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(54) Title: METHODS OF TREATING CANCER USING ANTI-CD22 ANTIBODY OLIGONUCLEOTIDE CONJUGATES

(57) Abstract: The present disclosure provides for methods for treating cancer using anti-CD22 antibody-oligonucleotide conjugates.

WO 2023/225577 A1

METHODS OF TREATING CANCER USING ANTI-CD22 ANTIBODY OLIGONUCLEOTIDE CONJUGATES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Application No. 63/343,506, filed May 18, 2022, which is hereby incorporated by reference in its entirety.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (186492001040seqlist.xml; Size: 319,072 bytes; and Date of Creation: May 3, 2023) are herein incorporated by reference in their entirety.

FIELD OF INVENTION

[0003] The present disclosure relates generally to methods for treating cancer using anti-CD22 antibody-oligonucleotide conjugates.

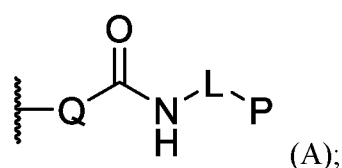
BACKGROUND

[0004] Immune-mediated elimination of cancer requires the coordination of the innate (*e.g.* dendritic cells, macrophages, myeloid derived suppressor cells) and adaptive (*i.e.* B cells, cytotoxic T cells, regulatory T cells) immune systems. Current gold-standard cancer treatments include the administration of immune checkpoint blockade therapy (anti-PD-1, anti-CTLA-4), but these therapies are only efficacious in up to 30% of patients and can have severe, even deadly, side effects in 10-30% of cancer patients. As well, such therapies predominantly act specifically to increase T lymphocyte activity, thereby neglecting the importance of coordinated immune response. Thus, there remains a need for a safe and effective treatment that utilizes the broad scope of possible immune involvement in cancer elimination.

BRIEF SUMMARY

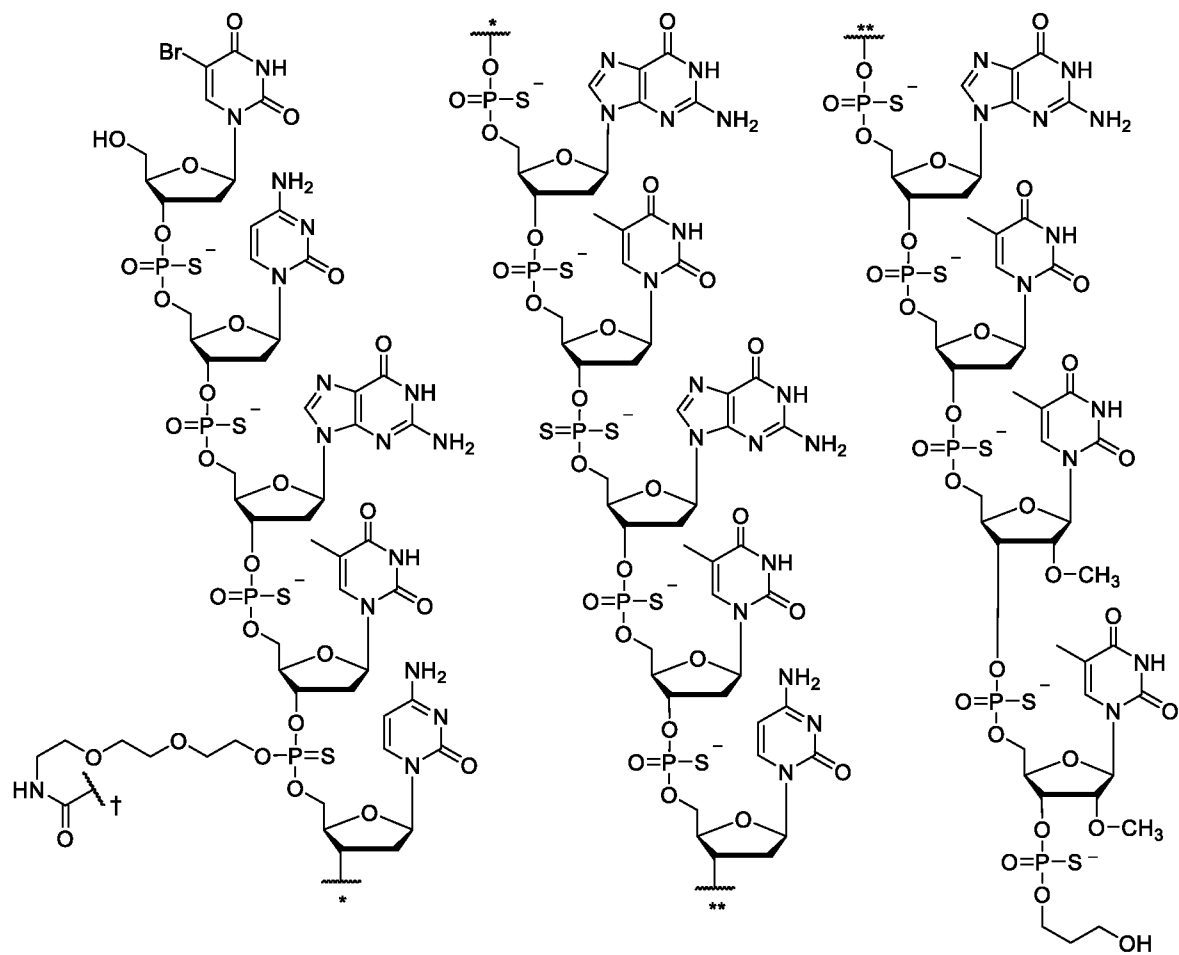
[0005] In one aspect, provided herein is a method of treating cancer in an individual comprising administering to the individual a conjugate comprising an anti-CD22 antibody (Ab) and an immunomodulating oligonucleotide (P) at a dose of between 0.1 mg/kg to 60 mg/kg; wherein the Ab comprises two antibody light chains, two antibody heavy chains, and two Q-tag peptides (Q); wherein each of the two Q-tag peptides comprises the amino acid sequence

RPQGFGPP (SEQ ID NO:49); wherein one Q-tag peptide is linked to the C-terminus of each of the two antibody heavy chains; wherein one of the two Q-tag peptides is linked to the immunomodulating oligonucleotide via an amide bond with the glutamine residue of the Q-tag peptide and a linker (L) as shown in Formula (A):

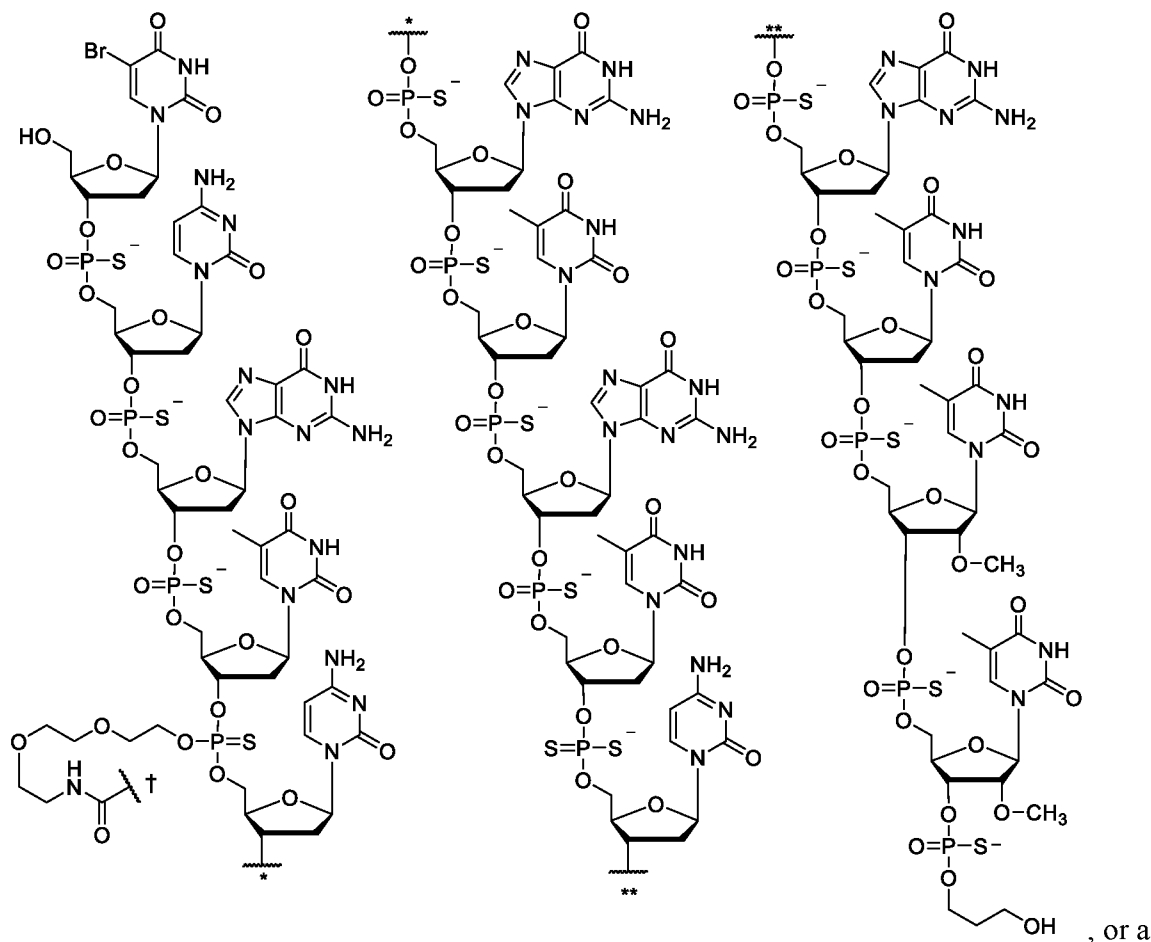


wherein $\sim$ indicates the point of attachment of Q to the antibody (Ab); wherein each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising an amino acid sequence selected from the group consisting

of SEQ ID NOs:120-122; wherein the linker L is $\sim \dagger$, wherein m is 24, and wherein $\sim \dagger$ indicates the point of attachment to the oligonucleotide P, and $\sim \ddagger$ indicates the point of attachment to the glutamine residue of the Q-tag; and wherein the oligonucleotide P comprises the structure:



or



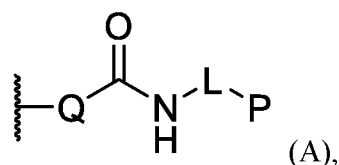
pharmaceutically acceptable salt thereof,

wherein $\sim^*$ and $\sim^{**}$ indicate the points of attachment within the oligonucleotide, wherein $\sim^\dagger$ indicates the point of attachment to the linker L.

[0006] In some embodiments, the individual has a solid tumor that is inoperable, locally advanced, metastatic, and/or recurrent. In some embodiments, the individual has a cancer selected from the group consisting of cutaneous melanoma, breast cancer, ovarian cancer, colorectal cancer, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), Merkel cell carcinoma, hepatocellular carcinoma (HCC), cervical squamous cell carcinoma, urothelial carcinoma, endometrial carcinoma, gastro-esophageal adenocarcinoma, and cholangiocarcinoma.

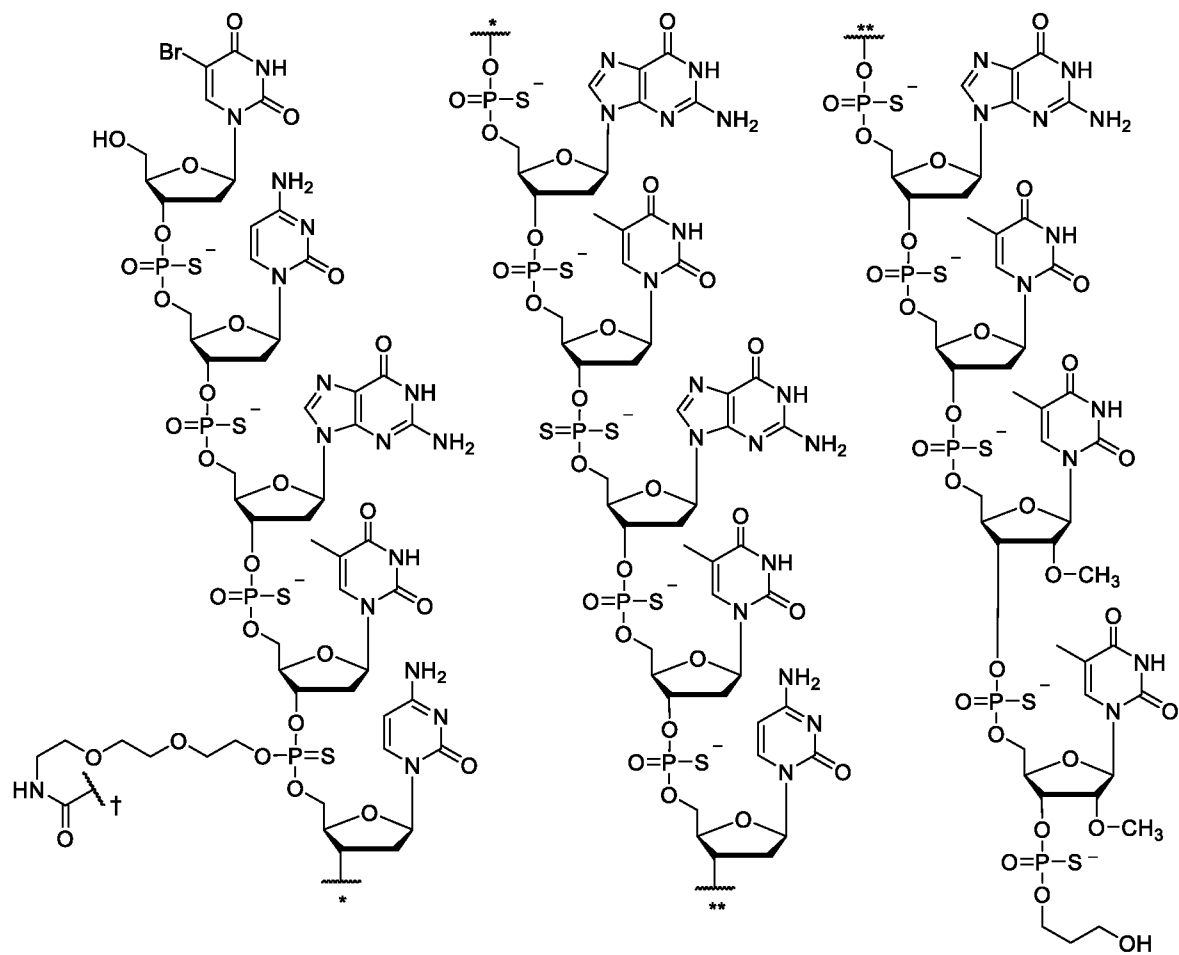
[0007] In another aspect, provided herein is a method of treating cancer in an individual comprising administering to the individual a conjugate comprising an anti-CD22 antibody (Ab) and an immunomodulating oligonucleotide (P); wherein the individual has a solid tumor that is inoperable, locally advanced, metastatic, and/or recurrent; wherein the Ab comprises two antibody

light chains, two antibody heavy chains, and two Q-tag peptides (Q); wherein each of the two Q-tag peptides comprises the amino acid sequence RPQGF₂GPP (SEQ ID NO:49); wherein one Q-tag peptide is linked to the C-terminus of each of the two antibody heavy chains; wherein one of the two Q-tag peptides is linked to the immunomodulating oligonucleotide via an amide bond with the glutamine residue of the Q-tag peptide and a linker (L) as shown in Formula (A):

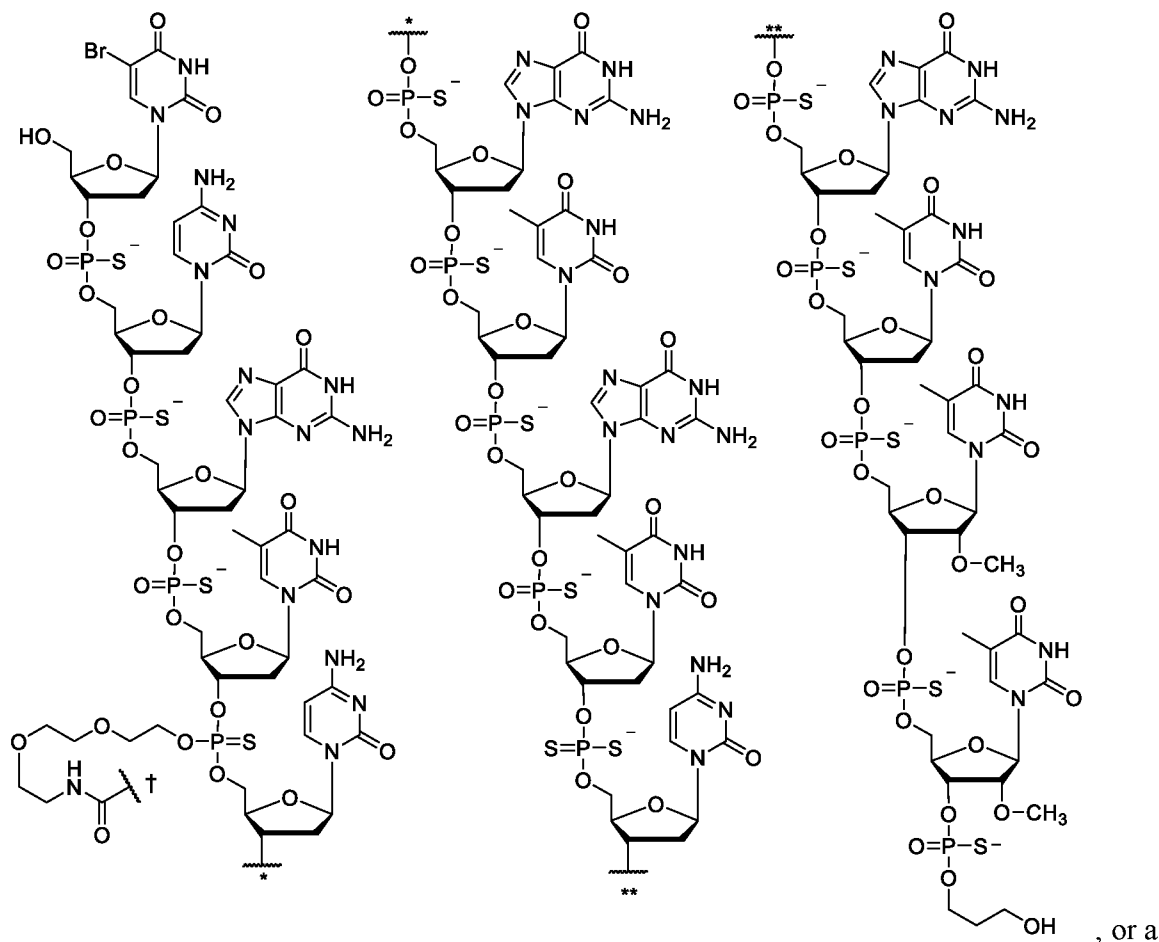


wherein $\sim$ indicates the point of attachment of Q to the antibody (Ab); wherein each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising an amino acid sequence selected from the group consisting

of SEQ ID NOs:120-122; wherein the linker L is $\ddagger \text{---} (\text{---CH}_2\text{---CH}_2\text{---O---})_m \text{---CH}_2\text{---CH}_2\text{---} \dagger$, wherein m is 24, and wherein $\sim \dagger$ indicates the point of attachment to the oligonucleotide P, and $\sim \ddagger$ indicates the point of attachment to the glutamine residue of the Q-tag; and wherein the oligonucleotide P comprises the structure:



or



pharmaceutically acceptable salt thereof,
 wherein $\sim^*$ and $\sim^{**}$ indicate the points of attachment within the oligonucleotide, and
 wherein $\sim^\dagger$ indicates the point of attachment to the linker L.

[0008] In some embodiments, the individual has a cancer selected from the group consisting of cutaneous melanoma, breast cancer, ovarian cancer, colorectal cancer, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), Merkel cell carcinoma, hepatocellular carcinoma (HCC), cervical squamous cell carcinoma, urothelial carcinoma, endometrial carcinoma, gastro-esophageal adenocarcinoma, and cholangiocarcinoma. In some embodiments, the conjugate is administered to the individual at a dose of between 0.1 mg/kg to 60 mg/kg.

[0009] In some embodiments according to any of the embodiments described herein, the individual has a solid tumor that has progressed on and/or is intolerant to standard therapy. In some embodiments, the conjugate is administered to the individual at a dose of 0.1, 0.3, 1.0, 3.0, 10.0, 30.0, or 60.0 mg/kg. In some embodiments, the conjugate is administered to the individual

once every two weeks. In some embodiments, each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising the amino acid sequence of SEQ ID NO:120. In some embodiments, each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising the amino acid sequence of SEQ ID NO:121. In some embodiments, each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising the amino acid sequence of SEQ ID NO:122. In some embodiments, each heavy chain of the Ab comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:65. In some embodiments, each light chain of the Ab comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:73. In some embodiments, each light chain of the Ab comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:87. In some embodiments, each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:179 or 180; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:181 or 182. In some embodiments, each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:179; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:181. In some embodiments, each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:179; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:182. In some embodiments, each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:180; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:181. In some embodiments, each heavy chain of the Ab including

the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:180; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:182. In some embodiments, the individual is a human. In some embodiments, the conjugate is administered in a formulation comprising the conjugate at a concentration of 30mg/mL; 20mM citrate; 150mM L-arginine; 50mM NaCl; and 0.02% polysorbate 80 (w/v); wherein the formulation is at pH 6.5. In some embodiments, the conjugate is administered to the individual intravenously.

DESCRIPTION OF THE FIGURES

[0010] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0011] **FIG. 1** shows a schematic diagram of an exemplary antibody:CpG conjugate with an engineered Q-tag (RPQGFQPP; SEQ ID NO:49) fused to the C-terminus of each heavy chain (with a DAR 1).

[0012] **FIG. 2A** shows the level of cell surface CD22 expression on peripheral B cells in patients after treatment with an anti-CD22-CpG conjugate.

[0013] **FIG. 2B** shows the level of cell surface CD22 expression on peripheral B cells in patients on Day 1 before treatment at the indicated doses with an anti-CD22-CpG conjugate (C1D1 pre), on Day 1 at 3 hours (leftmost 3 hrs), on Day 2 (C1D2), on Day 8 (C1D8), 15 hours prior to the administration of the second dose (i.e., the second cycle; C1D15 pre), 3 hours after administration of the second dose (rightmost 3 hrs), Day 16, during the second cycle (C2D16), and Day 22, during the second cycle (C2D22).

[0014] **FIG. 3A** shows CD86 expression on naïve B cells after treatment with an anti-CD22-CpG conjugate in patients at the indicated doses.

[0015] **FIG. 3B** shows CD86 expression on memory B cells after treatment with an anti-CD22-CpG conjugate in patients at the indicated doses.

[0016] **FIG. 3C** shows CD86 expression on naïve B cells after treatment with an anti-CD22-CpG conjugate in patients at the indicated doses and timepoints.

[0017] **FIG. 4** shows the concentration of an anti-CD22-CpG conjugate (TRAAC) in patients over time after administration of 0.1 mg/kg, 0.3 mg/kg, or 1 mg/kg of the conjugate.

DETAILED DESCRIPTION

[0018] The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

[0019] Provided herein are methods of treating solid tumors comprising administering a conjugate comprising an anti-CD22 antibody and an immunomodulating oligonucleotide. In some embodiments, the cancer is an advanced or metastatic solid tumor. In some embodiments, the conjugate is administered to an individual at dose between 0.1 mg/kg to 60 mg/kg.

[0020] Toll-like receptor 9 (TLR9), also designated as CD289, is a transmembrane and intracellular pattern recognition receptor that recognizes pathogen-associated molecular patterns (PAMPs) to engage an immune response in the absence of pathogens. TLR9 is an important receptor expressed by immune cells including dendritic cells (DCs), B lymphocytes, macrophages, natural killer cells, and other antigen presenting cells. TLR9 activation triggers intracellular signaling cascades that lead to activation, maturation, proliferation, and cytokine production in these immune cells, thus bridging and coordinating innate and adaptive immunity. Martinez-Campos *et al.*, *Viral Immunol.* 2016, 30, 98-105; Notley et al., *Sci. Rep.* 2017, 7, 42204. Thus, the identification of novel TLR9 agonist compounds may activate both innate and adaptive immunity and serve as potential anti-cancer therapeutics.

[0021] Natural TLR9 agonists include unmethylated cytosine-guanine dinucleotide (CpG)-containing oligodeoxynucleotides (CpG ODNs). CpG ODNs are often susceptible to degradation in serum and thus pharmacokinetics of CpG ODNs may be one of the limiting factors in their development as therapeutics. Additionally, CpG ODNs exhibit uneven tissue distribution that can result in increased PAMP-associated toxicity. These shortcoming(s) can be overcome by conjugating the CpG ODN to a targeting moiety for the treatment of a specific disease, *e.g.* conjugation to an anti-CD22 antibody for anti-cancer therapy. Indeed, CD22 is a transmembrane sialoglycoprotein receptor with restricted expression on B cells, including tumor-infiltrating B cells (TIBs) that will internalize in complex with an anti-CD22-CpG conjugate, thereby delivering TLR9 agonist to stimulate an anti-cancer immune response. Preclinical murine tumor models showed that an anti-CD22-CpG conjugate activated the TLR9 pathway in B cells to increase immune activation, cytokine production, antigen presentation, and anti-tumor efficacy. However,

there remains a need to assess the safety and efficacy of this drug compound in human cancer patients.

I. Definitions

[0022] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entireties. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in a patent, application, or other publication that is herein incorporated by reference, the definition set forth in this section prevails over the definition incorporated herein by reference.

[0023] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to particular method steps, reagents, or conditions are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed.

[0024] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0025] Throughout this application, unless the context indicates otherwise, references to a compound of Formula (A) include ionic forms, polymorphs, pseudopolymorphs, amorphous forms, solvates, co-crystals, chelates, isomers, tautomers, oxides (*e.g.*, N-oxides, S-oxides), esters, prodrugs, isotopes and/or protected forms thereof. In some embodiments, references to a compound of Formula (A) include polymorphs, solvates, co-crystals, isomers, tautomers and/or oxides thereof. In some embodiments, references to a compound of Formula (A) include polymorphs, solvates, and/or co-crystals thereof. In some embodiments, references to a compound

of Formula (A) include isomers, tautomers and/or oxides thereof. In some embodiments, references to a compound of Formula (A) include solvates thereof.

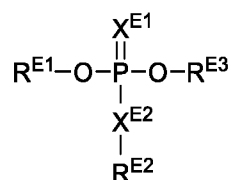
[0026] The term "*immunomodulating polynucleotide*" or "immunomodulating oligonucleotide" as used herein, represents a polynucleotide construct containing a total of from 6 to 50 contiguous nucleosides. The immunomodulating polynucleotides are capable of modulating an innate immune response, as determined by, e.g., a change in the activation of intracellular signaling pathway(s) including but not limited to NFκB, a change in the expression of an activation marker or a change in the secretion of at least one inflammatory cytokine or at least one type I interferon in an immune cell (e.g., antigen-presenting cell) to which an immunomodulating polynucleotide was delivered (e.g., in comparison to another immune cell (e.g., antigen-presenting cell) to which an immunomodulating polynucleotide was not delivered) or in an immune cell that interacts with an immune cell (e.g., antigen-presenting cell) to which an immunomodulating polynucleotide was delivered (including direct cell-to-cell interactions as well as indirect stimulation, e.g., from one or more cytokines secreted by the cell to which an immunomodulating polynucleotide was delivered).

[0027] The term "*immunostimulating polynucleotide*" or "immunostimulating oligonucleotide" as used herein, represents an immunomodulating polynucleotide capable of activating an immune response, as determined by, e.g., an increase in the activation of intracellular signaling pathway(s) such as NFκB or an increase in levels of cell surface marker(s) of activation or function or an increase in the secretion of at least one inflammatory cytokine or at least one type I interferon in an immune cell (e.g., antigen-presenting cell) to which an immunostimulating polynucleotide was delivered (e.g., in comparison to another immune cell (e.g., antigen-presenting cell) to which an immunostimulating polynucleotide was not delivered) or in an immune cell that interacts with an immune cell (e.g., antigen-presenting cell) to which an immunomodulating polynucleotide was delivered (including direct cell-to-cell interactions as well as indirect stimulation, e.g., from one or more cytokines secreted by the cell to which an immunomodulating polynucleotide was delivered).

[0028] It is to be understood that the terms "polynucleotide" and "oligonucleotide" may be used interchangeably herein. It is further to be understood that the terms "immunomodulating polynucleotide," "immunostimulating polynucleotide," "immunosuppressive polynucleotide,"

and “conjugate” encompass salts of the immunomodulating polynucleotide, immunostimulating polynucleotide, immunosuppressive polynucleotide and conjugate, respectively. For example, the terms “immunomodulating polynucleotide,” “immunostimulating polynucleotide,” “immunosuppressive polynucleotide,” and “conjugate” encompasses both the protonated, neutral form (P-XH moiety, where X is O or S) of a phosphate, phosphorothioate, or phosphorodithioate and the deprotonated, ionic form (P-X⁻ moiety, where X is O or S) of a phosphate, phosphorothioate, or phosphorodithioate. Accordingly, it is to be understood that the phosphoesters and phosphodiester described as having one or more of R^{E1}, R^{E2}, and R^{E3} as hydrogen encompass salts, in which the phosphate, phosphorothioate, or phosphorodithioate is present in a deprotonated, ionic form. In addition, the terms “free,” “naked,” and “unconjugated” referring to immunomodulating polynucleotides, immunostimulating polynucleotides, immunosuppressive polynucleotides, and/or oligonucleotides (*e.g.*, CpG oligonucleotides) may be used interchangeably herein.

[0029] The term “*phosphotriester*,” as used herein, refers to a phosphoester, in which all three valences are substituted with non-hydrogen substituents. The phosphotriester consists of phosphate, phosphorothioate, or phosphorodithioate; one or two bonds to nucleoside(s), or abasic spacer(s), and/or phosphoryl group(s); and one or two groups independently selected from the group consisting of a bioreversible group; a non-bioreversible group; an auxiliary moiety; a conjugating group; and a linker bonded to a targeting moiety and optionally to one or more (*e.g.*, 1 to 6) auxiliary moieties. A terminal phosphotriester includes one bond to a group containing a nucleoside and two groups independently selected from the group consisting of a bioreversible group; a non-bioreversible group; an auxiliary moiety; a conjugating group; a phosphoryl group; and a linker bonded to a targeting moiety and optionally to one or more (*e.g.*, 1 to 6) auxiliary moieties. In some embodiments, a terminal phosphotriester contains 1 or 0 linkers bonded to a targeting moiety and optionally to one or more (*e.g.*, 1 to 6) auxiliary moieties. An internucleoside phosphotriester includes two bonds to nucleoside-containing groups. A phosphotriester may be a group of the following structure:



wherein:

each of X^{E1} and X^{E2} is independently O or S;

each of R^{E1} and R^{E3} is independently a bond to a nucleoside; a sugar analogue of an abasic spacer; a bioreversible group; a non-bioreversible group; an auxiliary moiety; a conjugating group; a linker bonded to a targeting moiety; a linker bonded to a targeting moiety and one or more (e.g., 1 to 6) auxiliary moieties; or the phosphorus atom in a group of formula – $P(=X^{E1})(-X^{E2}-R^{E2}A)-O-$,

where $R^{E2}A$ is hydrogen; a bioreversible group; a non-bioreversible group; an auxiliary moiety; a conjugating group; a linker bonded to a targeting moiety; or a linker bonded to a targeting moiety and one or more (e.g., 1 to 6) auxiliary moieties; and

R^{E2} is a bioreversible group; a non-bioreversible group; an auxiliary moiety; a conjugating group; a linker bonded to a targeting moiety; or a linker bonded to a targeting moiety and one or more (e.g., 1 to 6) auxiliary moieties;

provided that at least one of R^{E1} and R^{E3} is a bond to a group containing at least one nucleoside.

If both R^{E1} and R^{E3} are bonds to groups containing at least one nucleoside, the phosphotriester is an internucleoside phosphotriester. If one and only one of R^{E1} and R^{E3} is a bond to a group containing a nucleoside, the phosphotriester is a terminal phosphotriester.

[0030] As used herein, the term "*amino acid*" refers to any amino acid (both standard and non-standard amino acids), including, but not limited to, α -amino acids, β -amino acids, γ -amino acids and δ -amino acids. Examples of suitable amino acids include, but are not limited to, alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Additional examples of suitable amino acids include, but are not limited to, ornithine, hypusine, 2-aminoisobutyric acid, dehydroalanine, gamma-aminobutyric acid, citrulline, beta-alanine, alpha-ethyl-glycine, alpha-propyl-glycine and norleucine.

[0031] The terms "*antibody*," "*immunoglobulin*," and "*Ig*" are used interchangeably herein, and are used in the broadest sense and specifically cover, for example, individual monoclonal antibodies (including agonist, antagonist, neutralizing antibodies, full length or intact monoclonal antibodies), antibody compositions with polyepitopic or monoepitopic specificity, polyclonal or monovalent antibodies, multivalent antibodies, multispecific antibodies (e.g., bispecific antibodies

so long as they exhibit the desired biological activity), formed from at least two intact antibodies, single chain antibodies, and fragments of antibodies. An antibody can be human, humanized, chimeric and/or affinity matured as well as an antibody from other species, for example, mouse and rabbit.

[0032] The term “*antibody*” is intended to include a polypeptide product of B cells within the immunoglobulin class of polypeptides that is able to bind to a specific antigen and is composed of two identical pairs of polypeptide chains, wherein each pair has one heavy chain (about 50-70 kDa) and one light chain (about 25 kDa) and each amino-terminal portion of each chain includes a variable region of about 100 to about 130 or more amino acids and each carboxyl-terminal portion of each chain includes a constant region. See Borrebaeck (ed.) (1995) *Antibody Engineering*, Second Ed., Oxford University Press.; Kuby (1997) *Immunology*, Third Ed., W.H. Freeman and Company, New York. Antibodies also include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinant antibodies, multispecific antibodies (including bi-specific antibodies), human antibodies, humanized antibodies, camelized antibodies, chimeric antibodies, intrabodies, anti-idiotypic (anti-Id) antibodies, and functional fragments thereof, which refers a portion of an antibody heavy or light chain polypeptide that retains some or all of the binding activity of the antibody from which the fragment is derived. Non-limiting examples of functional fragments of an antibody include single-chain Fvs (scFv) (*e.g.*, including monospecific or bispecific), Fab fragments, F(ab') fragments, F(ab)₂ fragments, F(ab')₂ fragments, disulfide-linked Fvs (sdFv), Fd fragments, Fv fragments, scRv-Fc, nanobody, diabody, triabody, tetrabody, and minibody. In some embodiments, the antibody comprises an Fc variant that has reduced or ablated effector function. In particular, antibodies provided herein include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, for example, antigen-binding domains or molecules that contain an antigen-binding site that binds to the antigen (*e.g.*, one or more complementarity determining regions (CDRs) of an anti-CD56 antibody or an anti-SIRPα antibody). Such antibody fragments are described in, for example, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, New York (1989); Myers (ed.), *Molec. Biology and Biotechnology: A Comprehensive Desk Reference*, New York: VCH Publisher, Inc.; Huston *et al.*, *Cell Biophysics* **1993**, 22, 189-224; Plückthun and Skerra, *Meth. Enzymol.* **1989**, 178, 497-515; and Day, *Advanced Immunochemistry*, Second Ed., Wiley-Liss, Inc., New York, NY (1990). The antibodies provided herein can be of any type (*e.g.*, IgG, IgE,

IgM, IgD, IgA, and IgY), any class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), or any subclass (*e.g.*, IgG2a and IgG2b) of an immunoglobulin molecule.

[0033] The term “*antigen*” refers to a predetermined target to which an antibody can selectively bind. A target antigen can be a polypeptide, carbohydrate, nucleic acid, lipid, hapten, or fragment thereof, or other naturally occurring or synthetic compound. In one embodiment, the target antigen is a polypeptide.

[0034] The terms “*antigen-binding fragment*,” “*antigen-binding domain*,” and “*antigen-binding region*” refer to a portion of an antibody that comprises the amino acid residues that interact with an antigen (*e.g.*, a polypeptide, carbohydrate, nucleic acid, lipid, hapten, or fragment thereof, or other naturally occurring or synthetic compound) and confer on the binding agent its specificity and affinity for the antigen (*e.g.*, complementarity determining regions (CDRs)).

[0035] The term “*specific binding*,” “*specifically binds to*,” or “*specific for*” a particular polypeptide or an epitope on a particular polypeptide target can be exhibited, for example, by a molecule (*e.g.*, an antibody) having a dissociation constant (K_d) for the target of at least about 10^{-4} M, at least about 10^{-5} M, at least about 10^{-6} M, at least about 10^{-7} M, at least about 10^{-8} M, at least about 10^{-9} M, at least about 10^{-10} M, at least about 10^{-11} M, or at least about 10^{-12} M. In one embodiment, the term “*specific binding*” refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

[0036] A 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (VH) followed by three constant domains (CH) for each of the α and γ chains and four CH domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (VL) followed by a constant domain (CL) at its other end. The VL is aligned with the VH and the CL is aligned with the first constant domain of the heavy chain (CH1). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a VH and VL together forms a single

antigen-binding site. For the structure and properties of the different classes of antibodies, *see, e.g., Basic and Clinical Immunology*, 8th edition, Stites *et al.* (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

[0037] The term “*variable region*” or “*variable domain*” refers to a portion of the light or heavy chains of an antibody that is generally located at the amino-terminal of the light or heavy chain and has a length of about 120 to 130 amino acids in the heavy chain and about 100 to 110 amino acids in the light chain, and are used in the binding and specificity of each particular antibody for its particular antigen. The variable region of the heavy chain may be referred to as “VH.” The variable region of the light chain may be referred to as “VL.” The term “variable” refers to the fact that certain segments of the variable regions differ extensively in sequence among antibodies. The V region mediates antigen binding and defines specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable regions. Instead, the V regions consist of less variable (*e.g., relatively invariant*) stretches called framework regions (FRs) of about 15-30 amino acids separated by shorter regions of greater variability (*e.g., extreme variability*) called “hypervariable regions” that are each about 9-12 amino acids long. The variable regions of heavy and light chains each comprise four FRs, largely adopting a β sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (*see, e.g., Kabat et al., Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991)). The constant regions are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). The variable regions differ extensively in sequence between different antibodies. The variability in sequence is concentrated in the CDRs while the less variable portions in the variable region are referred to as framework regions (FR). The CDRs of the light and heavy chains are primarily responsible for the interaction of the antibody with antigen. In specific embodiments, the variable region is a human variable region.

[0038] The term “*variable region residue numbering as in Kabat*” or “*amino acid position numbering as in Kabat*”, and variations thereof, refers to the numbering system used for heavy

chain variable regions or light chain variable regions 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 may 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 may 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 may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a “standard” Kabat numbered sequence. 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)). The “EU numbering system” or “EU index” is generally used when referring to a residue in an immunoglobulin heavy chain constant region (*e.g.*, the EU index reported in Kabat *et al.*, *supra*). The “EU index as in Kabat” refers to the residue numbering of the human IgG 1 EU antibody. Other numbering systems have been described, including, for example, by AbM, Chothia, Contact, IMGT and AHon.

[0039] An “*intact*” antibody is one comprising an antigen-binding site as well as a CL and at least heavy chain constant regions, CH1, CH2 and CH3. The constant regions may include human constant regions or amino acid sequence variants thereof. Preferably, an intact antibody has one or more effector functions.

[0040] The term “*antibody fragment*” refers to a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include, without limitation, Fab, Fab’, F(ab’)₂, and Fv fragments; diabodies and di-diabodies (*see, e.g.*, Holliger *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **1993**, 90, 6444-8; Lu *et al.*, *J. Biol. Chem.* **2005**, 280, 19665-72; Hudson *et al.*, *Nat. Med.* **2003**, 9, 129-134; WO 93/11161; and U.S. Pat. Nos. 5,837,242 and 6,492,123); single-chain antibody molecules (*see, e.g.*, U.S. Pat. Nos. 4,946,778; 5,260,203; 5,482,858 and 5,476,786); dual variable domain antibodies (*see, e.g.*, U.S. Pat. No. 7,612,181); single variable domain antibodies (SdAbs) (*see, e.g.*, Woolven *et al.*, *Immunogenetics* **1999**, 50, 98-101 Streltsov *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 12444-12449); and multispecific antibodies formed from antibody fragments.

[0041] The term “*functional fragment*,” “*binding fragment*,” or “*antigen-binding fragment*” of an antibody refers to a molecule that exhibits at least one of the biological functions attributed to the intact antibody, the function comprising at least binding to the target antigen.

[0042] The term “*heavy chain*” when used in reference to an antibody refers to a polypeptide chain of about 50-70 kDa, wherein the amino-terminal portion includes a variable region of about 120 to 130 or more amino acids and a carboxyl-terminal portion that includes a constant region. The constant region can be one of five distinct types, (*e.g.*, isotypes) referred to as alpha (α), delta (δ), epsilon (ϵ), gamma (γ) and mu (μ), based on the amino acid sequence of the heavy chain constant region. The distinct heavy chains differ in size: α , δ and γ contain approximately 450 amino acids, while μ and ϵ contain approximately 550 amino acids. When combined with a light chain, these distinct types of heavy chains give rise to five well known classes (*e.g.*, isotypes) of antibodies, IgA, IgD, IgE, IgG and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG2, IgG3, and IgG4. A heavy chain can be a human heavy chain.

[0043] The term “*light chain*” when used in reference to an antibody refers to a polypeptide chain of about 25 kDa, wherein the amino-terminal portion includes a variable region of about 100 to about 110 or more amino acids and a carboxyl-terminal portion that includes a constant region. The approximate length of a light chain is 211 to 217 amino acids. There are two distinct types, referred to as 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. A light chain can be a human light chain.

[0044] The term “*monoclonal antibody*” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *e.g.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts, and each monoclonal antibody will typically recognize a single epitope on the antigen. In specific embodiments, a “monoclonal antibody,” as used herein, is an antibody produced by a single hybridoma or other cell, wherein the antibody binds to only a beta klotho epitope as determined, for example, by ELISA or other antigen-binding or competitive binding assay known in the art. The term “monoclonal” is not limited to any particular method for making the antibody. For example, the monoclonal antibodies useful in the present disclosure may be prepared by the hybridoma methodology first described by Kohler *et al.*, *Nature* **1975**, 256, 495;

or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (*see, e.g.*, U.S. Pat. No. 4,816,567). The “monoclonal antibodies” may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, *Nature* **1991**, 352, 624-628 and Marks *et al.*, *J. Mol. Biol.* **1991**, 222, 581-597, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well known in the art (*see, for example*, Chapter 11 in: *Short Protocols in Molecular Biology*, (2002) 5th Ed., Ausubel *et al.*, eds., John Wiley and Sons, New York). Exemplary methods of producing monoclonal antibodies are provided in the Examples herein.

[0045] “*Humanized*” forms of nonhuman (*e.g.*, murine) antibodies are chimeric antibodies that include human immunoglobulins (*e.g.*, recipient antibody) in which the native CDR residues are replaced by residues from the corresponding CDR of a nonhuman species (*e.g.*, donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, one or more FR region residues of the human immunoglobulin are replaced by corresponding nonhuman residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. A humanized antibody heavy or light chain can comprise substantially all of at least one or more variable regions, in which all or substantially all of the CDRs correspond to those of a nonhuman immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. In certain embodiments, the humanized antibody will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, *see*, Jones *et al.*, *Nature* **1986**, 321, 522-525; Riechmann *et al.*, *Nature* **1988**, 332, 323-329; Presta, *Curr. Opin. Biotechnol.* **1992**, 3, 394-398; Carter *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **1992**, 89, 4285-4289; and U.S. Pat. Nos: 6,800,738, 6,719,971, 6,639,055, 6,407,213, and 6,054,297.

[0046] A “*human antibody*” is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries (Hoogenboom and Winter, *J. Mol. Biol.* **1991**, 227, 381; Marks *et al.*, *J. Mol. Biol.* **1991**, 222, 581) and yeast display libraries (Chao *et al.*, *Nature Protocols* **2006**, 1, 755-768). Also

available for the preparation of human monoclonal antibodies are methods described in Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner *et al.*, *J. Immunol.* **1991**, *147*, 86-95. See also van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* **2001**, *5*, 368-374. Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, *e.g.*, mice (see, *e.g.*, Jakobovits, *Curr. Opin. Biotechnol.* **1995**, *6*, 561-566; Brüggemann and Taussing, *Curr. Opin. Biotechnol.* **1997**, *8*, 455-458; and U.S. Pat. Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). See also, for example, Li *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 3557-3562 regarding human antibodies generated via a human B-cell hybridoma technology.

[0047] A “CDR” refers to one of three hypervariable regions (H1, H2, or H3) within the non-framework region of the immunoglobulin (Ig or antibody) VH β -sheet framework, or one of three hypervariable regions (L1, L2, or L3) within the non-framework region of the antibody VL β -sheet framework. Accordingly, CDRs are variable region sequences interspersed within the framework region sequences. CDR regions are well known to those skilled in the art and have been defined by, for example, Kabat as the regions of most hypervariability within the antibody variable (V) domains. Kabat *et al.*, *J. Biol. Chem.* **1977**, *252*, 6609-6616; Kabat, *Adv. Protein Chem.* **1978**, *32*, 1-75. CDR region sequences also have been defined structurally by Chothia as those residues that are not part of the conserved β -sheet framework, and thus are able to adapt different conformations. Chothia and Lesk, *J. Mol. Biol.* **1987**, *196*, 901-917. Both terminologies are well recognized in the art. CDR region sequences have also been defined by AbM, Contact and IMGT. The positions of CDRs within a canonical antibody variable region have been determined by comparison of numerous structures. Al-Lazikani *et al.*, *J. Mol. Biol.* **1997**, *273*, 927-948; Morea *et al.*, *Methods.* **2000**, *20*, 267-279. Because the number of residues within a hypervariable region varies in different antibodies, additional residues relative to the canonical positions are conventionally numbered with a, b, c and so forth next to the residue number in the canonical variable region numbering scheme. Al-Lazikani *et al.*, *supra* (1997). Such nomenclature is similarly well known to those skilled in the art.

[0048] The term “hypervariable region”, “HVR”, or “HV”, when used herein refers to the regions of an antibody variable region that are hypervariable in sequence and/or form structurally defined loops. Generally, antibodies comprise six hypervariable regions; three in the VH (H1, H2,

H3), and three in the VL (L1, L2, L3). A number of hypervariable region delineations are in use and are encompassed herein. The Kabat Complementarity Determining Regions (CDRs) are based on sequence variability and are the most commonly used (see, *e.g.*, Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). Chothia refers instead to the location of the structural loops. *See, e.g.*, Chothia and Lesk, *J. Mol. Biol.* **1987**, 196, 901-917. 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 (*see, e.g.*, Martin, in Antibody Engineering, Vol. 2, Chapter 3, Springer Verlag). The "contact" hypervariable regions are based on an analysis of the available complex crystal structures. The residues from each of these hypervariable regions or CDRs are noted below.

[0049] The term "*Fc region*" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including, for example, native sequence Fc regions, recombinant Fc regions, and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is often defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue.

[0050] The term "*DAR*" refers to a drug-antibody ratio of an oligonucleotide-antibody conjugate, more specifically an immunomodulating polynucleotide-antibody ratio. In some instances, for example, an oligonucleotide-antibody conjugate may be described herein as having a DAR of 1 or as a DAR1 conjugate, wherein the oligonucleotide-antibody ratio is 1-to-1. In other

instances, an an oligonucleotide-antibody conjugate may be described herein as having a DAR of 2 or as a DAR2 conjugate, wherein the oligonucleotide-antibody ratio is 2-to-1.

[0051] As used herein, the terms “*including*,” “*containing*,” and “*comprising*” are used in their open, non-limiting sense. It is also understood that aspects and embodiments of the invention described herein may include “*consisting*” and/or “*consisting essentially of*” aspects and embodiments.

[0052] It is understood that, whether the term “*about*” is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value.

[0053] As used herein, a “*carrier*” includes pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Non-limiting examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEENTM, polyethylene glycol (PEG), and PLURONICSTM.

[0054] As used herein, the term “*effective amount*” or “*therapeutically effective amount*” of a substance is at least the minimum concentration required to bring about a measurable improvement (*e.g.*, such as towards a therapeutic endpoint) or prevention of a particular disorder. An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the substance to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects. In reference to cancer, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such

as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation in cancer or to reach a particular threshold for a response criteria. In some embodiments, an effective amount is an amount sufficient to delay development of cancer. In some embodiments, an effective amount is an amount sufficient to prevent or delay recurrence. In some embodiments, an effective amount is an amount sufficient to reduce recurrence rate in the individual. An effective amount can be administered in one or more administrations. The effective amount of the drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and preferably stop cancer cell infiltration into peripheral organs; (iv) inhibit (*i.e.*, slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; (vii) reduce recurrence rate of tumor, and/or (viii) relieve to some extent one or more of the symptoms associated with the cancer. An effective amount can be administered in one or more administrations. For purposes of this disclosure, an effective amount of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective amount of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective amount” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0055] A “*package insert*” refers to instructions customarily included in commercial packages of medicaments that contain information about the indications customarily included in commercial packages of medicaments that contain information about the indications, usage, dosage, administration, contraindications, other medicaments to be combined with the packaged product, and/or warnings concerning the use of such medicaments, *etc.*

[0056] The terms “*protein*,” “*polypeptide*” and “*peptide*” are used herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may 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. Typically, a protein for use herein will have a molecular weight of at least about 5-20 kDa, alternatively at least about 20-100 kDa,

or at least about 100 kDa. Also included within the definition are, for example, proteins 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.

[0057] A “*pharmaceutically acceptable salt*” is a salt form that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. *See generally* Berge et al.(1977) *J. Pharm. Sci.* 66, 1. Particular pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of subjects without undue toxicity, irritation, or allergic response. Pharmaceutically acceptable salts include, without limitation, acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like. These salts may be derived from inorganic or organic acids. Non-limiting examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, and mandelates. In some embodiments, pharmaceutically acceptable salts are formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Salts derived from pharmaceutically acceptable organic non-toxic bases include, without limitation, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, trimethamine, dicyclohexylamine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N- ethylglucamine, N-methylglucamine, theobromine, purines, piperazine, piperidine, N- ethylpiperidine, polyamine resins, amino acids such as lysine, arginine, histidine, and the like. Examples of pharmaceutically

acceptable base addition salts include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. In some embodiments, the organic non-toxic bases are L-amino acids, such as L-lysine and L- arginine, tromethamine, N-ethylglucamine and N-methylglucamine. Acceptable inorganic bases include, without limitation, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Lists of other suitable pharmaceutically acceptable salts are found in *Remington's Pharmaceutical Sciences*, 17th Edition, Mack Publishing Company, Easton, Pa., 1985.

[0058] A “*solvate*” is formed by the interaction of a solvent and a compound. Suitable solvents include, for example, water and alcohols (*e.g.*, ethanol). Solvates include hydrates having any ratio of compound to water, such as monohydrates, dihydrates and hemi-hydrates.

[0059] A “*subject*,” “*patient*” or “*individual*” is a human. The individual can be male or female and can be any suitable age, including infant, juvenile, adolescent, adult, and geriatric subjects.

[0060] The term “*cancer*” or “*tumor*” refers to the presence of cells possessing characteristics typical of cancer-causing cells, such as uncontrolled proliferation, immortality, metastatic potential, rapid growth and proliferation rate, and certain characteristic morphological features. Cancer cells are often in the form of a solid tumor, which is detectable on the basis of tumor mass, *e.g.*, by procedures such as CAT scan, MR imaging, X-ray, ultrasound or palpation, and/or which is detectable because of the expression of one or more cancer-specific antigens in a sample obtainable from a patient. In some embodiments, a solid tumor does not need to have measurable dimensions. Cancer cells may also in the form of a liquid tumor, which cancer cells may exist alone or disseminated within an animal. As used herein, the terms “*disseminated tumor*” and “*liquid tumor*” are used interchangeably, and include, without limitation, leukemia and lymphoma and other blood cell cancers.

[0061] The terms “*cancer recurrence*” and “*cancer relapse*” are used interchangeably and refer to the return of a sign, symptom or disease after a remission. The recurrent cancer cells may re-appear in the same site of the primary tumor or in another location, such as in secondary cancer. The cancer cells may re-appear in the same diseased form as the primary cancer or a different diseased form. For example, in some embodiments, a primary cancer is a solid tumor, and the recurrent cancer is a liquid tumor. In other embodiments, a primary cancer is a liquid tumor, and

the recurrent cancer is a solid tumor. In yet other embodiments, the primary cancer and the recurrent cancer are both solid tumors, or both liquid tumors. In some embodiments, the recurrent tumor expresses at least one tumor-associated antigen that is also expressed by the primary tumor.

[0062] The term “*refractory cancer*” as used herein refers to a cancer that does not respond to a treatment, for example, a cancer that is resistant at the beginning of treatment (*e.g.*, treatment with an immunotherapy) or a cancer that may become resistant during treatment. The terms “*respond*,” “*response*” or “*responsiveness*” refer to an anti-cancer response, *e.g.* in the sense of reduction of tumor size or inhibiting tumor growth. The terms can also refer to an improved prognosis, for example, as reflected by an increased time to recurrence, which is the period to first recurrence censoring for second primary cancer as a first event or death without evidence of recurrence, or an increased overall survival, which is the period from treatment to death from any cause. To respond or to have a response means there is a beneficial endpoint attained when exposed to a stimulus. Alternatively, a negative or detrimental symptom is minimized, mitigated or attenuated on exposure to a stimulus. It will be appreciated that evaluating the likelihood that a tumor or subject will exhibit a favorable response is equivalent to evaluating the likelihood that the tumor or subject will not exhibit favorable response (*i.e.*, will exhibit a lack of response or be non-responsive).

[0063] As used herein, cancers include, but are not limited to, melanomas, breast cancer, lung cancer, bronchus cancer, colorectal cancer, prostate cancer, pancreatic cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, cancer of hematologic tissues, B cell cancer, *e.g.*, multiple myeloma, Waldenström's macroglobulinemia, the heavy chain diseases, such as, for example, alpha chain disease, gamma chain disease, and mu chain disease, benign monoclonal gammopathy, and immunocytic amyloidosis, and the like. Other non-limiting examples of types of cancers applicable to the methods encompassed by the present invention include human sarcomas and carcinomas, *e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma,

rhabdomyosarcoma, colon carcinoma, colorectal cancer, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, liver cancer, choriocarcinoma, sominoma, embryonal carcinoma, Wilms' tumor, cervical cancer, bone cancer, brain tumor, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, *e.g.*, acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease. In some embodiments, cancers are epithelial in nature and include but are not limited to, bladder cancer, breast cancer, cervical cancer, colon cancer, gynecologic cancers, renal cancer, laryngeal cancer, lung cancer, oral cancer, head and neck cancer, ovarian cancer, pancreatic cancer, prostate cancer, or skin cancer. In other embodiments, the cancer is breast cancer, prostate cancer, lung cancer, or colon cancer. In still other embodiments, the epithelial cancer is non-small-cell lung cancer, nonpapillary renal cell carcinoma, cervical carcinoma, ovarian carcinoma (*e.g.*, high grade serous ovarian carcinoma), or breast carcinoma. The epithelial cancers may be characterized in various other ways including, but not limited to, serous, endometrioid, mucinous, clear cell, Brenner, or undifferentiated.

[0064] The term “*cancer therapy*” or “*cancer therapeutic agent*” as used herein, refers to those therapies or agents that can exert anti-tumor effect or have an anti-tumor activity. Such anti-tumor effect or anti-tumor activity can be exhibited as a reduction in the rate of tumor cell proliferation, viability, or metastatic activity. A possible way of showing anti-tumor activity is to show a decline in growth rate of abnormal cells that arises during therapy or tumor size stability or reduction. Such activity can be assessed using accepted *in vitro* or *in vivo* tumor models, including but not limited to xenograft models, allograft models, MMTV models, and other known models known in the art to investigate anti-tumor activity.

[0065] The terms “*treat*,” “*treating*,” and “*treatment*” are meant to include alleviating or abrogating a condition, disorder, or disease, or one or more of the symptoms associated with the condition, disorder, or disease; or alleviating or eradicating the cause(s) of the condition, disorder, or disease itself. In some embodiments, treatment of a cancer results in a complete response (CR) or partial response (PR). In some embodiments, treatment of a cancer results in a CR, PR, or stable disease (SD). Exemplary criteria for CR, PR, and SD are provided herein.

[0066] The terms “*prevent*,” “*preventing*,” and “*prevention*” are meant to include a method of delaying and/or precluding the onset of a condition, disorder, or disease, and/or its attendant symptoms; barring a subject from acquiring a condition, disorder, or disease; or reducing a subject’s risk of acquiring a condition, disorder, or disease.

[0067] By “*optional*” or “*optionally*” is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” encompasses both “alkyl” and “substituted alkyl” as defined herein. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible, and/or inherently unstable. It will also be understood that where a group or moiety is optionally substituted, the disclosure includes both embodiments in which the group or moiety is substituted and embodiments in which the group or moiety is unsubstituted.

[0068] The term “*Q-tag*,” as used herein, refers to a portion of a polypeptide containing glutamine residue that, upon transglutaminase-mediated reaction with a compound containing -NH₂ amine, provides a conjugate containing the portion of polypeptide, in which the glutamine residue includes a side chain modified to include the amide bonded to the compound. Q-tags are known in the art. Non-limiting examples of Q-tags are LLQGG (SEQ ID NO:172), GGGLLQGG (SEQ ID NO:173), RPQGF (SEQ ID NO:47), and RPQGFQPP (SEQ ID NO:49). In some embodiments, the Q tag is attached to the C terminal of the heavy chain of the antibody. In some embodiments, the Q tag is attached to the light chain of the antibody. In some embodiments, the Q tag is naturally occurring. For example, mutation of N297 to N297A exposes Q295 of the antibody, where the conjugation could occur (numbering according to EU index, *e.g.*, as listed in Edelman, G.M. et al., Proc. Natl. Acad. USA, 63, 78-85 (1969) and Kabat, E.A. et al., Sequences

of proteins of immunological interest. 5th Edition - US Department of Health and Human Services, NIH publication n° 91-3242, pp 662,680,689 (1991)). In some embodiments, the Q tag is within the Fc domain of the antibody.

II. Methods of Treating Cancer

[0069] Provided herein are methods of treating cancer in an individual comprising administering a conjugate comprising an anti-CD22 antibody and an immunomodulating oligonucleotide (*e.g.*, CpG oligonucleotide). In some embodiments, the cancer is a tumor, *e.g.* an advanced or metastatic solid tumor. In some embodiments, the tumor is a histologically or cytologically-documented solid tumor that is inoperable, locally advanced, metastatic, or recurrent. In some embodiments, the conjugate is administered to an individual that has a solid tumor and the cancer in the individual has progressed on or the individual is intolerant to standard therapy, or has a cancer for which no standard therapy is available. In some embodiments, the cancer to be treated is cutaneous melanoma, breast cancer, ovarian cancer, colorectal cancer, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), Merkle cell carcinoma, hepatocellular carcinoma (HCC), cervical squamous cell carcinoma, urothelial carcinoma, endometrial carcinoma, gastro-esophageal adenocarcinoma, or cholangiocarcinoma. In some embodiments, the cancer to be treated is triple negative breast cancer, melanoma, ovarian cancer or colon cancer. In some embodiments, tumor tissue from the cancer to be treated is tested for the presence or level of PD-L1. In some embodiments, the conjugate is administered to an individual at dose between 0.1 mg/kg to 60 mg/kg (*e.g.*, 0.1, 0.3, 1.0, 3.0, 10.0, 30.0, or 60.0 mg/kg). In some embodiments, the conjugate is administered to an individual at dose between 0.1-1 mg/kg, between 1-10 mg/kg, between 10-30 mg/kg or between 30-60 mg/kg. In some embodiments, the dose administered is 0.1 mg/kg. In some embodiments, the dose administered is 0.3 mg/kg. In some embodiments, the dose administered is 1.0 mg/kg. In some embodiments, the dose administered is 3.0 mg/kg. In some embodiments, the dose administered is 10.0 mg/kg. In some embodiments, the dose administered is 30.0 mg/kg. In some embodiments, the dose administered is 60.0 mg/kg. In some embodiments, the dose is administered Q1W (weekly), or about once every 7 days. In some embodiments, the dose is administered Q2W (biweekly), or about once every 14 days. In some embodiments, the dose is administered Q3W (every 3 weeks), or about once every 21 days. In some embodiments, the dose is administered Q4W (once every 4 weeks), about once every 28 days, or about once a month. In

some embodiments, the dose is administered once, twice, 3 times, 4 times, 5 times or more than 5 times to an individual during a course of treatment. In some embodiments, the individual is a human. In some embodiments, the conjugate is administered to the individual intravenously (IV). In some embodiments, the conjugate is administered in a formulation comprising the conjugate at a concentration of 30mg/mL; 20mM citrate; 150mM L-arginine; 50mM NaCl; and 0.02% polysorbate 80 (w/v); wherein the formulation is at pH 6.5.

[0070] In some embodiments, treatment according to a method of the present disclosure results in a complete response (CR) in the individual. In some embodiments, a CR refers to disappearance of all non-nodal target lesions and a reduction in short axis to < 10 mm of any pathological lymph nodes assigned as target lesions.

[0071] In some embodiments, treatment according to a method of the present disclosure results in a partial response (PR) in the individual. In some embodiments, a PR refers to at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

[0072] In some embodiments, treatment according to a method of the present disclosure results in stable disease (SD) in the individual. In some embodiments, SD refers to insufficient target lesion shrinkage to qualify for PR or CR (*e.g.*, as described above) and insufficient increase in target lesion(s) to qualify for progressive disease (PD). In some embodiments, PD refers to at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline, as well as the sum demonstrating an absolute increase of at least 5 mm.

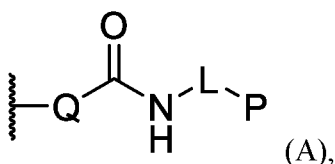
[0073] In some embodiments, the methods of the present disclosure are used to treat a cancer (*e.g.*, solid tumor) that is inoperable, locally advanced, metastatic, and/or recurrent.

[0074] In some embodiments, a locally advanced or advanced cancer refers to a cancer that has spread only to nearby tissues or lymph nodes. For example, for locally advanced breast cancer, cancers may involve the skin of the breast or the underlying muscles of the chest or involve multiple local lymph nodes (those located in the arm pit or the soft tissues above and below the collarbone). A second example is lung cancer; locally advanced lung cancer is when the cancer has grown into an airway, the chest wall or the membranes that surround the lung (the pleura).

[0075] In some embodiments, a metastatic cancer refers to a cancer that has spread to distant part(s) of the body. For example, the most common places metastatic breast cancer spread to are the bones, lung, brain and liver. A second example is metastatic lung cancer, where the cancer has spread to the brain, bones, liver, adrenal glands, other parts of the lung or the other lung.

[0076] In some embodiments, a cancer (*e.g.*, solid tumor) to be treated by the methods of the present disclosure is histologically and/or cytologically documented.

[0077] In some embodiments, in the immunomodulating oligonucleotide-antibody conjugate herein, the oligonucleotide and antibody are attached together via a linking moiety. In some embodiments, one antibody can be conjugated to one oligonucleotide (DAR 1) as shown in **FIG. 1**. In some embodiments, the oligonucleotide-antibody conjugate is a conjugate comprising an antibody or antigen-binding fragment thereof and one or more immunomodulating oligonucleotides (P), wherein the antibody or antigen-binding fragment is linked to one or more Q-tag peptides (Q) comprising at least one glutamine residue, wherein each immunomodulating oligonucleotide is linked to a Q-tag peptide via an amide bond with the glutamine residue of the Q-tag peptide and a linker (L) as shown in Formula (A):



or a stereoisomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof;

wherein:

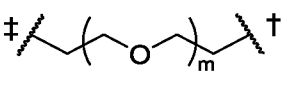
- ~~~~~ indicates the point of attachment of each Q to the antibody or antigen-binding fragment thereof (Ab);
- each Q is independently a Q-tag peptide sequence comprising at least one glutamine residue;
- each L is independently a bond or a linker moiety connected to Q via an amide bond with the glutamine residue; and
- each P is independently an immunomodulating oligonucleotide or a pharmaceutically acceptable salt thereof.

[0078] In another aspect, the oligonucleotide is conjugated to the polypeptide via a linking moiety. The length, rigidity and chemical composition of the linking moiety impact the conjugation reaction rates and the stability of the resulting conjugates.

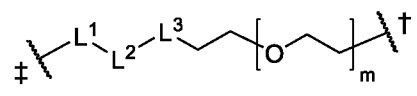
Linker moieties (L)

[0079] In some embodiments, the linking moiety comprises polyethylene glycol (PEG). In some embodiments, the PEG contains about 10-50 ethylene glycol units. In some embodiments, the linking moiety is an aliphatic chain.

[0080] For Formula (A), the linking moiety is represented by L. In some embodiments, the linker L comprises an oligoethylene glycol or polyethylene glycol moiety. In certain

embodiments, the linker L is a group having the structure , wherein  indicates the point of attachment to the oligonucleotide P, and  indicates the point of attachment to the glutamine residue of the Q-tag.

[0081] In other embodiments, the linker L is a group having the structure

 wherein  indicates the point of attachment to the oligonucleotide P, and  indicates the point of attachment to the glutamine residue of the Q-tag. In some embodiments, L¹ is absent. In some embodiments, L¹ is unsubstituted alkyl. In some embodiments, L¹ is independently an unsubstituted C₁₋₆ alkyl. In some embodiments, each L¹ is methyl or ethyl. In some embodiments, L¹ is independently a substituted alkyl. In some embodiments, L¹ is independently a substituted C₁₋₆ alkyl. In some embodiments, L¹ is C₁₋₆ alkyl substituted with one or more substituents selected from the group consisting of alkoxy, acyl, acyloxy, alkoxy carbonyl, carbonylalkoxy, acylamino, amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, cycloalkyl, cycloalkenyl, cyano, azido, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, alkyl, alkenyl, alkynyl, heterocyclyl, aminosulfonyl, sulfonylamino, sulfonyl and oxo.

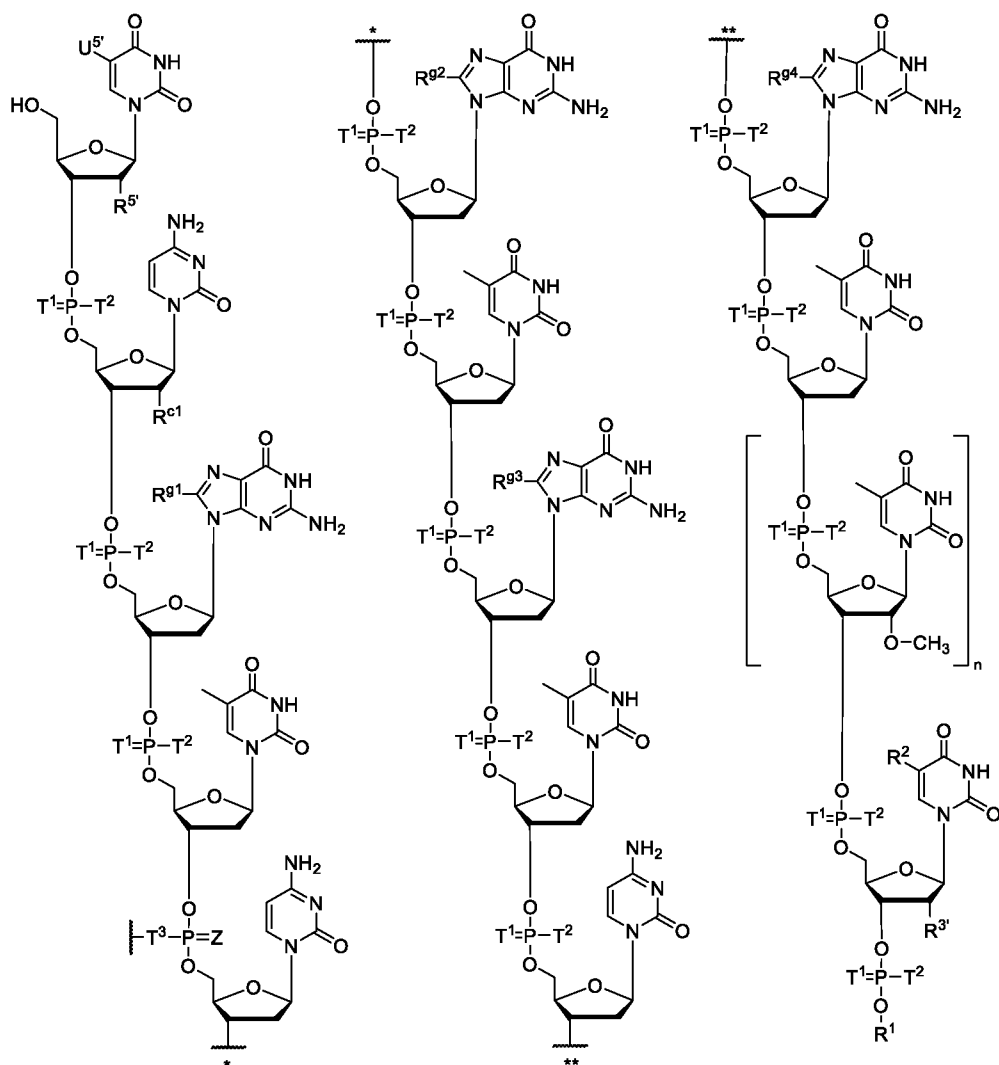
[0082] In some embodiments, L² is absent. In some embodiments, L² is unsubstituted or substituted alkyl.

[0083] In some embodiments, L^3 is absent. In some embodiments, L^3 is a linker moiety. In some embodiments, the linker moiety is an unsubstituted or substituted alkyl. In some embodiments, the linker moiety is independently an unsubstituted C_{1-6} alkyl. In some embodiments, the linker moiety is methyl or ethyl. In some embodiments, the linker moiety is independently a substituted alkyl. In some embodiments, the linker moiety is independently a substituted C_{1-6} alkyl. In some embodiments, the linker moiety is C_{1-6} alkyl substituted with one or more substituents selected from the group consisting of alkoxy, acyl, acyloxy, alkoxycarbonyl, carbonylalkoxy, acylamino, amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, cycloalkyl, cycloalkenyl, cyano, azido, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, alkyl, alkenyl, alkynyl, heterocyclyl, aminosulfonyl, sulfonylamino, sulfonyl and oxo. In some embodiments, the linker moiety is an amino acid residue. In some embodiments, the amino acid is selected from the group consisting of glycine, alanine, glutamic acid and proline. In some embodiments, the linker is methyl. In some embodiments, the linker moiety is $-R^5C(O)R^6NHR^7-$, wherein R^5 , and R^7 are independently absent or unsubstituted or substituted alkyl and R^6 is an amino acid residue. In some embodiments, the amino acid is selected from the group consisting of glycine, alanine, glutamic acid and proline. In some embodiments, the linker moiety is $-R^3C(O)NHR^4-$, wherein R^3 and R^4 are independently absent or unsubstituted or substituted alkyl. In some embodiments, R^3 is methylene and R^4 is $-(CH_2)_4-$. In some embodiments, R^3 is methylene and R^4 is absent. When more than one oligonucleotide (*i.e.*, $p = 2$), the two L^1 can be different or same, the two L^2 can be different or same and the two L^3 can be different or same.

[0084] In some embodiments, m is about 3-10, about 10-15, about 15-20, about 20-25, about 25-30, about 5-16, about 15-30, about 15-25 or about 20-30. In some embodiments, m is 20, 21, 22, 23, 24 or 25.

Immunomodulating oligonucleotides

[0085] In some embodiments, the immunomodulating oligonucleotide comprises the structure



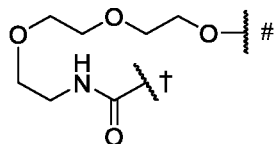
or a pharmaceutically acceptable salt thereof,

wherein

~~~~~\* and ~~~~~\*\* indicate the points of attachment within the oligonucleotide;

each  $T^1$  is independently O or S;

each  $T^2$  is  $O^-$  or  $S^-$ ;



$T^3$  is a group , wherein ~~~~† indicates the point of attachment to

L and wherein ~~~~# indicates the point of attachment to the rest of the oligonucleotide;

Z is O or S;

$U^{5'}$  is -H or halogen;

$R^{5'}$  is -H or methoxy;

$R^{c1}$  is -H or methoxy;

$R^{g1}$ ,  $R^{g2}$ ,  $R^{g3}$ , and  $R^{g4}$  are H or oxo, wherein

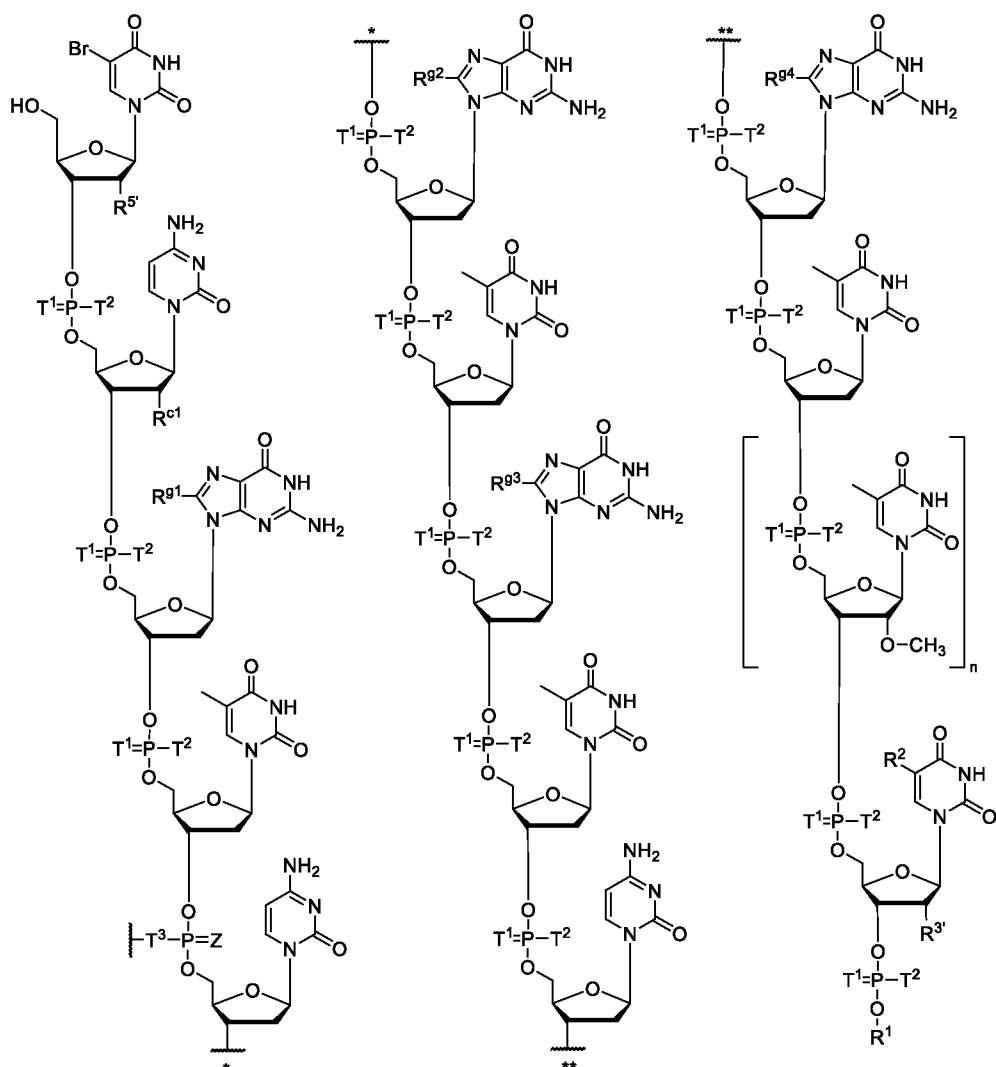
$R^{3'}$  is methoxy;

$R^1$  is  $C_{1-4}$ -alkylene-hydroxy;

$R^2$  is -H or methyl; and

$n$  is an integer from 0 to 2.

[0086] In other embodiments, the immunomodulating oligonucleotide comprises the structure



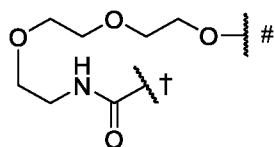
or a pharmaceutically acceptable salt thereof,

wherein

$\sim^*$  and  $\sim^{**}$  indicate the points of attachment within the oligonucleotide;

each  $T^1$  is independently O or S;

each  $T^2$  is  $O^-$  or  $S^-$ ;



$T^3$  is a group, wherein  $\sim^\dagger$  indicates the point of attachment to

L and wherein  $\sim^\#$  indicates the point of attachment to the rest of the oligonucleotide;

Z is O or S;

$R^{5'}$  is -H or methoxy;

$R^{c1}$  is -H or methoxy;

$R^{g1}$ ,  $R^{g2}$ ,  $R^{g3}$ , and  $R^{g4}$  are H or oxo, wherein

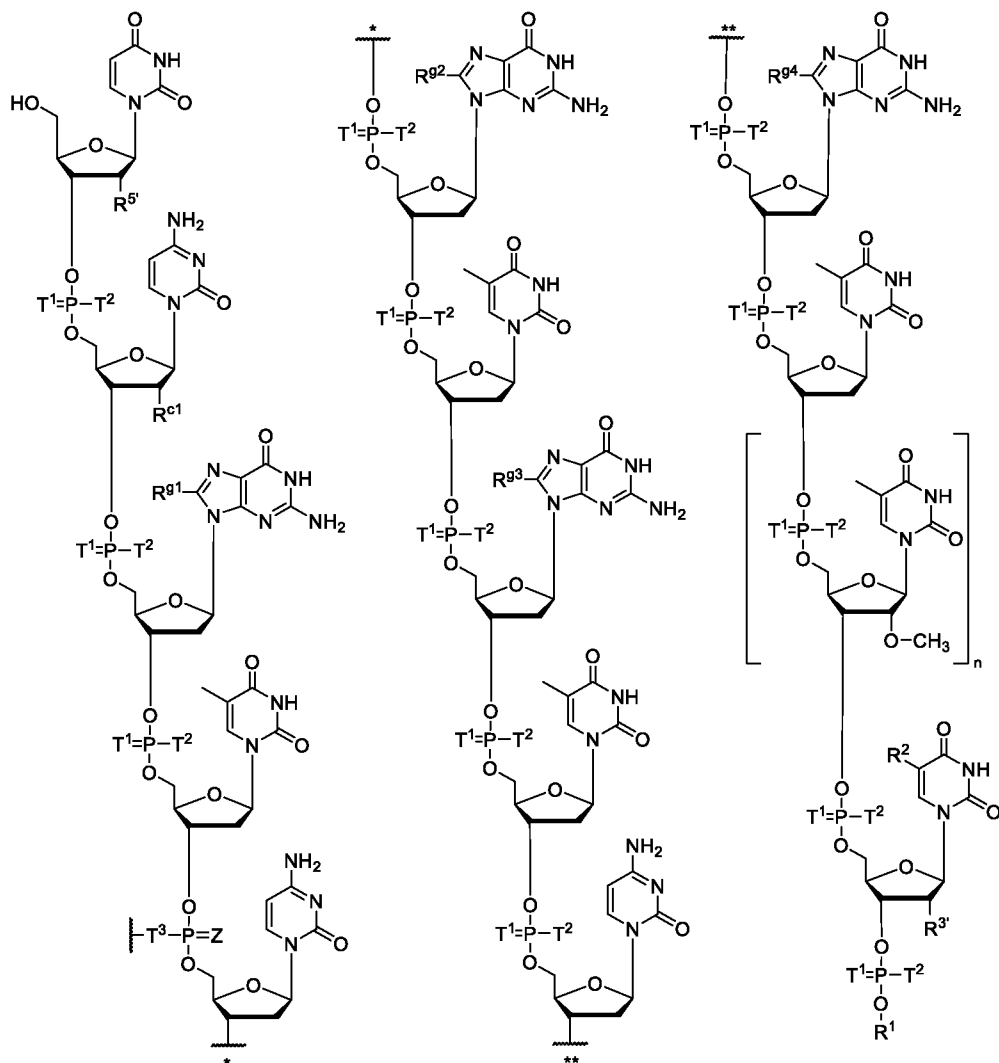
$R^{3'}$  is methoxy;

$R^1$  is  $C_{1-4}$ -alkylene-hydroxy;

$R^2$  is -H or methyl; and

n is an integer from 0 to 2.

[0087] In still other embodiments, the immunomodulating oligonucleotide comprises the structure



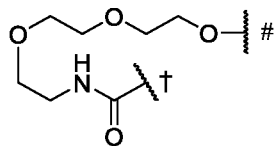
or a pharmaceutically acceptable salt thereof,

wherein

~\* and ~\*\* indicate the points of attachment within the oligonucleotide;

each T<sup>1</sup> is independently O or S;

each T<sup>2</sup> is O<sup>-</sup> or S<sup>-</sup>;



T<sup>3</sup> is a group

, wherein ~† indicates the point of attachment to

L and wherein ~# indicates the point of attachment to the rest of the oligonucleotide;

Z is O or S;

R<sup>5'</sup> is -H or methoxy;

R<sup>c1</sup> is -H or methoxy;

R<sup>g1</sup>, R<sup>g2</sup>, R<sup>g3</sup>, and R<sup>g4</sup> are H or oxo, wherein

R<sup>3'</sup> is methoxy;

R<sup>1</sup> is C<sub>1-4</sub>-alkylene-hydroxy;

R<sup>2</sup> is -H or methyl; and

n is an integer from 0 to 2.

**[0088]** In some embodiments, the immunomodulating oligonucleotide comprises an oligonucleotide sequence as shown in Table A, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide is an oligonucleotide as shown in Table A, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide comprises an oligonucleotide as shown in Table A, or a pharmaceutically acceptable salt thereof. In some embodiment, the immunomodulating oligonucleotide (P) plus linker comprises an oligonucleotide selected from the group consisting of SEQ ID NO:34-35, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide (P) plus linker comprises the oligonucleotide of SEQ ID NO:34, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide (P) plus linker comprises the oligonucleotide of SEQ ID NO:35, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide (P) is an oligonucleotide selected from the group consisting of SEQ ID Nos:14-25, 141-152, and 162, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide (P) comprises an oligonucleotide selected from the group consisting of SEQ ID Nos:14-25, 141-152, and 162, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide (P) comprises an oligonucleotide selected from the group consisting of SEQ ID Nos:14-25, 141-152, and 162, or a pharmaceutically acceptable salt thereof.

**Table A. Modified Oligonucleotides**

| SEQ ID NO. | Modified Oligonucleotide Sequence<br>(5'→3') | Cmpd # |
|------------|----------------------------------------------|--------|
| <b>3</b>   | <u>u</u> scsgstscsgstsgstscsgstsT-c3         | 1.1b   |

|     |                                      |       |
|-----|--------------------------------------|-------|
| 4   | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 2.1b  |
| 5   | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 2.2b  |
| 6   | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 2.3b  |
| 7   | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 2.4b  |
| 8   | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 3.1b  |
| 9   | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 3.2b  |
| 10  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 3.3b  |
| 11  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 4.1b  |
| 12  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 4.2b  |
| 13  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 4.3b  |
| 14  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.1a  |
| 15  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.2a  |
| 16  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.3a  |
| 17  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.4a  |
| 18  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.5a  |
| 19  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.6a  |
| 20  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.7a  |
| 21  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.8a  |
| 22  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.9a  |
| 23  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.10a |
| 24  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.11a |
| 25  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 5.12a |
| 26  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 6.1b  |
| 27  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 6.2b  |
| 28  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 6.3b  |
| 29  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.1b  |
| 30  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.2b  |
| 31  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.3b  |
| 32  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.4b  |
| 33  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.5b  |
| 34  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.6b  |
| 35  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.7b  |
| 36  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.8b  |
| 37  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.9b  |
| 38  | <u>uscsgstscsgstsgstscsgstst</u> -c3 | 7.10b |
| 130 | uscsgstscsgstsgstscsgstst-c3         | 8.1b  |
| 131 | uscsgstscsgstsgstscsgstst-c3         | 9.1b  |

|     |                                          |        |
|-----|------------------------------------------|--------|
| 132 | uscsgstscsgstsgstscsgstst-c3             | 9.2b   |
| 133 | uscsgstscsgstsgstscsgstst-c3             | 9.3b   |
| 134 | uscsgstscsgstsgstscsgstst-c3             | 9.4b   |
| 135 | uscsgstscsgstsgstscsgstst-c3             | 10.1b  |
| 136 | uscsgstscsgstsgstscsgstst-c3             | 10.2b  |
| 137 | uscsgstscsgstsgstscsgststst-c3           | 10.3b  |
| 138 | <u>uscsgstscsgstsgstscsgstst-c3</u>      | 12.1b  |
| 139 | <u>uscsgstscsgstsgstscsgststst-c3</u>    | 12.2b  |
| 140 | <u>uscsgstscsgstsgstscsgststst-c3</u>    | 12.3b  |
| 141 | uscs2gstscsgstsgstscsgstst-c3            | 13.1a  |
| 142 | uscs2tscsgstsgstscsgstst-c3              | 13.2a  |
| 143 | uscsgstscs2gstsgstscsgstst-c3            | 13.3a  |
| 144 | uscsgstscsgs2tsgstscsgstst-c3            | 13.4a  |
| 145 | uscsgstscsgsts2gstscsgstst-c3            | 13.5a  |
| 146 | uscsgstscsgstsgs2tscsgstst-c3            | 13.6a  |
| 147 | uscsgstscsgstsgsts2csgstst-c3            | 13.7a  |
| 148 | uscsgstscsgstsgstscs2gstst-c3            | 13.8a  |
| 149 | uscsgstscsgstsgstscsgs2tst-c3            | 13.9a  |
| 150 | uscsgstscsgstsgstscsgsts2t-c3            | 13.10a |
| 151 | uscsgstscsgstsgstscsgsts <u>us</u> 2-c3  | 13.11a |
| 152 | uscs2gstscsgstsgstscsgsts <u>us</u> 2-c3 | 13.12a |
| 153 | <u>uscsgs2tscsgstsgstscsgststst-c3</u>   | 14.1b  |
| 154 | <u>uscsgstscsgstsgsts2csgststst-c3</u>   | 14.2b  |
| 155 | <u>uscsgs2tscsgstsgsts2csgststst-c3</u>  | 14.3b  |
| 156 | uscs2gstscsgstsgstscsgststst-c3          | 15.1b  |
| 157 | uscsgstscsgstsgs2tscsgststst-c3          | 15.2b  |
| 158 | uscs2gstscsgstsgs2tscsgststst-c3         | 15.3b  |
| 159 | uscsgstscs2gstsgstscsgststst-c3          | 15.4b  |
| 160 | uscsgstscsgs2tsgstscsgststst-c3          | 15.5b  |
| 161 | uscsgstscsgsts2gstscsgststst-c3          | 15.6b  |
| 162 | uscsgstscsgstsgsts2csgststst-c3          | 15.7a  |
| 163 | uscsgstscsgstsgsts2csgststst-c3          | 15.7b  |
| 164 | uscs2gstscsgstsgsts2csgststst-c3         | 15.8b  |
| 165 | uscsgs2tscsgstsgstscsgststst-c3          | 15.9b  |
| 166 | uscsgstscsgstsgstscs2gststst-c3          | 15.10b |

\* u: 5-Bromo-2'-deoxyuridine

**g:** 8-oxo-7,8-dihydro-2'-deoxyguanosine

**u:** 5-Bromo 2'-OMe uridine

**c:** 2'-OMe- Cytidine

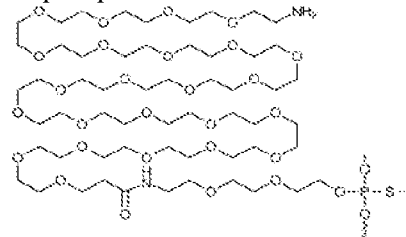
**t:** 2'-OMe- Thymidine

**u:** 2'-OMe- Uridine

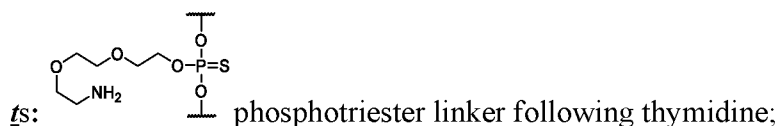
**u:** 2'-deoxyuridine

**T:** 2'-OMOE thymidine

**ts:** phosphotriester linker-PEG<sub>24</sub>-NH<sub>2</sub>



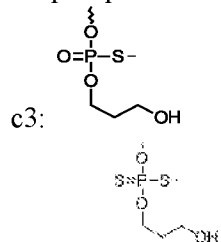
following thymidine;



Lower case: 2'-deoxy nucleotide

**s:** phosphorothioate linkage

**s2:** phosphorodithioate linkage



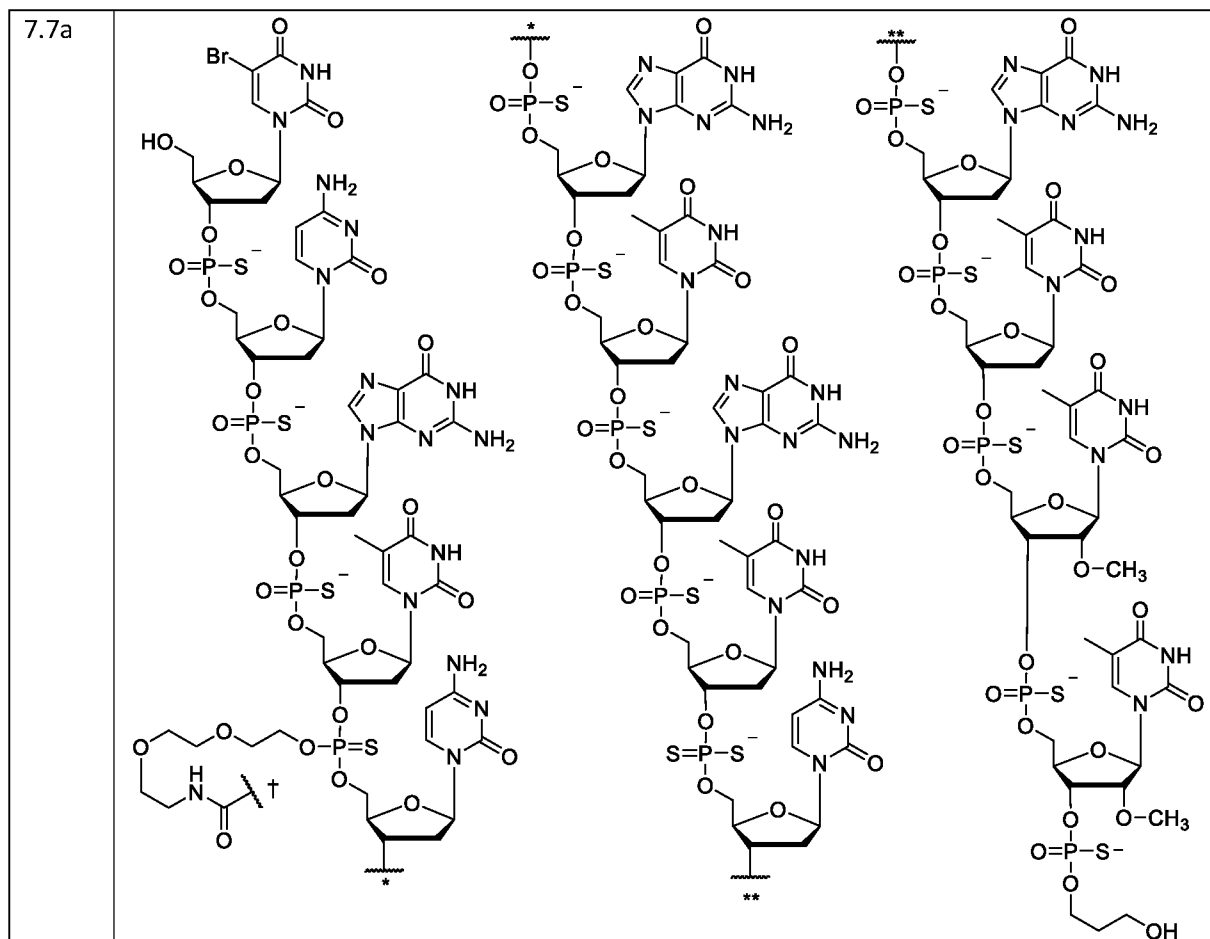
**s2-c3:**

**[0089]** In some embodiments, the immunomodulating oligonucleotide (*e.g.*, CpG oligonucleotide) comprises an oligonucleotide sequence as shown in Table A (compound numbers ending in “a”), or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide (*e.g.*, CpG oligonucleotide) is an oligonucleotide selected from the group consisting of the oligonucleotides of **Table 9**, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide (*e.g.*, CpG oligonucleotide) comprises an oligonucleotide selected from the group consisting of the oligonucleotides of **Table 9**, or a pharmaceutically acceptable salt thereof. In some embodiments, the immunomodulating oligonucleotide (*e.g.*, CpG oligonucleotide) is Compound 7.6a or Compound 7.7a, or a pharmaceutically acceptable salt thereof. In some embodiments, the

immunomodulating oligonucleotide (*e.g.*, CpG oligonucleotide) is Compound 7.7a, or a pharmaceutically acceptable salt thereof.

**Table 9. Modified Oligonucleotide Structures (with –PEG<sub>2</sub>NH<sub>2</sub>)**

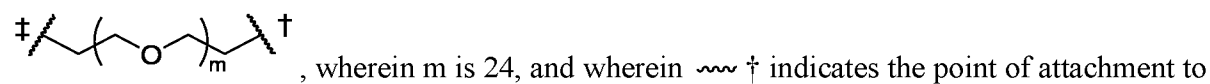
| Cmpd # | Structure |
|--------|-----------|
| 7.6a   |           |



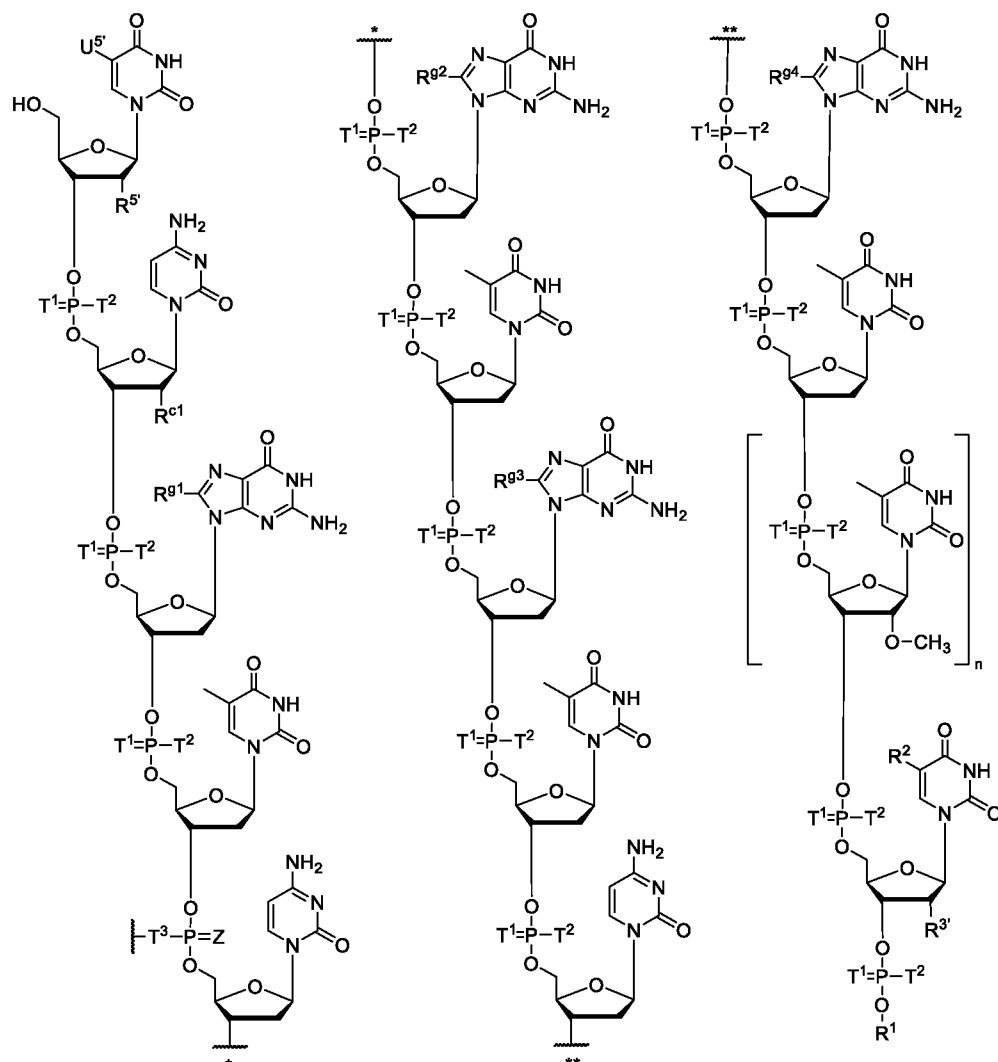
~~~~~\* and ~~~~~\*\* indicate the points of attachment within the oligonucleotide, wherein ~~~~~† indicates the point of attachment to the linker L.

[0090] In some embodiments, the oligonucleotide is functionalized with a chemical tag for attachment to the linking moiety. In some embodiments, the chemical tag is attached to an inter-nucleoside linkage of the oligonucleotide. In some embodiments, the chemical tag is attached to a 5' inter-nucleoside linkage. In some embodiments, the chemical tag is attached to a 3' inter-nucleoside linkage. In some embodiments, the inter-nucleoside linkage is a phosphorothioate linkage. In some embodiments, the inter-nucleoside linkage is a phosphorodithioate linkage. In some embodiments, the chemical tag is closer to the 5' end than the 3' end of the oligonucleotide. In some embodiments, the chemical tag is attached to a nucleobase.

[0091] In some embodiments of formula (A), the linker L is a group having the structure



the oligonucleotide P, and $\sim \ddagger$ indicates the point of attachment to the glutamine residue of the Q-tag; and wherein the oligonucleotide P comprises the structure:

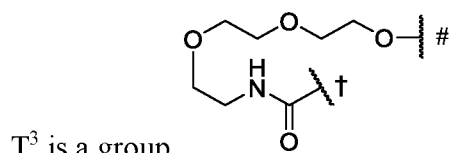


wherein

$\sim *$ and $\sim **$ indicate the points of attachment within the oligonucleotide;

each T^1 is independently O or S;

each T^2 is O^- or S^- ;



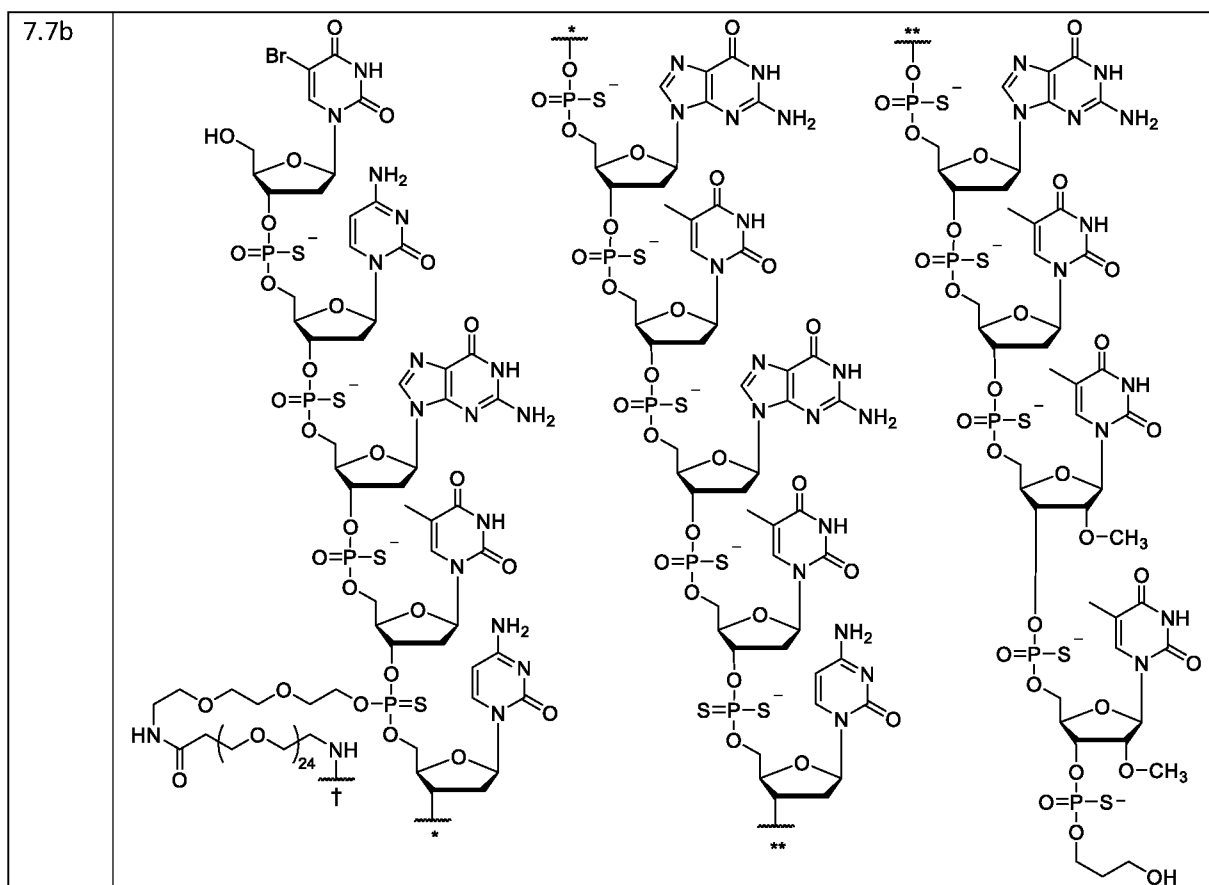
, wherein $\sim \ddagger$ indicates the point of attachment to L and wherein $\sim \#$ indicates the point of attachment to the rest of the oligonucleotide;

Z is O or S;
 U^{5'} is -H or halogen;
 R^{5'} is -H or methoxy;
 R^{c1} is -H or methoxy;
 R^{g1}, R^{g2}, R^{g3}, and R^{g4} are H or oxo, wherein
 R^{3'} is methoxy;
 R¹ is C₁₋₄-alkylene-hydroxy;
 R² is -H or methyl; and
 n is an integer from 0 to 2.

[0092] In some embodiments, the linker-oligonucleotide L-P comprises an oligonucleotide sequence as shown in Table A, or a pharmaceutically acceptable salt thereof. In some embodiments, the linker-oligonucleotide L-P is a compound as shown in **Table 10**, or a pharmaceutically acceptable salt thereof. In some embodiments, the linker-oligonucleotide L-P is Compound 7.6b or Compound 7.7b, or a pharmaceutically acceptable salt thereof. In some embodiments, the linker-oligonucleotide L-P is Compound 7.6b, or a pharmaceutically acceptable salt thereof. In some embodiments, the linker-oligonucleotide L-P is Compound 7.7b, or a pharmaceutically acceptable salt thereof. In some embodiments, the linker-oligonucleotide L-P comprises the oligonucleotide of SEQ ID NO:34, or a pharmaceutically acceptable salt thereof. In some embodiments, the linker-oligonucleotide L-P comprises the oligonucleotide of SEQ ID NO:35, or a pharmaceutically acceptable salt thereof. In some embodiments, the linker-oligonucleotide L-P comprises an oligonucleotide selected from the group consisting of SEQ ID Nos:3-13, 26-38, 130-140, 153-161, and 163-166, or a pharmaceutically acceptable salt thereof.

Table 10. Modified Oligonucleotide Structures (with -PEG₂NHCOPEG₂₄NH₂)

| Cmpd
| Structure |
|-----------|--|
| 7.6b | <p>The image displays three chemical structures of compound 7.6b, which is a branched nucleotide derivative. Each structure features a central sugar moiety (ribose or deoxyribose) linked to multiple nucleoside units via phosphate and sulfonate groups. The structures are labeled with asterisks and double asterisks, indicating specific modifications or linkages. The leftmost structure includes a brominated nucleoside unit and a long polyether chain. The middle structure shows a sulfonate group and a double asterisk label. The rightmost structure features a methyl group and a double asterisk label.</p> |



~~~~~\* and ~~~~~\*\* indicate the points of attachment within the oligonucleotide, wherein ~~~~~† indicates the point of attachment to the linker L.

#### Anti-CD22 antibodies with O-tags

**[0093]** In some embodiments, an oligonucleotide of the present disclosure is conjugated to anti-CD22 antibody. In some embodiments, the oligonucleotide is conjugated to an antibody via one or more Q tags. In some embodiments, the Q tag comprises a glutamine residue which is linked to the rest of the conjugate. In still further embodiments of the present aspect, which may be combined with any of the preceding embodiments, each Q tag independently comprises or is a peptide sequence selected from the group consisting of SEQ ID NOs: 39-55. In some embodiments, each Q tag independently comprises or is a peptide sequence selected from the group consisting of the peptide sequences of **Table 3**. In other embodiments of the present aspect, each Q tag independently comprises or is a peptide sequence selected from the group consisting of SEQ ID NOs: 40-55. In yet other embodiments, each Q tag independently comprises or is a peptide sequence selected from the group consisting of SEQ ID NOs: 47-49. In some

embodiments, the Q-tag comprises LLQGG (SEQ ID NO:172), GGGLLQGG (SEQ ID NO:173), RPQGF (SEQ ID NO:47), or RPQGFGPP (SEQ ID NO:49). In some embodiments, the Q-tag comprises a peptide sequence RPQGF (SEQ ID NO:47). In certain embodiments, the Q-tag comprising a peptide sequence RPQGF (SEQ ID NO:47) is selected from the group consisting of RPQGF (SEQ ID NO:47), RPQGFPP (SEQ ID NO:48), and RPQGFGPP (SEQ ID NO:49). In some embodiments, the Q-tag comprises a peptide sequence RPQGFGPP (SEQ ID NO:49).

[0094] In some embodiments, the Q-tag comprises one or more sequences shown in **Table 3**.

**Table 3. Q-tag Peptide Sequences**

| SEQ ID NO. | Peptide Sequences |
|------------|-------------------|
| 39         | LSLSPGLLQGG-OH    |
| 40         | WPAQGPT           |
| 41         | WPQGPT            |
| 42         | WAPQGPT           |
| 43         | WAQGPT            |
| 44         | TPGQAPW           |
| 45         | PNPQLPF           |
| 46         | RPQQF             |
| 47         | RPQGF             |
| 48         | RPQGFPP           |
| 49         | RPQGFGPP          |
| 50         | RPRPQQF           |
| 51         | LSQSKVLG          |
| 52         | WGGQLL            |
| 53         | WALQRPHYSYPD      |
| 54         | WALQRPYTLTES      |
| 55         | WALQGPYTLTES      |

[0095] Certain aspects of the present disclosure relate to CD22 and anti-CD22 antibodies. In some embodiments, CD22 refers to human CD22, and the antibodies bind human CD22. CD22 is also known as Siglec-2, and CD22 gene and polypeptide sequences (*e.g.*, human gene and polypeptide sequences) are known in the art. *See, e.g.*, NCBI Gene ID No. 933 and NCBI Ref. Seq. Accession No. NP\_001172028. Any of the anti-CD22 antibodies provided herein may find use in the conjugates and methods of the present disclosure.

[0096] In some embodiments, an antibody or conjugate of the present disclosure comprises a VH domain comprising 1, 2, or 3 CDRs of a single antibody shown in **Table 4**. In some embodiments, an antibody or conjugate of the present disclosure comprises a VH domain comprising the 3 CDRs of a single antibody shown in **Table 4**. In some embodiments, an antibody or conjugate of the present disclosure comprises a VL domain comprising 1, 2, or 3 CDRs of a single antibody shown in **Table 4**. In some embodiments, an antibody or conjugate of the present disclosure comprises a VL domain comprising the 3 CDRs of a single antibody shown in **Table 4**. In some embodiments, an antibody or conjugate of the present disclosure comprises a VH domain comprising 1, 2, or 3 CDRs of a single antibody shown in **Table 4** and a VL domain comprising 1, 2, or 3 CDRs of a single antibody shown in **Table 4**. In some embodiments, an antibody or conjugate of the present disclosure comprises a VH domain comprising the 3 CDRs of a single antibody shown in **Table 4** and a VL domain comprising the 3 CDRs of a single antibody shown in **Table 4**. In some embodiments, an antibody or conjugate of the present disclosure comprises a VH domain comprising a CDR-H1 comprising the sequence of SEQ ID NO:113, a CDR-H2 comprising the sequence of SEQ ID NO:115, and a CDR-H3 comprising the sequence of SEQ ID NO:116. In some embodiments, an antibody or conjugate of the present disclosure comprises a VH domain comprising a CDR-H1 comprising the sequence of SEQ ID NO:114, a CDR-H2 comprising the sequence of SEQ ID NO:189, and a CDR-H3 comprising the sequence of SEQ ID NO:116. In some embodiments, an antibody or conjugate of the present disclosure comprises a VL domain comprising a CDR-L1 comprising the sequence of SEQ ID NO:117, a CDR-L2 comprising the sequence of SEQ ID NO:119, and a CDR-L3 comprising the sequence of SEQ ID NO:120. In some embodiments, an antibody or conjugate of the present disclosure comprises a VL domain comprising a CDR-L1 comprising the sequence of SEQ ID NO:118, a CDR-L2 comprising the sequence of SEQ ID NO:177, and a CDR-L3 comprising the sequence of SEQ ID NO:120. In some embodiments, an antibody or conjugate of the present disclosure comprises a VL domain comprising a CDR-L1 comprising the sequence of SEQ ID NO:117, a CDR-L2 comprising the sequence of SEQ ID NO:119, and a CDR-L3 comprising the sequence of SEQ ID NO:121. In some embodiments, an antibody or conjugate of the present disclosure comprises a VL domain comprising a CDR-L1 comprising the sequence of SEQ ID NO:117, a CDR-L2 comprising the sequence of SEQ ID NO:119, and a CDR-L3 comprising the sequence of SEQ ID NO:122. In some embodiments, an antibody or

conjugate of the present disclosure comprises a VH domain comprising a CDR-H1 comprising the sequence of SEQ ID NO:113, a CDR-H2 comprising the sequence of SEQ ID NO:115, and a CDR-H3 comprising the sequence of SEQ ID NO:116 and a VL domain comprising a CDR-L1 comprising the sequence of SEQ ID NO:117, a CDR-L2 comprising the sequence of SEQ ID NO:119, and a CDR-L3 comprising the sequence of SEQ ID NO:120. In some embodiments, an antibody or conjugate of the present disclosure comprises a VH domain comprising a CDR-H1 comprising the sequence of SEQ ID NO:113, a CDR-H2 comprising the sequence of SEQ ID NO:115, and a CDR-H3 comprising the sequence of SEQ ID NO:116 and a VL domain comprising a CDR-L1 comprising the sequence of SEQ ID NO:117, a CDR-L2 comprising the sequence of SEQ ID NO:119, and a CDR-L3 comprising the sequence of SEQ ID NO:121. In some embodiments, an antibody or conjugate of the present disclosure comprises a VH domain comprising a CDR-H1 comprising the sequence of SEQ ID NO:113, a CDR-H2 comprising the sequence of SEQ ID NO:115, and a CDR-H3 comprising the sequence of SEQ ID NO:116 and a VL domain comprising a CDR-L1 comprising the sequence of SEQ ID NO:117, a CDR-L2 comprising the sequence of SEQ ID NO:119, and a CDR-L3 comprising the sequence of SEQ ID NO:122.

**Table 4.** Anti-CD22 antibody CDR sequences

| Antibody | CDR-H1                      | CDR-H2                      | CDR-H3                              | CDR-L1                    | CDR-L2              | CDR-L3                       |
|----------|-----------------------------|-----------------------------|-------------------------------------|---------------------------|---------------------|------------------------------|
| RH1      | GFAFSIYD<br>(SEQ ID NO:113) | ISSGGGTT<br>(SEQ ID NO:115) | ARHSGYGTHWGVLFAY<br>(SEQ ID NO:116) | --                        | --                  | --                           |
| RH2      | GFAFSIYD<br>(SEQ ID NO:113) | ISSGGGTT<br>(SEQ ID NO:115) | ARHSGYGTHWGVLFAY<br>(SEQ ID NO:116) | --                        | --                  | --                           |
| RH3      | GFTFSSYE<br>(SEQ ID NO:114) | ISSSGSTI<br>(SEQ ID NO:189) | ARHSGYGTHWGVLFAY<br>(SEQ ID NO:116) | --                        | --                  | --                           |
| RH4      | GFAFSIYD<br>(SEQ ID NO:113) | ISSGGGTT<br>(SEQ ID NO:115) | ARHSGYGTHWGVLFAY<br>(SEQ ID NO:116) | --                        | --                  | --                           |
| RL1      | --                          | --                          | --                                  | QDIHGY<br>(SEQ ID NO:117) | YTS (SEQ ID NO:119) | QQGNTLPWT<br>(SEQ ID NO:120) |
| RL1'     |                             |                             |                                     | QDIHGY<br>(SEQ ID NO:117) | YTS (SEQ ID NO:119) | QQGATLPWT<br>(SEQ ID NO:121) |

|       |    |    |    |                              |                           |                                 |
|-------|----|----|----|------------------------------|---------------------------|---------------------------------|
| RL1'' |    |    |    | QDIHGY<br>(SEQ ID<br>NO:117) | YTS (SEQ<br>ID<br>NO:119) | QQGSTLPWT<br>(SEQ ID<br>NO:122) |
| RL2   | -- | -- | -- | QDIHGY<br>(SEQ ID<br>NO:117) | YTS (SEQ<br>ID<br>NO:119) | QQGNTLPWT<br>(SEQ ID<br>NO:120) |
| RL3   | -- | -- | -- | QSISSY<br>(SEQ ID<br>NO:118) | AAS (SEQ<br>ID<br>NO:177) | QQGNTLPWT<br>(SEQ ID<br>NO:120) |
| RL4   | -- | -- | -- | QDIHGY<br>(SEQ ID<br>NO:117) | YTS (SEQ<br>ID<br>NO:119) | QQGNTLPWT<br>(SEQ ID<br>NO:120) |
| RL5   | -- | -- | -- | QDIHGY<br>(SEQ ID<br>NO:117) | YTS (SEQ<br>ID<br>NO:119) | QQGNTLPWT<br>(SEQ ID<br>NO:120) |

[0097] In certain embodiments, the anti-CD22 antibody is an antibody comprising a VH and VL as shown below in **Table 5**.

**Table 5. Anti-CD22 Antibody Sequences**

| Name        | Domain | SEQ ID<br>NO: | Sequence                                                                                                                             |
|-------------|--------|---------------|--------------------------------------------------------------------------------------------------------------------------------------|
| RFB4        | VH     | 56            | EVQLVESGGGLVKGPGSLKLSAASGFAFSIYDMSWVRQTPE<br>KRLEWVAYISSGGGTTYYPDTVKGRFTISRDNANTLYLQMSS<br>LKSEDTAMYYCARHSGYGSSYGVLFAFWGQGTTLTVSS    |
| RFB4        | VL     | 57            | DIQMTQTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGTV<br>KLLIYTSILHSGVPSRFSGSGSGTDYSLTISNLEQEDFATYFCQQG<br>NTLPWTFGGGTTKLEIK                   |
| epratuzumab | VH     | 58            | QVQLVQSGAEVKKPGSSVKVSKASGYTFTSYWLHWVRQAPG<br>QGLEWIGYINPRNDYTEYNQNFKDKATITADESTNTAYMELSSL<br>RSEDTAFYFCARRDITTFYWGQGTTLTVSS          |
| epratuzumab | VL     | 59            | DIQLTQSPSSLSASVGDRTVMCKSSQSVLYSANHKNYLAWYQQ<br>KPGKAPKLLIYWASTRESGVPSRFSGSGSGTDFTLTISLQPEDIA<br>YYCHQYLSSWTFGGGTTKLEIK               |
| m971        | VH     | 60            | QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPS<br>RGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNS<br>VTPEDTAVYYCAREVTGDLEDAFDIWGQGTMTVTVSS |
| m971        | VL     | 61            | DIQMTQSPSSLSASVGDRTITCRASQTIWSYLNWYQQRPKGA<br>PNLLIYAASSLQSGVPSRFSGRGSGTDFTLTISLQAEAFATYYCQ<br>QSYSIPQTFGQGTKEIK                     |
| 10F4        | VH     | 62            | EVQLVESGGGLVQPGGSLRLSAAAGYEFSSRW/MNWVRQAPG<br>KGLEWVGRIYPGDGDTNYSKGKGRFTISADTSKNTAYLQMNSL<br>RAEDTAVYYCARDGSSWDWYFDVWGQGTTLTVSS      |
| 10F4        | VL     | 63            | MDIQMTQSPSSLSASVGDRTITCRSSQIVHSGNTFLEWYQQ<br>KPGKAPKLLIYKVSNRFSGVPSRFSGSGSGTDFTLTISLQPEDFAT<br>YYCFQGSQFPYTFGQGTKEIK                 |

| Name | Domain | SEQ ID NO: | Sequence                                                                                                                          |
|------|--------|------------|-----------------------------------------------------------------------------------------------------------------------------------|
| RH1  | VH     | 64         | EVQLVESGGGLVQPGGSLRLSCAASGFAFSIYDMSWVRQAPGK<br>GLEWVAYISSGGGTYYPDVTVKGRFTISRDNKNTLYLQMNSLR<br>AEDTAVYYCARHSGYGTHWGVLFAYWGRGTLTVSS |
| RH2  | VH     | 65         | QVQLLESQGGVQPGGSLRLSCAASGFAFSIYDMNWVRQAPG<br>KGLEWVSAISSGGGTYYADSVKGRFTISRDNKNSLYLQMNSLR<br>RAEDTAVYYCARHSGYGTHWGVLFAYWGRGTLTVSS  |
| RH3  | VH     | 66         | EVQLVESGGGLVQPGGSLRLSCAASGFTFSYEMNWVRQAPGK<br>GLEWVSYISSSGSTIYYADSVKGRFTISRDNKNSLYLQMNSLRAE<br>DTAVYYCARHSGYGTHWGVLFAYWGRGTLTVSS  |
| RH4  | VH     | 67         | QVQLQESGPGLVKPSDTLSLTCTVSGFAFSIYDMSWIRQPPGKG<br>LEWIAYISSGGGTYYNPSLKSRTISVDTSKNQFSLKLSVTAADT<br>AVYYCARHSGYGTHWGVLFAYWGRGTLTVSS   |
| RL1  | VL     | 68         | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKA<br>PKLLIYYTSLHSGVPSRFSGSGSGTDFTLTISLQPEDFATYFCQQ<br>GNTLPWTFGQGTKLEIK                  |
| RL2  | VL     | 69         | DIQMTQSPSSVSASVGDRVTITCRASQDIHGYNWYQQKPGKA<br>PKLLIYYTSSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYFCQQ<br>GNTLPWTFGQGTKLEIK                 |
| RL3  | VL     | 70         | DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP<br>KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYFCQQ<br>GNTLPWTFGQGTKLEIK                |
| RL4  | VL     | 71         | EIVLTQSPATLSLSPGERATLSCRASQDIHGYNWYQQKPGQAP<br>RLLIYYTSLHSGIPARFSGSGPGTDFTLTISLQPEDFAVYYCQQG<br>NTLPWTFGGGGTKLEIK                 |
| RL5  | VL     | 72         | DIVMTQTPLSLSVTPGQPASISCRASQDIHGYNWYQQKPGQSP<br>QLLIYYTSLHSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCQQ<br>GNTLPWTFGGGGTKLEIK                |

**[0098]** In some embodiments, the anti-CD22 antibody or conjugate comprises a VH domain shown in Table 6 and a VL domain shown in Table 7. For example, in some embodiments, the anti-CD22 antibody or conjugate comprises a VH domain comprising a sequence selected from the group consisting of SEQ ID Nos:64-67 and a VL domain comprising a sequence selected from the group consisting of 68-91. In some embodiments, the anti-CD22 antibody or conjugate comprises a VH domain comprising the sequence of SEQ ID NO:65 and a VL domain comprising the sequence of SEQ ID NO:73 or 87. In some embodiments, the anti-CD22 antibody or conjugate comprises a VH domain comprising the sequence of SEQ ID NO:65 and a VL domain comprising the sequence of SEQ ID NO:73. In some embodiments, the anti-CD22 antibody or conjugate comprises a VH domain comprising the sequence of SEQ ID NO:65 and a VL domain comprising the sequence of SEQ ID NO:87.

**Table 6. Anti-CD22 Antibody VH Sequences.**

| Name | Sequence                                                                                                                          | SEQ ID NO |
|------|-----------------------------------------------------------------------------------------------------------------------------------|-----------|
| RH1  | EVQLVESGGGLVQPGGSLRLSCAASGFAFSIYDMSWVRQAPGKGLEWVAYISSGG<br>GTTYYPDTVKGRTISRDNKNTLYLQMNSLRAEDTAVYYCARHSGYGTHWGVLFAY<br>WGRGTLTVSS  | 64        |
| RH2  | QVQLLESQGGGVVQPGGSLRLSCAASGFAFSIYDMNWVRQAPGKGLEWVSAISSGG<br>GTTYADSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARHSGYGTHWGVLFAY<br>WGRGTLTVSS | 65        |
| RH3  | EVQLVESGGGLVQPGGSLRLSCAASGFTSSYEMNWVRQAPGKGLEWVSYISSSGS<br>TIYYADSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARHSGYGTHWGVLFAY<br>WGRGTLTVSS  | 66        |
| RH4  | QVQLQESGPGLVKPSDTLSLTCTVSGFAFSIYDMSWIRQPPGKGLEWVAYISSGGGT<br>TYYNPSLSRVTSVDTSKNQFSLKSSVTAADTAVYYCARHSGYGTHWGVLFAYW<br>GRGTLTVSS   | 67        |

**Table 7. Anti-CD22 Antibody VL Sequences.**

| Name        | Sequence                                                                                                       | SEQ ID NO |
|-------------|----------------------------------------------------------------------------------------------------------------|-----------|
| RL1         | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGNTLPWTFGQGTKLEIK    | 68        |
| RL2         | DIQMTQSPSSVSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSSLQSG<br>VPSRFGSGSGTDFTLTISLQPEDFATYFCQQGNTLPWTFGQGTKLEIK   | 69        |
| RL3         | DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGNTLPWTFGQGTKLEIK  | 70        |
| RL4         | EIVLTQSPATLSLSPGERATLSCRASQDIHGYNWYQQKPGQAPRLIYYTILHSGIP<br>ARFSGSGPGTDFTLTISLQPEDFAVYYCQQGNTLPWTFGGGTKLEIK    | 71        |
| RL5         | DIVMTQTPLSLSVTPGGQPASISCRASQDIHGYNWYQQKPGQSPQLLIYYTILHSGV<br>PDRFGSGSGTDFTLTKISRVEAEDVGYYFCQQGNTLPWTFGGGTKLEIK | 72        |
| RL1<br>N92A | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGATLPWTFGQGTKLEIK    | 73        |
| RL1<br>N92C | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGCTLPWTFGQGTKLEIK    | 74        |
| RL1<br>N92D | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGDTLPWTFGQGTKLEIK    | 75        |
| RL1<br>N92E | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGETLPWTFGQGTKLEIK    | 76        |
| RL1<br>N92F | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGFTLPWTFGQGTKLEIK    | 77        |
| RL1<br>N92G | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGGTLPWTFGQGTKLEIK    | 78        |
| RL1<br>N92H | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGHTLPWTFGQGTKLEIK    | 79        |
| RL1<br>N92I | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGITLPWTFGQGTKLEIK    | 80        |
| RL1<br>N92K | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTILHSGV<br>PSRFGSGSGTDFTLTISLQPEDFATYFCQQGKTLPWTFGQGTKLEIK    | 81        |

|             |                                                                                                                |    |
|-------------|----------------------------------------------------------------------------------------------------------------|----|
| RL1<br>N92L | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGLTLPWTFGQGTKLEIK  | 82 |
| RL1<br>N92M | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGMTLPWTFGQGTKLEIK  | 83 |
| RL1<br>N92P | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGPTLPWTFGQGTKLEIK  | 84 |
| RL1<br>N92Q | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGQTLPWTFGQGTKLEIK  | 85 |
| RL1<br>N92R | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGRTLTPWTFGQGTKLEIK | 86 |
| RL1<br>N92S | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGSTLPWTFGQGTKLEIK  | 87 |
| RL1<br>N92T | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGTTLPWTFGQGTKLEIK  | 88 |
| RL1<br>N92V | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGVTLPWTFGQGTKLEIK  | 89 |
| RL1<br>N92W | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGWTLPWTFGQGTKLEIK  | 90 |
| RL1<br>N92Y | DIQMTQSPSSLSASVGDRVTITCRASQDIHGYNWYQQKPGKAPKLLIYYTSILHSGV<br>PSRFGSGSGTDFTLTISSLQPEDFATYFCQQGYTLPWTFGQGTKLEIK  | 91 |

[0099] In some embodiments, the anti-CD22 antibody or conjugate comprises a heavy chain comprising a VH domain shown in Table 6 and a heavy chain constant domain sequence shown in Table 8A. In some embodiments, the anti-CD22 antibody or conjugate comprises a heavy chain comprising a VL domain shown in Table 7 and a light chain constant domain sequence shown in Table 8A.

**Table 8A. Antibody constant domain sequences.**

| Name           | SEQ ID NO: | Sequence                                                                                                                                                                                                                                                                                                                                                              |
|----------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| IgG1 wildtype  | 92         | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA<br>LTSGVHTFPAVLQSSGLYSLSSVTPVSSSLGTQTYICNVNHKPSN<br>TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY<br>NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREE<br>MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDS<br>GSFFLYSKLTVDKSRW<br>QQGNVFSCSVMHEALHNHYTQKSLSLSPG |
| IgG1_AAA_N297A | 93         | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA<br>LTSGVHTFPAVLQSSGLYSLSSVTPVSSSLGTQTYICNVNHKPSN<br>TKVDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMI<br>SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY<br>ASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ<br>PENNYKTTPVLDSGSFFLYSKLTVDKSRWQQGNVFSCSVMHE<br>ALHNHYTQKSLSLSPG     |

| Name             | SEQ ID NO: | Sequence                                                                                                                                                                                                                                                                                                                                                                     |
|------------------|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| IgG1_AAA         | 94         | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA<br>LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN<br>TKVDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY<br>NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ<br>PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE<br>ALHNHYTQKSLSLSPG        |
| IgG1_AAA + S-tag | 95         | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA<br>LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN<br>TKVDKKVEPKSCDKTHTCPPCPAPEAAGAPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY<br>NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ<br>PENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE<br>ALHNHYTQKSLSLSPGRPQGFPP |
| IgG1_N297A       | 96         | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA<br>LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN<br>TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY<br>ASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREE<br>MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD<br>GSFFLYSKLTVDKSRW<br>QQGNVFSCSVMHEALHNHYTQKSLSLSPG    |
| IgG1_D265A       | 97         | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA<br>LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN<br>TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY<br>NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREE<br>MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD<br>GSFFLYSKLTVDKSRW<br>QQGNVFSCSVMHEALHNHYTQKSLSLSPG    |
| IgG1_N297A/D265A | 98         | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA<br>LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN<br>TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY<br>ASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREE<br>MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD<br>GSFFLYSKLTVDKSRW<br>QQGNVFSCSVMHEALHNHYTQKSLSLSPG    |
| IgG2             | 99         | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSG<br>LYSLSSVVTVPSSNFGTQTYTCNVNHHKPSNTKVDKTKVERKCCVEC<br>PPCPAPPVAGPSVFL<br>FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN<br>AKTKPREEQFNSTFRV<br>VSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ<br>VYTLPPSREEMTKNQ                                                                                              |

| Name             | SEQ ID NO: | Sequence                                                                                                                                                                                                                                                                                                                                                                        |
|------------------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                  |            | VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSGSSFFLY<br>SKLTVDKSRWQQGNV<br>FSCSVMHEALHNHYTQKSLSLSPG                                                                                                                                                                                                                                                                                    |
| IgG2Da           | 100        | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNT<br>KVDKTVVERKCCVECPAPPPVAGPSVFLFPPKPKDTLMISRTPE<br>VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR<br>VVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKTKGQPREP<br>QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN<br>YKTTPPMLDSGSSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN<br>HYTQKSLSLSPG                |
| IgG2Da_N297A     | 101        | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNT<br>KVDKTVVERKCCVECPAPPPVAGPSVFLFPPKPKDTLMISRTPE<br>VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFASTFR<br>VVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKTKGQPREP<br>QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN<br>YKTTPPMLDSGSSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN<br>HYTQKSLSLSPG                |
| IgG2_N297A       | 102        | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSG<br>LYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVVERKCCVECP<br>PCPAPPPVAGPSVFL<br>FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN<br>AKTKPREEQFASTFRV<br>VSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ<br>VYTLPPSREEMTKNQ<br>VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSGSSFFLY<br>SKLTVDKSRWQQGNV<br>FSCSVMHEALHNHYTQKSLSLSPG |
| IgG2Da_D265A     | 103        | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNT<br>KVDKTVVERKCCVECPAPPPVAGPSVFLFPPKPKDTLMISRTPE<br>VTCVVAVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR<br>VVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKTKGQPREP<br>QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN<br>YKTTPPMLDSGSSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN<br>HYTQKSLSLSPG                 |
| IgG4_S228P       | 104        | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNT<br>KVDKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPE<br>VTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR<br>VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP<br>QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN<br>YKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN<br>HYTQKSLSLSLG               |
| IgG4_S228P_D265A | 105        | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNT<br>KVDKRVESKYGPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPE<br>VTCVVAVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR<br>VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP<br>QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN                                                                                |

| Name               | SEQ ID NO: | Sequence                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    |            | YKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN<br>HYTQKSLSLSLG                                                                                                                                                                                                                                                                                                                    |
| IgG4_S228P, L235E  | 106        | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSGLYSLSSVVPSSSLGKTYTCNVDHKPSNT<br>KVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPE<br>VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR<br>VVSFLTTLHQLDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPREP<br>QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN<br>YKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN<br>HYTQKSLSLSLG                 |
| IgG4_S228P,N297A   | 107        | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL<br>TSGVHTFPAVLQSSGLYSLSSVVPSSSLGKTYTCNVDHKPSNT<br>KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE<br>VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFASTYR<br>VVSFLTTLHQLDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPREP<br>QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN<br>YKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN<br>HYTQKSLSLSLG                 |
| IgG1_wt + S-tag    | 178        | ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA<br>LTSGVHTFPAVLQSSGLYSLSSVVPSSSLGTQTYICNVNHKPSN<br>TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI<br>SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY<br>NSTYRVVSFLTTLHQLDWLNGKEYCKVSNKALPAPIEKTISKAKG<br>QPREPQVYTLPPSREE<br>MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSD<br>GSFFLYSKLTVDKSRW<br>QQGNVFSCSVMHEALHNHYTQKSLSLSPGRPQGFGPP |
| Human Kappa        | 108        | RTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKVDN<br>ALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVT<br>HQLSSPVTKSFNRGEC                                                                                                                                                                                                                                                              |
| Human Lambda IGLC1 | 109        | GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD<br>GSPVKAGVETTKPSKQSNKNYAASSYLSLTPEQWKSHRSYSCQVT<br>HEGSTVEKTVAPTECS                                                                                                                                                                                                                                                             |
| Human Lambda IGLC2 | 110        | GQPKAAPSVTTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD<br>SSPVKAGVETTTTPSKQSNKNYAASSYLSLTPEQWKSHRSYSCQVT<br>HEGSTVEKTVAPTECS                                                                                                                                                                                                                                                           |

**[0100]** In some embodiments, the anti-CD22 antibody or conjugate comprises a heavy chain (including Q-tag) shown in Table 8B, and a light chain shown in Table 8B. In some embodiments, the anti-CD22 antibody or conjugate comprises a heavy chain comprising the sequence of SEQ ID NO:179 or 180, and a light chain comprising the sequence of SEQ ID NO:181 or 182. In some embodiments, the anti-CD22 antibody or conjugate comprises a heavy chain comprising the sequence of SEQ ID NO:179, and a light chain comprising the sequence of SEQ ID NO:181. In some embodiments, the anti-CD22 antibody or conjugate comprises a heavy chain comprising the sequence of SEQ ID NO:179, and a light chain comprising the

sequence of SEQ ID NO:182. In some embodiments, the anti-CD22 antibody or conjugate comprises a heavy chain comprising the sequence of SEQ ID NO:180, and a light chain comprising the sequence of SEQ ID NO:181. In some embodiments, the anti-CD22 antibody or conjugate comprises a heavy chain comprising the sequence of SEQ ID NO:180, and a light chain comprising the sequence of SEQ ID NO:182. In some embodiments, the anti-CD22 antibody or conjugate comprises two heavy chains, each comprising the sequence of SEQ ID NO:179 or 180, and two light chains, each comprising the sequence of SEQ ID NO:181 or 182. In some embodiments, the anti-CD22 antibody or conjugate comprises two heavy chains, each comprising the sequence of SEQ ID NO:179, and two light chains, each comprising the sequence of SEQ ID NO:181. In some embodiments, the anti-CD22 antibody or conjugate comprises two heavy chains, each comprising the sequence of SEQ ID NO:179, and two light chains, each comprising the sequence of SEQ ID NO:182. In some embodiments, the anti-CD22 antibody or conjugate comprises two heavy chains, each comprising the sequence of SEQ ID NO:180, and two light chains, each comprising the sequence of SEQ ID NO:181. In some embodiments, the anti-CD22 antibody or conjugate comprises two heavy chains, each comprising the sequence of SEQ ID NO:180, and two light chains, each comprising the sequence of SEQ ID NO:182.

**Table 8B. Anti-CD22 antibody sequences (including C-terminal Q-tag on heavy chains)**

| Heavy chain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Light chain                                                                                                                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| QVQLLES GGGV VQPGGSLRLSCAASGFAFSIYDMNWVRQ<br>APGKGLEWVSAISSGGGTTYADSVKGRFTISRDNAKNSLY<br>LQMNSLRAEDTAVYYCARHSGYGTHWGVLFAYWGRGTL<br>VTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV<br>TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT<br>QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLG<br>GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN<br>WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL<br>NGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE<br>EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPP<br>VLDSGGSFFLYSLKLTVDKSRWQQGNVFCFSVMHEALHNH<br>YTQKSLSLSPGRPQGFGPP (SEQ ID NO:179) | DIQMTQSPSSLSASVGDRVITTCRASQDIHGYN<br>WYQQKPGKAPKLLIYYTILHSGVPSRFSGSGSGT<br>DFTLTISLQPEDFATYFCQQGATLPWTFGQGTKL<br>EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY<br>PREAKVQWKVDNALQSGNSQESVTEQDSKDSY<br>SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF<br>NRGEC (SEQ ID NO:181) |
| QVQLLES GGGV VQPGGSLRLSCAASGFAFSIYDMNWVRQ<br>APGKGLEWVSAISSGGGTTYADSVKGRFTISRDNAKNSLY<br>LQMNSLRAEDTAVYYCARHSGYGTHWGVLFAYWGRGTL<br>VTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV<br>TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT<br>QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAEEA<br>GAPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN<br>WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL                                                                                                                                                                             | DIQMTQSPSSLSASVGDRVITTCRASQDIHGYN<br>WYQQKPGKAPKLLIYYTILHSGVPSRFSGSGSGT<br>DFTLTISLQPEDFATYFCQQGSTLPWTFGQGTKL<br>EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY<br>PREAKVQWKVDNALQSGNSQESVTEQDSKDSY<br>SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF<br>NRGEC (SEQ ID NO:182) |

|                                                                                                                                                                          |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE<br>EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP<br>VLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH<br>YTQKSLSLSPGRPQGFGPP (SEQ ID NO:180) |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

**[0101]** In some embodiments, a conjugate according to Table 11 (*e.g.*, conjugates A-F) is used in the methods of the present disclosure.

**Table 11.** Exemplary anti-CD22 antibody-CpG oligonucleotide conjugates.

| Conjugate | VH           | VL           | Heavy chain constant domain | Linker-CpG   | Q-tag        |
|-----------|--------------|--------------|-----------------------------|--------------|--------------|
| A         | SEQ ID NO:65 | SEQ ID NO:73 | SEQ ID NO:92                | SEQ ID NO:34 | SEQ ID NO:49 |
| B         | SEQ ID NO:65 | SEQ ID NO:87 | SEQ ID NO:92                | SEQ ID NO:35 | SEQ ID NO:49 |
| C         | SEQ ID NO:65 | SEQ ID NO:87 | SEQ ID NO:94                | SEQ ID NO:35 | SEQ ID NO:49 |
| D         | SEQ ID NO:65 | SEQ ID NO:87 | SEQ ID NO:94                | SEQ ID NO:34 | SEQ ID NO:49 |
| E         | SEQ ID NO:65 | SEQ ID NO:73 | SEQ ID NO:96                | SEQ ID NO:34 | SEQ ID NO:47 |
| F         | SEQ ID NO:65 | SEQ ID NO:87 | SEQ ID NO:92                | SEQ ID NO:35 | SEQ ID NO:47 |

### III. KITS

**[0102]** Also provided herein is a kit comprising a conjugate as described above for use in any of methods described herein.

**[0103]** In another aspect, the kit further comprises a package insert including, without limitation, appropriate instructions for preparation and administration of the formulation, side effects of the formulation, and any other relevant information. The instructions may be in any suitable format, including, but not limited to, printed matter, videotape, computer readable disk, optical disc or directions to internet-based instructions.

**[0104]** In another aspect, kits for treating an individual who suffers from or is susceptible to the conditions described herein are provided, comprising a first container comprising a dosage

amount of a composition or formulation as disclosed herein, and a package insert for use. The container may be any of those known in the art and appropriate for storage and delivery of intravenous formulation. In certain embodiments, the kit further comprises a second container comprising a pharmaceutically acceptable carrier, diluent, adjuvant, etc. for preparation of the formulation to be administered to the individual.

**[0105]** In another aspect, kits may also be provided that contain sufficient dosages of the compositions described herein (including pharmaceutical compositions thereof) to provide effective treatment for an individual for an extended period, such as 1–3 days, 1–5 days, a week, 2 weeks, 3, weeks, 4 weeks, 6 weeks, 8 weeks, 1 cycle, 2 cycles, 3 cycles, 4 cycles, 5 cycles, 6 cycles, 7 cycles, 8 cycles or more.

**[0106]** In some embodiments, the kits may also include multiple doses and may be packaged in quantities sufficient for storage and use in pharmacies, for example, hospital pharmacies and compounding pharmacies. In certain embodiments the kits may include a dosage amount of at least one composition as disclosed herein.

## EXAMPLES

[0107] The presently disclosed subject matter will be better understood by reference to the following Examples, which are provided as exemplary of the invention, and not by way of limitation.

**Example 1: An open-label, dose escalation study to assess the safety, tolerability, pharmacokinetics, preliminary efficacy, and pharmacodynamics of an anti-CD22-CpG conjugate in patients with advanced or metastatic solid tumors**

[0108] The conjugate comprising an anti-CD22 antibody (Ab) and an immunomodulating oligonucleotide (also referred to as the “anti-CD22-CpG conjugate) used in this study is a Toll like Receptor (TLR) Agonist Antibody Conjugate (TRAAC) designed to deliver TLR9 activation in targeted immune cells via systemic administration. The anti-CD22-CpG conjugate comprises a TLR9 agonist oligonucleotide (14-mer) site specifically conjugated to an anti-CD22 antibody at the C-terminus via a Q-tag peptide as described herein. Pre-clinical murine tumor models showed that anti-CD22-CpG conjugate treatment activated the TLR9 pathway in B cells to increase immune activation, cytokine production, antigen presentation, and anti-tumor efficacy. This study was designed to test the safety, tolerability, pharmacokinetics, preliminary efficacy, and pharmacodynamics of anti-CD22-CpG conjugate treatment in patients with advanced or metastatic solid tumors.

[0109] In some embodiments, one of Conjugates A-F was administered, as shown in Table 11.

[0110] The anti-CD22-CpG Conjugate C was administered to patients every 2 weeks (Q2W) by intravenous infusion over approximately 90 min, starting at 0.1 mg/kg. During the first week after receiving the first dose, patients were monitored for daily temperature and any CRS symptoms. Patients were monitored for 28 days to assure no dose limiting toxicities (DLT) arose, with a DLT target rate of 25%. All patients were also monitored for late DLTs during Days 29-60. In the absence of any DLTs or  $\geq$  Grade 2 cytokine release syndrome (CRS), the next group of patients were escalated to the next dose of 0.3 mg/kg Q2W with 28 days of monitoring. This process continued, increasing approximately 3-fold per dose (*i.e.* dose 1 = 0.1 mg/kg, dose 2 = 0.3 mg/kg, dose 3 = 1.0 mg/kg, dose 4 = 3.0 mg/kg). Additional escalations are dose 5 = 10.0 mg/kg, dose 6 = 30.0 mg/kg and optionally dose 7 = a maximum of 60.0 mg/kg. If a DLT or  $\geq$

Grade 2 CRS is observed, then the subsequent dose level increase will be a maximum of 2-fold (*e.g.* if a DLT is observed on dose 1 = 0.1 mg/kg, then the maximum dose 2 = 0.2 mg/kg). Dose level 7 is optional, does not exceed 60 mg/kg, and depends upon the available safety, pharmacokinetics, and efficacy data collected from the other dose cohorts. A Bayesian Optimal Interval (BOIN) design with the 3+3 design run-in was applied to inform dose escalation/de-escalation decisions to the dose levels. Up to 30 patients may be enrolled in the dose escalation phase to determine the maximum tolerated dose (MTD). To ascertain the most ideal dose for further evaluation or define a recommended phase 2 dose (RP2D), at least two dose optimization cohorts will be enrolled at dose levels equivalent to or lower than the MTD. A total of 100 patients may be enrolled in the dose escalation and dose optimization phase, with up to 5 patients to be initially enrolled at a specific dose with a staggered start of 48 hrs between the first and subsequent patients to assess for any initial safety concerns.

**[0111]** This study included a screening period, a treatment period, and a follow-up period. All patients completed up to 28 days of screening. During the treatment period, patients received the anti-CD22-CpG conjugate biweekly (Q2W) until treatment discontinuation criteria were met. Patients then entered a follow-up period, to be continued for up to 2 years or until study discontinuation criteria are met.

**[0112]** Inclusion criteria included:

- (a) Age ( $\geq 18$  years old);
- (b) Sex (all);
- (c) Histologically or cytologically-documented solid tumors that are inoperable, locally advanced, metastatic, or recurrent of the following cancers:
  - (i) Cutaneous melanoma;
  - (ii) Breast cancer;
  - (iii) Ovarian cancer;
  - (iv) Colorectal cancer;
  - (v) Non-small cell lung cancer (NSCLC);
  - (vi) Renal cell carcinoma (RCC);
  - (vii) Head and neck squamous cell carcinoma (HNSCC);
  - (viii) Merkel cell carcinoma;

- (ix) Hepatocellular carcinoma (HCC);
  - (x) Cervical squamous cell carcinoma;
  - (xi) Urothelial carcinoma;
  - (xii) Endometrial carcinoma
  - (xiii) Gastro-esophageal adenocarcinoma; and
  - (xiv) Cholangiocarcinoma;
- (d) Patients must have at least one measurable lesion, as defined by RECIST v1.1
- (e) Adult male or female patients  $\geq 18$  years of age on day of signing informed consent.
- (f) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1;
- (g) Demonstration of adequate organ function.

**[0113]** Exclusion criteria included:

- (a) Prior history of or active malignant disease other than that being treated in this study;
- (b) Known brain metastases or cranial epidural disease;
- (c) Receiving chronic systemic steroid therapy ( $>10$  mg/day prednisone or equivalent) or any immunosuppressive therapy within 7 days prior to the first dose of study drug;
- (d) Active autoimmune disease requiring systemic treatment in the past 2 years;
- (e) History of Grade 3 or higher immune mediated adverse events that were considered drug-related to prior immunotherapy;
- (f) Infection with HIV-1 or HIV-2, unless HIV is well-controlled and viral load is undetectable; infection with hepatitis B unless disease is undetectable; infection with hepatitis C unless disease is well-controlled and viral load is minimal;
- (g) Active infection requiring systemic therapy;
- (h) Significant cardiovascular disease within the last 6 months;
- (i) Receipt of any type of systemic anti-cancer therapy within 4 weeks of the first dose of study drug;
- (j) Current or previous participation in an interventional clinical trial with an investigational compound or device within 4 weeks of the first dose of study drug;
- (k) Radiation for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks of the first dose of study drug;
- (l) Major surgery within 2 weeks of the first dose of study drug;

- (m) Receipt of any live vaccines within 4 weeks or any other vaccines within 2 days of the first dose of study drug;
- (n) Any prior treatment with TLR9 agonists or anti-CD22 antibodies;
- (o) A known hypersensitivity to the components of the study therapy or its analogs;
- (p) A history or current evidence of any condition therapy, lab abnormality, or other circumstance exposing the subject to risk by participating in the trial, confound the results of the trial, or interfere with the patient's participation for the full duration of the trial; and
- (q) Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

**[0114]** The primary outcome measure included an analysis of safety and tolerability of increasing dose levels of the anti-CD22-CpG conjugate in order to identify the recommended dose for a Phase 2 expansion study. This outcome measure included the assessment of 28-day dose limiting toxicities (DLTs), adverse events (AEs), and laboratory abnormalities. AEs are characterized by type, frequency, and severity per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0, and laboratory abnormalities are graded by CTCAE v 5.0.

**[0115]** Secondary outcome measures included the following:

- (a) Characterization of single and multiple dose pharmacokinetics of the anti-CD22-CpG conjugate, including pharmacokinetic parameters such as serum concentration ( $C_{\max}$ ), shortest time to peak plasma concentration ( $T_{\max}$ ), area under curve (AUC), drug clearance (CL), and half-life ( $t_{1/2}$ ) as data allow;
- (b) Evaluation of immunogenicity of the anti-CD22-CpG conjugate and the incidence of antidrug antibodies against this anti-CD22-CpG conjugate; and
- (c) Evaluation of preliminary anti-tumor activity as assessed for all cohorts by best overall response rate (ORR) per RECIST v1.1 and iRECIST and by duration of response (DOR) and the clinical benefit rate, and as assessed for ovarian cancer patients by combined RECIST v1.1 and Gynecologic Cancer Intergroup (GCIG) CA-125 ORR and DOR criteria. Response criteria are shown in Tables E1-E2C below.

**[0116]** Exploratory outcome measures included the following:

- (a) Characterization of other efficacy outcomes, such as progression-free survival (PFS) and overall survival (OS);
- (b) Characterization of the degree of target engagement by the anti-CD22-CpG conjugate via measurement CD22 expression on B cells in peripheral blood;
- (c) Exploration of the impact of the anti-CD22-CpG conjugate on systemic soluble immune factors, including pre- and post-dose quantification of soluble immune factors in serum;
- (d) Assessment of the pharmacodynamics effect of the anti-CD22-CpG conjugate on immune cell markers, including levels of phenotypic markers on B cells and lymphocyte counts in peripheral blood; and
- (e) Exploration of the impact of the anti-CD22-CpG conjugate on pharmacodynamics markers in tumor tissues, including pre- and post-dose levels of pharmacodynamics markers that include but are not limited to (i) tumor mutational burden (TMB) and (ii) PD-L1 and other immune modulatory markers.

**Table E1.** Response criteria for the evaluation of target lesions.

| Response Criteria        | Evaluation of Target Lesions                                                                                                                                                                                                                                                                                        |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Complete Response (CR)   | Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. <sup>1</sup>                                                                                                                                    |
| Partial Response (PR)    | At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.                                                                                                                                                                                            |
| Progressive Disease (PD) | At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. <sup>2</sup> |
| Stable Disease (SD)      | Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.                                                                                                                                                                                                         |
| Unknown (UNK)            | Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.                                                                                                                                                             |

<sup>1</sup> SOD for CR may not be zero when nodal lesions are part of target lesions

<sup>2</sup> Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are < 10 mm in size. In this case, the target lesion response is CR.

**Table E2A.** Evaluation of overall cancer response. Acronyms refer to Table E1.

| Target Lesion               | Non-Target Lesion                          | New Lesion | Objective Status |
|-----------------------------|--------------------------------------------|------------|------------------|
| CR                          | CR                                         | No         | CR               |
| CR                          | Non-CR/Non-PD <sup>3</sup>                 | No         | PR               |
| CR                          | Indeterminate or missing                   | No         | PR               |
| PR                          | Non-CR/Non-PD,<br>indeterminate or missing | No         | PR               |
| SD                          | Non-CR/Non-PD,<br>indeterminate or missing | No         | SD               |
| Indeterminate<br>or missing | Non-PD                                     | No         | Indeterminate    |
| PD                          | Any                                        | Yes or No  | PD               |
| Any                         | PD                                         | Yes or No  | PD               |
| Any                         | Any                                        | Yes        | PD               |

<sup>3</sup> Criteria for neither CR nor PD have been met.

All noted regressions should be confirmed  $\geq 4$  weeks after criteria for response are first met or at the next tumor assessment.

**Table E2B.** Assignment of time point response using iRECIST. Acronyms refer to Table E1.

|                                                                                                  | Timepoint<br>response<br>with no previous<br>iUPD in any<br>category | Timepoint response with previous<br>iUPD in any category <sup>4</sup>                                                                                                                                     |
|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Target lesions: iCR; non-target<br>lesions: iCR;<br>new lesions: no                              | iCR                                                                  | iCR                                                                                                                                                                                                       |
| Target lesions: iCR; non-target<br>lesions:<br>non-iCR/non-iUPD; new<br>lesions: no              | iPR                                                                  | iPR                                                                                                                                                                                                       |
| Target lesions: iPR; non-target<br>lesions:<br>non-iCR/non-iUPD; new<br>lesions: no              | iPR                                                                  | iPR                                                                                                                                                                                                       |
| Target lesions: iSD; non-target<br>lesions:<br>non-iCR/non-iUPD; new<br>lesions: no              | iSD                                                                  | iSD                                                                                                                                                                                                       |
| Target lesions: iUPD with no<br>change, or with a<br>decrease from last timepoint;<br>non-target | Not applicable                                                       | New lesions confirm iCPD if new<br>lesions were previously identified and<br>they have increased in size ( $\geq 5$ mm in<br>sum of measures for new lesion target<br>or any increase for new lesion non- |

|                                                                                                        |      |                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------------------------------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes                        |      | target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD                                                                                                                                                                                        |
| Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no                               | iUPD | Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST v1.1 criteria for unequivocal progression)                                                                                                                         |
| Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no                    | iUPD | Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures $\geq 5$ mm; otherwise, assignment remains iUPD                                                                                                                                                                 |
| Target lesions: iUPD; non-target lesions: iUPD; new lesions: no                                        | iUPD | Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures $\geq 5$ mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)                                                                    |
| Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes                                       | iUPD | Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures $\geq 5$ mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified |
| Target lesions: non-iUPD or progression; Non-target lesions: non-iUPD or progression; new lesions: yes | iUPD | Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified                                                                                                                                                                                |

<sup>4</sup> Previously identified in assessment immediately before this timepoint. The “i” indicates immune responses assigned using iRECIST.

Abbreviations: iCR = complete response; iPR = partial response; iSD = stable disease; iUPD = unconfirmed progression; non-iCR/non-iPD = criteria for neither CR nor PD have been met; iCPD = confirmed progression; RECIST = Response Evaluation Criteria in Solid Tumors.

**Table E2C.** Overall response in patients with initial measurable disease and evaluable by CA-125, combining both CA-125 and RECIST criteria. Acronyms refer to Table E1.

| Target lesion <sup>5</sup> | Non-target lesion <sup>6</sup> | New lesion | CA-125 | Overall best response |  |
|----------------------------|--------------------------------|------------|--------|-----------------------|--|
| CR                         | CR                             | No         | Normal | CR                    |  |

|                                                |                  |           |               |    |                                                                                                              |
|------------------------------------------------|------------------|-----------|---------------|----|--------------------------------------------------------------------------------------------------------------|
| CR                                             | Non CR<br>Non PD | No        | Not PD        | PR | Best RECIST response for this category also requires it to be confirmed and maintained for at least 28 days. |
| CR                                             | CR               | No        | PR not normal | PR |                                                                                                              |
| PR                                             | Non PD           | No        | Not PD        | PR |                                                                                                              |
| NE                                             | Non PD           | No        | PR            | PR |                                                                                                              |
| PD or New >28 days from CA-125 PR <sup>7</sup> |                  |           | PR            | PR |                                                                                                              |
| SD                                             | Non PD           | No        | PR            | PR |                                                                                                              |
| SD                                             | Non PD           | No        | Not PR or PD  | SD |                                                                                                              |
| PD or New ≤28 days from CA-125 PR <sup>7</sup> |                  |           | PR            | PD |                                                                                                              |
| PD                                             | Any              | Yes or No | Any           | PD |                                                                                                              |
| NE                                             | PD               | Yes or no | Any           | PD |                                                                                                              |
| NE                                             | Any              | Yes       | Any           | PD |                                                                                                              |
| NE                                             | Any              | Yes or no | PD            | PD |                                                                                                              |

<sup>5</sup> Target lesions include up to 5 measurable lesions as defined by RECIST.

<sup>6</sup> Non-target lesions include ascites and peritoneal thickening which are not measurable according to RECIST.

<sup>7</sup> Patients who have a CA-125 response that occurs more than 28 days from PD according to RECIST are considered a PR according to best response, but PD if the RECIST PD is within 28 days of CA-125 response.

Best RECIST response also requires confirmation and maintenance for at least 28 days.

### Example 2: CD22 Target Engagement

[0117] The ability of the administered anti-CD22-CpG conjugate to exhibit and maintain CD22 target (CD22) engagement was assessed. Using the protocol of Example 1, the anti-CD22-CpG Conjugate C was administered to patients as a biweekly (Q2W) intravenous infusion over approximately 90 min, at 0.1 mg/kg (1 patient), 0.3 mg/kg (1 patient), 1 mg/kg (7 patients) or 3 mg/kg (4 patients). Peripheral whole blood (PB) was drawn on Cycle 1 before the first dose on Day 1 (C1D1 pre), and after administration at 3 hours (C1D1 3hrs) then on Days 2 (C1D2), 8 (C1D8), 15 prior to the administration of the second dose (C1D15 pre), as well as blood draws on time points in subsequent cycles.

[0118] CD19<sup>+</sup> B cells from PB were analyzed for surface expression of CD22 by fluorescence-activated cell sorting (FACS) analysis using a Navios flow cytometer (Beckman Coulter) or CytoFLEX LX cytometer (Beckman Coulter). Data analysis was performed using either WinList (Verity Software) or FlowLogic softwares. B cells were identified as CD45<sup>+</sup>CD19<sup>+</sup> lymphocytes. Molecules of Equivalent Soluble Fluorochrome (MESF) values of

cell surface CD22 expression were determined using SpheroTech Rainbow Calibration Beads URCP-38-2K (SpheroTech) per manufacturer's recommendation. Data were tabulated using GraphPad Prism software. Data were expressed as mean percent change of CD22 cell surface expression from pre-dose value +/- standard deviation (SD).

[0119] As shown in **FIG. 2A**, the level of cell surface CD22 expression on peripheral B cells decreased after dosing with the anti-CD22-CpG conjugate. The higher doses trended toward prolonged target engagement, as shown by a slower rate of return to pre-dose levels of cell surface CD22. The patients at 0.3 mg/kg and 1 mg/kg doses were reassessed after the second cycle of administration. **FIG. 2B** demonstrates that the anti-CD22-CpG conjugate at the 0.3 mg/kg and 1 mg/kg dose levels exhibited similar levels of target engagement upon administration of the 1<sup>st</sup> and 4<sup>th</sup> doses. At the higher dose level of 3 mg/kg, the anti-CD22-CpG conjugate, the data indicates that the conjugate maintained target engagement prior to and through the second cycle of treatment (4 doses; 2 cycles of biweekly administration).

### **Example 3: B Cell Activation**

[0120] B cell activation in response to administration of the anti-CD22-CpG conjugate was assessed. The B cells from PB collected from patients in Example 2 were analyzed for activation by measuring CD86 expression by FACS analysis using either a Navios flow cytometer (Beckman Coulter) or a CytoFLEX LX cytometer (Beckman Coulter). Data analysis was performed using either WinList (Verity Software) or FlowLogic softwares. Naïve B cells were identified as CD45<sup>+</sup>CD19<sup>+</sup>CD27<sup>-</sup> and memory B cells were identified as CD45<sup>+</sup>CD19<sup>+</sup>CD27<sup>+</sup>. CD86 expression was derived by gating on percent of naïve and memory B cells expressing CD86. Data were tabulated using GraphPad Prism software and were expressed as fold- change of marker expressopm from pre-dose.

[0121] As shown in **FIGS. 3A** and **3B**, all doses of anti-CD22-CpG conjugate elicited B cell activation, exhibited by increased CD86 expression. **FIG. 3C** provides evidence of B cell activation after the second cycle of administration (4 doses; 2 cycles of biweekly administration).

### **Example 4: Pharmacokinetics**

[0122] The pharmacokinetics of the anti-CD22-CpG conjugate were assessed by measuring the concentration of the conjugate in patients administered 0.1, 0.3, and 1 mg/kg from Example

2. A MesoScale Discoveries (MSD) assay was used to detect the conjugate, using a Human CD22 ECD (TNT9, Tallac Therapeutics) ligand binding format and electrochemiluminescence (ECL) technology. The conjugate was detected using a biotin-conjugated anti-sense oligo (primary detection agent) and Sulfo-TAG-labeled Streptavidin. Electrochemiluminescent signal, following the addition of Read Buffer T, was read on an MSD Sector Imager plate reader. The results are provided in Table E4 and **FIG. 4**.

**Table E3.** Pharmacokinetics of the anti-CD22-CpG conjugate

| <b>Dose<br/>(mg/kg)</b> | <b>N</b> | <b>C<sub>max</sub><br/>(µg/mL)</b> | <b>AUC<sub>last</sub><br/>(h*µg/mL)</b> | <b>CL<br/>(mL/h/kg)</b> | <b>V<sub>z</sub><br/>(mL/kg)</b> | <b>T<sub>1/2</sub><br/>(h)</b> |
|-------------------------|----------|------------------------------------|-----------------------------------------|-------------------------|----------------------------------|--------------------------------|
| 0.1                     | 1        | 1.74                               | 6.01                                    | 16.2                    | 120                              | 5.1                            |
| 0.3                     | 1        | 5.04                               | 44.9                                    | 6.15                    | 58.7                             | 6.62                           |
| 1                       | 3        | 19.6 (4.93)                        | NA                                      | NA                      | NA                               | NA                             |

C<sub>max</sub> at 1 mg/kg presented as mean (SD)

**[0123]** The C<sub>max</sub> increase for the conjugate was approximately dose proportional between the 0.1 and 1 mg/kg doses. The AUC increase was greater than dose-proportional for the 0.1 and 1 mg/kg doses. A similar trend was observed when the samples were assayed for total antibody.

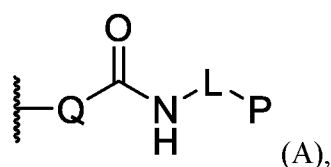
**[0124]** At the time of filing this application, three of the eight evaluable subjects demonstrated stable disease according to the criteria in Example 1. These subjects were at the 0.3, 1 and 3 mg/kg dose levels.

## CLAIMS

What is claimed is:

1. A method of treating cancer in an individual comprising administering to the individual a conjugate comprising an anti-CD22 antibody (Ab) and an immunomodulating oligonucleotide (P) at a dose of between 0.1 mg/kg to 60 mg/kg;

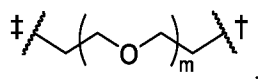
wherein the Ab comprises two antibody light chains, two antibody heavy chains, and two Q-tag peptides (Q); wherein each of the two Q-tag peptides comprises the amino acid sequence RPQGFGPP (SEQ ID NO:49); wherein one Q-tag peptide is linked to the C-terminus of each of the two antibody heavy chains; wherein one of the two Q-tag peptides is linked to the immunomodulating oligonucleotide via an amide bond with the glutamine residue of the Q-tag peptide and a linker (L) as shown in Formula (A):



wherein  $\sim$  indicates the point of attachment of Q to the antibody (Ab);

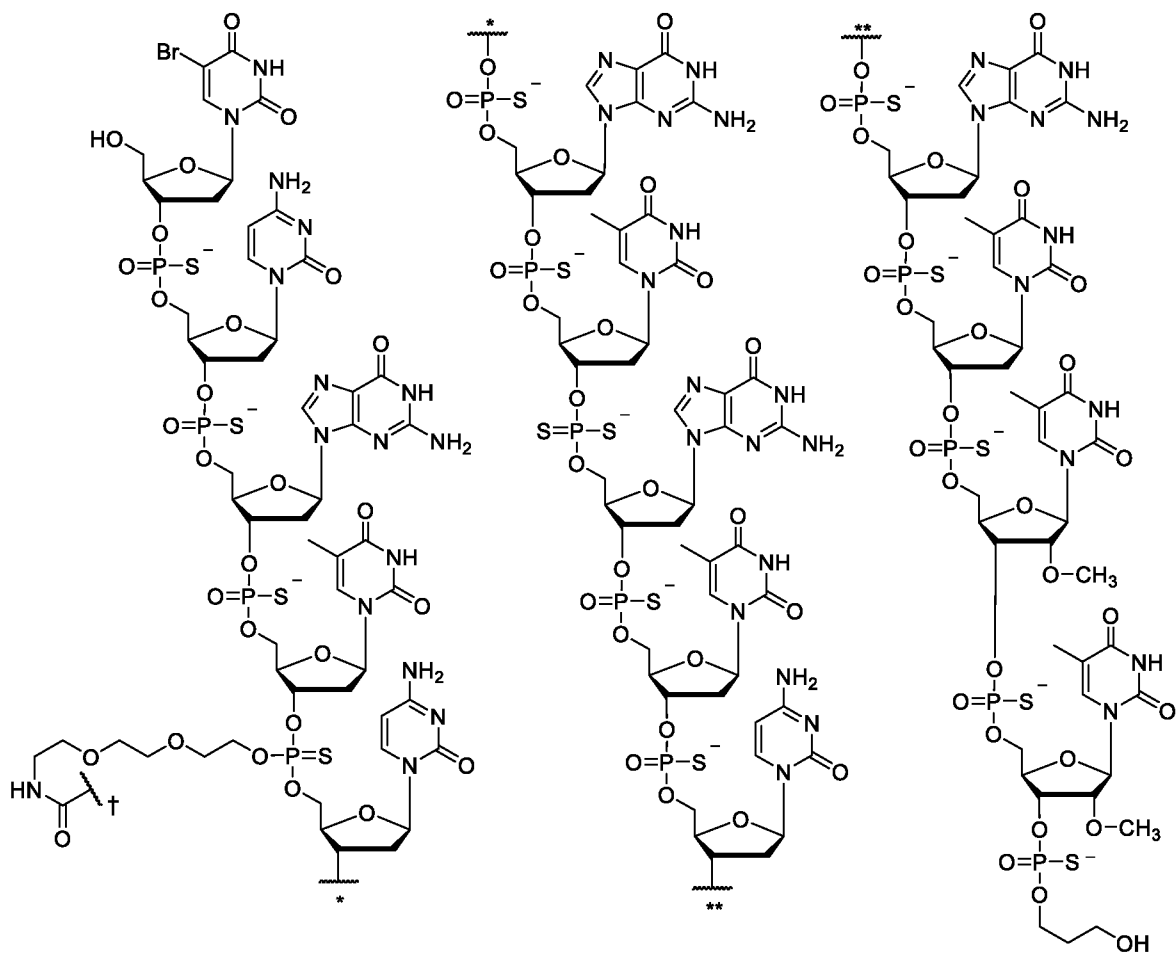
wherein each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:120-122;

wherein the linker L is

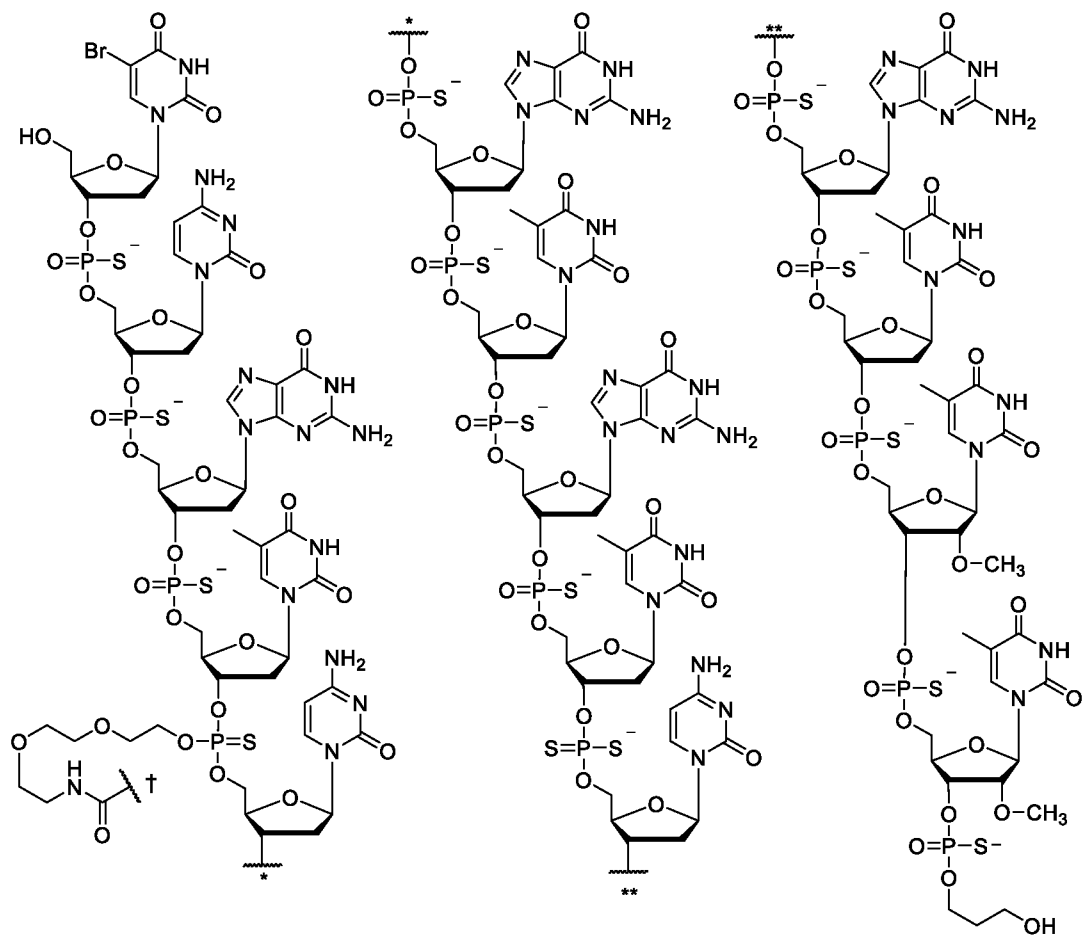


wherein m is 24, and wherein  $\sim \dagger$  indicates the point of attachment to the oligonucleotide P, and  $\sim \ddagger$  indicates the point of attachment to the glutamine residue of the Q-tag; and

wherein the oligonucleotide P comprises the structure:



or



or a pharmaceutically acceptable salt thereof,

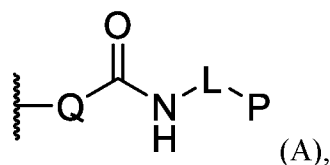
wherein  $\sim^*$  and  $\sim^{**}$  indicate the points of attachment within the oligonucleotide, wherein  $\sim^\dagger$  indicates the point of attachment to the linker L.

2. The method of claim 1, wherein the individual has a solid tumor that is inoperable, locally advanced, metastatic, and/or recurrent.

3. The method of claim 1 or claim 2, wherein the individual has a cancer selected from the group consisting of cutaneous melanoma, breast cancer, ovarian cancer, colorectal cancer, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), Merkel cell carcinoma, hepatocellular carcinoma (HCC), cervical squamous cell carcinoma, urothelial carcinoma, endometrial carcinoma, gastro-esophageal adenocarcinoma, and cholangiocarcinoma.

4. A method of treating cancer in an individual comprising administering to the individual a conjugate comprising an anti-CD22 antibody (Ab) and an immunomodulating oligonucleotide (P); wherein the individual has a solid tumor that is inoperable, locally advanced, metastatic, and/or recurrent;

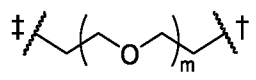
wherein the Ab comprises two antibody light chains, two antibody heavy chains, and two Q-tag peptides (Q); wherein each of the two Q-tag peptides comprises the amino acid sequence RPQGFGPP (SEQ ID NO:49); wherein one Q-tag peptide is linked to the C-terminus of each of the two antibody heavy chains; wherein one of the two Q-tag peptides is linked to the immunomodulating oligonucleotide via an amide bond with the glutamine residue of the Q-tag peptide and a linker (L) as shown in Formula (A):



wherein ~~~~ indicates the point of attachment of Q to the antibody (Ab);

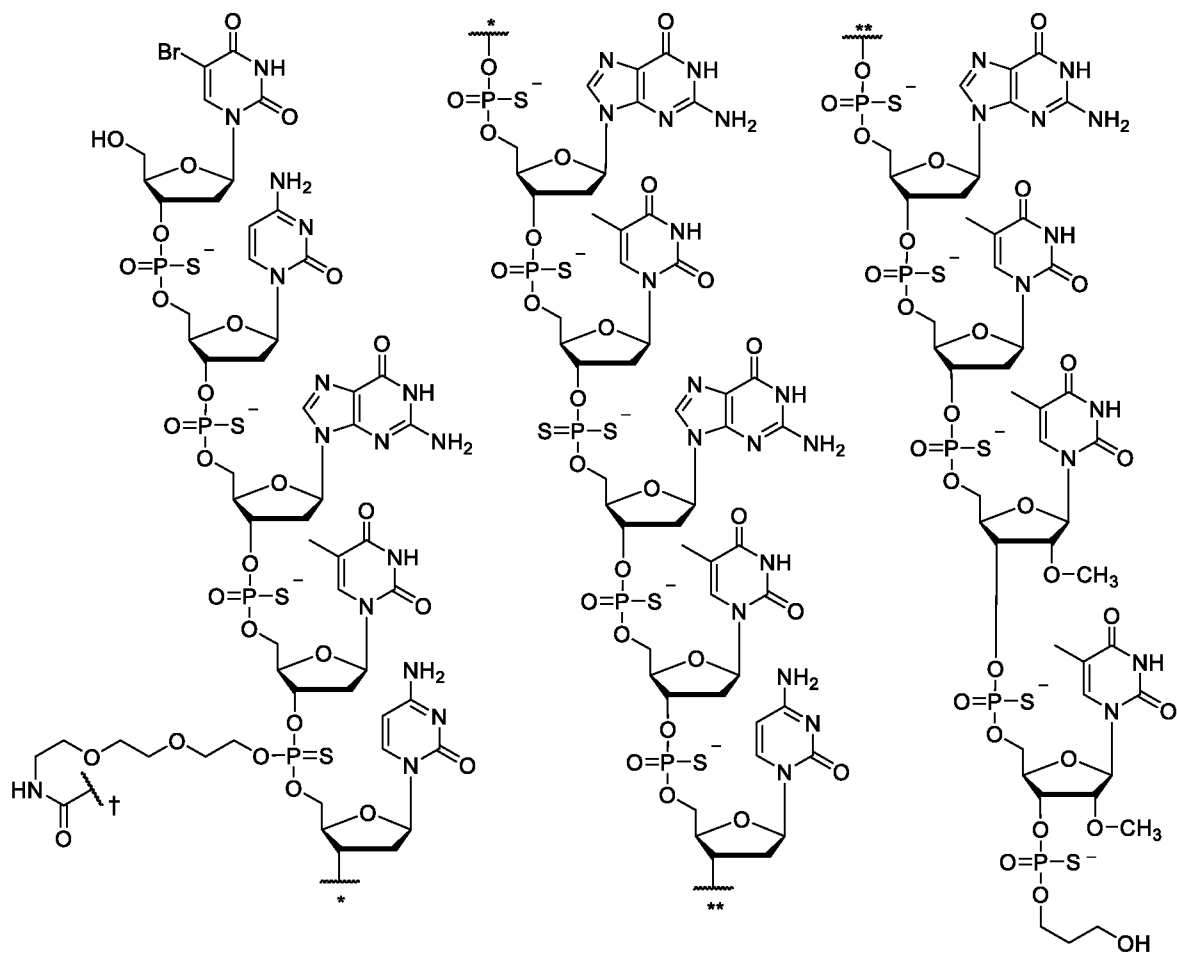
wherein each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:120-122;

wherein the linker L is

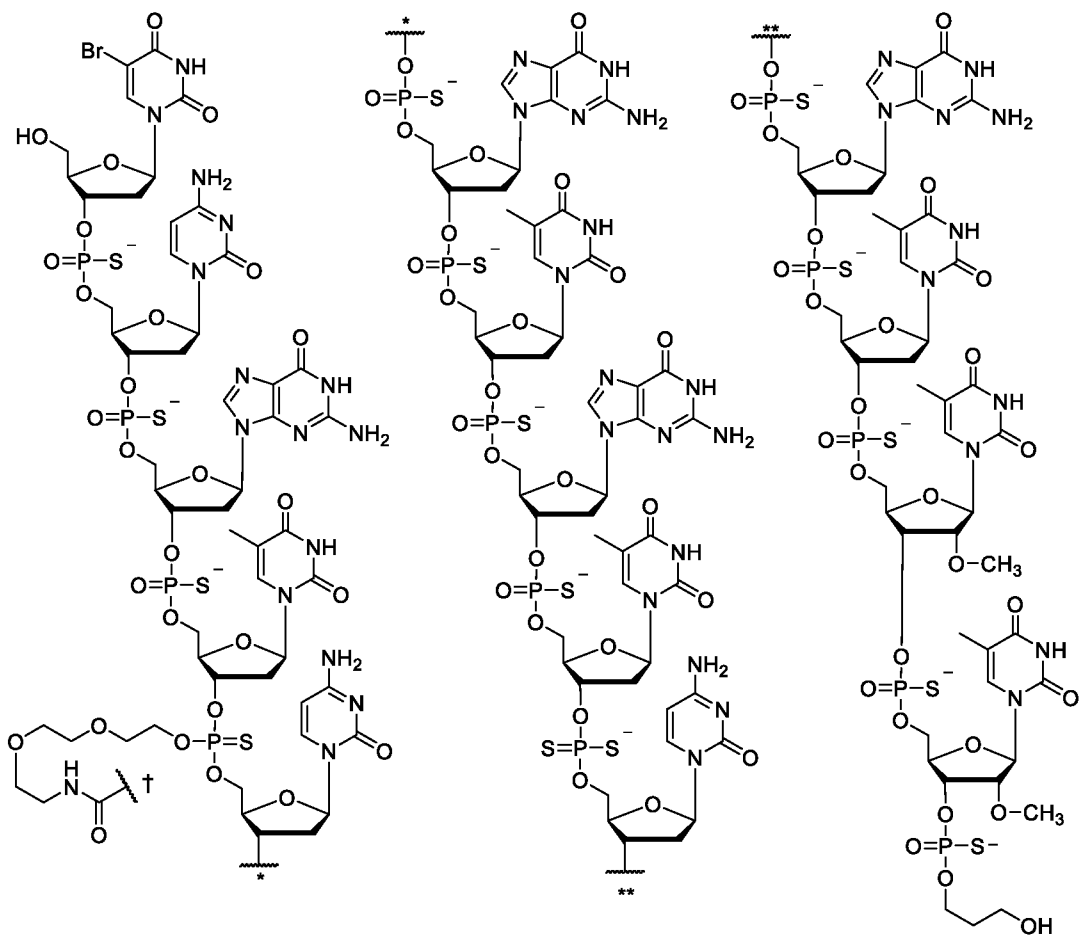


wherein m is 24, and wherein ~~~~ † indicates the point of attachment to the oligonucleotide P, and ~~~~ ‡ indicates the point of attachment to the glutamine residue of the Q-tag; and

wherein the oligonucleotide P comprises the structure:



or



or a pharmaceutically acceptable salt thereof,

wherein  $\sim^*$  and  $\sim^{**}$  indicate the points of attachment within the oligonucleotide, and  
 wherein  $\sim^\dagger$  indicates the point of attachment to the linker L.

5. The method of claim 4, wherein the individual has a cancer selected from the group consisting of cutaneous melanoma, breast cancer, ovarian cancer, colorectal cancer, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), Merkel cell carcinoma, hepatocellular carcinoma (HCC), cervical squamous cell carcinoma, urothelial carcinoma, endometrial carcinoma, gastro-esophageal adenocarcinoma, and cholangiocarcinoma.

6. The method of claim 4 or claim 5, wherein the conjugate is administered to the individual at a dose of between 0.1 mg/kg to 60 mg/kg.

7. The method of any one of claims 1-6, wherein the individual has a solid tumor that has progressed on and/or is intolerant to standard therapy.
8. The method of any one of claims 1-7, wherein the conjugate is administered to the individual at a dose of 0.1, 0.3, 1.0, 3.0, 10.0, 30.0, or 60.0 mg/kg.
9. The method of any one of claims 1-8, wherein the conjugate is administered to the individual once every two weeks.
10. The method of any one of claims 1-9, wherein each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising the amino acid sequence of SEQ ID NO:120.
11. The method of any one of claims 1-9, wherein each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising the amino acid sequence of SEQ ID NO:121.
12. The method of any one of claims 1-9, wherein each heavy chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:113, a CDR2 comprising the amino acid sequence of SEQ ID NO:115, and a CDR3 comprising the amino acid sequence of SEQ ID NO:116, and each light chain of the Ab comprises a CDR1 comprising the amino acid sequence of SEQ ID NO:117, a CDR2 comprising the amino acid sequence of SEQ ID NO:119, and a CDR3 comprising the amino acid sequence of SEQ ID NO:122.

13. The method of any one of claims 1-9, wherein each heavy chain of the Ab comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:65.
14. The method of any one of claims 1-9 and 13, wherein each light chain of the Ab comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:73.
15. The method of any one of claims 1-9 and 13, wherein each light chain of the Ab comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:87.
16. The method of any one of claims 1-9, wherein each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:179 or 180; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:181 or 182.
17. The method of claim 16, wherein each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:179; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:181.
18. The method of claim 16, wherein each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:179; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:182.
19. The method of claim 16, wherein each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:180; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:181.
20. The method of claim 16, wherein each heavy chain of the Ab including the Q-tag peptide comprises the amino acid sequence of SEQ ID NO:180; and wherein each light chain of the Ab comprises the amino acid sequence of SEQ ID NO:182.
21. The method of any one of claims 1-20, wherein the individual is a human.

22. The method of any one of claims 1-21, wherein the conjugate is administered in a formulation comprising:

- (a) the conjugate at a concentration of 30mg/mL;
- (b) 20mM citrate;
- (c) 150mM L-arginine;
- (d) 50mM NaCl; and
- (e) 0.02% polysorbate 80 (w/v);

wherein the formulation is at pH 6.5.

23. The method of any one of claims 1-22, wherein the conjugate is administered to the individual intravenously.

Engineered Q-tag (RPQGFGPP)

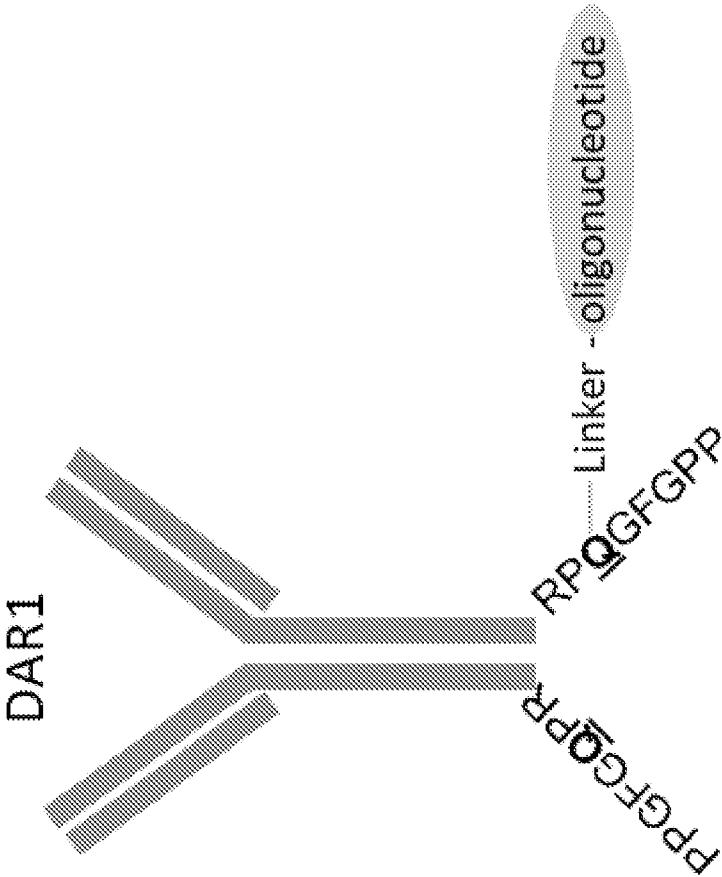


FIG. 1

FIG. 2A

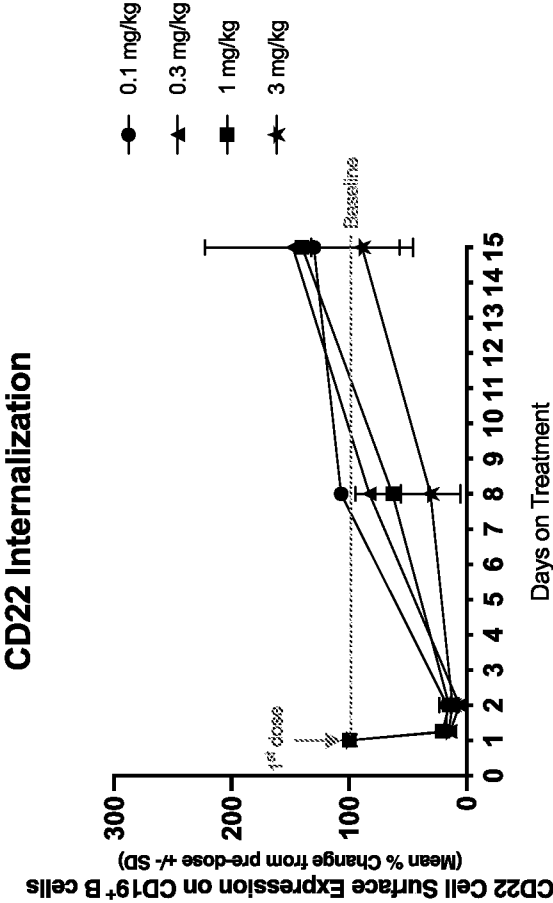


FIG. 2B

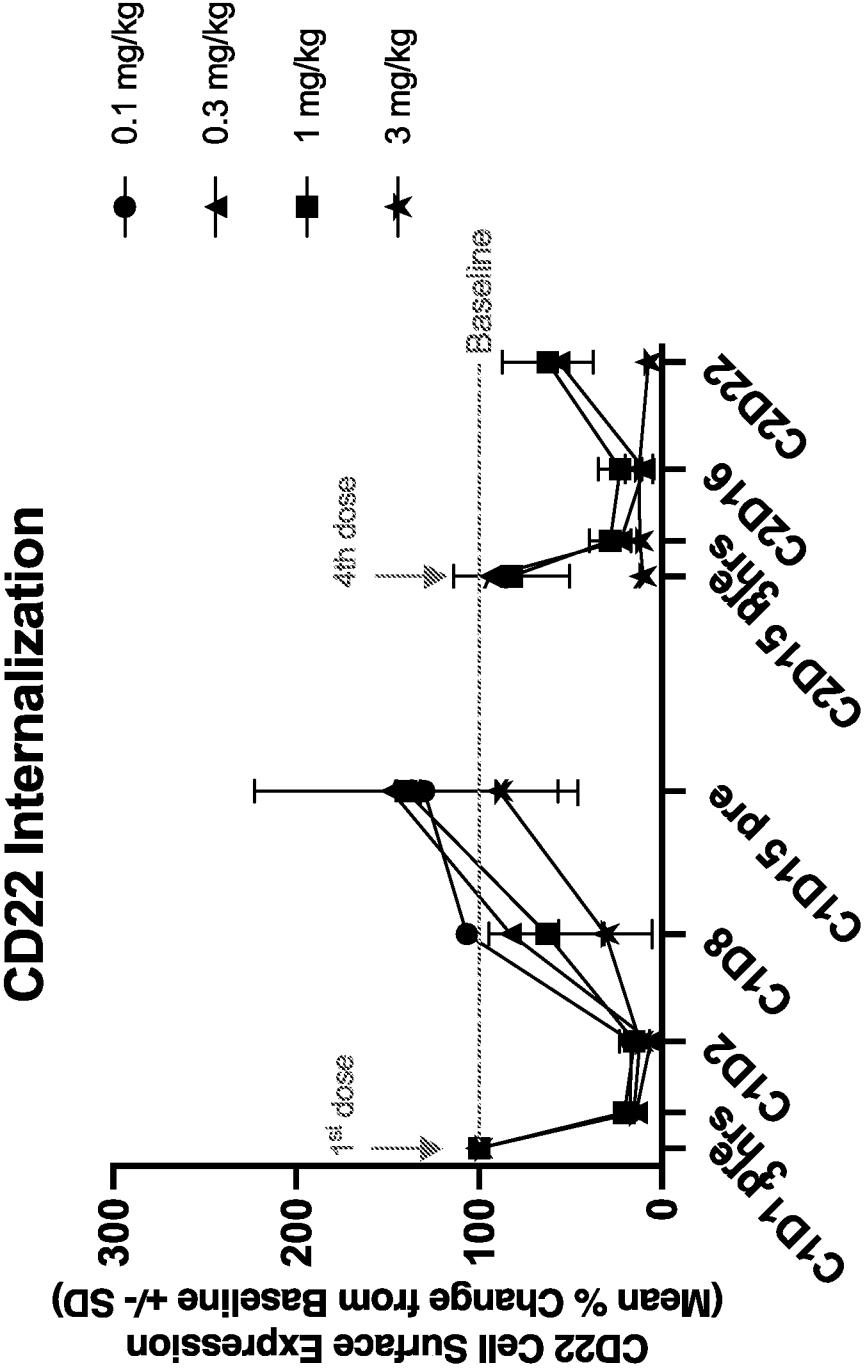


FIG. 3A

Naive B cells: CD86 Expression

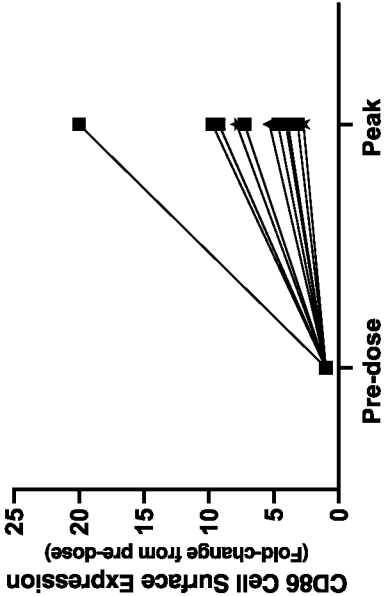
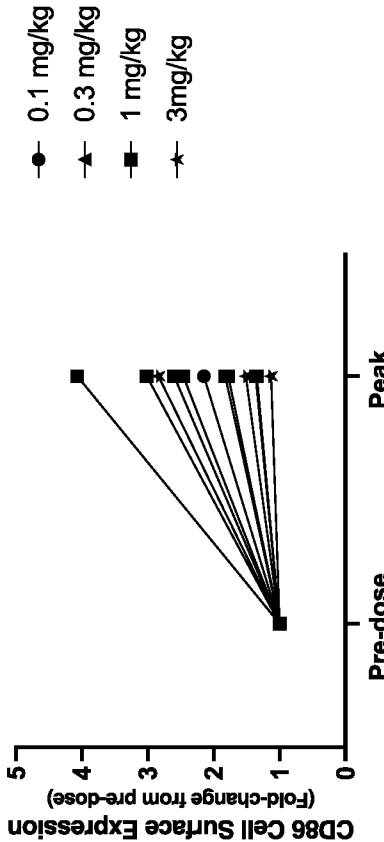


FIG. 3B

Memory B cells: CD86 Expression



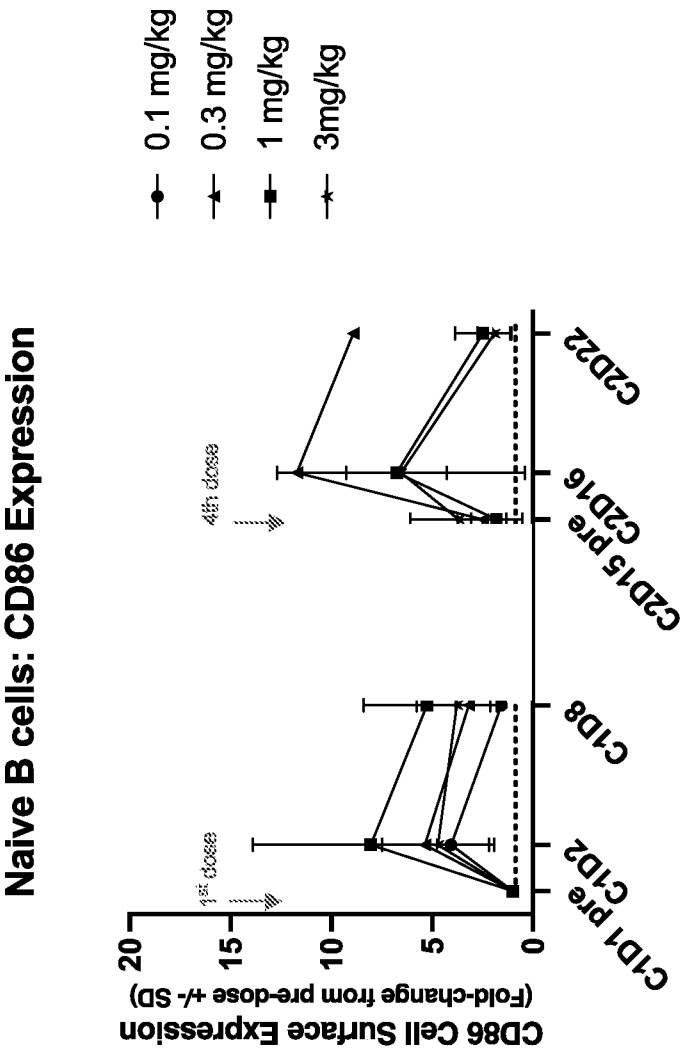
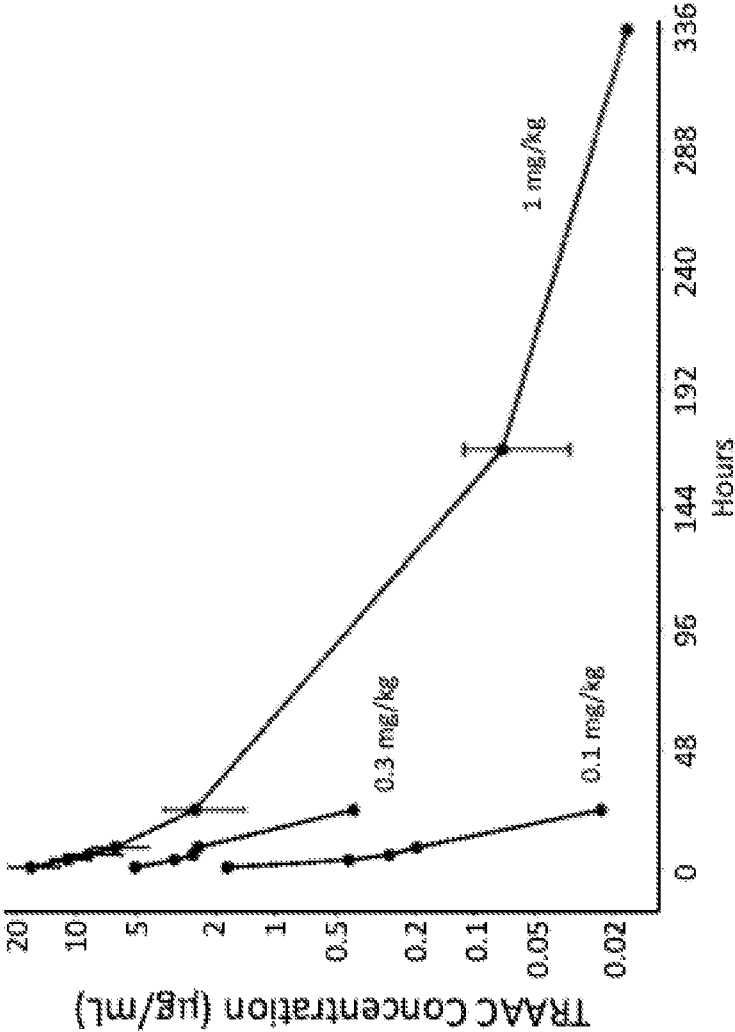


FIG. 3C

FIG. 4



## A. CLASSIFICATION OF SUBJECT MATTER

A61K 47/68 (2017.01) A61K 39/00 (2006.01) A61P 35/00 (2006.01) C07K 16/28 (2006.01) C12N 15/117 (2010.01)

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)

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)

DATABASES: MEDLINE, EPODOC, WPIAP, PATENW (EPODOC, WPIAP and all English language full text databases), CAPLUS, BIOSIS, EMBASE, GENOMEQUEST (nucleic acid and protein databases). KEYWORDS: CD22, Siglec 2, antibody, immunoglobulin, linked, fused, conjugated immune modulating oligonucleotide, CPG, Q tag, RPQGFGPP as well as synonyms and similar terms. SEQ ID NOs: 113, 115, 116 and 117, 119, 120-122 relating to the CDRs of the anti-CD22 antibody and SEQ ID NO. 46 relating to the Q-tag peptide. Applicant and/or Inventor searches of the patent and non-patent literature was performed in DOCDB and DWPI, PubMed, and in internal databases provided by IP Australia.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------|-----------------------|
|           | Documents are listed in the continuation of Box C                                  |                       |



Further documents are listed in the continuation of Box C



See patent family annex

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                              |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"D" document cited by the applicant in the international application</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> |                                                                                                                                                                                                                                              |  |
| "T"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                                              |  |
| "X"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone                                                                     |  |
| "Y"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |  |
| "&"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | document member of the same patent family                                                                                                                                                                                                    |  |

|                                                                                                                                                         |                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Date of the actual completion of the international search<br>28 August 2023                                                                             | Date of mailing of the international search report<br>28 August 2023                                                                         |
| Name and mailing address of the ISA/AU<br><br>AUSTRALIAN PATENT OFFICE<br>PO BOX 200, WODEN ACT 2606, AUSTRALIA<br>Email address: pct@ipaustalia.gov.au | Authorised officer<br><br>Monica Graham<br>AUSTRALIAN PATENT OFFICE<br>(ISO 9001 Quality Certified Service)<br>Telephone No. +61 2 6283 3179 |

| INTERNATIONAL SEARCH REPORT                           |                                                                                                                                                                                                                                                                                                                                                                                                                                           | International application No. |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                           | PCT/US2023/067146             |
| Category*                                             | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                        | Relevant to claim No.         |
| X                                                     | WO 2021/174091 A1 (TALLAC THERAPEUTICS, INC) 02 September 2021<br>(D1: see abstract, paragraphs [0012], [0025]-[0026], [0035], [0054], [0056], [0064]-[0066], [0068], [0173]-[0176], [0292]-[0293], [0396]-[0409], [0419]-[0420], [0426], and claims; Q tag sequence SEQ ID NO. 46, CpG oligonucleotide SEQ ID NO. 34 and 35; heavy chains SEQ ID NO. 64, 65, 67, 179, 180 and light chains SEQ ID NO. 68, 69, 71, 72, 73, 87, 181, 182). | 1-23                          |
| A                                                     | WO 2022/040173 A1 (TALLAC THERAPEUTICS INC) 24 February 2022<br>(D2: see abstract, paragraphs [0009]-[0014], [0020], [0180], Example 3 and claims).                                                                                                                                                                                                                                                                                       | 1-23                          |
| A                                                     | WO 2020/081744 A1 (TOLLNINE INC.) 23 April 2020<br>(D3: see abstract, paragraphs [0011]-[0015], [00284] and claims)                                                                                                                                                                                                                                                                                                                       | 1-23                          |
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**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
  - a. ☒ forming part of the international application as filed.
  - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).  
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:  
SEQ ID NOs: 113, 115, 116 and 117, 119, 120-122 relating to the CDRs of the anti-CD22 antibody and SEQ ID NO. 46 relating to the Q-tag peptide was searched.

| INTERNATIONAL SEARCH REPORT                                                                                                                                                                                                                                           |                   | International application No. |                  |
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| Information on patent family members                                                                                                                                                                                                                                  |                   | PCT/US2023/067146             |                  |
| This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information. |                   |                               |                  |
| Patent Document/s Cited in Search Report                                                                                                                                                                                                                              |                   | Patent Family Member/s        |                  |
| Publication Number                                                                                                                                                                                                                                                    | Publication Date  | Publication Number            | Publication Date |
| WO 2021/174091 A1                                                                                                                                                                                                                                                     | 02 September 2021 | WO 2021174091 A1              | 02 Sep 2021      |
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| WO 2023/028511 A1                                                                                                                                                                                                                                                     | 02 March 2023     | WO 2023028511 A1              | 02 Mar 2023      |
| End of Annex                                                                                                                                                                                                                                                          |                   |                               |                  |
| Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.                                                                                                                                             |                   |                               |                  |