior to the administration of the immunoconjugate. In certain instances, the corticosteroid is administered from about 30 to about 60 minutes prior to administration of the immunoconjugate. In certain instances, the immunoconjugate is administered intravenously, and the corticosteroid is administered peri-infusionally. In certain instances, the corticosteroid is administered after the administration of the immunoconjugate. In certain instances, the corticosteroid is administered from about one day to about four days after administration of the immunoconjugate. In certain instances, the corticosteroid is administered on days 2 and 3 following the administration of the immunoconjugate.

[0017] In certain instances, the corticosteroid is selected from the group consisting of prednisone, prednisolone, methylprednisolone, beclamethasone, betamethasone, dexamethasone, fludrocortisone, hydrocortisone, and triamcinolone. In certain instances, the corticosteroid is dexamethasone.

[0018] In certain instances, the methods further comprise administering a growth factor to the patient. In certain instances, the growth factor is selected from the group consisting of granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), filgrastim, and pegfilgrastim. In certain instances, the growth factor is G-CSF.

[0019] In certain instances, the cancer is a B cell malignancy. In certain instances, the cancer is leukemia or lymphoma. In certain instances, the cancer is a Non-Hodgkin's lymphoma (NHL). In certain instances, the NHL is relapsed NHL. In certain instances, the NHL is refractory NHL. In certain instances, the cancer is diffuse large B-cell lymphoma

(DLBCL). In certain instances, the DLBCL is relapsed DLBCL. In certain instances, the DLBCL is refractory DLBCL. In certain instances, the cancer is selected from the group consisting of relapsed and/or refractory DLBCL, Follicular Lymphoma (FL), Marginal Zone Lymphoma/Mucosa-associated lymphoid tissue (MZL/MALT), or Mantle Cell Lymphoma (MCL). In certain instances, the cancer is selected from the group consisting of precursor B-cell lymphoblastic leukemia/lymphoma and mature B-cell neoplasms, such as B-cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), including low-grade, intermediate-grade and high-grade FL, cutaneous follicle center lymphoma, marginal zone B-cell lymphoma (MALT type, nodal and splenic type), hairy cell leukemia, diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant lymphoproliferative disorder, Waldenstrom's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL).

[0020] In certain instances, the cancer expresses CD37.

[0021] In certain instances, the weekly administration of the anti-CD37 immunoconjugate maintains exposure over three weeks. In certain instances, the weekly administration of the anti-CD37 immunoconjugate limits neutropenia and/or other adverse events. In certain instances, the weekly administration of the anti-CD37 immunoconjugate prolongs the synergistic effect with rituximab as compared to administration of the anti-CD37 immunoconjugate every three weeks.

[0022] In certain instances, the anti-CD37 immunoconjugate is administered weekly for at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven or at least twelve three-week cycles. In certain instances, the anti-CD37 immunoconjugate is administered at a dose of 0.7 mg/kg once every three weeks after the at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven or at least twelve three-week cycles of weekly administration. In certain instances, the anti-CD37 immunoconjugate is administered at a dose of 0.7 mg/kg once every three weeks after a complete response, a partial response, or stable disease is observed following weekly administration.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

- [0023]** Figure 1 shows simulations of Debio 1562 (“ADC”) blood concentration in patients as a result of administration of three weekly doses of 0.2 mg/kg for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (top panel) or administration of three weekly doses of 0.3, 0.2, and 0.2 mg/kg, respectively, for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (bottom panel).
- [0024]** Figure 2 shows simulations of Debio 1562 (“ADC”) blood concentration in patients as a result of administration of three weekly doses of 0.3, 0.3, and 0.2 mg/kg, respectively, for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (top panel) or administration of three weekly doses of 0.3 mg/kg for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (bottom panel).
- [0025]** Figure 3 shows simulations of Debio 1562 (“ADC”) blood concentration in patients as a result of administration of three weekly doses of 0.4, 0.2, and 0.2 mg/kg, respectively, for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (top panel) or administration of three weekly doses of 0.4, 0.3, and 0.2 mg/kg, respectively, for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (bottom panel).
- [0026]** Figure 4 shows simulations of Debio 1562 (“ADC”) blood concentration in patients as a result of administration of three weekly doses of 0.4, 0.3, and 0.3 mg/kg, respectively, for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (top panel) or administration of three weekly doses of 0.5, 0.2, and 0.2 mg/kg, respectively, for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (bottom panel).
- [0027]** Figure 5 shows simulations of Debio 1562 (“ADC”) blood concentration in patients as a result of administration of three weekly doses of 0.5, 0.3, and 0.2 mg/kg, respectively, for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (top panel) or administration of three weekly doses of 0.6, 0.2, and 0.2 mg/kg, respectively, for six cycles as compared to administration of 0.7 mg/kg once every three weeks for six cycles (bottom panel).

[0028] Figure 6 shows pharmacokinetic parameters reflecting patient exposure to Debio 1562 in Cohort A (Q3W - once per 3 weeks regimen) and in Cohort B (QW - weekly administration in 3 weeks regimen). AUC_{cycle} = Area Under the Curve during a cycle of 3 weeks; C_{last} = last concentration measured during a cycle before the next Debio 1562 administration; C_{max} = maximal concentration observed per cycle; N represents the number of observations used to build the corresponding box plot - multiple values might be observed per subject. Box plots represent the median value and the 25th - 75th percentiles.

[0029] Figure 7 shows the percentage of CD37 receptor occupancy (RO) on CD3+ T cells measured in Cohort A (Q3W) and in Cohort B (QW).

[0030] Figure 8 shows categorical plots of best overall response (BOR) and overall response rate (ORR) as per 2014 Lugano classification in the Q3W regimen (Cohort A in light grey) and in the QW regimen (Cohort B in dark gray). Left panel shows data as number of patients per category. Right panel shows data as percentage of patients in each category relative to the total number of evaluable patients in the corresponding cohort. This plot is based on the data in 10 patients in Cohort A and 6 patients in Cohort B.

DETAILED DESCRIPTION OF THE INVENTION

[0031] The present invention provides new dosing regimens for CD37 binding immunoconjugates.

I. Definitions

[0032] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0033] The term "CD37" as used herein, refers to any native CD37, unless otherwise indicated. CD37 is also referred to as GP52-40, leukocyte antigen CD37, and Tetraspanin-26. The term "CD37" encompasses "full-length," unprocessed CD37 as well as any form of CD37 that results from processing in the cell. The term also encompasses naturally occurring variants of CD37, e.g., splice variants, allelic variants, and isoforms. The CD37 polypeptides described herein can be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

[0034] The term "CD20" as used herein, refers to any native CD20 polypeptide, unless otherwise indicated. CD20 is also referred to as membrane-spanning 4-domains, subfamily

A, member 1 (MS4A1), B-lymphocyte surface antigen B1, and Leukocyte surface antigen Leu-16. The term "CD20" encompasses "full-length," unprocessed CD20 polypeptide as well as any form or isoform of CD20 polypeptide that results from processing in the cell. The term also encompasses naturally occurring variants of CD20 polypeptide, e.g., those encoded by splice variants and allelic variants. The CD20 polypeptides described herein can be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. Where specifically indicated, "CD20" can be used to refer to a nucleic acid that encodes a CD20 protein.

[0035] The term "antibody" means an immunoglobulin molecule that recognizes and specifically binds to a target, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or combinations of the foregoing through at least one antigen recognition site within the variable region of the immunoglobulin molecule. As used herein, the term "antibody" encompasses intact polyclonal antibodies, intact monoclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, fusion proteins comprising an antibody, and any other modified immunoglobulin molecule so long as the antibodies exhibit the desired biological activity. An antibody can be of any the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well known subunit structures and three-dimensional configurations. Antibodies can be naked or conjugated to other molecules such as toxins, radioisotopes, etc.

[0036] The term "antibody fragment" refers to a portion of an intact antibody. An "antigen-binding fragment," "antigen-binding domain," or "antigen-binding region," refers to a portion of an intact antibody that binds to an antigen. An antigen-binding fragment can contain the antigenic determining regions of an intact antibody (e.g., the complementarity determining regions (CDR)). Examples of antigen-binding fragments of antibodies include, but are not limited to Fab, Fab', F(ab')₂, and Fv fragments, linear antibodies, and single chain antibodies. An antigen-binding fragment of an antibody can be derived from any animal species, such as rodents (e.g., mouse, rat, or hamster) and humans or can be artificially produced.

[0037] The term "anti-CD37 antibody" or "an antibody that binds to CD37" refers to an antibody that is capable of binding CD37 with sufficient affinity such that the antibody is

useful as a diagnostic and/or therapeutic agent in targeting CD37. The extent of binding of an anti-CD37 antibody to an unrelated, non-CD37 protein can be less than about 10% of the binding of the antibody to CD37 as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds to CD37 has a dissociation constant (K_d) of $\leq 1 \mu\text{M}$, $\leq 100 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 1 \text{ nM}$, or $\leq 0.1 \text{ nM}$. Similarly, the term "anti-CD20 antibody" or "an antibody that binds to CD20" refers to an antibody that is capable of binding CD20 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting CD20. The extent of binding of an anti-CD20 antibody to an unrelated, non-CD20 protein can be less than about 10% of the binding of the antibody to CD20 as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds to CD20 has a dissociation constant (K_d) of $\leq 1 \mu\text{M}$, $\leq 100 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 1 \text{ nM}$, or $\leq 0.1 \text{ nM}$.

[0038] A "monoclonal antibody" refers to a homogeneous antibody population involved in the highly specific recognition and binding of a single antigenic determinant, or epitope. This is in contrast to polyclonal antibodies that typically include different antibodies directed against different antigenic determinants. The term "monoclonal" antibody or antigen-binding fragment thereof encompasses both intact and full-length monoclonal antibodies as well as antibody fragments (such as Fab, Fab', F(ab')₂, Fv), single chain (scFv) mutants, fusion proteins comprising an antibody portion, and any other modified immunoglobulin molecule comprising an antigen recognition site. Furthermore, "monoclonal" antibody refers to such antibodies made in any number of manners including but not limited to by hybridoma, phage selection, recombinant expression, and transgenic animals.

[0039] As used herein, the terms "variable region" or "variable domain" are used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids or 110 to 125 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain

embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

[0040] The terms “VL” and “VL domain” are used interchangeably to refer to the light chain variable region of an antibody.

[0041] The terms “VH” and “VH domain” are used interchangeably to refer to the heavy chain variable region of an antibody.

[0042] The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.*, Kabat et al., Sequences of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)).

[0043] The amino acid position numbering as in Kabat, refers to the numbering system used for heavy chain variable domains or light chain variable domains of the compilation of antibodies in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991). Using this numbering system, the actual linear amino acid sequence can contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or CDR of the variable domain. For example, a heavy chain variable domain can include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (*e.g.* residues 82a, 82b, and 82c, etc. according to Kabat) after heavy chain FR residue 82. The Kabat numbering of residues can be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence. Chothia refers instead to the location of the structural loops (Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software.

Loop	Kabat	AbM	Chothia
L1	L24-L34	L24-L34	L24-L34
L2	L50-L56	L50-L56	L50-L56
L3	L89-L97	L89-L97	L89-L97
H1	H31-H35B	H26-H35B (Kabat Numbering)	H26-H32..34
H1	H31-H35	H26-H35 (Chothia Numbering)	H26-H32
H2	H50-H65	H50-H58	H52-H56
H3	H95-H102	H95-H102	H95-H102

[0044] As used herein, the term “constant region” or “constant domain” are interchangeable and have its meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain. In certain aspects, an antibody or antigen-binding fragment comprises a constant region or portion thereof that is sufficient for antibody-dependent cell-mediated cytotoxicity (ADCC).

[0045] As used herein, the term “heavy chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ϵ), gamma (γ), and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG₁, IgG₂, IgG₃, and IgG₄. Heavy chain amino acid sequences are well known in the art. In specific embodiments, the heavy chain is a human heavy chain.

[0046] As used herein, the term “light chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

[0047] The term "chimeric" antibodies or antigen-binding fragments thereof refers to antibodies or antigen-binding fragments thereof wherein the amino acid sequence is derived from two or more species. Typically, the variable region of both light and heavy chains corresponds to the variable region of antibodies or antigen-binding fragments thereof

derived from one species of mammals (e.g. mouse, rat, rabbit, etc.) with the desired specificity, affinity, and capability while the constant regions are homologous to the sequences in antibodies or antigen-binding fragments thereof derived from another (usually human) to avoid eliciting an immune response in that species.

[0048] The term "humanized" antibody or antigen-binding fragment thereof refers to forms of non-human (e.g. murine) antibodies or antigen-binding fragments that are specific immunoglobulin chains, chimeric immunoglobulins, or fragments thereof that contain minimal non-human (e.g., murine) sequences. Typically, humanized antibodies or antigen-binding fragments thereof are human immunoglobulins in which residues from the complementary determining region (CDR) are replaced by residues from the CDR of a non-human species (e.g. mouse, rat, rabbit, hamster) that have the desired specificity, affinity, and capability ("CDR grafted") (Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-327 (1988); Verhoeyen et al., *Science* 239:1534-1536 (1988)). In some instances, the Fv framework region (FR) residues of a human immunoglobulin are replaced with the corresponding residues in an antibody or fragment from a non-human species that has the desired specificity, affinity, and capability. The humanized antibody or antigen-binding fragment thereof can be further modified by the substitution of additional residues either in the Fv framework region and/or within the replaced non-human residues to refine and optimize antibody or antigen-binding fragment thereof specificity, affinity, and/or capability. In general, the humanized antibody or antigen-binding fragment thereof will comprise substantially all of at least one, and typically two or three, variable domains containing all or substantially all of the CDR regions that correspond to the non-human immunoglobulin whereas all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody or antigen-binding fragment thereof can also comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Examples of methods used to generate humanized antibodies are described in U.S. Pat. 5,225,539; Roguska et al., *Proc. Natl. Acad. Sci., USA*, 91(3):969-973 (1994), and Roguska et al., *Protein Eng.* 9(10):895-904 (1996). In certain instances, a "humanized antibody" is a resurfaced antibody.

[0049] The term "human" antibody or antigen-binding fragment thereof means an antibody or antigen-binding fragment thereof having an amino acid sequence derived from a human immunoglobulin gene locus, where such antibody or antigen-binding fragment is

made using any technique known in the art. This definition of a human antibody or antigen-binding fragment thereof includes intact or full-length antibodies and fragments thereof.

[0050] The term "biosimilar" as used herein refers to a biological medicine highly similar to another biological medicine in terms of structure, biological activity and efficacy, safety and immunogenicity profile.

[0051] "Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present invention.

[0052] "Or better" when used herein to refer to binding affinity refers to a stronger binding between a molecule and its binding partner. "Or better" when used herein refers to a stronger binding, represented by a smaller numerical Kd value. For example, an antibody which has an affinity for an antigen of "0.6 nM or better", the antibody's affinity for the antigen is <0.6 nM, i.e. 0.59 nM, 0.58 nM, 0.57 nM etc. or any value less than 0.6 nM.

[0053] By "specifically binds," it is generally meant that an antibody binds to an epitope via its antigen binding domain, and that the binding entails some complementarity between the antigen binding domain and the epitope. According to this definition, an antibody is said to "specifically bind" to an epitope when it binds to that epitope, via its antigen binding domain more readily than it would bind to a random, unrelated epitope. The term "specificity" is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody "A" may be deemed to have a higher specificity for a given epitope than antibody "B," or antibody "A" may be said to bind to epitope "C" with a higher specificity than it has for related epitope "D."

[0054] By "preferentially binds," it is meant that the antibody specifically binds to an epitope more readily than it would bind to a related, similar, homologous, or analogous epitope. Thus, an antibody which "preferentially binds" to a given epitope would more likely

bind to that epitope than to a related epitope, even though such an antibody may cross-react with the related epitope.

[0055] A polypeptide, antibody, polynucleotide, vector, cell, or composition which is "isolated" is a polypeptide, antibody, polynucleotide, vector, cell, or composition which is in a form not found in nature. Isolated polypeptides, antibodies, polynucleotides, vectors, cell or compositions include those which have been purified to a degree that they are no longer in a form in which they are found in nature. In certain instances, an antibody, polynucleotide, vector, cell, or composition which is isolated is substantially pure.

[0056] As used herein, "substantially pure" refers to material which is at least 50% pure (i.e., free from contaminants), at least 60% pure, at least 70% pure, at least 80% pure, at least 90% pure, at least 95% pure, at least 98% pure, or at least 99% pure.

[0057] The term "immunoconjugate" or "conjugate" as used herein refers to a compound or a derivative thereof that is linked to a cell binding agent (i.e., an anti-CD37 antibody or fragment thereof) and is defined by a generic formula: C-L-A, wherein C = cytotoxin, L = linker, and A = anti-CD37 antibody or antibody fragment. Immunoconjugates can also be defined by the generic formula in reverse order: A-L-C.

[0058] The term "Debio 1562" refers to the immunoconjugate described herein containing the huCD37-3 antibody (comprising the CDRs represented by SEQ ID NOs:2-7, the VH of SEQ ID NO:8 and the VL of SEQ ID NO:10), the SMCC linker, and the DM1 maytansinoid. It is also known as naratuximab emtansine and was previously known as IMG529.

[0059] A "linker" is any chemical moiety that is capable of linking a compound, usually a drug, such as a maytansinoid, to a cell-binding agent such as an anti CD37 antibody or a fragment thereof in a stable, covalent manner. Linkers can be susceptible to or be substantially resistant to acid-induced cleavage, light-induced cleavage, peptidase-induced cleavage, esterase-induced cleavage, and disulfide bond cleavage, at conditions under which the compound or the antibody remains active. Suitable linkers are well known in the art and include, for example, disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups and esterase labile groups. Linkers also include charged linkers, and hydrophilic forms thereof as described herein and known in the art.

[0060] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals in which a population of cells are characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma,

sarcoma, and leukemia. "Tumor" and "neoplasm" refer to one or more cells that result from excessive cell growth or proliferation, either benign (noncancerous) or malignant (cancerous) including pre-cancerous lesions. Examples of "cancer" or "tumorigenic" diseases which can be treated and/or prevented include B-cell lymphomas including NHL, precursor B-cell lymphoblastic leukemia/lymphoma and mature B-cell neoplasms, such as B-cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), including low-grade, intermediate-grade and high-grade FL, cutaneous follicle center lymphoma, marginal zone B-cell lymphoma (MALT type, nodal and splenic type), hairy cell leukemia, diffuse large B-cell lymphoma, Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant lymphoproliferative disorder, Waldenstrom's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL).

[0061] The terms "cancer cell," "tumor cell," and grammatical equivalents refer to the total population of cells derived from a tumor or a pre-cancerous lesion, including both non-tumorigenic cells, which comprise the bulk of the tumor cell population, and tumorigenic stem cells (cancer stem cells). As used herein, the term "tumor cell" will be modified by the term "non-tumorigenic" when referring solely to those tumor cells lacking the capacity to differentiate to distinguish those tumor cells from cancer stem cells.

[0062] The term "subject" refers to any animal (e.g., a mammal), including, but not limited to humans, non-human primates, rodents, and the like, which is to be the recipient of a particular treatment. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject.

[0063] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

[0064] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. The formulation can be sterile.

[0065] An "effective amount" of an antibody or immunoconjugate as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" can be determined empirically and in a routine manner, in relation to the stated purpose.

[0066] The term "therapeutically effective amount" refers to an amount of an antibody or other drug effective to "treat" a disease or disorder in a subject or mammal. In the case of

cancer, the therapeutically effective amount of the drug can reduce the number of cancer cells; reduce the tumor size or burden; inhibit (i.e., slow to some extent and in a certain embodiment, stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and in a certain embodiment, stop) tumor metastasis; inhibit, to some extent, tumor growth; relieve to some extent one or more of the symptoms associated with the cancer; and/or result in a favorable response such as increased progression-free survival (PFS), disease-free survival (DFS), or overall survival (OS), complete response (CR), partial response (PR), or, in some cases, stable disease (SD), a decrease in progressive disease (PD), a reduced time to progression (TTP) or any combination thereof. See the definition herein of "treating". To the extent the drug can prevent growth and/or kill existing cancer cells, it can be cytostatic and/or cytotoxic. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[0067] The term "respond favorably" generally refers to causing a beneficial state in a subject. With respect to cancer treatment, the term refers to providing a therapeutic effect on the subject. Positive therapeutic effects in cancer can be measured in a number of ways (*See*, W.A. Weber, J. Nucl. Med. 50:1S-10S (2009)). For example, tumor growth inhibition, molecular marker expression, serum marker expression, and molecular imaging techniques can all be used to assess therapeutic efficacy of an anti-cancer therapeutic. A favorable response can be assessed in the clinic, for example, by increased progression-free survival (PFS), disease-free survival (DFS), or overall survival (OS), complete response (CR), partial response (PR), or, in some cases, stable disease (SD), a decrease in progressive disease (PD), a reduced time to progression (TTP) or any combination thereof.

[0068] PFS, DFS, DoR, and OS can be measured by standards set by the National Cancer Institute and the U.S. Food and Drug Administration for the approval of new drugs. See Johnson et al, (2003) J. Clin. Oncol. 21(7):1404-1411.

[0069] "Progression free survival" (PFS) refers to the time from enrollment to disease progression or death. PFS is generally summarized using the Kaplan-Meier method. Generally, progression free survival refers to the situation wherein a patient remains alive, without the cancer getting worse.

- [0070] "Time to Tumor Progression" (TTP) is defined as the time from enrollment to disease progression. TTP is generally measured using the RECIST 1.1 criteria.
- [0071] A "complete response" or "complete remission" or "CR" indicates the disappearance of all signs of tumor or cancer in response to treatment. This does not always mean the cancer has been cured. For example, any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to <10 mm. Complete response in solid tumors is generally measured using the RECIST 1.1 criteria. Eisenhauer, E.A., Eur. J. Cancer, 45: 228-47 (2009). Complete response in NHL is generally measured using the Lugano classification. Cheson, B.D et al., J Clin Oncol., 32: 3059-3067 (2014). Other tumor response criteria may also be used as appropriate for the relevant indication.
- [0072] A "partial response" or "PR" refers to a decrease in the size or volume of one or more tumors or lesions, or in the extent of cancer in the body, in response to treatment. Eisenhauer, E.A., Eur. J. Cancer, 45: 228-47 (2009). Cheson, B.D et al., J Clin Oncol., 32: 3059-3067 (2014).
- [0073] "Stable disease" or "SD" refers to disease without progression or relapse. In stable disease there is neither sufficient tumor shrinkage to qualify for partial response nor sufficient tumor increase to qualify as progressive disease taking as reference the smallest sum diameters while on the study. Eisenhauer, E.A., Eur. J. Cancer, 45: 228-47 (2009). Cheson, B.D et al., J Clin Oncol., 32: 3059-3067 (2014).
- [0074] "Progressive disease" or "PD" refers to the appearance of one more new lesions or tumors and/or the unequivocal progression of existing non-target lesions and/or at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). Eisenhauer, E.A., Eur. J. Cancer, 45: 228-47 (2009). Cheson, B.D et al., J Clin Oncol., 32: 3059-3067 (2014).
- [0075] "Disease free survival" (DFS) refers to the length of time during and after treatment that the patient remains free of disease.
- [0076] "Duration of response" (DoR) refers to the time from earlier response (PR or better) to disease progression or death.
- [0077] "Overall Survival" (OS) refers to the time from patient enrollment to death or censored at the date last known alive. OS includes a prolongation in life expectancy as

compared to naive or untreated individuals or patients. Overall survival refers to the situation wherein a patient remains alive for a defined period of time, such as one year, five years, etc., e.g., from the time of randomization or treatment.

[0078] The term "overexpression" of CD37 in a particular tumor, tissue, or cell sample refers to CD37 (a CD37 polypeptide or a nucleic acid encoding such a polypeptide) that is present at a level higher than that which is present in non-diseased tissue or cells of the same type or origin. Such overexpression can be caused, for example, by mutation, gene amplification, increased transcription, or increased translation.

[0079] Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder. Thus, those in need of treatment include those already diagnosed with or suspected of having the disorder. In certain embodiments, a subject is successfully "treated" for cancer according to the methods of the present invention if the patient shows one or more of the following: a reduction in the number of or complete absence of cancer cells; a reduction in the tumor burden; inhibition of or an absence of cancer cell infiltration into peripheral organs including, for example, the spread of cancer into soft tissue and bone; inhibition of or an absence of tumor metastasis; inhibition or an absence of tumor growth; relief of one or more symptoms associated with the specific cancer; reduced morbidity and mortality; improvement in quality of life; reduction in tumorigenicity, tumorigenic frequency, or tumorigenic capacity, of a tumor; reduction in the number or frequency of cancer stem cells in a tumor; differentiation of tumorigenic cells to a non-tumorigenic state; increased progression-free survival (PFS), disease-free survival (DFS), or overall survival (OS), complete response (CR), partial response (PR), stable disease (SD), a decrease in progressive disease (PD), a reduced time to progression (TTP), or any combination thereof.

[0080] The terms "pre-treat" and "pre-treatment" refer to therapeutic measures that occur prior to the administration of an anti-CD37 therapeutic. For example, as described in more detail herein, a prophylactic such as a steroid (e.g., corticosteroid) can be administered within about a week, about five days, about three days, about two days, or about one day or 24 hours prior to the administration of the anti-CD37 therapeutic. The prophylactic can also be administered prior to the anti-CD37 therapeutic on the same day as the anti-CD37 therapeutic.

[0081] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer can be linear or branched, it can comprise modified amino acids, and it can be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that, because the polypeptides of this invention are based upon antibodies, in certain embodiments, the polypeptides can occur as single chains or associated chains.

[0082] As used in the present disclosure and claims, the singular forms "a," "an," and "the" include plural forms unless the context clearly dictates otherwise.

[0083] It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0084] The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both "A and B," "A or B," "A," and "B." Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

II. Anti-CD37 Immunoconjugates

[0085] The methods described herein provide methods of administering immunoconjugates that specifically bind to CD37. These agents are referred to herein as "CD37-immunoconjugates" or "anti-CD37-immunoconjugates." Such immunoconjugates comprise an anti-CD37 antibody or antigen-binding fragment thereof and a drug (e.g., a maytansinoid). The drug (e.g., a maytansinoid) can be attached to the anti-CD37 antibody or antigen-binding fragment thereof by a linker (e.g., an SMCC linker). An immunoconjugate can contain multiple drugs (e.g., 1-10 maytansinoids), wherein each drug (e.g., maytansinoid) can be linked to the antibody or antigen-binding fragment thereof by a linker (e.g., an SMCC linker).

[0086] The anti-CD37 immunoconjugate can bind, for example, to human CD37. The full-length amino acid sequence for human CD37 is known in the art (NP_001765.1) and is also provided herein as SEQ ID NO:1.

MSAQESCLSLIKYFLFVFNLFVFLGSLIFCFGIWILIDKTSFVSFVGLAFVPLQIWS
 KVLAISGIFTMGIALLGCVGALKELRCLLGLYFGMLLLLFATQITLGILISTQRAQL
 ERSLRDVVEKTIQKYGTNPEETA AEESWDYVQFQLRCCGWHYPQDWFQVLILRG
 NGSEAHRVPCSCYNLSATNDSTILDKVILPQLSRLGHLARSRHSADICAVPAESHI
 YREGCAQGLQKWLHNNLISIVGICLGVGLLELGFMTLSIFLCRNLDHVYNRLAYR
 (SEQ ID NO:1)

[0087] In certain instances, the anti-CD37 immunoconjugates (e.g., Debio 1562) have one or more of the following effects: inhibit proliferation of tumor cells, reduce the tumorigenicity of a tumor by reducing the frequency of cancer stem cells in the tumor, inhibit tumor growth, increase survival, trigger cell death of tumor cells, differentiate tumorigenic cells to a non-tumorigenic state, or prevent metastasis of tumor cells. In certain instances, the anti-CD37 immunoconjugates (e.g., Debio 1562) trigger cell death via a cytotoxic agent. In certain instances, the anti-CD37 immunoconjugates (e.g., Debio 1562) are capable of inhibiting tumor growth. In certain instances, the anti-CD37 immunoconjugates (e.g., Debio 1562) are capable of inhibiting tumor growth *in vivo* (e.g., in a xenograft mouse model and/or in a human having cancer). The anti-CD37 immunoconjugates (e.g., Debio 1562) can comprise the antibody huCD37-3 or fragments, variants and derivatives thereof, as described previously in U.S. Publication No. 2011/0256153, which is herein incorporated by reference in its entirety.

[0088] In some instances, an anti-CD37 immunoconjugate comprises a humanized anti-CD37 antibody or antigen-binding fragment thereof.

[0089] In some instances, an anti-CD37 immunoconjugate (e.g., Debio 1562) comprises the heavy chain and light chain variable region CDR sequences of the humanized anti-CD37-3 antibodies (“huCD37-3”). The CDR sequences of huCD37-3 are provided in Tables 1 and 2 below.

Table 1: Variable heavy chain CDR amino acid sequences

Antibody	VH-CDR1	VH-CDR2	VH-CDR3
CD37-3	TSGVS (SEQ ID NO:2)	VIWGDGSTN (SEQ ID NO:3)	GGYSLAH (SEQ ID NO:4)

Table 2: Variable light chain CDR amino acid sequences

Antibody	VL-CDR1	VL-CDR2	VL-CDR3
CD37-3	RASENIRSNLA (SEQ ID NO:5)	VATNLAD (SEQ ID NO:6)	QHYPWGTTWT (SEQ ID NO:7)

[0090] In some instances, an anti-CD37 immunoconjugate (e.g., Debio 1562) comprises an antibody or antigen-binding fragment thereof comprising variable heavy chain CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 2, 3, and 4, respectively, and variable light chain CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 5, 6, and 7 respectively.

[0091] In some instances, an anti-CD37 immunoconjugate (e.g., Debio 1562) comprises a variable light chain or a variable heavy chain described herein. In some instances, an anti-CD37 immunoconjugate (e.g., Debio 1562) comprises both a variable light chain and a variable heavy chain provided herein. The variable light chain and variable heavy chain sequences of huCD37-3 antibodies (version 1.0 and version 1.1) are provided in Tables 3 and 4 below.

Table 3: Variable heavy chain amino acid sequences

Antibody	VH Amino Acid Sequence (SEQ ID NO)
huCD37-3 (version 1.0)	QVQVQESGPGLVAPSQTLTITCTVSGFSLTTSVSWVRQPPGKGLEW LGVIWGDGSTNYHPSLKSRLSIKKDHSKSQVFLKLNLSLTAADTATYY CAKGGYSLAHWGQGLVTVSS (SEQ ID NO:8)
huCD37-3 (version 1.1)	QVQVQESGPGLVAPSQTLTITCTVSGFSLTTSVSWVRQPPGKGLEW LGVIWGDGSTNYHSSLKSRLSIKKDHSKSQVFLKLNLSLTAADTATYY CAKGGYSLAHWGQGLVTVSS (SEQ ID NO:9)

Table 4: Variable light chain amino acid sequence

Antibody	VL Amino Acid Sequence (SEQ ID NO)
huCD37-3	DIQMTQSPSSLSVSVGERVTITCRASENIRSNLAWYQQKPGKSPKLLV NVATNLADGVPSRFSGSGSGTDYSLKINSLQPEDFGTYCYCQHYPWGTT WTFGQGTKLEIKR (SEQ ID NO:10)

[0092] An anti-CD37 immunoconjugate (e.g., Debio 1562) can also comprise a full-length light chain or a full-length heavy chain. In certain instances, an anti-CD37 immunoconjugate (e.g., Debio 1562) can comprise both a full-length light chain and a full-length heavy chain. The

full-length light chain and heavy chain sequences of huCD37-3 (version 1.0) are provided in Tables 5 and 6 below.

Table 5: Full-length heavy chain amino acid sequence

Antibody	Full-Length Heavy Chain Amino Acid Sequence (SEQ ID NO)
huCD37-3 (version 1.0)	QVQVQESGPGLVAPSQTL SITCTVSGFSLT TSGVSWVRQPPGKGLEW LGVIWGDGSTNYHPSLKSRLSIKKDHSKSQVFLKLNLSLTAADTATYY CAKGGYSLAHWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVDFCS VMHEALHNHYTQKSLSLSPG (SEQ ID NO:11)

Table 6: Full-length light chain amino acid sequence

Antibody	Full-length Light Chain Amino Acid Sequence (SEQ ID NO)
huCD37-3	DIQMTQSPSSLSVSVGERVTITCRASENIRSNLAWYQQKPGKSPKLLV NVATNLADGVPSRFSGSGSGTDYSLKINSIQPEDFGTYCYCQHYWGTT WTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPRE AKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:12)

[0093] In certain instances, the anti-CD37 immunoconjugate (e.g., Debio 1562) can comprise an anti-CD37 antibody or antigen-binding fragment thereof comprising a light chain or light chain variable region having the same amino acid sequence as the amino acid sequence encoded by the recombinant plasmid DNA phuCD37-3LC (ATCC Deposit Designation PTA-10722, deposited with the ATCC on March 18, 2010). In certain instances, the anti-CD37 antibody or antigen-binding fragment thereof can comprise a heavy chain or heavy chain variable region comprising the same amino acid sequence as the amino acid sequence encoded by the recombinant plasmid DNA phuCD37-3HCv.1.0 (ATCC Deposit Designation PTA-10723, deposited with the ATCC on March 18, 2010). In certain instances, the anti-CD37 antibody or antigen-binding fragment thereof can comprise a light chain or light chain variable region comprising the same amino acid sequence as the amino acid sequence encoded by the recombinant plasmid DNA phuCD37-3LC (PTA-10722) and a heavy chain or heavy chain variable region comprising the same amino acid sequence as the

amino acid sequence encoded by the recombinant plasmid DNA phuCD37-3HCv.1.0 (PTA-10723). In certain instances, the anti-CD37 antibody or antigen-binding fragment thereof can comprise (i) VL-CDRs comprising the same amino acid sequences as the VL-CDRs encoded by the recombinant plasmid DNA phuCD37-3LC (PTA-10722) and (ii) VH-CDRs comprising the same amino acid sequences as the VH-CDRs encoded by the recombinant plasmid DNA phuCD37-3HCv.1.0 (PTA-10723).

[0094] As provided herein, in certain instances, about 1 to about 8 drug molecules e.g., maytansinoids, are linked to an anti-CD37 antibody or antigen-binding fragment thereof. In one aspect, an immunoconjugate comprises 1, 2, 3, 4, 5, 6, 7, or 8 maytansinoids per antibody or antigen-binding fragment thereof. In one aspect, an immunoconjugate comprises about 1 to about 8 maytansinoids per antibody or antigen-binding fragment thereof, about 2 to about 7 maytansinoids per antibody or antigen-binding fragment thereof, about 2 to about 6 maytansinoids per antibody or antigen-binding fragment thereof, about 2 to about 5 maytansinoids per antibody or antigen-binding fragment thereof, about 3 to about 5 maytansinoids per antibody or antigen-binding fragment thereof, or about 3 to about 4 maytansinoids per antibody or antigen-binding fragment thereof.

[0095] In certain instances a composition provided herein comprises anti-CD37 immunoconjugates comprising about 1 to about 10 maytansinoids per antibody or antigen-binding fragment thereof, for example, wherein the average number of maytansinoids per antibody or antigen-binding fragment thereof is from about 2 to about 8 (e.g., 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1).

[0096] In certain instances, a composition provided herein comprises anti-CD37 immunoconjugates with an average of about 2 ± 0.5 , about 3 ± 0.5 , about 4 ± 0.5 , about 5 ± 0.5 , about 6 ± 0.5 , about 7 ± 0.5 , or about 8 ± 0.5 drug molecules (e.g., maytansinoids) attached per antibody or antigen-binding fragment thereof. In certain aspects, a composition provided herein comprises anti-CD37 immunoconjugates with an average of about 3.5 ± 0.5 drug molecules (e.g., maytansinoids) per antibody. In certain aspects, a composition provided herein comprises anti-CD37 immunoconjugates with an average of 3.5 ± 0.5 drug molecules (e.g., maytansinoids) per antibody.

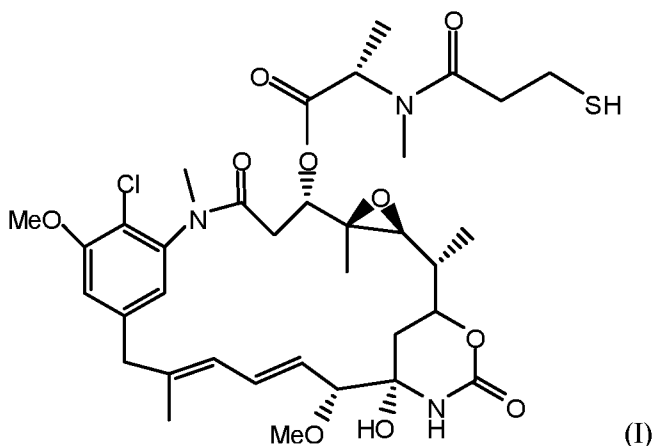
[0097] As used herein, the expression "linked to a cell-binding agent" or "linked to an anti-CD37 antibody or fragment" refers to the conjugate molecule comprising at least one

drug derivative bound to a cell-binding agent anti-CD37 antibody or fragment via a suitable linking group, or a precursor thereof. One linking group is SMCC.

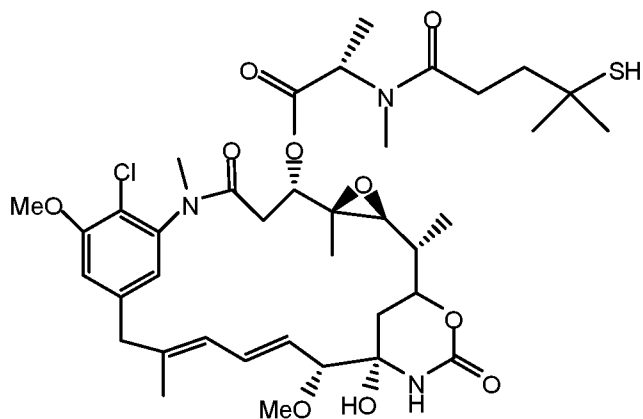
[0098] Examples of suitable maytansinoids include esters of maytansinol and maytansinol analogs. Included are any drugs that inhibit microtubule formation and that are highly toxic to mammalian cells, as are maytansinol and maytansinol analogs.

[0099] Examples of suitable maytansinol esters include those having a modified aromatic ring and those having modifications at other positions. Such suitable maytansinoids are disclosed in U.S. Patent Nos. 4,424,219; 4,256,746; 4,294,757; 4,307,016; 4,313,946; 4,315,929; 4,331,598; 4,361,650; 4,362,663; 4,364,866; 4,450,254; 4,322,348; 4,371,533; 5,208,020; 5,416,064; 5,475,092; 5,585,499; 5,846,545; 6,333,410; 7,276,497 and 7,473,796.

[0100] In a certain instance, the immunoconjugates of the invention utilize the thiol-containing maytansinoid (DM1), formally termed *N*^{2'}-deacetyl-*N*^{2'}-(3-mercapto-1-oxopropyl)-maytansine, as the cytotoxic agent. DM1 is represented by the following structural formula (I):

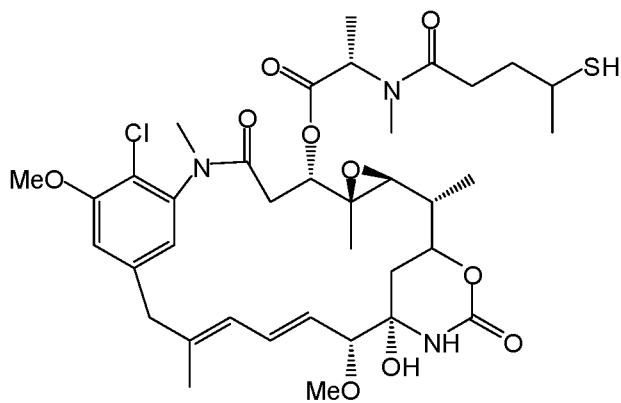


[0101] In another instance, the conjugates of the present invention utilize the thiol-containing maytansinoid *N*^{2'}-deacetyl-*N*^{2'}-(4-methyl-4-mercapto-1-oxopentyl)-maytansine (e.g., DM4) as the cytotoxic agent. DM4 is represented by the following structural formula (II):



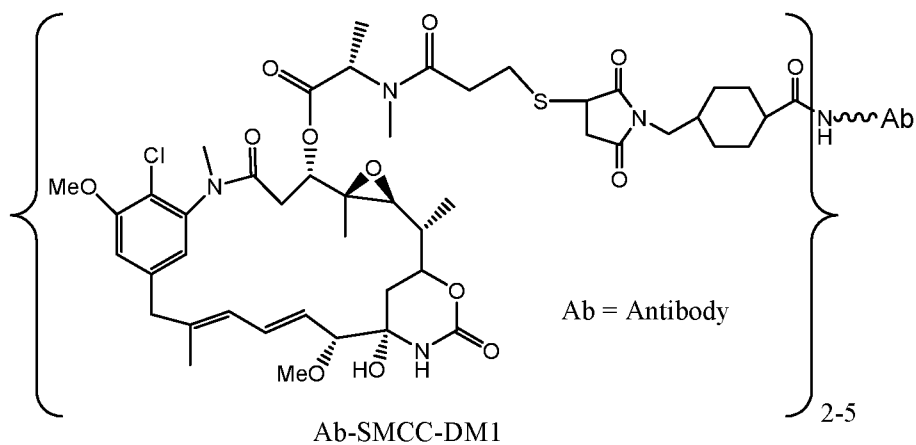
(II)

[0102] Another maytansinoid comprising a side chain that contains a sterically hindered thiol bond is $N^{2'}$ -deacetyl- $N^{2'}$ (4-mercapto-1-oxopentyl)-maytansine (termed DM3), represented by the following structural formula (III):

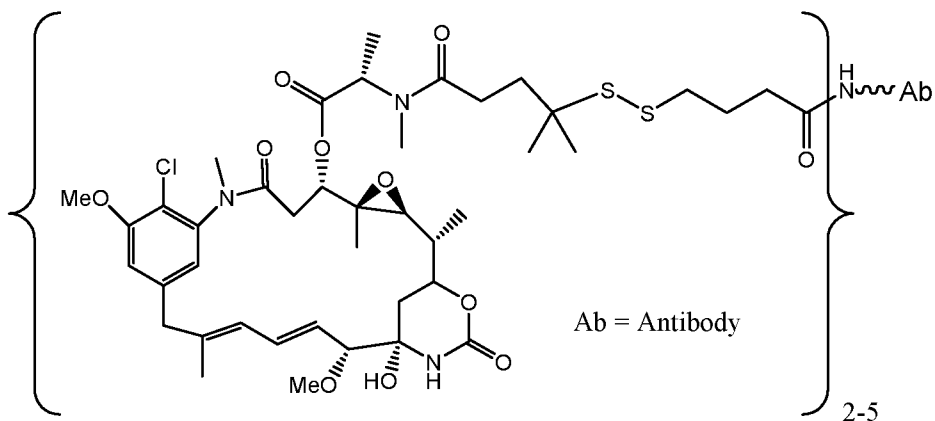


(III)

[0103] Structural representations of some conjugates are shown below:

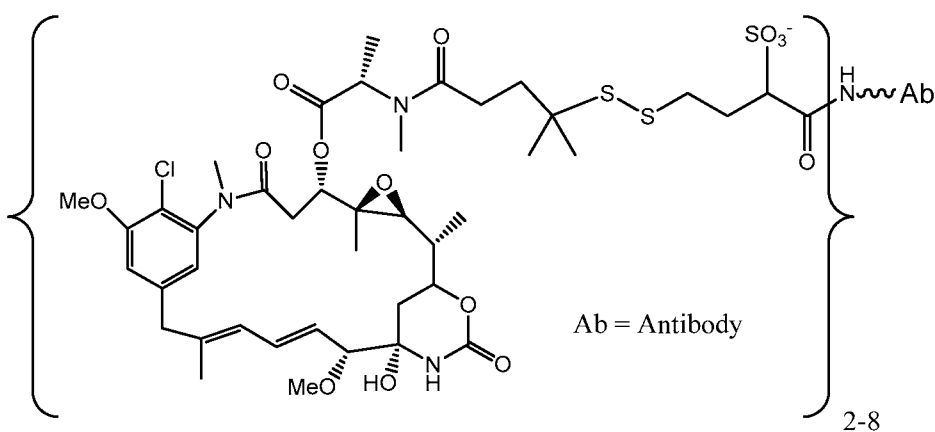


(IV)



Ab-SPDB-DM4

(V)



Ab-sulfo-SPDB-DM4

(VI)

[0104] Also included in the present invention are any stereoisomers and mixtures thereof for any compounds or conjugates depicted by any structures above.

[0105] The maytansinoid can be, e.g., $N^{2'}$ -deacetyl- $N^{2'}$ -(3-mercapto-1-oxopropyl)-maytansine (DM1).

[0106] The immunoconjugates can, according to some instances described herein, be internalized into cells. The immunoconjugate, therefore, can exert a therapeutic effect when it is taken up by, or internalized, by a CD37-expressing cell.

III. Anti-CD20 therapy

[0107] In certain instances, the methods described herein comprise administering an anti-CD37 immunoconjugate (e.g., Debio 1562) in combination with an anti-CD20 therapy.

[0108] In certain instances, the anti-CD20 therapy is rituximab, an antigen-binding fragment thereof, or a biosimilar thereof. In certain instances, the anti-CD20 therapy is ofatumumab, an antigen-binding fragment thereof, or a biosimilar thereof. In certain instances, the anti-CD20 therapy is obinutuzumab, an antigen-binding fragment thereof, or a

biosimilar thereof. In certain instances, the anti-CD20 therapy is veltuzumab an antigen-binding fragment thereof, or a biosimilar thereof.

[0109] In certain instances, the methods described herein comprise administering an anti-CD37 immunoconjugate (e.g., Debio 1562) in combination with rituximab. Rituximab is an anti-CD20 antibody marketed as Rituxan®. The variable heavy and variable light chain amino acid sequences of rituximab are provided in Table 7.

Table 7: Rituximab variable heavy chain and variable light chain amino acid sequences

Rituximab variable heavy chain	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSA (SEQ ID NO:13)
Rituximab variable light chain	QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWVFQKPGSSPKPWIYATSNLASGVPVRFSGSGSGTSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK (SEQ ID NO:14)

[0110] As used herein, the administration of rituximab “in combination” with an anti-CD37 immunoconjugate (e.g., Debio 1562) encompasses simultaneous or sequential administration of the rituximab and the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the rituximab and the anti-CD37 immunoconjugate (e.g., Debio 1562) are administered sequentially in separate pharmaceutical compositions, e.g., with the rituximab being administered after the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) on the same day as the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered.

[0111] Use of an anti-CD37 immunoconjugate (e.g., Debio 1562) in combination with rituximab can provide "synergy" and prove "synergistic", i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. This has been described in WO 2016/200676, which is herein incorporated by reference in its entirety. The combination of Debio 1562 and rituximab demonstrated synergistic pro-apoptotic activity in a panel of cell lines representative of diverse NHL subtypes, including activated B-cell like (ABC) and germinal center B-cell-like (GCB) DLBCL, CLL and MCL.

IV. Methods of administering pharmaceutical compositions comprising anti-CD37 immunoconjugates

[0112] The present disclosure relates to a weekly dosage regimen for administering an anti-CD37 immunoconjugate (e.g. Debio 1562) (optionally in combination with an anti-

CD20 therapy (e.g., rituximab)) to a human patient to treat cancer. The cancer can be, for example, a B-cell malignancy.

[0113] In certain instances, the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered once a week in a three-week cycle, for example, on Day 1, Day 8, and Day 15 of a 21-day cycle. Weekly administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) can maintain a constant and prolonged exposure of the CD37 antigen to Debio 1562. Weekly administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) can also limit the risk of safety issue (e.g. neutropenia) while maintaining the saturation of CD37 antigens on target cells. Rituximab can also be administered, for example every three weeks (e.g., on Day 1 of the 21-day cycle after the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered). Weekly administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) in combination with rituximab can prolong the synergistic effect with rituximab. Rituximab can also be administered once every four weeks (one month), once every two months, or once every three months.

[0114] Patients can be treated for at least two three-week (21-day) cycles. Patients can be treated for at least three three-week (21-day) cycles. Patients can be treated for at least four three-week (21-day) cycles. Patients can be treated for at least five three-week (21-day) cycles. Patients can be treated for at least six three-week (21-day) cycles.

[0115] Patients can be treated for one to six three-week (21-day) cycles. Patients can be treated for two to six three-week (21-day) cycles. Patients can be treated for three to six three-week (21-day) cycles. Patients can be treated for four to six three-week (21-day) cycles. Patients can be treated for five to six three-week (21-day) cycles.

[0116] In certain instances, 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0117] In certain instances, 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the

third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0118] In certain instances, 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0119] In certain instances, 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0120] In certain instances, 0.4 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0121] In certain instances, 0.4 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0122] In certain instances, 0.4 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.2 mg/kg of the anti-CD37

immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0123] In certain instances, 0.5 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.3 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0124] In certain instances, 0.5 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0125] In certain instances, 0.6 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the first week (e.g., on Day 1), 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the second week (e.g., on Day 8), and 0.2 mg/kg of the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered in the third week (e.g., on Day 15). Rituximab can also be administered in the first week (e.g., on Day 1 after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562)), at a dose, for example, of 375 mg/m².

[0126] In certain instances, the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered intravenously. In certain instances, the rituximab is administered intravenously. In certain instances, both the anti-CD37 immunoconjugate (e.g., Debio 1562) and the rituximab are administered intravenously (e.g., on the same day in separate compositions with the rituximab being administered after the anti-CD37 immunoconjugate (e.g., Debio 1562)).

[0127] In certain instances, after the anti-CD37 immunoconjugate is administered weekly in a 3-week cycle, the anti-CD37 immunoconjugate can be administered at a dose of 0.7 mg/kg once every three weeks. For example, the anti-CD37 immunoconjugate can be administered weekly in a single 3-week cycle and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in two consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in three consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in four consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in five consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in six consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in seven consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in eight consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in nine consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in ten consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in eleven consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in twelve consecutive 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks.

[0128] The anti-CD37 immunoconjugate can be administered weekly in at least one 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least two 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least three 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least four 3-week cycles and then

administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least five 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least six 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least seven 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least eight 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least nine 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least ten 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least eleven 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks. The anti-CD37 immunoconjugate can be administered weekly in at least twelve 3-week cycles and then administered at a dose of 0.7 mg/kg once every three weeks.

[0129] The anti-CD37 immunoconjugate can be administered weekly in one or more 3-week cycles until a favorable result (e.g., a complete response, a partial response, or stable disease) is observed and then administered at a dose of 0.7 mg/kg once every three weeks.

[0130] The present invention provides for methods of treating cancer in a human subject comprising administering a therapeutically effective amount of a CD37-binding agent to a subject (e.g., a subject in need of treatment). In certain embodiments, the cancer is a B-cell malignancy. In certain embodiments, the cancer is leukemia or lymphoma. In certain embodiments, the cancer is selected from the group consisting of B cell lymphomas, NHL, precursor B cell lymphoblastic leukemia/lymphoma and mature B cell neoplasms, B cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), small cell lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), low grade, intermediate-grade and high-grade (FL), cutaneous follicle center lymphoma, marginal zone B cell lymphoma, MALT type marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, splenic type marginal zone B cell lymphoma, hairy cell leukemia, diffuse large B cell lymphoma, Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant

lymphoproliferative disorder, Waldenstrom's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL). In certain embodiments, the cancer is selected from the group consisting of diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), unspecified NHL, MALT lymphoma, mantle cell lymphoma (MCL), Burkitt's lymphoma (BL), and chronic lymphocytic leukemia (CLL). In certain embodiments, the cancer is relapsed or refractory NHL.

[0131] In certain instances, the cancer is a diffuse large B-cell lymphoma (DLBCL). The DLBCL can be a relapsed DLBCL. The DLBCL can be a refractory (i.e. not responding to or showing disease progression after first line of treatment) DLBCL. In certain instances, the DLBCL is not a refractory DLBCL.

[0132] In certain instances, administration of the anti-CD37 immunoconjugate, optionally in combination with an anti-CD20 therapy, increases progression-free survival (PFS), disease-free survival (DFS), duration of response (DOR), overall survival (OS), complete responses (CR), partial responses (PR), or, stable diseases (SD).

[0133] In certain instances, the human subject has received at least one prior treatment regimen for the cancer. In certain instances, the human subject has received no more than six prior treatment regimens for the cancer. In certain instances, the human subject has received at least one prior treatment, but no more than six prior treatment regimens for the cancer. In certain instances, the human subject has already received treatment with an anti-CD20 therapy. In certain instances, the anti-CD20 therapy included treatment with an anti-CD20 antibody, such as rituximab.

[0134] As provided herein, anti-CD37 immunoconjugates can be administered in a pharmaceutical composition. In certain instances, a pharmaceutical composition comprises anti-CD37 immunoconjugates (e.g., Debio 1562) and a pharmaceutically acceptable vehicle. Accordingly, provided herein are methods of administering pharmaceutical compositions comprising anti-CD37 immunoconjugates (e.g., Debio 1562) thereof having the desired degree of purity in a physiologically acceptable carrier, excipient, or stabilizer (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed. (See, e.g., Gennaro, Remington: The Science and Practice of Pharmacy with Facts and Comparisons: Drugfacts Plus, 20th ed. (2003); Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippencott Williams and Wilkins (2004); Kibbe et al., Handbook of Pharmaceutical Excipients, 3rd ed., Pharmaceutical Press

(2000)). The compositions to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.*, sterile filtration membranes.

[0135] In certain instances, provided herein are methods of administering a pharmaceutical composition comprising anti-CD37 immunoconjugates (*e.g.*, Debio 1562), wherein the anti-CD37 immunoconjugates in the pharmaceutical composition comprise 1-10 maytansinoids per antibody or antigen-binding fragment thereof. In certain instances, the anti-CD37 immunoconjugates in the pharmaceutical composition comprise 2-8 maytansinoids per antibody or antigen-binding fragment thereof.

[0136] In certain instances, provided herein are methods of administering a pharmaceutical composition comprising anti-CD37 immunoconjugates (*e.g.*, Debio 1562), wherein the anti-CD37 immunoconjugates in the pharmaceutical composition comprise an average of 2-6 maytansinoids per antibody or antigen-binding fragment thereof. In certain instances, the anti-CD37 immunoconjugates in the pharmaceutical composition comprise an average of 2-5 maytansinoids per antibody or antigen-binding fragment thereof. In certain instances, the anti-CD37 immunoconjugates in the pharmaceutical composition comprise an average of 3-4 maytansinoids per antibody or antigen-binding fragment thereof. In certain instances, the anti-CD37 immunoconjugates in the pharmaceutical composition comprise an average of 3.5 maytansinoids per antibody or antigen-binding fragment thereof.

[0137] In certain instances, the methods further comprise administering a corticosteroid to the patient. In certain instances, the corticosteroid can be selected from the group consisting of prednisone, prednisolone, methylprednisolone, beclomethasone, betamethasone, dexamethasone, fludrocortisone, hydrocortisone, and triamcinolone. In certain instances, the corticosteroid can be dexamethasone. In certain instances, the corticosteroid can be administered as a pre-treatment, *i.e.*, prior to the administration of the anti-CD37 immunoconjugates (*e.g.*, Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugates (*e.g.*, Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugates (*e.g.*, Debio 1562) and at least one additional time from about one day after to about five days after the administration of the anti-CD37 immunoconjugates (*e.g.*, Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugates (*e.g.*, Debio 1562) and at least one additional time from about one day after to about four days after the administration of the anti-CD37 immunoconjugates (*e.g.*, Debio 1562). In certain instances,

the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugates (e.g., Debio 1562) and at least one additional time from about one day after to about three days after the administration of the anti-CD37 immunoconjugates (e.g., Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and at least one additional time from about one day after to about two days after the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and at least one additional time from about two days after to about five days after the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and at least one additional time from about two days after to about four days after the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and at least one additional time from about two days after to about three days after the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and at about two days after and at about three days after the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the corticosteroid can be administered during the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and at about two days after and at about three days after the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the corticosteroid can be administered by peri-infusion. In certain instances, the corticosteroid is administered 30 to 60 minutes prior to administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the corticosteroid is administered 30 to 60 minutes prior to administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and on at least one additional time on days 1 to 3 following administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). Pre-infusion intravenous steroid administration was found to eliminate hematological adverse effects. In certain instances, the corticosteroid is administered on at least one of days 2 and 3 following infusion.

[0138] In certain instances the corticosteroid is administered by IV. In certain instances, the steroid is administered orally.

- [0139] In certain instances, the corticosteroid is administered intravenously 30 to 60 minutes prior to the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and the corticosteroid is administered orally on days 2 and 3 of a 3-week anti-CD37 immunoconjugate administration cycle.
- [0140] In certain instances, the corticosteroid to be administered can be dexamethasone. In certain instances, the corticosteroid to be administered can be methylprednisolone. In certain instances, the corticosteroid to be administered can be prednisolone.
- [0141] In certain instances, from about 5 mg to about 10 mg dexamethasone is administered. In certain instances, from about 8 mg to about 10 mg dexamethasone is administered. In certain instances, about 10 mg dexamethasone is administered. In certain instances, about 8 mg dexamethasone is administered. In certain instances about 10 mg dexamethasone is administered by IV 30 to 60 minutes prior to administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances about 10 mg dexamethasone is administered by IV at the time of administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and again about 1 to about 5 days after administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the corticosteroid is administered by IV 30 to 60 minutes prior to administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and one dose of 8 mg of dexamethasone is delivered orally on days 2 and 3 following infusion.
- [0142] In certain instances, 10 mg dexamethasone is administered intravenously 30 to 60 minutes prior to the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562) and 8 mg dexamethasone is administered orally on days 2 and 3 of a 3-week anti-CD37 immunoconjugate administration cycle.
- [0143] In certain instances, the methods further comprise administering a growth factor to the patient. Methods of administering white blood cell growth factors are reviewed, for example, in Smith *et al.*, *J. Clin. Oncol.* 24: 3187-3205 (2006), which is herein incorporated by reference in its entirety. Growth factor treatment may decrease the likelihood of neutropenias. In certain instances, the growth factor can be granulocyte colony-stimulating factor (G-CSF). In certain instances, the growth factor can be granulocyte-macrophage colony-stimulating factor (GM-CSF). In certain instances, the growth factor can be macrophage colony-stimulating factor (M-CSF). In certain instances, the growth factor can be filgrastim. In certain instances, the growth factor can be pegylated, e.g., pegylated G-CSF. In certain instances, the growth factor can be pegfilgrastim, marketed as Neulasta®.

[0144] In certain instances, the growth factor can be administered as a pre-treatment, i.e., prior to the administration of the anti-CD37 immunoconjugate (e.g., Debio 1562). In certain instances, the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered on a 3-week (about 21-day) cycle and the growth factor can be administered at any point during the 3-week (about 21-day) cycle. In certain instances, the anti-CD37 immunoconjugate (e.g., Debio 1562) is administered on a 3-week (about 21-day) cycle and the growth factor can be administered early to middle cycle of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 1 to about day 21 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 1 to about day 20 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 1 to about day 19 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 1 to about day 18 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 1 to about day 17 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 1 to about day 16 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 1 to about day 14 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 1 to about day 12 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day about 15 to about day 21 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from about day 3 to about day 10 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered at least twice from about day 3 to about day 10 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered at least three times from about day 3 to about day 10 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from about day 4 to about day 10 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day from day 5 to day 8 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on at least one day selected from day 5, day 6, and day 8 of the 3-week (about 21-day) cycle. In certain instances, the growth factor can be administered on days 5, 6, and 8 of the 3-week (about 21-day) cycle.

- [0145] In certain instances, G-CSF is administered at a dose of about 1 $\mu\text{g}/\text{kg}$ body weight to about 15 $\mu\text{g}/\text{kg}$ body weight, per day that the growth factor is administered. In certain instances, G-CSF is administered at a dose of about 5 $\mu\text{g}/\text{kg}/\text{day}$. In certain instances, G-CSF is administered at a dose of about 10 $\mu\text{g}/\text{kg}/\text{day}$.
- [0146] In certain instances, G-CSF is administered at a dose of about 200 μg to about 600 μg per day. In certain instances, G-CSF is administered at a dose of about 300 μg to about 500 μg per day. In certain instances, G-CSF is administered at a dose of about 300 μg to about 480 μg per day. In certain instances, G-CSF is administered at a dose of about 300 $\mu\text{g}/\text{day}$. In certain instances, G-CSF is administered at a dose of about 400 $\mu\text{g}/\text{day}$. In certain instances, G-CSF is administered at a dose of about 480 $\mu\text{g}/\text{day}$. In certain instances, G-CSF is administered at a dose of about 500 $\mu\text{g}/\text{day}$.
- [0147] In certain instances, GM-CSF is administered at a dose of about 100 $\mu\text{g}/\text{m}^2$ to about 500 $\mu\text{g}/\text{m}^2$, per day that the growth factor is administered. In certain instances, GM-CSF is administered at a dose of about 250 $\mu\text{g}/\text{m}^2/\text{day}$.
- [0148] In certain instances, GM-CSF is administered at a dose of about 200 μg to about 600 μg per day. In certain instances, GM-CSF is administered at a dose of about 300 μg to about 500 μg per day. In certain instances, GM-CSF is administered at a dose of about 300 μg to about 480 μg per day. In certain instances, GM-CSF is administered at a dose of about 300 $\mu\text{g}/\text{day}$. In certain instances, G-CSF is administered at a dose of about 400 $\mu\text{g}/\text{day}$. In certain instances, GM-CSF is administered at a dose of about 480 $\mu\text{g}/\text{day}$. In certain instances, GM-CSF is administered at a dose of about 500 $\mu\text{g}/\text{day}$.
- [0149] In certain instances, pegfilgrastim is administered at a dose of about 6 mg per cycle. In certain instances, pegfilgrastim is administered at a dose of about 10 $\mu\text{g}/\text{kg}$ to about 500 $\mu\text{g}/\text{kg}$ per cycle. In certain instances, pegfilgrastim is administered at a dose of about 10 $\mu\text{g}/\text{kg}$ to about 400 $\mu\text{g}/\text{kg}$ per cycle. In certain instances, pegfilgrastim is administered at a dose of about 50 $\mu\text{g}/\text{kg}$ to about 300 $\mu\text{g}/\text{kg}$ per cycle. In certain instances, pegfilgrastim is administered at a dose of about 50 $\mu\text{g}/\text{kg}$ to about 200 $\mu\text{g}/\text{kg}$ per cycle. In certain instances, pegfilgrastim is administered at a dose of about 50 $\mu\text{g}/\text{kg}$ to about 150 $\mu\text{g}/\text{kg}$ per cycle. In certain instances, pegfilgrastim is administered at a dose of about 100 $\mu\text{g}/\text{kg}$ per cycle.
- [0150] In certain instances, administration of corticosteroids and/or G-CSF to the dosing protocol allows a higher dose to be administered. In certain instances, patients stay on the treatment longer due to the administration of corticosteroids and/or G-CSF. In certain instances, less neutropenia is observed due to the administration of corticosteroids and/or G-

CSF. In certain instances, more clinical benefits are observed due to the administration of corticosteroids and/or G-CSF.

[0151] Embodiments of the present disclosure can be further defined by reference to the following non-limiting examples, which describe in detail preparation of certain antibodies of the present disclosure and methods for using antibodies of the present disclosure. It will be apparent to those skilled in the art that many modifications, both to materials and methods, can be practiced without departing from the scope of the present disclosure.

Examples

[0152] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

Example 1: Design of a Weekly Dosing Schedule

[0153] A weekly dosing schedule of Debio 1562 was designed to improve the safety profile and optimize the duration of tumor exposure to Debio 1562 in order to enhance efficacy.

[0154] Based on all the pharmacokinetics (PK), pharmacodynamics (PD) and safety data gathered in previous studies, a modeling algorithm was designed that allows dosing schedule simulations. Simulation of Debio 1562 drug concentrations in patients at various weekly dosing schedules as compared to administration every three weeks are shown in Figures 1-5. Each scenario was simulated 1000 times, and simulations were summarized as mean and 90% prediction intervals. Simulations were performed for 6 treatment cycles. Compared with the 3-weekly schedule, the simulations show that these weekly dosing schedules of Debio 1562 should prolong exposure of CD37 receptors to Debio 1562 over each three-week cycle and decrease the C_{max} (if C_{max} is too high, it may be associated with toxicities).

[0155] As an example of such weekly dosage regimen, 0.4/0.2/0.2 mg/kg, on week 1, 2, and 3 of each cycle respectively (cumulative 0.8 mg/kg over three weeks) would be expected to optimize the benefit-risk of Debio 1562 for DLBCL patients.

- [0156] With regard to safety, the total dose over three weeks would not exceed 1mg/kg, which was previously determined as the maximum tolerated dose (MTD) for Debio 1562 (without G-CSF) in Phase 1. It is also worth noting that the majority of patients experienced no decrease in neutrophil count during single Q3W dosing with 0.2-0.4 mg/kg dose in the Phase 1 study. As such, a more frequent QW dosing schedule with 0.4/0.2/0.2 mg/kg (combined with rituximab Q3W at 375 mg/m²) should not increase the risk of neutropenia.
- [0157] With regard to efficacy: in the monotherapy Phase 1 study, “theoretical” Receptor Occupancy (RO) values derived from observed C_{max} showed that even at low dose levels, a saturation of >> 95% of the CD37 sites was expected (between 96.2% and 99.9% on average). Therefore, a 0.4 mg/kg loading dose followed by 2 weekly doses of 0.2 mg/kg is expected to provide adequate target saturation across a 3-weeks cycle.
- [0158] As such, more frequent dosing is expected to prolong the synergistic effect and effector-mediated activities of Debio 1562 combined with 3-weekly (Q3W) dosing of rituximab at 375 mg/m², resulting in improved efficacy.

Example 2: Study of Debio 1562 (QW) in combination with rituximab in patients with relapsed or refractory DLBCL

- [0159] A Phase 2 clinical trial was initiated and is being conducted including the weekly Debio 1562 dosing schedule developed in Example 1 (in combination with Q3W rituximab at 375 mg/m²) to confirm the efficacy and tolerability of Debio 1562 in combination with rituximab in patients with relapsed and/or refractory diffuse large B-cell lymphoma (DLBCL) and other forms of Non-Hodgkin’s Lymphoma (NCT 02564744). The trial includes 3 parts. Part 1 is a safety run-in in which about 15 patients with a diagnosis of R/R DLBCL, Follicular Lymphoma (FL), Marginal Zone Lymphoma/Mucosa-associated lymphoid tissue (MZL/ MALT), Mantle Cell Lymphoma (MCL) or other NHL subtypes with the Sponsor’s approval are enrolled. Part 2 is an initial assessment of safety and efficacy of administering Debio 1562 once every three weeks (Q3W) and once every week (QW). About 30 patients with a diagnosis of relapsed DLBCL are enrolled. Part 3 is an expansion phase in which about 30 additional patients with a diagnosis of relapsed DLBCL are enrolled.

Study Design

[0160] In Part 1, the safety run-in, patients with DLBCL, FL, MCL, MZL/MALT or other NHL subtypes participate. At least six DLBCL and six FL NHL patients are enrolled. Patients are given Debio 1562 and rituximab on the same day (i.e., Day 1) once every three weeks (Q3W) intravenously (IV). Debio 1562 is given at a dose of 0.7 mg/kg, followed by 375 mg/m² of rituximab. Following review of safety and PK data, the Q3W dosing schedule will continue with the 0.7 mg/kg dose of IMGN or an alternate higher (1.0 mg/kg) or lower dose of Debio 1562.

[0161] In Part 2, the initial assessment of safety and efficacy of Q3W and QW dosing regimens, patients with relapsed DLBCL are enrolled into two parallel cohorts according to the dosing regimen of Debio 1562: cohort A (21-day treatment cycle with a Q3W dosing schedule) and cohort B (21-day treatment cycle with a once weekly [QW] dosing schedule). Patients in cohort A receive Debio 1562 and rituximab IV on the same day (Day 1) on a Q3W dosing schedule. Debio 1562 is given at a dose of 0.7 mg/kg (followed by 375 mg/m² of rituximab). Cohort B receives a QW dosing schedule of Debio 1562: 0.4, 0.2, and 0.2 mg/kg of Debio 1562 is administered IV to patients on Day 1, Day 8 and Day 15 of a 21-day treatment cycle, respectively. Rituximab is administered IV at a dose of 375 mg/m² on Day 1 of each treatment cycle (following IMGN529). Patients in both cohorts will be treated for a maximum of six 21-day cycles.

[0162] In Part 3, the expansion, additional relapsed DLBCL patients are enrolled. Patients are treated with six 21-day cycles of Q3W and/or QW Debio 1562 along with rituximab.

[0163] In all parts, anti-tumor activity is assessed by the Lugano Classification.

[0164] In all parts, patients receive steroid prophylaxis. Prior to receiving Debio 1562 and rituximab, patients are given dexamethasone IV at 8 mg (or equivalent), acetaminophen PO or IV 325 – 650 mg, and an antihistamine (e.g. 25-50 mg diphenhydramine or equivalent) approximately 30-60 minutes prior to the Debio 1562 infusion. Patients are also instructed to take oral dexamethasone at 8 mg/day on Days 2 and 3, following the infusion. If needed, patients are also treated with granulocyte colony-stimulating factor support to mitigate neutropenia.

Patients

[0165] Adult (\geq 18 years) patients have histopathologically confirmed relapsed and/or refractory DLBCL, FL, MZL/MALT, MCL, or other NHL subtypes according to the World

Health Organization (WHO) classification 2008. Patients have received no more than six prior treatment regimens and have an evaluable or measurable disease in accordance with the International Working Group Guidelines for Lymphoma. Patients have an ECOG Performance Status of 0-2.

[0166] For Part 2 and Part 3 of the study, patients have histopathologically and clinically confirmed diagnosis of relapsed DLBCL. Patients are considered to have a relapsed disease if they show a duration of response of at least 24 weeks after their first line of therapy.

[0167] No patients have CLL or SLL. No patients received prior anti-CD36 therapy or anti-CD20 monoclonal antibody therapy within 14 days of participation.

Safety and Pharmacokinetic Evaluation

[0168] Adverse events are monitored continuously throughout the study. Adverse events include any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. PK parameters that are evaluated include, but are not limited to: C_{max} , T_{max} , Terminal half-life ($t_{1/2}$), V_{ss} , CL, AUC_{0-t} , AUC_{inf} . These will be derived from plasma concentrations of Debio 1562, total and/or naked humanized CD37 antibody (huCD37-3), DM1 (free and bound), as well as potential catabolites, and total rituximab.

Efficacy Evaluation

[0169] The best Overall Response (OR) is determined for each evaluable patient as CR, PR, stable disease (SD), or relapsed disease/PD. The overall response rate (ORR) is tabulated by dose cohort as well as the dose at which the response occurred along with the 95% confidence interval (CI). To meet the definition of response-evaluable, patients must have undergone radiographic assessment at baseline, received at least one dose of Debio 1562 and rituximab, and must have had at least one post-dose tumor assessment. Overall survival (OS) at one year is analyzed using the Kaplan-Meier method. Median OS and 95% CI (if feasible). The duration of response (DoR) is estimated for all evaluable patients who achieve an objective response (PR or CR). Progression free survival (PFS) at six months and one year are analyzed using the Kaplan-Meier method.

[0170] The exposure, C_{max} , efficacy and safety of the QW dosing schedule are compared to the Q3W schedule.

Example 3: Study of Debio 1562 Pharmacokinetics and Pharmacodynamics in Q3W and QW dosing regimens

- [0171] The pharmacokinetics and pharmacodynamics studies were conducted with subjects from Cohorts A and B in Example 2. Blood was taken at several time points during the cycle and used for pharmacokinetic measurements.
- [0172] The preliminary results revealed that the rate of exposure (C_{max}) is approximately dose proportional between the Q3W dosing regimen and the QW dosing regimen (Figure 6). Surprisingly though, the extent of exposure over a three-week cycle in the plasma as characterized by the area under the curve (AUC) for the QW dosing regimen was similar to that of the Q3W dosing regimen (Figure 6). This was surprising because, even if the total dose administered over three weeks is approximately the same (0.7 mg/kg for Q3W vs. $0.4 + 0.2 + 0.2 = 0.8$ mg/kg for QW), previous reports found that clearance of Debio 1562 was substantially higher at low doses such as 0.4 mg/kg and 0.2 mg/kg, and the half-life was lower (*see Stathis et al., Invest New Drugs 36: 869-876 (2018)*). Nonetheless, the administration of such lower doses as per the Cohort B schedule did not result in a substantial decrease in exposure (AUC). In addition, the C_{last} (last Debio 1562 concentration measured during a cycle before the next Debio 1562 administration) revealed that the QW dosing regimen allowed to maintain a higher Debio 1562 concentration throughout the 3-week cycle than the Q3W dosing regimen (Figure 6).
- [0173] This data demonstrated that fractionating the once every 3 week dose into three weekly doses had an exposure benefit. Although the extent of exposure (AUC) is maintained in both dosing regimens, the higher C_{last} in the QW regimen indicates that the QW dosing regimen maintains a higher average concentration pressure on tumor cells throughout the 3-week cycle. This is expected to improve the efficacy of Debio 1562, e.g., when combined with an anti-CD20 therapy. Moreover, the C_{max} was lower in the QW regimen than the Q3W regimen, indicating that the QW administration would not increase the risk of adverse effects.
- [0174] The receptor occupancy (RO) of Debio 1562 was measured on CD19+ B, CD3+ T, and CD56+ NK cells on samples obtained from subjects in Cohort A and B. Because of the rapid depletion of B cells, RO evaluation of this specific lymphocyte population was not possible. In Cohorts A and B, greater than 80% of the CD37 molecule expressed on CD3+ T and CD56+ NK lymphocyte populations are rapidly C1D1 (cycle 1-dose 1) occupied by

Debio 1562 after administration. The maximum RO observed at C1D2 (cycle 1-dose 2) and C1D3 was greater than 90% for both cohorts. No RO was observed in samples collected just before the re-administration of Debio 1562 in cycle 2 and cycle 3 in the patients analyzed. Thus, a rapid (C1D1) and complete (>80%) RO was observed in both cohorts without any obvious differences between them. Figure 7 shows the preliminary individual RO measurement at cycles 1, 2, and 3 in CD3+ cells.

[0175] The pharmacokinetic and RO data suggest that fractionating the Q3W dose into weekly administrations (QW) would not jeopardize either the exposure or the target attainment. A weekly administration would maintain "exposure pressure" on CD37-bearing cells during the 3-week cycle, e.g., when combined with rituximab.

[0176] Pharmacokinetic exposure was also compared in patients with varying responses to Debio 1562 (Figure 8). The preliminary response rate appeared to be higher in the QW regimen. Exposure (AUC) in the complete responders (CR) of the QW regimen was higher than in the CRs of the Q3W regimen. In parallel, safety was comparable in the QW regimen and the Q3W regimen.

[0177] In sum, these results demonstrate that fractionated administration of Debio 1562 once weekly in a three-week cycle results in a lower rate of exposure (C_{max}), a similar extent of exposure (AUC), and an increased concentration pressure on tumor cells (C_{last}) per three-week cycle as compared to administration once every three weeks.

[0178] It is to be appreciated that the Detailed Description section, and not the Summary and Abstract sections, is intended to be used to interpret the claims. The Summary and Abstract sections sets forth one or more, but not all, exemplary embodiments of the present invention as contemplated by the inventor(s), and thus, are not intended to limit the present invention and the appended claims in any way.

[0179] The present invention has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

[0180] The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the

art, readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0181] The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method for treating a cancer in a human patient comprising administering to the patient a pharmaceutical composition comprising an anti-CD37 immunoconjugate once a week in a three-week cycle, wherein:
 - a) 0.4 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week;
 - b) 0.2 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week;
 - c) 0.3 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg are administered in the second week, and 0.3 mg/kg are administered in the third week;
 - d) 0.3 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week;
 - e) 0.3 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week;
 - f) 0.4 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg are administered in the second week, and 0.3 mg/kg are administered in the third week;
 - g) 0.4 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week;
 - h) 0.5 mg/kg of the immunoconjugate are administered in the first week, 0.3 mg/kg is administered in the second week, and 0.2 mg/kg are administered in the third week;
 - i) 0.5 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week; or
 - j) 0.6 mg/kg of the immunoconjugate are administered in the first week, 0.2 mg/kg are administered in the second week, and 0.2 mg/kg are administered in the third week;wherein the immunoconjugate comprises (i) an antibody or antigen-binding fragment thereof comprising a VH-CDR1 comprising the amino acid sequence of SEQ ID NO:2, a

VH-CDR2 comprising the amino acid sequence of SEQ ID NO:3, a VH-CDR3 comprising the amino acid sequence of SEQ ID NO:4, a VL-CDR1 comprising the amino acid sequence of SEQ ID NO:5, a VL-CDR2 comprising the amino acid sequence of SEQ ID NO:6, and a VL-CDR3 comprising the amino acid sequence of SEQ ID NO:7 and (ii) a maytansinoid.

2. The method of claim 1, wherein the antibody or antigen-binding fragment comprises a variable heavy chain comprising the amino acid sequence of SEQ ID NO:8.
3. The method of claim 1 or 2, wherein the antibody or antigen-binding fragment thereof comprises a variable light chain comprising the amino acid sequence of SEQ ID NO:10.
4. The method of any one of claims 1-3, wherein the antibody or antigen-binding fragment comprises a full length heavy chain comprising the amino acid sequence of SEQ ID NO:11.
5. The method of any one of claims 1-4, wherein the antibody or antigen-binding fragment comprises a full length light chain comprising the amino acid sequence of SEQ ID NO:12.
6. The method of claim 1, wherein the antibody comprises a light chain comprising the same amino acid sequence as the light chain encoded by the phuCD37-3LC plasmid deposited as ATCC deposit PTA-10722 and a heavy chain comprising the same amino acid sequence as the heavy chain encoded by the phuCD37-3HCv1.0 deposited as ATCC deposit PTA-10723.
7. The method of any one of claims 1-6, wherein the maytansinoid is DM1.
8. The method of any one of claims 1-7, wherein the maytansinoid is linked to the antibody or antigen-binding fragment by an SMCC linker.
9. The method of claim 1, wherein the antibody comprises a full length heavy chain comprising the amino acid sequence of SEQ ID NO:11 and a full length light chain comprising the amino acid sequence of SEQ ID NO:12, wherein the maytansinoid is DM1, and wherein the DM1 is linked to the antibody by an SMCC linker.

10. The method of any one of claims 1-9, wherein the immunoconjugate comprises 1-10 maytansinoids per antibody.
11. The method of any one of claims 1-9, wherein the pharmaceutical composition comprises at least two of the immunoconjugates and the immunoconjugates comprise an average of 3 to 4 maytansinoids per antibody.
12. The method of any one of claims 1-9, wherein the pharmaceutical composition comprises at least two of the immunoconjugates and the immunoconjugates comprise an average of 3.5 maytansinoids per antibody.
13. The method of any one of claims 1-12, wherein the immunoconjugate is administered for six three-week cycles.
14. The method of any one of claims 1-13 wherein the immunoconjugate is administered intravenously.
15. The method of any one of claims 1-14, wherein the immunoconjugate is administered in combination with an anti-CD20 therapy.
16. The method of claim 15, wherein the anti-CD20 therapy and the immunoconjugate are administered in separate pharmaceutical compositions.
17. The method of claim 15 or 16, wherein the anti-CD20 therapy is rituximab.
18. The method of claim 17, wherein 375 mg/m^2 of the rituximab is administered.
19. The method of any one of claims 17-18, wherein the rituximab is administered once every three weeks.
20. The method of any one of claims 17-19, wherein the rituximab is administered on day one of the three-week cycle.
21. The method of any one of claims 17-20, wherein the immunoconjugate and the rituximab are administered on the same day.
22. The method of any one of claims 17-19, wherein the rituximab is administered after the immunoconjugate is administered.

23. The method of any one of claims 17-22, wherein the rituximab is administered for six three-week cycles.
24. The method of any one of claims 17-22, wherein the rituximab is administered once every four weeks (one month), once every two months, or once every three months.
25. The method of claim 15 or 16, wherein the anti-CD20 therapy is an antigen-binding fragment of rituximab or a biosimilar of rituximab.
26. The method of claim 15 or 16, wherein the anti-CD20 therapy is ofatumumab, obinutuzumab, veltuzumab, an antigen-binding fragment of ofatumumab, obinutuzumab, or veltuzumab, or a biosimilar of ofatumumab, obinutuzumab, or veltuzumab .
27. The method of claim 1, wherein the pharmaceutical composition comprises at least two of the immunoconjugates and the immunoconjugates comprise an average of 3 to 4 maytansinoids per antibody wherein the antibody comprises a full length heavy chain comprising the amino acid sequence of SEQ ID NO:11 and a full length light chain comprising the amino acid sequence of SEQ ID NO:12, wherein the maytansinoid is DM1, and wherein the DM1 is linked to the antibody by an SMCC linker, wherein the immunoconjugate is administered in combination with 375 mg/m² of rituximab administered once every three weeks on day one of the three-week cycle after administration of the immunoconjugate.
28. The method of any one of claims 1-27, further comprising administering a corticosteroid to the patient.
29. The method of claim 28, wherein the corticosteroid is administered prior to the administration of the immunoconjugate.
30. The method of claim 29, wherein the corticosteroid is administered from about 30 to about 60 minutes prior to administration of the immunoconjugate.
31. The method of any one of claims 28-30, wherein the immunoconjugate is administered intravenously, and the corticosteroid is administered peri-infusionally.

32. The method of any one of claims 28-31, wherein the corticosteroid is administered after the administration of the immunoconjugate.
33. The method of claim 32, wherein the corticosteroid is administered from about one day to about four days after administration of the immunoconjugate.
34. The method of claim 32, wherein the corticosteroid is administered on days 2 and 3 following the administration of the immunoconjugate.
35. The method of any one of claims 28-34, wherein the corticosteroid is selected from the group consisting of prednisone, prednisolone, methylprednisolone, beclamethasone, betamethasone, dexamethasone, fludrocortisone, hydrocortisone, and triamcinolone.
36. The method of claim 35, wherein the corticosteroid is dexamethasone.
37. The method of any one of claims 1-36 further comprising administering a growth factor to the patient.
38. The method of claim 37, wherein the growth factor is selected from the group consisting of granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), filgrastim, and pegfilgrastim.
39. The method of claim 38, wherein the growth factor is G-CSF.
40. The method of any one of claims 1-39, wherein the cancer is a B cell malignancy.
41. The method of any one of claims 1-39, wherein the cancer is leukemia or lymphoma.
42. The method of any one of claims 1-39, wherein the cancer is a Non-Hodgkin's lymphoma (NHL).
43. The method of any one of claims 1-39, wherein the cancer is diffuse large B-cell lymphoma (DLBCL).
44. The method of claim 42 or 43, wherein the NHL is relapsed NHL or the DLBCL is relapsed DLBCL.

45. The method of claim 42 or 43, wherein the NHL is refractory NHL or the DLBCL is refractory DLBCL.
46. The method of any one of claims 1-39, wherein the cancer is selected from the group consisting of relapsed and/or refractory DLBCL, Follicular Lymphoma (FL), Marginal Zone Lymphoma/Mucosa-associated lymphoid tissue (MZL/MALT), or Mantle Cell Lymphoma (MCL).
47. The method of any one of claims 1-39, wherein the cancer is selected from the group consisting of precursor B-cell lymphoblastic leukemia/lymphoma and mature B-cell neoplasms, such as B-cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), including low-grade, intermediate-grade and high-grade FL, cutaneous follicle center lymphoma, marginal zone B-cell lymphoma (MALT type, nodal and splenic type), hairy cell leukemia, diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant lymphoproliferative disorder, Waldenstrom's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL).
48. The method of any one of claims 1-47, wherein the cancer expresses CD37.
49. The method of any one of claims 1-48, wherein the weekly administration of the anti-CD37 immunoconjugate maintains exposure over three weeks.
50. The method of any one of claims 1-49, wherein the weekly administration of the anti-CD37 immunoconjugate limits neutropenia.
51. The method of any one of claims 1-50, wherein the anti-CD37 immunoconjugate is administered once a week in a three-week cycle for at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, or at least twelve three-week cycles.
52. The method of claim 51, further comprising administering the anti-CD37 immunoconjugate at a dose of 0.7 mg/kg once every three weeks after the at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight,

at least nine, at least ten, at least eleven or at least twelve three-week cycles of weekly administration.

53. The method of any one of claims 1-51, wherein the anti-CD37 immunoconjugate is administered once a week in a three-week cycle until a complete response, a partial response, or stable disease is observed, and then the anti-CD37 immunoconjugate is administered at a dose of 0.7 mg/kg once every three weeks.

Figure 1

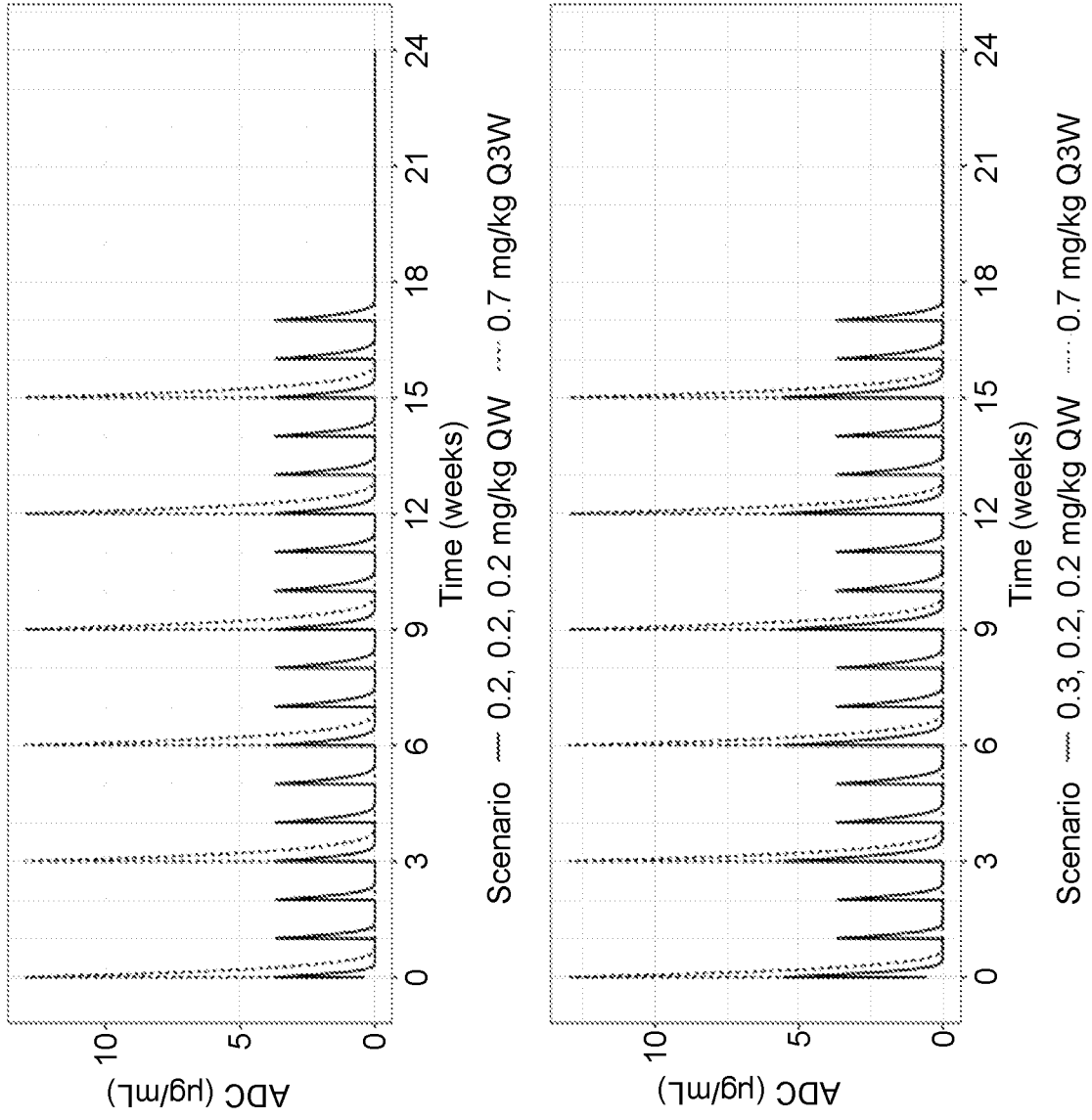


Figure 2

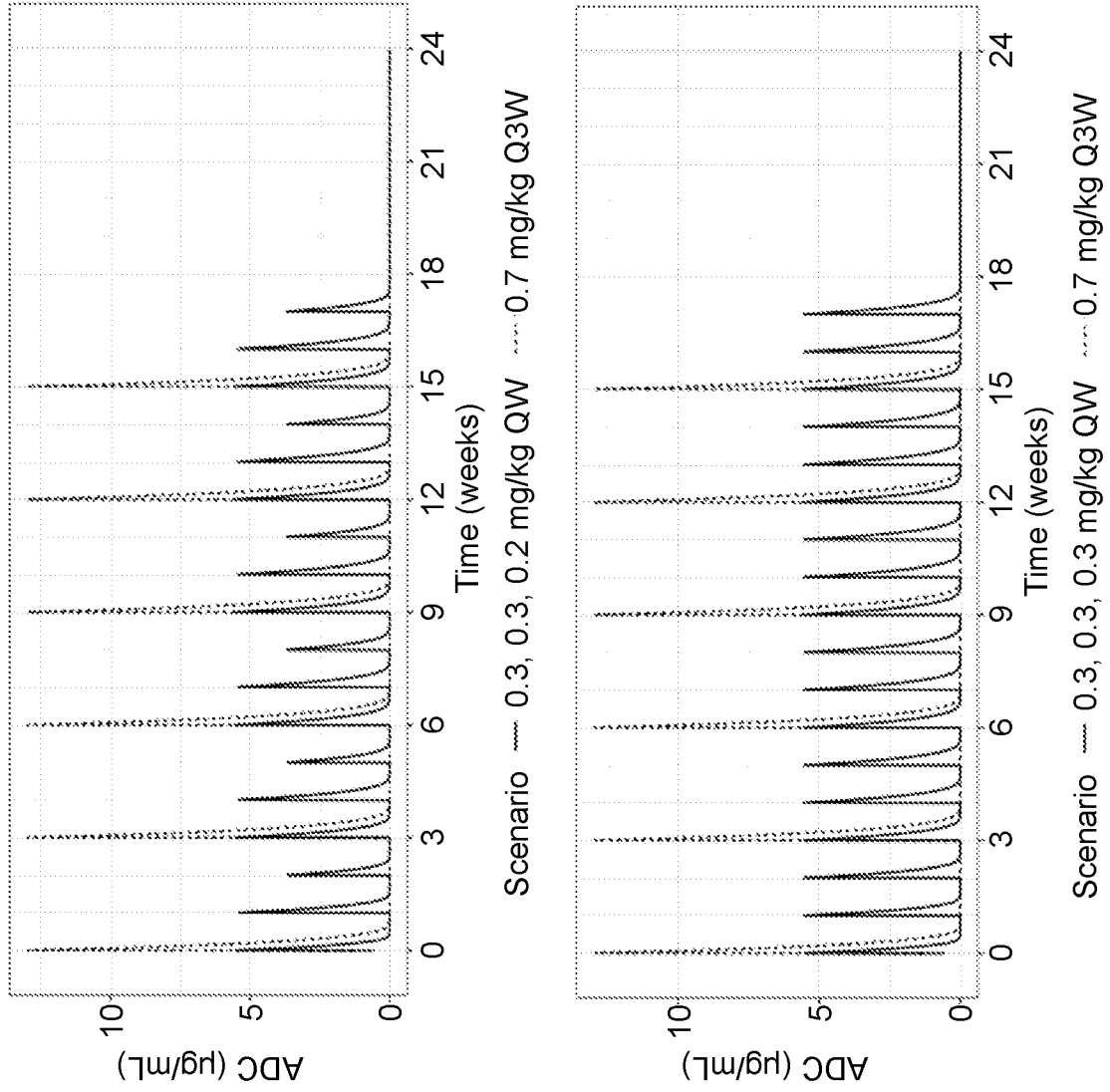


Figure 3

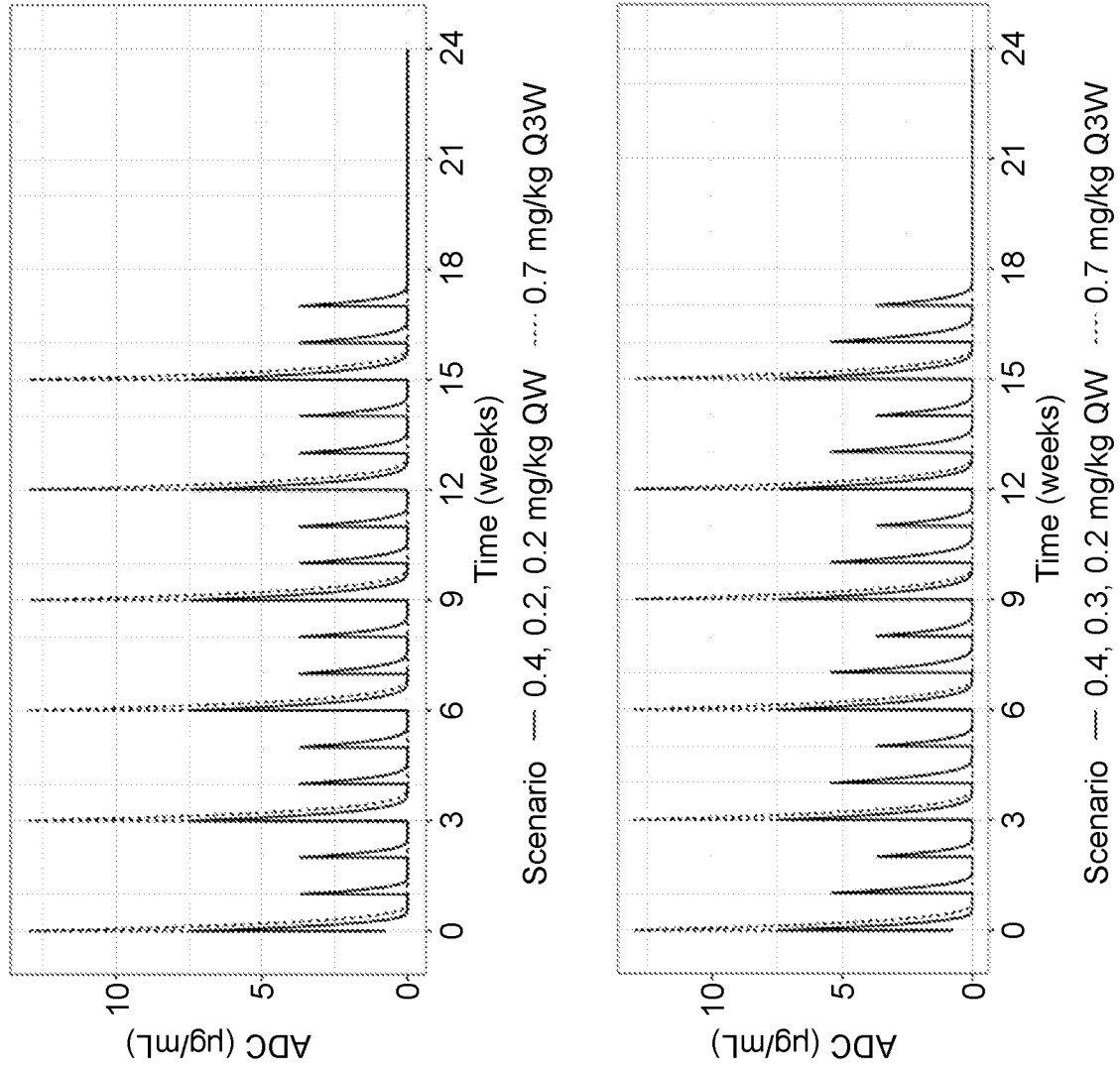


Figure 4

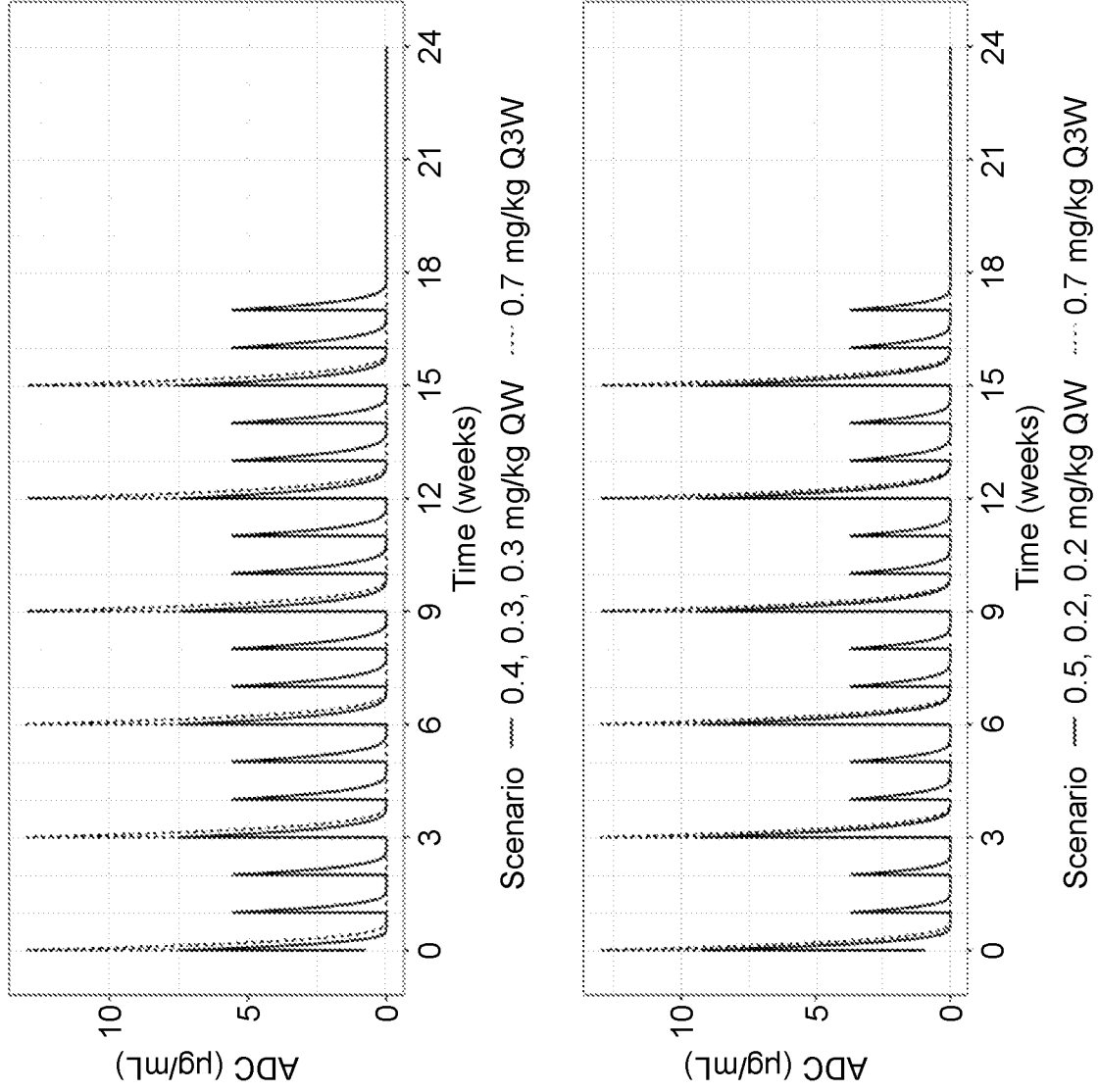
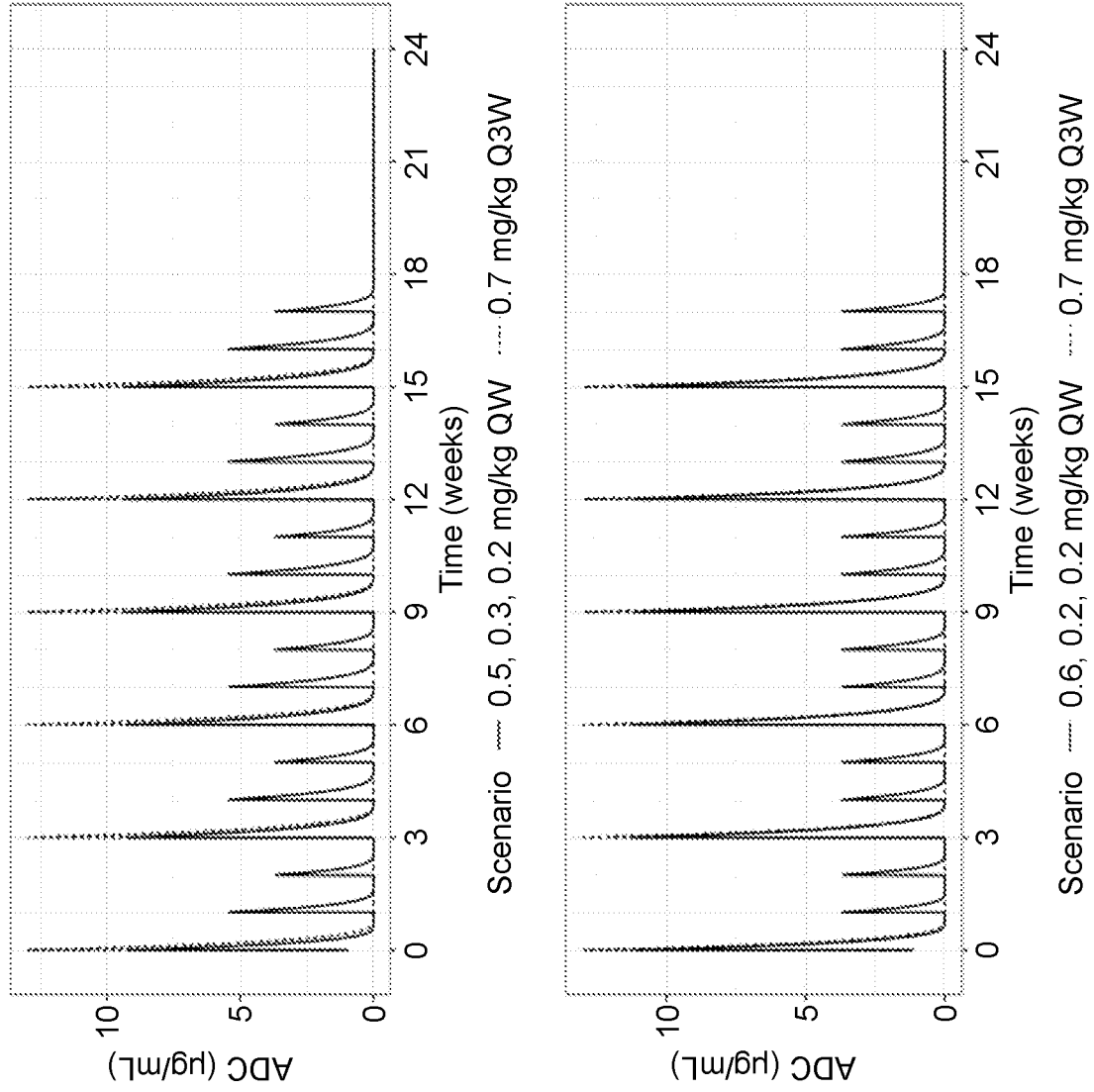


Figure 5



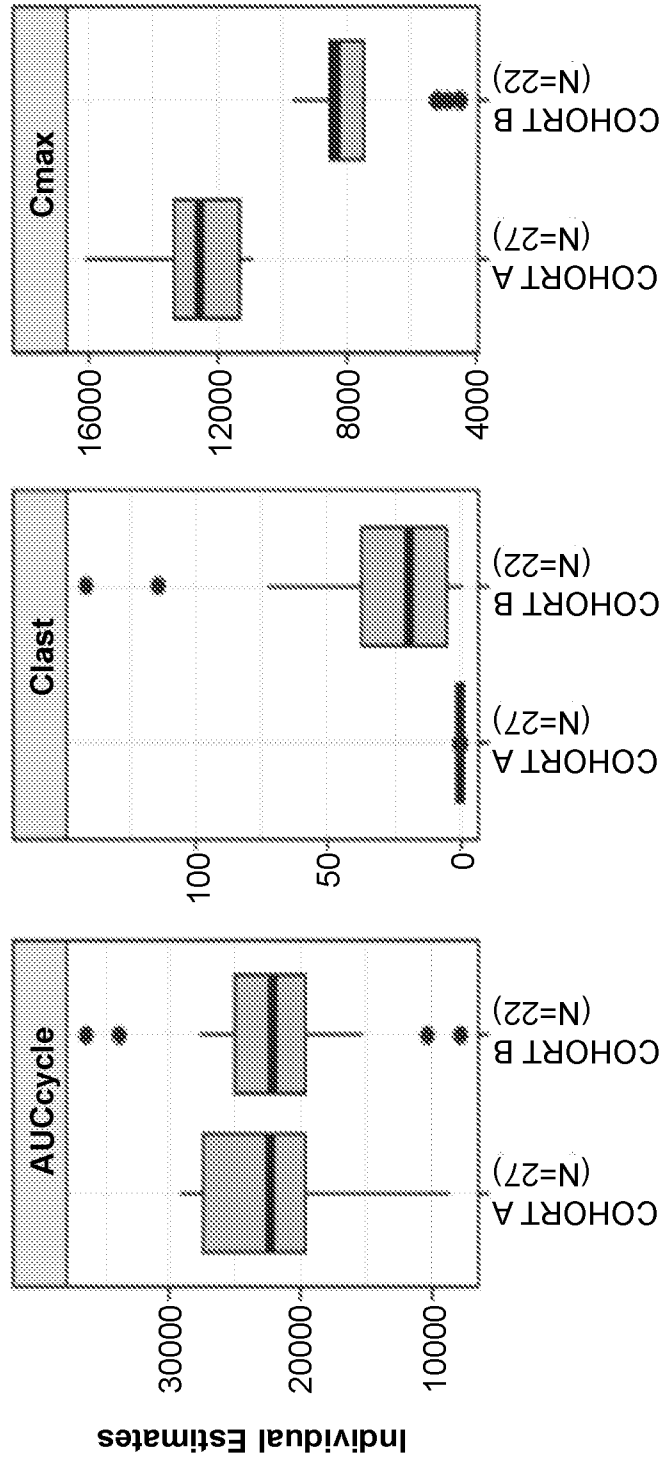


Figure 6

Figure 7

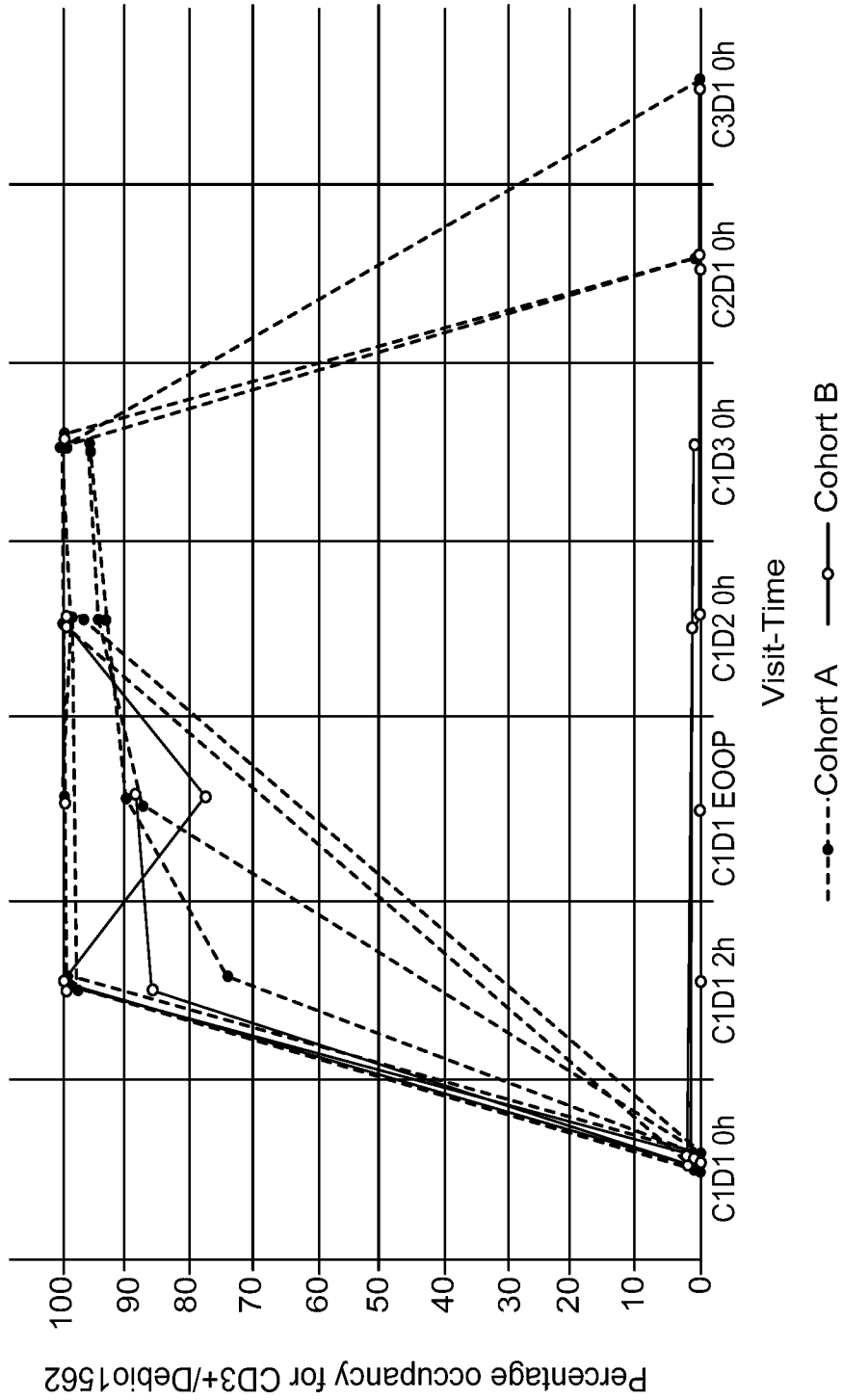
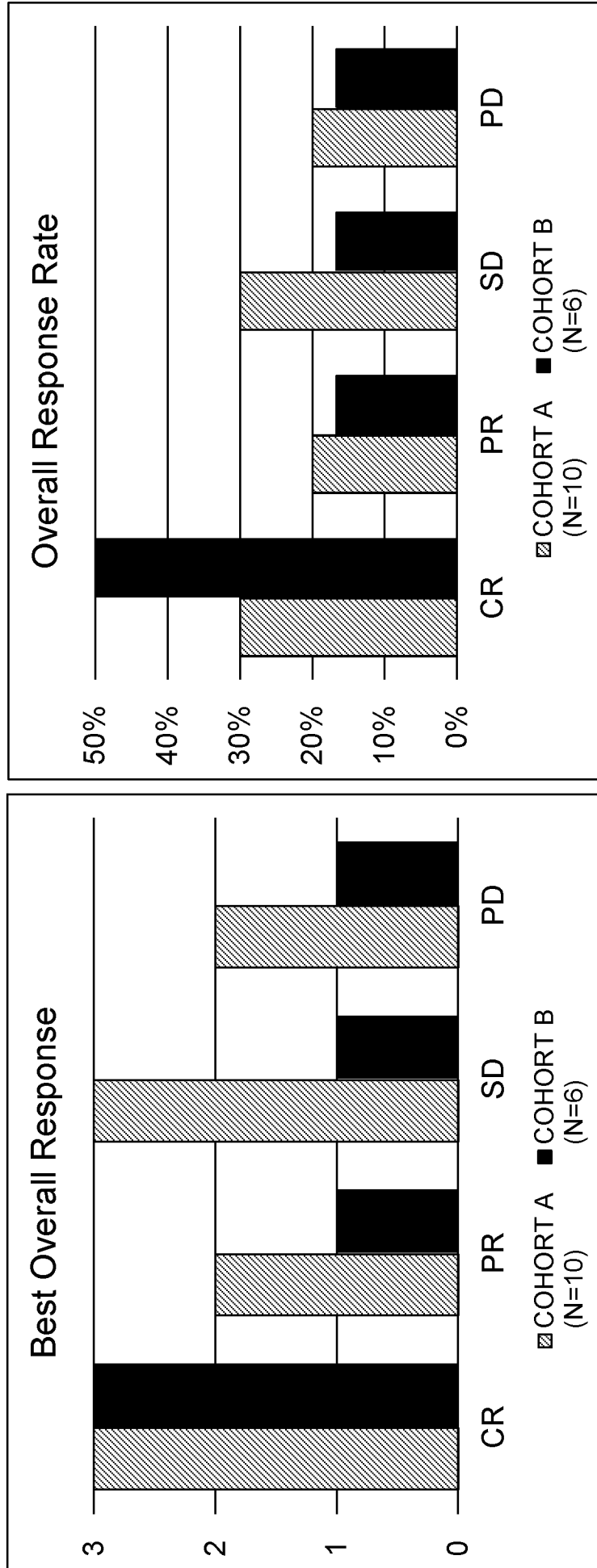


Figure 8



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/054457

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K47/68 A61K39/395 A61K38/18 A61K31/573 A61P35/00
 A61P35/02
 ADD.
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 EPO-Internal, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STATHIS ANASTASIOS ET AL: "Safety, tolerability, and preliminary activity of IMGN529, a CD37-targeted antibody-drug conjugate, in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: a dose-escalation, phase I study", INVESTIGATIONAL NEW DRUGS, MARTINUS NIJHOFF PUBLISHERS, BOSTON, US, vol. 36, no. 5, 17 February 2018 (2018-02-17), pages 869-876, XP036590591, ISSN: 0167-6997, DOI: 10.1007/S10637-018-0570-4 [retrieved on 2018-02-17] the whole document ----- -/--	1-53

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

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 9 August 2019	Date of mailing of the international search report 21/08/2019
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Villard, Anne-Laure
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/054457

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/175533 A2 (IMMUNOGEN INC [US]) 19 November 2015 (2015-11-19) paragraphs [0011] - [0018], [0061], [0112], [0135], [0137] examples -----	1-53
X	WO 2016/200676 A1 (IMMUNOGEN INC [US]) 15 December 2016 (2016-12-15) cited in the application	1-53
Y	paragraphs [0027] - [0029], [0080], [0133], [0143], [0145], [0180] - [0188], [0197] - [0207] examples -----	15-27
X	WO 2018/083633 A1 (DEBIOPHARM INT S A [CH]) 11 May 2018 (2018-05-11)	1-14, 28-53
Y	paragraphs [0028], [0029], [0070], [0128], [0132], [0135], [0242], [0243], [0245], [0253], [0256] - [0266] example 1 -----	15-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/054457

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 2016200676 A1	15-12-2016	AU 2016276158 A1 BR 112017026027 A2 CA 2986437 A1 CN 108472361 A EA 201792300 A1 EP 3302561 A1 JP 2018517714 A KR 20180011315 A US 2017000900 A1 US 2019183788 A1 WO 2016200676 A1	14-12-2017 14-08-2018 15-12-2016 31-08-2018 28-09-2018 11-04-2018 05-07-2018 31-01-2018 05-01-2017 20-06-2019 15-12-2016

WO 2018083633 A1	11-05-2018	NONE	
