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(71) **Applicant** *(for all designated States except AL, AT, BA, BE, BG, CH, CN, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IN, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR)*: **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, CA 94080 (US).

(71) **Applicant** *(for AL, AT, BA, BE, BG, CH, CN, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IN, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR only)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) **Inventors**: **WALSH, Kevin**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **DE ALMEIDA, Patricia**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **DU, Changchun**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **KIM, Jeong**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **ZHU, Jing**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **BEVERS, Jack**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **ANDYA, James**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US). **SHEN, Ye**; c/o Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 (US).

(74) **Agents**: **ZHOU, Jie** et al.; Morrison & Foerster LLP, 425 Market Street, San Francisco, CA 94105-2482 (US).

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(54) **Title**: COMBINATION THERAPY COMPRISING ANTI-ANGIOGENESIS AGENTS AND OX40 BINDING AGONISTS

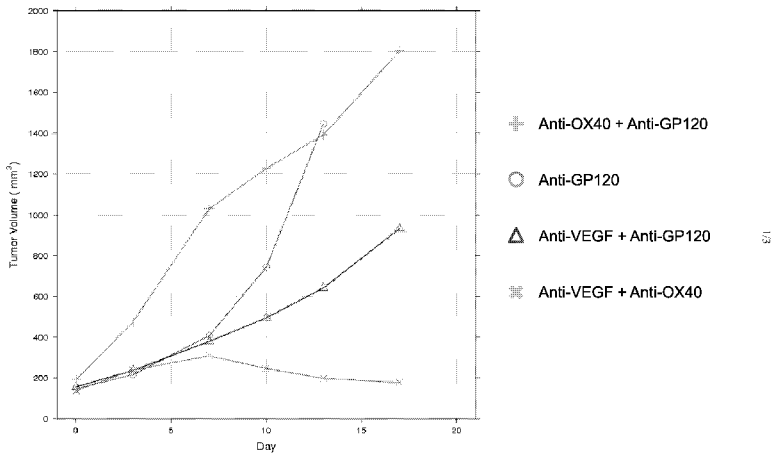

FIG. 1

(57) **Abstract**: The disclosure provides compositions and methods for treating cancers. The method comprises administering an anti-angiogenesis agent and an OX40 binding agonist.

WO 2015/153514 A1

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COMBINATION THERAPY COMPRISING ANTI-ANGIOGENESIS AGENTS AND OX40 BINDING AGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Application Serial Nos. 61/973,193, filed March 31, 2014; 61/989,448, filed May 6, 2014; 62/073,873, filed October 31, 2014; 62/080,171, filed November 14, 2014; and 62/113,345, filed February 6, 2015; each of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 146392031540SEQLIST.txt, date recorded: March 26, 2015, size: 188 KB).

FIELD OF THE INVENTION

[0003] This invention relates to methods of treating cancers by administering an anti-angiogenesis agent and an OX40 binding agonist.

BACKGROUND

[0004] Angiogenesis is necessary for cancer development, regulating not only primary tumor size and growth, but also impacting invasive and metastatic potential. Accordingly, the mechanisms mediating angiogenic processes have been investigated as potential targets for directed anti-cancer therapies. Early in the study of angiogenic modulators, the vascular endothelial growth factor (VEGF) signaling pathway was discovered to regulate angiogenic activity in multiple cancer types, and multiple therapeutics have been developed to modulate this pathway at various points. Although the use of angiogenesis inhibitors in the clinic has shown success, not all patients respond or fully respond to this therapy. The mechanism(s) underlying such incomplete response is unknown. Therefore, there is a need for the identification of patient subgroups sensitive or responsive to anti-angiogenic cancer therapy. Further, there remains a need for combination therapies that may increase the efficacy of anti-angiogenic cancer therapy.

[0005] Bevacizumab (Avastin®) is a recombinant humanized monoclonal IgG1 antibody that specifically binds to and blocks the biological effects of VEGF. Bevacizumab has been approved in Europe for the treatment of the advanced stages of six common types of cancer: colorectal cancer, breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, cervical cancer, and kidney cancer, which collectively cause over 2.5 million deaths each year. In the United States, bevacizumab was the first anti-angiogenesis therapy approved by the FDA, and it is now approved for the treatment of six tumor types: colorectal cancer, NSCLC, brain cancer (glioblastoma), kidney cancer (renal cell

carcinoma), ovarian cancer, and cervical cancer. Over half a million patients have been treated with bevacizumab so far, and a comprehensive clinical program is investigating the further use of bevacizumab in the treatment of multiple cancer types.

[0006] Bevacizumab has shown promise as a co-therapeutic, demonstrating efficacy when combined with a broad range of chemotherapies and other anti-cancer treatments. For example, phase-III studies have demonstrated the beneficial effects of combining bevacizumab with standard chemotherapeutic regimens (see, e.g., Saltz et al., 2008, J. Clin. Oncol., 26:2013-2019; Yang et al., 2008, Clin. Cancer Res., 14:5893-5899; Hurwitz et al., 2004, N. Engl. J. Med., 350:2335-2342). However, as in previous studies of angiogenesis inhibitors, some of these phase-III studies have shown that a portion of patients experience incomplete response to the addition of bevacizumab to their chemotherapeutic regimens. Accordingly, there is a need for methods of identifying those patients that are likely to respond or have an improved response to not only angiogenesis inhibitors (e.g., bevacizumab) alone, but also combination therapies comprising angiogenesis inhibitors (e.g., bevacizumab).

[0007] Accordingly, there is a need for combination therapies that may increase the efficacy of anti-angiogenic cancer therapy. Combination therapies may increase responsiveness in patients that show incomplete response and/or further increase responsiveness in patients that do respond to anti-angiogenic cancer therapy.

[0008] OX40 (also known as CD34, TNFRSF4 and ACT35) is a member of the tumor necrosis factor receptor superfamily. OX40 is not constitutively expressed on naïve T cells, but is induced after engagement of the T cell receptor (TCR). The ligand for OX40, OX40L, is predominantly expressed on antigen presenting cells. OX40 is highly expressed by activated CD4+ T cells, activated CD8+ T cells, memory T cells, and regulatory T cells. OX40 signaling can provide costimulatory signals to CD4 and CD8 T cells, leading to enhanced cell proliferation, survival, effector function and migration. OX40 signaling also enhances memory T cell development and function.

[0009] Regulatory T cells (Treg) cells are highly enriched in tumors and tumor draining lymph nodes derived from multiple cancer indications, including melanoma, NSCLC, renal, ovarian, colon, pancreatic, hepatocellular, and breast cancer. In a subset of these indications, increased intratumoral T reg cell densities are associated with poor patient prognosis, suggesting that these cells play an important role in suppressing antitumor immunity. OX40 positive tumor infiltrating lymphocytes have been described.

[0010] Modulating OX40 signaling with other signaling pathways that are deregulated in tumor cells (*e.g.,* angiogenic pathways) may further enhance treatment efficacy. Thus, there remains a need for such an optimal therapy for treating or delaying development of various cancers, immune related diseases, and T cell dysfunctional disorders.

[0011] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

SUMMARY

[0012] In one aspect, provided herein is a method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of an anti-angiogenesis agent and an OX40 binding agonist.

[0013] In another aspect, provided herein is a use of an anti-angiogenesis agent in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and wherein the treatment comprises administration of the medicament in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier. Further provided herein is a use of an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein the treatment comprises administration of the medicament in combination with a composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier.

[0014] In still another aspect, provided herein is a composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the treatment comprises administration of said composition in combination with a second composition, wherein the second composition comprises OX40 binding agonist and an optional pharmaceutically acceptable carrier. Further provided herein is a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the treatment comprises administration of said composition in combination with a second composition, wherein the second composition comprises an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier.

[0015] In yet another aspect, provided herein is a kit comprising a medicament comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration of the medicament in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual. Further provided here is a kit comprising a first medicament comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and a second medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier. In some embodiments, the kit further comprises a package insert comprising instructions for administration of the first medicament and the second medicament for treating or delaying progression of cancer in an individual. Still further provided herein is a kit comprising a medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration of the medicament

in combination with a composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.

[0016] In some embodiments, the anti-angiogenesis agent is selected from the group consisting of an anti-VEGFR2 antibody; an anti-VEGFR1 antibody; a VEGF-trap; a bispecific VEGF antibody; a bispecific antibody comprising a combination of two arms selected from the group consisting of an anti-VEGF arm, an anti-VEGFR1 arm, and an anti-VEGFR2 arm; an anti-VEGF-A antibody; an anti-VEGFB antibody; an anti-VEGFC antibody; an anti-VEGFD antibody; a nonpeptide small molecule VEGF antagonist; an anti-PDGFR inhibitor; and a native angiogenesis inhibitor. In some embodiments, the anti-angiogenesis agent is selected from the group consisting of ramucirumab, tanibirumab, aflibercept, icrucumab, ziv-aflibercept, MP-0250, vanucizumab, sevacizumab, VGX-100, pazopanib, axitinib, vandetanib, stivarga, cabozantinib, lenvatinib, nintedanib, orantinib, telatinib, dovitinig, cediranib, motesanib, sulfatinib, apatinib, foretinib, famitinib, imatinib, and tivozanib.

[0017] In some embodiments, the anti-angiogenesis agent is an anti-angiogenesis antibody. In some embodiments, the anti-angiogenesis antibody is a monoclonal antibody. In some embodiments, the anti-angiogenesis antibody is a human or humanized antibody. In some embodiments, the anti-angiogenesis agent is a VEGF antagonist. In some embodiments, the VEGF antagonist reduces the expression level or biological activity of VEGF by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%. In some embodiments, the VEGF is VEGF (8-109), VEGF (1-109), or $VEGF_{165}$. In some embodiments, the VEGF antagonist increases MHC class II expression on dendritic cells as compared to MHC class II expression on dendritic cells prior to treatment with the VEGF antagonist. In some embodiments, the VEGF antagonist increases OX40L expression on dendritic cells as compared to OX40L expression on dendritic cells prior to treatment with the VEGF antagonist. In some embodiments, the dendritic cells are myeloid dendritic cells. In some embodiments, the dendritic cells are non-myeloid dendritic cells. In some embodiments, the VEGF antagonist comprises a soluble VEGF receptor or a soluble VEGF receptor fragment that specifically binds to VEGF. In some embodiments, the VEGF antagonist is a chimeric VEGF receptor protein. In some embodiments, the VEGF antagonist is administered by gene therapy.

[0018] In some embodiments, the VEGF antagonist is an anti-VEGF antibody. In some embodiments, the anti-VEGF antibody is a human or humanized antibody. In some embodiments, the anti-VEGF antibody binds to the A4.6.1 epitope. In some embodiments, the anti-VEGF antibody binds to a functional epitope comprising residues F17, M18, D19, Y21, Y25, Q89, I91, K101, E103, and C104 of human VEGF. In some embodiments, the anti-VEGF antibody binds to a functional epitope comprising residues F17, Y21, Q22, Y25, D63, I83, and Q89 of human VEGF. In some embodiments, the anti-VEGF antibody is a G6 series antibody. In some embodiments, the anti-VEGF antibody is a B20 series antibody. In some embodiments, the anti-VEGF antibody is a monoclonal anti-VEGF antibody. In some embodiments, the monoclonal anti-VEGF antibody is bevacizumab. In

some embodiments, the anti-VEGF antibody comprises a light chain variable region comprising the amino acid sequence of DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR. (SEQ ID NO:214). In some embodiments, the anti-VEGF antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:215). In some embodiments, the anti-VEGF antibody comprises a light chain variable region comprising the amino acid sequence of DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR. (SEQ ID NO:214) and a heavy chain variable region comprising the amino acid sequence of EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:215). In some embodiments, the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of bevacizumab. In some embodiments, the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of selected from (a) HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO:216); (b) HVR-H2 comprising the amino acid sequence of WINTYTGEPTYAADFKR (SEQ ID NO:217); (c) HVR-H3 comprising the amino acid sequence of YPHYYGSSHWYFDV (SEQ ID NO:218); (d) HVR-L1 comprising the amino acid sequence of SASQDISNYLN (SEQ ID NO:219); (e) HVR-L2 comprising the amino acid sequence of FTSSLHS (SEQ ID NO:220); and (f) HVR-L3 comprising the amino acid sequence of QQYSTVPWT (SEQ ID NO:221). In some embodiments, the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of an antibody described in U.S. Pat. No. 6,884,879. In some embodiments, the anti-VEGF antibody comprises one, two, or three hypervariable region (HVR) sequences of a light chain variable region comprising the following amino acid sequence: DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR. (SEQ ID NO:214) and/or one, two, or three hypervariable region (HVR) sequences of a heavy chain variable region comprising the following amino acid sequence: EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:215). In some embodiments, the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of bevacizumab.

[0019] In some embodiments, the OX40 binding agonist is selected from the group consisting of an OX40 agonist antibody, an OX40L agonist fragment, an OX40 oligomeric receptor, and an OX40 immunoadhesin. In some embodiments, the OX40 binding agonist is a trimeric OX40L-Fc protein.

In some embodiments, the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L. In some embodiments, the OX40 binding agonist is an OX40 agonist antibody that binds human OX40. In some embodiments, the OX40 agonist antibody depletes cells that express human OX40. In some embodiments, the OX40 agonist antibody depletes cells that express human OX40 *in vitro*. In some embodiments, the cells are CD4+ effector T cells. In some embodiments, the cells are Treg cells. In some embodiments, the depleting is by ADCC and/or phagocytosis. In some embodiments, the depleting is by ADCC. In some embodiments, the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 1 nM. In some embodiments, the OX40 agonist antibody depletes cells that express human OX40 *in vitro* and binds human OX40 with an affinity of less than or equal to about 1 nM. In some embodiments, the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM. In some embodiments, the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM. In some embodiments, OX40 agonist antibody binding affinity is determined using radioimmunoassay. In some embodiments, binding to human OX40 has an EC50 of less than or equal to 0.2 ug/ml. In some embodiments, binding to human OX40 has an EC50 of less than or equal to 0.3 ug/ml. In some embodiments, the OX40 agonist antibody increases CD4+ effector T cell proliferation and/or increasing cytokine production by the CD4+ effector T cell as compared to proliferation and/or cytokine production prior to treatment with anti-human OX40 agonist antibody. In some embodiments, the cytokine is gamma interferon. In some embodiments, the OX40 agonist antibody increases memory T cell proliferation and/or increasing cytokine production by the memory cell. In some embodiments, the cytokine is gamma interferon. In some embodiments, the OX40 agonist antibody inhibits Treg function. In some embodiments, the OX40 agonist antibody inhibits Treg suppression of effector T cell function. In some embodiments, effector T cell function is effector T cell proliferation and/or cytokine production. In some embodiments, the effector T cell is a CD4+ effector T cell. In some embodiments, the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40. In some embodiments, OX40 signal transduction is detected by monitoring NFkB downstream signaling. In some embodiments, the OX40 agonist antibody is stable after treatment at 40°C for two weeks. In some embodiments, the OX40 agonist antibody comprises a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells, and wherein the antibody has diminished activity relative to an anti-human OX40 agonist antibody comprising a native sequence IgG1 Fc portion. In some embodiments, the OX40 agonist antibody comprises a variant Fc portion comprising a DANA mutation. In some embodiments, OX40 agonist antibody cross-linking is required for anti-human OX40 agonist antibody function. In some embodiments, the OX40 agonist antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 2, 8 or 9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 4, 15, or 19; and (iv) HVR-L1 comprising the amino acid

sequence of SEQ ID NO:5, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28. In some embodiments, the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:7. In some embodiments, the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:26. In some embodiments, the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:27. In some embodiments, the OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 108, 114, 116, 233, or 234. In some embodiments, the OX40 agonist antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 109, 115 or 117. In some embodiments, the OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56. In some embodiments, the OX40 agonist VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to human OX40. In some embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:56. In some embodiments, the OX40 agonist VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4. In some embodiments, the OX40 agonist antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57. In some embodiments, the OX40 agonist VL sequence

having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to human OX40. In some embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 57. In some embodiments, the OX40 agonist VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7. In some embodiments, the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 56. In some embodiments, the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 57. In some embodiments, the OX40 agonist antibody comprises a VH sequence of SEQ ID NO:56 and a VL sequence of SEQ ID NO: 57. In some embodiments, the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 94. In some embodiments, the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 95. In some embodiments, the OX40 agonist antibody comprises a VH sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO: 95. In some embodiments, the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 96. In some embodiments, the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 97. In some embodiments, the OX40 agonist antibody comprises a VH sequence of SEQ ID NO:96 and a VL sequence of SEQ ID NO: 97. In some embodiments, the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

[0020] In some embodiments, the OX40 agonist is in a pharmaceutical formulation that comprises any of the anti-human OX40 antibodies (e.g., agonist antibodies) provided herein and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein at a concentration between about 10 mg/mL and about 100 mg/mL, (b) a polysorbate, wherein the polysorbate concentration is about 0.02% to about 0.06%; (c) a histidine buffer at about pH 5.0 to about pH 6.0; and (d) a saccharide, wherein the saccharide concentration is about 120mM to about 320 mM. In some embodiments, the histidine buffer is at pH 5.0 to 6.0. In some embodiments, the saccharide is sucrose. In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.02%; (c) a histidine acetate buffer at pH 6.0; and (d) sucrose, wherein the sucrose concentration is about 320 mM. In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.02%; (c) a histidine acetate buffer at pH 5.5; and (d) sucrose, wherein the sucrose concentration is about 240 mM. In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.04%; (c) a histidine acetate buffer at pH 6.0; and (d) sucrose, wherein the sucrose concentration is about 120 mM. In some embodiments,

the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 40, wherein the polysorbate concentration is about 0.04%; (c) a histidine acetate buffer at pH 5.0; and (d) sucrose, wherein the sucrose concentration is about 240 mM. In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 40, wherein the polysorbate concentration is about 0.04%; (c) a histidine acetate buffer at pH 6.0; and (d) sucrose, wherein the sucrose concentration is about 120 mM. In some embodiments, the antibody of the formulation comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 2, 8 or 9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 4, 15, or 19; and (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28. In some embodiments, the antibody of the formulation comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:7. In some embodiments, the antibody of the formulation comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:26. In some embodiments, the antibody of the formulation comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:27. In some embodiments, the antibody of the formulation comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 108, 114, 116, 183, or 184. In some embodiments, the antibody of the formulation comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 109, 115 or 117. In some embodiments, the antibody of the formulation comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID

NO:56. In some embodments, the VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to human OX40. In some embodiments, total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:56. In some embodiments, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4. In some embodiments, the antibody of the formulation comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57. In some embodiments, the VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to human OX40. In some embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 57. In some embodiments, the VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO: 56. In some embodiments, the antibody of the formulation comprises a VL sequence of SEQ ID NO: 57. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO:56 and a VL sequence of SEQ ID NO: 57. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO: 94. In some embodiments, the antibody of the formulation comprises a VL sequence of SEQ ID NO: 95. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO: 95. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO: 96. In some embodiments, the antibody of the formulation comprises a VL sequence of SEQ ID NO: 97. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO:96 and a VL sequence of SEQ ID NO: 97. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO: 179. In some embodiments, the antibody of the formulation comprises a VL sequence of SEQ ID NO: 180. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO:179 and a VL sequence of SEQ ID NO: 180. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO: 181. In some embodiments, the antibody of the formulation comprises a VL sequence of SEQ ID NO: 182. In some embodiments, the antibody of the formulation comprises a VH sequence of SEQ ID NO:181 and a VL sequence of SEQ ID NO: 182.

[0021] In some embodiments, the cancer is lung cancer, glioblastoma, cervical cancer, ovarian cancer, breast cancer, colon cancer, colorectal cancer, fallopian tube cancer, peritoneal cancer, kidney cancer, renal cancer, non-Hodgkins lymphoma, prostate cancer, pancreatic cancer, soft-tissue sarcoma, kaposi's sarcoma, carcinoid carcinoma, head and neck cancer, mesothelioma, multiple myeloma, non-small cell lung cancer, neuroblastoma, melanoma, gastric cancer, or liver cancer. In some embodiments, the cancer is a gynecologic cancer. In some embodiments, the cancer is advanced, refractory, recurrent, chemotherapy-resistant, and/or platinum-resistant. In some embodiments, the individual has cancer or has been diagnosed with cancer. In some embodiments, the treatment results in a sustained response in the individual after cessation of the treatment. In some embodiments, the OX40 binding agonist is administered before the anti-angiogenesis agent, simultaneous with the anti-angiogenesis agent, or after the anti-angiogenesis agent. In some embodiments, the individual is a human. In some embodiments, the anti-angiogenesis agent and/or the OX40 binding agonist are administered intravenously, intramuscularly, subcutaneously, intracerobrospinally, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, intra-articularly, intrasynovially, or intranasally. In some embodiments, the method further comprises administering a chemotherapeutic agent for treating or delaying progression of cancer.

[0022] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention. These and other aspects of the invention will become apparent to one of skill in the art. These and other embodiments of the invention are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE FIGURES

[0023] **FIG. 1** shows the efficacy of different treatments on inhibiting tumor growth in a CT26 tumor model. Average tumor volumes (y-axis) over time (x-axis) are plotted for each experimental group. Experimental groups were anti-OX40 and anti-GP120 treatment (pluses), anti-GP120 treatment (circles), anti-VEGF and anti-GP120 treatment (triangles), and anti-VEGF and anti-OX40 treatment (X's).

[0024] **FIGS. 2A-2D** track tumor volumes from individual mice over time in the following treatment groups: anti-GP120 (control; **FIG. 2A**), anti-VEGF + anti-GP120 (**FIG. 2B**), anti-OX40 + anti-GP120 (**FIG. 2C**), and anti-VEGF + anti-OX40 (**FIG. 2D**). Solid black and dashed and dotted lines represent tumors from individual mice within each experimental group. Solid black lines represent mice that remained alive at the termination of the experiment, and dashed and dotted lines represent mice that were euthanized prior to experiment termination due to tumor ulceration or tumor size exceeding 2000 mm^3. Evenly dashed lines depict the average tumor volume over time in mice that received anti-GP120 alone (as labeled by arrows). Unevenly dashed lines are representative of the average tumor volume over time within each experimental group (as labeled by arrows).

Percentages in top left corner of each individual graph are % tumor growth inhibition (TGI), as judged against mice that received anti-GP120 alone.

[0025] **FIGS. 3A & 3B** show increased intratumoral dendritic cell activation following anti-VEGF treatment in a CT26 tumor model. **FIG. 3A** shows increased activation of myeloid dendritic cells (CD11b+). **FIG. 3B** shows increased activation of non-myeloid dendritic cells (CD11b-). Asterisks indicate statistical significance determined using a Student's t-test, assuming unequal variance and a significance level of 0.05 (* indicates $p<0.05$).

DETAILED DESCRIPTION

[0026] In one aspect, provided herein are methods, compositions and uses for treating or delaying progression of cancer in an individual comprising administering an effective amount of an anti-angiogenesis agent and an OX40 binding agonist.

I. Definitions

[0027] The term "dysfunction" in the context of immune dysfunction, refers to a state of reduced immune responsiveness to antigenic stimulation.

[0028] The term "dysfunctional", as used herein, also includes refractory or unresponsive to antigen recognition, specifically, impaired capacity to translate antigen recognition into downstream T-cell effector functions, such as proliferation, cytokine production (*e.g.*, gamma interferon) and/or target cell killing.

[0029] "Enhancing T cell function" means to induce, cause or stimulate an effector or memory T cell to have a renewed, sustained or amplified biological function. Examples of enhancing T-cell function include: increased secretion of γ-interferon from $CD8^+$ effector T cells, increased secretion of γ-interferon from CD4+ memory and/or effector T-cells, increased proliferation of CD4+ effector and/or memory T cells, increased proliferation of CD8+ effector T-cells, increased antigen responsiveness (*e.g.*, clearance), relative to such levels before the intervention. In one embodiment, the level of enhancement is at least 50%, alternatively 60%, 70%, 80%, 90%, 100%, 120%, 150%, 200%. The manner of measuring this enhancement is known to one of ordinary skill in the art.

[0030] "Tumor immunity" refers to the process in which tumors evade immune recognition and clearance. Thus, as a therapeutic concept, tumor immunity is "treated" when such evasion is attenuated, and the tumors are recognized and attacked by the immune system. Examples of tumor recognition include tumor binding, tumor shrinkage and tumor clearance.

[0031] "Immunogenicity" refers to the ability of a particular substance to provoke an immune response. Tumors are immunogenic and enhancing tumor immunogenicity aids in the clearance of the tumor cells by the immune response.

[0032] "Sustained response" refers to the sustained effect on reducing tumor growth after cessation of a treatment. For example, the tumor size may remain to be the same or smaller as compared to the size at the *beginning* of the administration phase. In some embodiments, the sustained response has a

duration at least the same as the treatment duration, at least 1.5X, 2.0X, 2.5X, or 3.0X length of the treatment duration.

[0033] An "acceptor human framework" for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as defined below. An acceptor human framework "derived from" a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some embodiments, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0034] "Affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

[0035] An "agonist antibody," as used herein, is an antibody which activates a biological activity of the antigen it binds.

[0036] "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted immunoglobulin bound onto Fc receptors (FcRs) present on certain cytotoxic cells (*e.g.* NK cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII, and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 or U.S. Patent No. 6,737,056 (Presta), may be performed. Useful effector cells for such assays include PBMC and NK cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.*, in an animal model such as that disclosed in Clynes *et al. PNAS (USA)* 95:652-656 (1998). An exemplary assay for assessing ADCC activity is provided in the examples herein.

[0037] The terms "anti-OX40 antibody" and "an antibody that binds to OX40" refer to an antibody that is capable of binding OX40 with sufficient affinity such that the antibody is useful as a diagnostic

and/or therapeutic agent in targeting OX40. In one embodiment, the extent of binding of an anti-OX40 antibody to an unrelated, non-OX40 protein is less than about 10% of the binding of the antibody to OX40 as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds to OX40 has a dissociation constant (Kd) of $\leq$ 1μM, $\leq$ 100 nM, $\leq$ 10 nM, $\leq$ 1 nM, $\leq$ 0.1 nM, $\leq$ 0.01 nM, or $\leq$ 0.001 nM (e.g. 10^{-8} M or less, e.g. from 10^{-8} M to 10^{-13} M, e.g., from 10^{-9} M to 10^{-13} M). In certain embodiments, an anti-OX40 antibody binds to an epitope of OX40 that is conserved among OX40 from different species.

[0038] As use herein, the term "binds", "specifically binds to" or is "specific for" refers to measurable and reproducible interactions such as binding between a target and an antibody, which is determinative of the presence of the target in the presence of a heterogeneous population of molecules including biological molecules. For example, an antibody that binds to or specifically binds to a target (which can be an epitope) is an antibody that binds this target with greater affinity, avidity, more readily, and/or with greater duration than it binds to other targets. In one embodiment, the extent of binding of an antibody to an unrelated target is less than about 10% of the binding of the antibody to the target as measured, *e.g.,* by a radioimmunoassay (RIA). In certain embodiments, an antibody that specifically binds to a target has a dissociation constant (Kd) of $\leq$ 1μM, $\leq$ 100 nM, $\leq$ 10 nM, $\leq$ 1 nM, or $\leq$ 0.1 nM. In certain embodiments, an antibody specifically binds to an epitope on a protein that is conserved among the protein from different species. In another embodiment, specific binding can include, but does not require exclusive binding.

[0039] The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

[0040] An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, $F(ab')_2$; diabodies; linear antibodies; single-chain antibody molecules (e.g. scFv); and multispecific antibodies formed from antibody fragments.

[0041] An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. An exemplary competition assay is provided herein.

[0042] The term "binding domain" refers to the region of a polypeptide that binds to another molecule. In the case of an FcR, the binding domain can comprise a portion of a polypeptide chain thereof (*e.g.* the alpha chain thereof) which is responsible for binding an Fc region. One useful binding domain is the extracellular domain of an FcR alpha chain.

[0043] A polypeptide with a variant IgG Fc with "altered" FcR, ADCC or phagocytosis activity is one which has either enhanced or diminished FcR binding activity (e.g, FcγR) and/or ADCC activity and/or phagocytosis activity compared to a parent polypeptide or to a polypeptide comprising a native sequence Fc region.

[0044] The term "OX40," as used herein, refers to any native OX40 from any vertebrate source, including mammals such as primates (e.g. humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses "full-length," unprocessed OX40 as well as any form of OX40 that results from processing in the cell. The term also encompasses naturally occurring variants of OX40, e.g., splice variants or allelic variants. The amino acid sequence of an exemplary human OX40 (minus the signal peptide) is as shown in SEQ ID NO:1.

[0045] "OX40 activation" refers to activation, of the OX40 receptor. Generally, OX40 activation results in signal transduction.

[0046] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Included in this definition are benign and malignant cancers. Examples of cancer include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer (including platinum sensitive and platinum resistant ovarian cancer), liver cancer, bladder cancer, hepatoma, neuroblastoma, melanoma, breast cancer, colon cancer, colorectal cancer, fallopian tube, peritoneal, endometrial or uterine carcinoma, gynecologic cancers (e.g., ovarian, peritoneal, fallopian tube, cervical, endometrial, vaginal, and vulvar cancer), salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, soft-tissue sarcoma, kaposi's sarcoma, carcinoid carcinoma, mesothelioma, multiple myeloma, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome.

[0047] The terms "cell proliferative disorder" and "proliferative disorder" refer to disorders that are associated with some degree of abnormal cell proliferation. In one embodiment, the cell proliferative disorder is cancer.

[0048] The term "chimeric" antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0049] The "class" of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively.

[0050] "Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass), which are bound to their cognate antigen. To assess complement activation, a CDC assay, *e.g.*, as described in Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996), may be performed. Polypeptide variants with altered Fc region amino acid sequences (polypeptides with a variant Fc region) and increased or decreased C1q binding capability are described, *e.g.*, in US Patent No. 6,194,551 B1 and WO 1999/51642. See also, *e.g.*, Idusogie *et al. J. Immunol.* 164: 4178-4184 (2000).

[0051] The term "cytostatic agent" refers to a compound or composition which arrests growth of a cell either in vitro or in vivo. Thus, a cytostatic agent may be one which significantly reduces the percentage of cells in S phase. Further examples of cytostatic agents include agents that block cell cycle progression by inducing G0/G1 arrest or M-phase arrest. The humanized anti-Her2 antibody trastuzumab (HERCEPTIN®) is an example of a cytostatic agent that induces G0/G1 arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Certain agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in Mendelsohn and Israel, eds., *The Molecular Basis of Cancer*, Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (W.B. Saunders, Philadelphia, 1995), *e.g.*, p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb). Paclitaxel and docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

[0052] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu); chemotherapeutic agents or drugs (e.g., methotrexate, adriamicin, vinca alkaloids

(vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and the various antitumor or anticancer agents disclosed below.

[0053] A "depleting anti-OX40 antibody," is an anti-OX40 antibody that kills or depletes OX40-expressing cells. Depletion of OX40 expressing cells can be achieved by various mechanisms, such as antibody-dependent cell-mediated cytotoxicity and/or phagocytosis. Depletion of OX40-expressing cells may be assayed in vitro, and exemplary methods for in vitro ADCC and phagocytosis assays are provided herein. In some embodiments, the OX40-expressing cell is a human CD4+ effector T cell. In some embodiments, the OX40-expressing cell is a transgenic BT474 cell that expresses human OX40.

[0054] "Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g. B cell receptor); and B cell activation.

[0055] An "effective amount" is at least the minimum amount required to effect a measurable improvement 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 antibody 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. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. In the case of cancer or tumor, an effective amount of the drug may have the effect in reducing the number of cancer cells; reducing the tumor size; inhibiting (*i.e.*, slow to some extent or desirably stop) cancer cell infiltration into peripheral organs; inhibit (*i.e.*, slow to some extent and desirably stop) tumor metastasis; inhibiting to some extent tumor growth; and/or relieving to some extent one or more of the symptoms associated with the disorder. An effective amount can be administered in one or more administrations. For purposes of this invention, 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.

[0056] "Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. In some embodiments, an FcR is a native human FcR. In some embodiments, an FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of those receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (see, *e.g.*, Daëron, *Annu. Rev. Immunol.* 15:203-234 (1997)). FcRs are reviewed, for example, in Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991); Capel *et al., Immunomethods* 4:25-34 (1994); and de Haas *et al., J. Lab. Clin. Med.* 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term "Fc receptor" or "FcR" also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer *et al., J. Immunol.* 117:587 (1976) and Kim *et al., J. Immunol.* 24:249 (1994)) and regulation of homeostasis of immunoglobulins. Methods of measuring binding to FcRn are known (see, *e.g.*, Ghetie and Ward., *Immunol. Today* 18(12):592-598 (1997); Ghetie *et al.*, *Nature Biotechnology*, 15(7):637-640 (1997); Hinton *et al.*, *J. Biol. Chem.* 279(8):6213-6216 (2004); WO 2004/92219 (Hinton *et al.*). Binding to human FcRn *in vivo* and serum half life of human FcRn high affinity binding polypeptides can be assayed, *e.g.*, in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides with a variant Fc region are administered. WO 2000/42072 (Presta) describes antibody variants with improved or diminished binding to FcRs. See also, *e.g.*, Shields *et al. J. Biol. Chem.* 9(2):6591-6604 (2001).

[0057] The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. In one embodiment, a human IgG heavy chain Fc region extends from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., *Sequences of Proteins of*

Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991.

[0058] A "functional Fc region" possesses an "effector function" of a native sequence Fc region. Exemplary "effector functions" include C1q binding; CDC; Fc receptor binding; ADCC; phagocytosis; down regulation of cell surface receptors (e.g. B cell receptor; BCR), etc. Such effector functions generally require the Fc region to be combined with a binding domain (*e.g.*, an antibody variable domain) and can be assessed using various assays as disclosed, for example, in definitions herein.

[0059] "Human effector cells" refer to leukocytes that express one or more FcRs and perform effector functions. In certain embodiments, the cells express at least FcγRIII and perform ADCC effector function(s). Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells, and neutrophils. The effector cells may be isolated from a native source, e.g., from blood.

[0060] "Framework" or "FR" refers to variable domain residues other than hypervariable region (HVR) residues. The FR of a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the HVR and FR sequences generally appear in the following sequence in VH (or VL): FR1-H1(L1)-FR2-H2(L2)-FR3-H3(L3)-FR4.

[0061] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0062] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0063] A "human antibody" is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[0064] A "human consensus framework" is a framework which represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, Fifth Edition, NIH Publication 91-

3242, Bethesda MD (1991), vols. 1-3. In one embodiment, for the VL, the subgroup is subgroup kappa I as in Kabat et al., *supra.* In one embodiment, for the VH, the subgroup is subgroup III as in Kabat et al., *supra.*

[0065] A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization.

[0066] The term "hypervariable region" or "HVR" as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence ("complementarity determining regions" or "CDRs") and/or form structurally defined loops ("hypervariable loops") and/or contain the antigen-contacting residues ("antigen contacts"). Generally, antibodies comprise six HVRs: three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). Exemplary HVRs herein include:
(a) hypervariable loops occurring at amino acid residues 26-32 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987));
(b) CDRs occurring at amino acid residues 24-34 (L1), 50-56 (L2), 89-97 (L3), 31-35b (H1), 50-65 (H2), and 95-102 (H3) (Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991));
(c) antigen contacts occurring at amino acid residues 27c-36 (L1), 46-55 (L2), 89-96 (L3), 30-35b (H1), 47-58 (H2), and 93-101 (H3) (MacCallum et al. *J. Mol. Biol.* 262: 732-745 (1996)); and
(d) combinations of (a), (b), and/or (c), including HVR amino acid residues 46-56 (L2), 47-56 (L2), 48-56 (L2), 49-56 (L2), 26-35 (H1), 26-35b (H1), 49-65 (H2), 93-102 (H3), and 94-102 (H3).
Unless otherwise indicated, HVR residues and other residues in the variable domain (e.g., FR residues) are numbered herein according to Kabat et al., *supra.*

[0067] An "immunoconjugate" is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

[0068] An "individual" or "subject" is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual or subject is a human.

[0069] "Promoting cell growth or proliferation" means increasing a cell's growth or proliferation by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100%.

[0070] An "isolated" antibody is one which has been separated from a component of its natural environment. In some embodiments, an antibody is purified to greater than 95% or 99% purity as

determined by, for example, electrophoretic (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (e.g., ion exchange or reverse phase HPLC). For review of methods for assessment of antibody purity, see, e.g., Flatman et al., *J. Chromatogr. B* 848:79-87 (2007).

[0071] An "isolated" nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0072] "Isolated nucleic acid encoding an anti-OX40 antibody" refers to one or more nucleic acid molecules encoding antibody heavy and light chains (or fragments thereof), including such nucleic acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.

[0073] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0074] A "naked antibody" refers to an antibody that is not conjugated to a heterologous moiety (e.g., a cytotoxic moiety) or radiolabel. The naked antibody may be present in a pharmaceutical formulation.

[0075] "Native antibodies" refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG antibodies are heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light chains and two identical heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3). Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a

variable light domain or a light chain variable domain, followed by a constant light (CL) domain. The light chain of an antibody may be assigned to one of two types, called kappa (κ) and lambda (λ), based on the amino acid sequence of its constant domain. A "native sequence Fc region" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

[0076] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0077] "Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, California, or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0078] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino

acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0079] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[0080] A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0081] As used herein, "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antibodies of the invention are used to delay development of a disease or to slow the progression of a disease.

[0082] As used herein, "in conjunction with" refers to administration of one treatment modality in addition to another treatment modality. As such, "in conjunction with" refers to administration of one treatment modality before, during, or after administration of the other treatment modality to the individual. For example, an anti-angiogenesis agent may be administered in conjunction with an OX40 binding agonist. An anti-angiogenesis agent and an OX40 binding agonist may be administered in conjunction with another a chemotherapeutic agent.

[0083] The term "tumor" refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. The terms "cancer," "cancerous," "cell proliferative disorder," "proliferative disorder" and "tumor" are not mutually exclusive as referred to herein.

[0084] The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (See, e.g., Kindt et al. *Kuby Immunology*, 6th ed., W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding

specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. See, e.g., Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., *Nature* 352:624-628 (1991).

[0085] A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, e.g. from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

[0086] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

[0087] A "VH subgroup III consensus framework" comprises the consensus sequence obtained from the amino acid sequences in variable heavy subgroup III of Kabat et al. In one embodiment, the VH subgroup III consensus framework amino acid sequence comprises at least a portion or all of each of the following sequences: EVQLVESGGGLVQPGGSLRLSCAAS (SEQ ID NO:222)-H1-WVRQAPGKGLEWV (SEQ ID NO:223)-H2-RFTISRDNSKNTLYLQMNSLRAEDTAVYYC (SEQ ID NO:224)-H3-WGQGTLVTVSS (SEQ ID NO:225).

[0088] A "VL subgroup I consensus framework" comprises the consensus sequence obtained from the amino acid sequences in variable light kappa subgroup I of Kabat et al. In one embodiment, the VH subgroup I consensus framework amino acid sequence comprises at least a portion or all of each of the following sequences:
DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO:226)-L1-WYQQKPGKAPKLLIY (SEQ ID NO:227)-L2-GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO:228)-L3-FGQGTKVEIK (SEQ ID NO:229).

[0089] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At211, I131, I125, Y90, Re186, Re188, Sm153, Bi212, P32, Pb212 and radioactive isotopes of Lu); chemotherapeutic agents; growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or

variants thereof. Exemplary cytotoxic agents can be selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, inhibitors of LDH-A; inhibitors of fatty acid biosynthesis; cell cycle signalling inhibitors; HDAC inhibitors, proteasome inhibitors; and inhibitors of cancer metabolism.

[0090] In one embodiment the cytotoxic agent is selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, inhibitors of LDH-A, inhibitors of fatty acid biosynthesis, cell cycle signalling inhibitors, HDAC inhibitors, proteasome inhibitors, and inhibitors of cancer metabolism. In one embodiment the cytotoxic agent is a taxane. In one embodiment the taxane is paclitaxel or docetaxel. In one embodiment the cytotoxic agent is a platinum agent. In one embodiment the cytotoxic agent is an antagonist of EGFR. In one embodiment the antagonist of EGFR is N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (e.g., erlotinib). In one embodiment the cytotoxic agent is a RAF inhibitor. In one embodiment, the RAF inhibitor is a BRAF and/or CRAF inhibitor. In one embodiment the RAF inhibitor is vemurafenib. In one embodiment the cytotoxic agent is a PI3K inhibitor.

[0091] "Chemotherapeutic agent" includes chemical compounds useful in the treatment of cancer. Examples of chemotherapeutic agents include erlotinib (TARCEVA®, Genentech/OSI Pharm.), bortezomib (VELCADE®, Millennium Pharm.), disulfiram, epigallocatechin gallate , salinosporamide A, carfilzomib, 17-AAG (geldanamycin), radicicol, lactate dehydrogenase A (LDH-A), fulvestrant (FASLODEX®, AstraZeneca), sunitib (SUTENT®, Pfizer/Sugen), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), finasunate (VATALANIB®, Novartis), oxaliplatin (ELOXATIN®, Sanofi), 5-FU (5-fluorouracil), leucovorin, Rapamycin (Sirolimus, RAPAMUNE®, Wyeth), Lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), Lonafamib (SCH 66336), sorafenib (NEXAVAR®, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), AG1478, alkylating agents such as thiotepa and CYTOXAN® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including topotecan and irinotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); adrenocorticosteroids (including prednisone and prednisolone); cyproterone acetate; 5α-reductases including finasteride and dutasteride); vorinostat, romidepsin, panobinostat, valproic acid, mocetinostat dolastatin; aldesleukin,

talc duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlomaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin γ1I and calicheamicin ω1I (Angew Chem. Intl. Ed. Engl. 1994 33:183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamnol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE® (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Ill.), and TAXOTERE® (docetaxel, doxetaxel; Sanofi-Aventis); chloranmbucil; GEMZAR® (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000;

difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0092] Chemotherapeutic agent also includes (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, iodoxyfene , 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide and goserelin; buserelin, tripterelin, medroxyprogesterone acetate, diethylstilbestrol, premarin, fluoxymesterone, all transretionic acid, fenretinide, as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN®, rIL-2; a topoisomerase 1 inhibitor such as LURTOTECAN®; ABARELIX® rmRH; and (ix) pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0093] Chemotherapeutic agent also includes antibodies such as alemtuzumab (Campath), cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG®, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab, bapineuzumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti–interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a

recombinant exclusively human-sequence, full-length IgG1 λ antibody genetically modified to recognize interleukin-12 p40 protein.

[0094] Chemotherapeutic agent also includes "EGFR inhibitors," which refers to compounds that bind to or otherwise interact directly with EGFR and prevent or reduce its signaling activity, and is alternatively referred to as an "EGFR antagonist." Examples of such agents include antibodies and small molecules that bind to EGFR. Examples of antibodies which bind to EGFR include MAb 579 (ATCC CRL HB 8506), MAb 455 (ATCC CRL HB8507), MAb 225 (ATCC CRL 8508), MAb 528 (ATCC CRL 8509) (see, US Patent No. 4,943, 533, Mendelsohn et al.) and variants thereof, such as chimerized 225 (C225 or Cetuximab; ERBUTIX®) and reshaped human 225 (H225) (see, WO 96/40210, Imclone Systems Inc.); IMC-11F8, a fully human, EGFR-targeted antibody (Imclone); antibodies that bind type II mutant EGFR (US Patent No. 5,212,290); humanized and chimeric antibodies that bind EGFR as described in US Patent No. 5,891,996; and human antibodies that bind EGFR, such as ABX-EGF or Panitumumab (see WO98/50433, Abgenix/Amgen); EMD 55900 (Stragliotto et al. Eur. J. Cancer 32A:636-640 (1996)); EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR that competes with both EGF and TGF-alpha for EGFR binding (EMD/Merck); human EGFR antibody, HuMax-EGFR (GenMab); fully human antibodies known as E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6. 3 and E7.6. 3 and described in US 6,235,883; MDX-447 (Medarex Inc); and mAb 806 or humanized mAb 806 (Johns et al., J. Biol. Chem. 279(29):30375-30384 (2004)). The anti-EGFR antibody may be conjugated with a cytotoxic agent, thus generating an immunoconjugate (see, e.g., EP659,439A2, Merck Patent GmbH). EGFR antagonists include small molecules such as compounds described in US Patent Nos: 5,616,582, 5,457,105, 5,475,001, 5,654,307, 5,679,683, 6,084,095, 6,265,410, 6,455,534, 6,521,620, 6,596,726, 6,713,484, 5,770,599, 6,140,332, 5,866,572, 6,399,602, 6,344,459, 6,602,863, 6,391,874, 6,344,455, 5,760,041, 6,002,008, and 5,747,498, as well as the following PCT publications: WO98/14451, WO98/50038, WO99/09016, and WO99/24037. Particular small molecule EGFR antagonists include OSI-774 (CP-358774, erlotinib, TARCEVA® Genentech/OSI Pharmaceuticals); PD 183805 (CI 1033, 2-propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, Pfizer Inc.); ZD1839, gefitinib (IRESSA®) 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, AstraZeneca); ZM 105180 ((6-amino-4-(3-methylphenyl-amino)-quinazoline, Zeneca); BIBX-1382 (N8-(3-chloro-4-fluoro-phenyl)-N2-(1-methyl-piperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine, Boehringer Ingelheim); PKI-166 ((R)-4-[4-[(1-phenylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol); (R)-6-(4-hydroxyphenyl)-4-[(1-phenylethyl)amino]-7H-pyrrolo[2,3-d]pyrimidine); CL-387785 (N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butynamide); EKB-569 (N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butenamide) (Wyeth); AG1478 (Pfizer); AG1571 (SU 5271; Pfizer); dual EGFR/HER2 tyrosine kinase inhibitors such as

lapatinib (TYKERB®, GSK572016 or N-[3-chloro-4-[(3 fluorophenyl)methoxy]phenyl]-6[5[[[2methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine).

[0095] Chemotherapeutic agents also include "tyrosine kinase inhibitors" including the EGFR-targeted drugs noted in the preceding paragraph; small molecule HER2 tyrosine kinase inhibitor such as TAK165 available from Takeda; CP-724,714, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase (Pfizer and OSI); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; lapatinib (GSK572016; available from Glaxo-SmithKline), an oral HER2 and EGFR tyrosine kinase inhibitor; PKI-166 (available from Novartis); pan-HER inhibitors such as canertinib (CI-1033; Pharmacia); Raf-1 inhibitors such as antisense agent ISIS-5132 available from ISIS Pharmaceuticals which inhibit Raf-1 signaling; non-HER targeted TK inhibitors; multi-targeted tyrosine kinase inhibitors such as sunitinib (SUTENT®, available from Pfizer); VEGF receptor tyrosine kinase inhibitors such as vatalanib (PTK787/ZK222584, available from Novartis/Schering AG); MAPK extracellular regulated kinase I inhibitor CI-1040 (available from Pharmacia); quinazolines, such as PD 153035,4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo[2,3-d] pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties; PD-0183805 (Warner-Lamber); antisense molecules (e.g. those that bind to HER-encoding nucleic acid); quinoxalines (US Patent No. 5,804,396); tryphostins (US Patent No. 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering AG); pan-HER inhibitors such as CI-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); imatinib mesylate (GLEEVEC®); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); CI-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Pfizer); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone), rapamycin (sirolimus, RAPAMUNE®); or as described in any of the following patent publications: US Patent No. 5,804,396; WO 1999/09016 (American Cyanamid); WO 1998/43960 (American Cyanamid); WO 1997/38983 (Warner Lambert); WO 1999/06378 (Warner Lambert); WO 1999/06396 (Warner Lambert); WO 1996/30347 (Pfizer, Inc); WO 1996/33978 (Zeneca); WO 1996/3397 (Zeneca) and WO 1996/33980 (Zeneca).

[0096] Chemotherapeutic agents also include dexamethasone, interferons, colchicine, metoprine, cyclosporine, amphotericin, metronidazole, alemtuzumab, alitretinoin, allopurinol, amifostine, arsenic trioxide, asparaginase, BCG live, bevacuzimab, bexarotene, cladribine, clofarabine, darbepoetin alfa, denileukin, dexrazoxane, epoetin alfa, elotinib, filgrastim, histrelin acetate, ibritumomab, interferon alfa-2a, interferon alfa-2b, lenalidomide, levamisole, mesna, methoxsalen, nandrolone, nelarabine, nofetumomab, oprelvekin, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, plicamycin, porfimer sodium, quinacrine, rasburicase, sargramostim, temozolomide, VM-26, 6-TG, toremifene, tretinoin, ATRA, valrubicin, zoledronate, and zoledronic acid, and pharmaceutically acceptable salts thereof.

[0097] Chemotherapeutic agents also include hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-butyrate, hydrocortisone-17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate and fluprednidene acetate; immune selective anti-inflammatory peptides (ImSAIDs) such as phenylalanine-glutamine-glycine (FEG) and its D-isomeric form (feG) (IMULAN BioTherapeutics, LLC); anti-rheumatic drugs such as azathioprine, ciclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomideminocycline, sulfasalazine, tumor necrosis factor alpha (TNFα) blockers such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1) blockers such as anakinra (Kineret), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMERA®); Interleukin 13 (IL-13) blockers such as lebrikizumab; Interferon alpha (IFN) blockers such as Rontalizumab; Beta 7 integrin blockers such as rhuMAb Beta7; IgE pathway blockers such as Anti-M1 prime; Secreted homotrimeric LTa3 and membrane bound heterotrimer LTa1/β2 blockers such as Anti-lymphotoxin alpha (LTa); radioactive isotopes (e.g., At211, I131, I125, Y90, Re186, Re188, Sm153, Bi212, P32, Pb212 and radioactive isotopes of Lu); miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18- OCH3, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; autophagy inhibitors such as chloroquine; delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; acetylcamptothecin, scopolectin, and 9-aminocamptothecin); podophyllotoxin; tegafur (UFTORAL®); bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine; perifosine, COX-2 inhibitor (e.g. celecoxib or etoricoxib), proteosome inhibitor (e.g. PS341); CCI-779; tipifarnib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASARTM); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATINTM) combined with 5-FU and leucovorin.

[0098] Chemotherapeutic agents also include non-steroidal anti-inflammatory drugswith analgesic, antipyretic and anti-inflammatory effects. NSAIDs include non-selective inhibitors of the enzyme cyclooxygenase. Specific examples of NSAIDs include aspirin, propionic acid derivatives such as ibuprofen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin and naproxen, acetic acid derivatives such as indomethacin, sulindac, etodolac, diclofenac, enolic acid derivatives such as piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam and isoxicam, fenamic acid derivatives such as mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, and COX-2 inhibitors such as celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, rofecoxib, and valdecoxib. NSAIDs can be indicated for the symptomatic relief of conditions such as rheumatoid arthritis, osteoarthritis, inflammatory arthropathies, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhoea, metastatic bone pain, headache and migraine, postoperative pain, mild-to-moderate pain due to inflammation and tissue injury, pyrexia, ileus, and renal colic.

[0099] The term “cytokine” is a generic term for proteins released by one cell population that act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines; interleukins (ILs) such as IL-1, IL-1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12, IL-15; a tumor necrosis factor such as TNF-α or TNF-β; and other polypeptide factors including LIF and kit ligand (KL) and gamma interferon. As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native-sequence cytokines, including synthetically produced small-molecule entities and pharmaceutically acceptable derivatives and salts thereof.

[0100] An "anti-angiogenesis agent" or "angiogenesis inhibitor" refers to a small molecular weight substance, a polynucleotide, a polypeptide, an isolated protein, a recombinant protein, an antibody, or conjugates or fusion proteins thereof, that inhibits angiogenesis, vasculogenesis, or undesirable vascular permeability, either directly or indirectly. It should be understood that the anti-angiogenesis agent includes those agents that bind and block the angiogenic activity of the angiogenic factor or its receptor. For example, an anti-angiogenesis agent is an antibody or other antagonist to an angiogenic agent as defined throughout the specification or known in the art, e.g., but are not limited to, antibodies to VEGF-A or to the VEGF-A receptor (e.g., KDR receptor or Flt-1 receptor), VEGF-trap, anti-PDGFR inhibitors such as Gleevec™ (Imatinib Mesylate). Anti-angiogenesis agents also include native angiogenesis inhibitors, e.g., angiostatin, endostatin, etc. See, e.g., Klagsbrun and D'Amore, Annu. Rev. Physiol., 53:217-39 (1991); Streit and Detmar, Oncogene, 22:3172-3179 (2003) (e.g., Table 3 listing anti-angiogenic therapy in malignant melanoma); Ferrara & Alitalo, Nature Medicine 5:1359-1364 (1999); Tonini et al., Oncogene, 22:6549-6556 (2003) (e.g., Table 2 listing known antiangiogenic factors); and Sato. Int. J. Clin. Oncol., 8:200-206 (2003) (e.g., Table 1 lists anti-angiogenic agents used in clinical trials).

[0101] The term "VEGF" or "VEGF-A" is used to refer to the 165-amino acid human vascular endothelial cell growth factor and related 121-, 145-, 189-, and 206-amino acid human vascular

endothelial cell growth factors, as described by, e.g., Leung et al. Science, 246:1306 (1989), and Houck et al. Mol. Endocrin., 5:1806 (1991), together with the naturally occurring allelic and processed forms thereof. VEGF-A is part of a gene family including VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and PlGF. VEGF-A primarily binds to two high affinity receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR), the latter being the major transmitter of vascular endothelial cell mitogenic signals of VEGF-A. Additionally, neuropilin-1 has been identified as a receptor for heparin-binding VEGF-A isoforms, and may play a role in vascular development. The term "VEGF" or "VEGF-A" also refers to VEGFs from non-human species such as mouse, rat, or primate. Sometimes the VEGF from a specific species is indicated by terms such as hVEGF for human VEGF or mVEGF for murine VEGF. Typically, VEGF refers to human VEGF. The term "VEGF" is also used to refer to truncated forms or fragments of the polypeptide comprising amino acids 8 to 109 or 1 to 109 of the 165-amino acid human vascular endothelial cell growth factor. Reference to any such forms of VEGF may be identified in the application, e.g., by "VEGF (8-109)," "VEGF (1-109)" or "VEGF165." The amino acid positions for a "truncated" native VEGF are numbered as indicated in the native VEGF sequence. For example, amino acid position 17 (methionine) in truncated native VEGF is also position 17 (methionine) in native VEGF. The truncated native VEGF has binding affinity for the KDR and Flt-1 receptors comparable to native VEGF.

[0102] A "chimeric VEGF receptor protein" is a VEGF receptor molecule having amino acid sequences derived from at least two different proteins, at least one of which is a VEGF receptor protein. In certain embodiments, the chimeric VEGF receptor protein is capable of binding to and inhibiting the biological activity of VEGF.

[0103] A "VEGF antagonist" or "VEGF-specific antagonist" refers to a molecule capable of binding to VEGF, reducing VEGF expression levels, or neutralizing, blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities, including, but not limited to, VEGF binding to one or more VEGF receptors, VEGF signaling, and VEGF mediated angiogenesis and endothelial cell survival or proliferation. For example, a molecule capable of neutralizing, blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities can exert its effects by binding to one or more VEGF receptor (VEGFR) (e.g., VEGFR1, VEGFR2, VEGFR3, membrane-bound VEGF receptor (mbVEGFR), or soluble VEGF receptor (sVEGFR)). Included as VEGF-specific antagonists useful in the methods of the invention are polypeptides that specifically bind to VEGF, anti-VEGF antibodies and antigen-binding fragments thereof, receptor molecules and derivatives which bind specifically to VEGF thereby sequestering its binding to one or more receptors, fusions proteins (e.g., VEGF-Trap (Regeneron)), and $VEGF_{121}$-gelonin (Peregrine). VEGF-specific antagonists also include antagonist variants of VEGF polypeptides, antisense nucleobase oligomers complementary to at least a fragment of a nucleic acid molecule encoding a VEGF polypeptide; small RNAs complementary to at least a fragment of a nucleic acid molecule encoding a VEGF polypeptide; ribozymes that target

VEGF; peptibodies to VEGF; and VEGF aptamers. VEGF antagonists also include polypeptides that bind to VEGFR, anti-VEGFR antibodies, and antigen-binding fragments thereof, and derivatives which bind to VEGFR thereby blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities (e.g., VEGF signaling), or fusions proteins. VEGF-specific antagonists also include nonpeptide small molecules that bind to VEGF or VEGFR and are capable of blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities. Thus, the term "VEGF activities" specifically includes VEGF mediated biological activities of VEGF. In certain embodiments, the VEGF antagonist reduces or inhibits, by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more, the expression level or biological activity of VEGF. In some embodiments, the VEGF inhibited by the VEGF-specific antagonist is VEGF (8-109), VEGF (1-109), or $VEGF_{165}$.

[0104] As used herein VEGF antagonists can include, but are not limited to, anti-VEGFR2 antibodies and related molecules (e.g., ramucirumab, tanibirumab, aflibercept), anti-VEGFR1 antibodies and related molecules (e.g., icrucumab, aflibercept (VEGF Trap-Eye; EYLEA®), and ziv-aflibercept (VEGF Trap; ZALTRAP®)), bispecific VEGF antibodies (e.g., MP-0250, vanucizumab (VEGF-ANG2), and bispecific antibodies disclosed in US 2001/0236388), bispecific antibodies including combinations of two of anti-VEGF, anti-VEGFR1, and anti-VEGFR2 arms, anti-VEGFA antibodies (e.g., bevacizumab, sevacizumab), anti-VEGFB antibodies, anti-VEGFC antibodies (e.g., VGX-100), anti-VEGFD antibodies, and nonpeptide small molecule VEGF antagonists (e.g., pazopanib, axitinib, vandetanib, stivarga, cabozantinib, lenvatinib, nintedanib, orantinib, telatinib, dovitinig, cediranib, motesanib, sulfatinib, apatinib, foretinib, famitinib, and tivozanib).

[0105] An "anti-VEGF antibody" is an antibody that binds to VEGF with sufficient affinity and specificity. In certain embodiments, the antibody will have a sufficiently high binding affinity for VEGF, for example, the antibody may bind hVEGF with a K_d value of between 100 nM-1 pM. Antibody affinities may be determined, e.g., by a surface plasmon resonance based assay (such as the BIAcore assay as described in PCT Application Publication No. WO2005/012359); enzyme-linked immunoabsorbent assay (ELISA); and competition assays (e.g. RIA's). In certain embodiments, the anti-VEGF antibody can be used as a therapeutic agent in targeting and interfering with diseases or conditions wherein the VEGF activity is involved. Also, the antibody may be subjected to other biological activity assays, e.g., in order to evaluate its effectiveness as a therapeutic. Such assays are known in the art and depend on the target antigen and intended use for the antibody. Examples include the HUVEC inhibition assay; tumor cell growth inhibition assays (as described in WO 89/06692, for example); antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity (CDC) assays (U.S. Pat. No. 5,500,362); and agonistic activity or hematopoiesis assays (see WO 95/27062). An anti-VEGF antibody will usually not bind to other VEGF homologues such as VEGF-B or VEGF-C, nor other growth factors such as PlGF, PDGF, or bFGF. In one embodiment, anti-VEGF antibody is a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709. In another

embodiment, the anti-VEGF antibody is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (1997) *Cancer Res.* 57:4593-4599, including but not limited to the antibody known as bevacizumab (BV; AVASTIN®).

[0106] The anti-VEGF antibody "Bevacizumab (BV)," also known as "rhuMAb VEGF" or "AVASTIN®," is a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (1997) *Cancer Res.* 57:4593-4599. It comprises mutated human IgG1 framework regions and antigen-binding complementarity-determining regions from the murine anti-hVEGF monoclonal antibody A.4.6.1 that blocks binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence of bevacizumab, including most of the framework regions, is derived from human IgG1, and about 7% of the sequence is derived from the murine antibody A4.6.1. Bevacizumab has a molecular mass of about 149,000 daltons and is glycosylated. Bevacizumab and other humanized anti-VEGF antibodies are further described in U.S. Pat. No. 6,884,879 issued Feb. 26, 2005, the entire disclosure of which is expressly incorporated herein by reference. Additional preferred antibodies include the G6 or B20 series antibodies (e.g., G6-31, B20-4.1), as described in PCT Application Publication No. WO 2005/012359. For additional preferred antibodies see U.S. Pat. Nos. 7,060,269, 6,582,959, 6,703,020; 6,054,297; WO98/45332; WO 96/30046; WO94/10202; EP 0666868B1; U.S. Patent Application Publication Nos. 2006009360, 20050186208, 20030206899, 20030190317, 20030203409, and 20050112126; and Popkov et al., Journal of Immunological Methods 288:149-164 (2004). Other preferred antibodies include those that bind to a functional epitope on human VEGF comprising of residues F17, M18, D19, Y21, Y25, Q89, 191, K101, E103, and C104 or, alternatively, comprising residues F17, Y21, Q22, Y25, D63, 183, and Q89.

[0107] The "epitope A4.6.1" refers to the epitope recognized by the anti-VEGF antibody bevacizumab (AVASTIN®) (see Muller Y et al., Structure 15 September 1998, 6:1153–1167). In certain embodiments of the invention, the anti-VEGF antibodies include, but are not limited to, a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709; a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (1997) Cancer Res. 57:4593-4599.

[0108] By "standard of care" herein is intended the anti-tumor agent or agents that are routinely used to treat a particular form of cancer. For example, for platinum-resistant ovarian cancer, a standard of care is topotecan or liposomal doxorubicin.

[0109] By "platinum-based chemotherapeutic agent" or "platin" is meant an antineoplastic drug that is a coordination complex of platinum. Examples of platinum-based chemotherapeutic agents include carboplatin, cisplatin, and oxaliplatinum.

[0110] By "platinum-based chemotherapy" is meant therapy with one or more platinum-based chemotherapeutic agent, optionally in combination with one or more other chemotherapeutic agents.

[0111] By "chemotherapy-resistant" cancer is meant cancer in a patient that has progressed while the patient is receiving a chemotherapy regimen (i.e., the patient is "chemotherapy refractory"), or the

patient has progressed within 12 months (for instance, within 6 months) after completing a chemotherapy regimen.

[0112] By "platinum-resistant" cancer is meant cancer in a patient that has progressed while receiving platinum-based chemotherapy (i.e., the patient is "platinum refractory"), or the patient has progressed within 12 months (for instance, within 6 months) after completing a platinum-based chemotherapy regimen.

[0113] By "radiation therapy" is meant the use of directed gamma rays or beta rays to induce sufficient damage to a cell so as to limit its ability to function normally or to destroy the cell altogether. It will be appreciated that there will be many ways known in the art to determine the dosage and duration of treatment. Typical treatments are given as a one-time administration and typical dosages range from 10 to 200 units (Grays) per day.

[0114] As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a molecule" optionally includes a combination of two or more such molecules, and the like.

[0115] The term "about" as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se.

[0116] It is understood that aspects and embodiments of the invention described herein include "comprising," "consisting," and "consisting essentially of" aspects and embodiments.

II. Anti-angiogenesis Agents

[0117] Provided herein are methods treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of an anti-angiogenesis agent and an OX40 binding agonist.

[0118] As described *supra*, an anti-angiogenesis agent may include a compound such as a small molecular weight substance, a polynucleotide, a polypeptide, an isolated protein, a recombinant protein, an antibody, or conjugates or fusion proteins thereof. In some embodiments, the anti-angiogenesis agent is an anti-VEGFR2 antibody; an anti-VEGFR1 antibody; a VEGF-trap; a bispecific VEGF antibody; a bispecific antibody comprising a combination of two arms selected from an anti-VEGF arm, an anti-VEGFR1 arm, and an anti-VEGFR2 arm; an anti-VEGF-A antibody (*e.g.,* an anti-KDR receptor or anti-Flt-1 receptor antibody); an anti-VEGFB antibody; an anti-VEGFC antibody; an anti-VEGFD antibody; a nonpeptide small molecule VEGF antagonist; an anti-PDGFR inhibitor; or a native angiogenesis inhibitor. In certain embodiments, the anti-angiogenesis agent is ramucirumab, tanibirumab, aflibercept (*e.g.,* VEGF Trap-Eye; EYLEA®), icrucumab, ziv-aflibercept (*e.g.,* VEGF Trap; ZALTRAP®), MP-0250, vanucizumab, sevacizumab, VGX-100, pazopanib, axitinib, vandetanib, stivarga, cabozantinib, lenvatinib, nintedanib, orantinib, telatinib, dovitinig,

cediranib, motesanib, sulfatinib, apatinib, foretinib, famitinib, imatinib (*e.g.,* Imatinib Mesylate; Gleevec™), and tivozanib.

[0119] In some embodiments, the anti-angiogenesis agent is an anti-angiogenesis antibody. Descriptions of antibodies and methods for generating antibodies are further provided *infra*. In some embodiments, the anti-angiogenesis antibody is a monoclonal antibody. In some embodiments, the anti-angiogenesis antibody is a human or humanized antibody (described in more detail below).

[0120] In some embodiments, the anti-angiogenesis agent is a VEGF antagonist. For example, VEGF antagonists of the present disclosure may include without limitation polypeptides that specifically bind to VEGF, anti-VEGF antibodies and antigen-binding fragments thereof; receptor molecules and derivatives which bind specifically to VEGF, thereby sequestering its binding to one or more receptors; fusion proteins (e.g., VEGF-Trap (Regeneron)), $VEGF_{121}$-gelonin (Peregrine), antagonist variants of VEGF polypeptides, antisense nucleobase oligomers complementary to at least a fragment of a nucleic acid molecule encoding a VEGF polypeptide; small RNAs complementary to at least a fragment of a nucleic acid molecule encoding a VEGF polypeptide (*e.g.,* an RNAi, siRNA, shRNA, or miRNA); ribozymes that target VEGF; peptibodies to VEGF; VEGF aptamers; polypeptides that bind to VEGFR; anti-VEGFR antibodies and antigen-binding fragments thereof; derivatives which bind to VEGFR thereby blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities (e.g., VEGF signaling); fusion proteins; and nonpeptide small molecules that bind to VEGF or VEGFR and are capable of blocking, inhibiting, abrogating, reducing, or interfering with VEGF biological activities.

[0121] In certain embodiments, the VEGF antagonist reduces or inhibits, by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more, the expression level or biological activity of VEGF. For example, in some embodiments, the VEGF antagonist may reduce or inhibit the expression level or biological activity of VEGF by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. In some embodiments, the VEGF inhibited by the VEGF-specific antagonist is VEGF (8-109), VEGF (1-109), or $VEGF_{165}$.

[0122] Certain aspects of the methods, uses, and kits of the present disclosure are based, at least in part, on the surprising discovery that anti-VEGF treatment can improve the functional phenotype of tumoral dendritic cells (*e.g.,* by leading to increased expression of MHC Class II and/or OX40L). Without wishing to be bound to theory, this property, *inter alia*, may make combination therapies including an anti-angiogenesis agent and an OX40 binding agonist particularly advantageous for the treatment of cancer, *e.g.,* by resulting in enhanced anti-tumor responses such as anti-tumoral T cell responses.

[0123] Therefore, in some embodiments, the VEGF antagonist increases MHC class II expression on intratumoral dendritic cells, *e.g.,* as compared to MHC class II expression on dendritic cells from a tumor treated with a control antibody (*e.g.,* an isotype control). MHC class II is known as a family of

related molecules (typically heterodimers containing alpha and beta chains) that present antigen to T cells. As used herein, MHC class II expression may refer to expression of any MHC class II molecule or chain, including without limitation a polypeptide encoded by the human genes HLA-DM alpha (*e.g.,* NCBI Gene ID No. 3108), HLA-DM beta (*e.g.,* NCBI Gene ID No. 3109), HLA-DO alpha (*e.g.,* NCBI Gene ID No. 3111), HLA-DO beta (*e.g.,* NCBI Gene ID No. 3112), HLA-DP alpha 1 (*e.g.,* NCBI Gene ID No. 3113), HLA-DP beta 1 (*e.g.,* NCBI Gene ID No. 3115), HLA-DQ alpha 1 (*e.g.,* NCBI Gene ID No. 3117), HLA-DQ alpha 2 (*e.g.,* NCBI Gene ID No. 3118), HLA-DQ beta 1 (*e.g.,* NCBI Gene ID No. 3119), HLA-DQ beta 2 (*e.g.,* NCBI Gene ID No. 3120), HLA-DR alpha (*e.g.,* NCBI Gene ID No. 3122), HLA-DR beta 1 (*e.g.,* NCBI Gene ID No. 3123), HLA-DR beta 3 (*e.g.,* NCBI Gene ID No. 3125), HLA-DR beta 4 (*e.g.,* NCBI Gene ID No. 3126), or HLA-DR beta 5 (*e.g.,* NCBI Gene ID No. 3127). It will be appreciated by one of skill in the art that MHC genes are highly variable across populations, and thus the specific genes and sequences listed are merely exemplary and in no way intended to be limiting.

[0124] In some embodiments, the VEGF antagonist increases OX40L expression on intratumoral dendritic cells, *e.g.,* as compared to OX40L expression on dendritic cells from a tumor treated with a control antibody (*e.g.,* an isotype control). OX40L (also known as tumor necrosis factor ligand superfamily member 4 or CD252) is known as the binding partner or ligand of OX40. Examples of OX40L polypeptides including without limitation polypeptides having the amino acid sequence represented by UniProt Accession No. P43488 and/or a polypeptide encoded by gene *TNFSF4* (*e.g.,* NCBI Gene ID No. 7292).

[0125] Methods for measuring MHC class II or OX40L expression are known in the art and may include without limitation FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometery, HPLC, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, and FISH, and combinations thereof.

[0126] In some embodiments, the dendritic cells are myeloid dendritic cells. In other embodiments, the dendritic cells are non-myeloid dendritic cells (*e.g.,* lymphoid or plasmacytoid dendritic cells). The cell-surface antigens expressed by dendritic cells, and those that distinguish myeloid and non-myeloid dendritic cells, are known in the art. For example, dendritic cells may be identified by expression of CD45, CD11c, and MHC class II. They may be distinguished from other cell types (*e.g.,* macrophages, neutrophils, and granulocytic myeloid cells) by their lack of significant F4/80 and Gr1 expression. In some embodiments, myeloid dendritic cells are dendritic cells that express CD11b, and non-myeloid dendritic cells are dendritic cells that lack significant CD11b expression. For further descriptions of myeloid and non-myeloid dendritic cells, see, *e.g.,* Steinman, R.M. and Inaba, K. (1999) *J. Leukoc. Biol.* 66:205-8.

VEGF Receptor Molecules

[0127] In some embodiments, the anti-angiogenesis agent is a VEGF antagonist. In some embodiments, the VEGF antagonist comprises a soluble VEGF receptor or a soluble VEGF receptor fragment that specifically binds to VEGF. The two best characterized VEGF receptors are VEGFR1 (also known as Flt-1) and VEGFR2 (also known as KDR and FLK-1 for the murine homolog). The specificity of each receptor for each VEGF family member varies but VEGF-A binds to both Flt-1 and KDR. Both Flt-I and KDR belong to the family of receptor tyrosine kinases (RTKs). The RTKs comprise a large family of transmembrane receptors with diverse biological activities. At least nineteen (19) distinct RTK subfamilies have been identified. The receptor tyrosine kinase (RTK) family includes receptors that are crucial for the growth and differentiation of a variety of cell types (Yarden and Ullrich (1988) Ann. Rev. Biochem. 57:433-478; Ullrich and Schlessinger (1990) Cell 61:243-254). The intrinsic function of RTKs is activated upon ligand binding, which results in phosphorylation of the receptor and multiple cellular substrates, and subsequently in a variety of cellular responses (Ullrich & Schlessinger (1990) Cell 61:203-212). Thus, receptor tyrosine kinase mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), typically followed by receptor dimerization, stimulation of the intrinsic protein tyrosine kinase activity and receptor trans-phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response. (e.g., cell division, differentiation, metabolic effects, changes in the extracellular microenvironment) see, Schlessinger and Ullrich (1992) Neuron 9:1-20. Structurally, both Flt-1 and KDR have seven immunoglobulin-like domains in the extracellular domain, a single transmembrane region, and a consensus tyrosine kinase sequence which is interrupted by a kinase-insert domain. Matthews et al. (1991) PNAS USA 88:9026-9030; Terman et al. (1991) Oncogene 6:1677-1683. The extracellular domain is involved in the binding of VEGF and the intracellular domain is involved in signal transduction.

[0128] VEGF receptor molecules, or fragments thereof, that specifically bind to VEGF can be used in the methods of the invention to bind to and sequester the VEGF protein, thereby preventing it from signaling. In certain embodiments, the VEGF receptor molecule, or VEGF binding fragment thereof, is a soluble form, such as sFlt-1. A soluble form of the receptor exerts an inhibitory effect on the biological activity of the VEGF protein by binding to VEGF, thereby preventing it from binding to its natural receptors present on the surface of target cells. Also included are VEGF receptor fusion proteins, examples of which are described below.

[0129] In some embodiments, the VEGF antagonist is a chimeric VEGF receptor protein. A chimeric VEGF receptor protein is a receptor molecule having amino acid sequences derived from at least two different proteins, at least one of which is a VEGF receptor protein (e.g., the flt-1 or KDR receptor), that is capable of binding to and inhibiting the biological activity of VEGF. In certain embodiments, the chimeric VEGF receptor proteins of the invention consist of amino acid sequences

derived from only two different VEGF receptor molecules; however, amino acid sequences comprising one, two, three, four, five, six, or all seven Ig-like domains from the extracellular ligand-binding region of the flt-1 and/or KDR receptor can be linked to amino acid sequences from other unrelated proteins, for example, immunoglobulin sequences. Other amino acid sequences to which Ig-like domains are combined will be readily apparent to those of ordinary skill in the art. Examples of chimeric VEGF receptor proteins include, e.g., soluble Flt-1/Fc, KDR/Fc, or FLt-1/KDR/Fc (also known as VEGF Trap). (See for example PCT Application Publication No. WO97/44453).

[0130] A soluble VEGF receptor protein or chimeric VEGF receptor proteins of the invention includes VEGF receptor proteins which are not fixed to the surface of cells via a transmembrane domain. As such, soluble forms of the VEGF receptor, including chimeric receptor proteins, while capable of binding to and inactivating VEGF, do not comprise a transmembrane domain and thus generally do not become associated with the cell membrane of cells in which the molecule is expressed.

[0131] In some embodiments, the VEGF antagonist (I, an anti-VEGF antibody, such as bevacizumab) is administered by gene therapy. See, for example, WO 96/07321 published Mar. 14, 1996 concerning the use of gene therapy to generate intracellular antibodies. There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells; in vivo and ex vivo. For in vivo delivery the nucleic acid is injected directly into the patient, usually at the site where the antibody is required. For ex vivo treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes which are implanted into the patient (see, e.g. U.S. Pat. Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells in vitro, or in vivo in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells in vitro include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. A commonly used vector for ex vivo delivery of the gene is a retrovirus. The currently preferred in vivo nucleic acid transfer techniques include transfection with viral vectors (such as adenovirus, Herpes simplex I virus, or adeno-associated virus) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are DOTMA, DOPE and DC-Chol, for example). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by

Wu et al., *J. Biol. Chem.* 262:44294432 (1987); and Wagner et al., *Proc. Natl. Acad. Sci. USA* 87:3410-3414 (1990). For review of the currently known gene marking and gene therapy protocols see Anderson et al., *Science* 256:808-813 (1992). See also WO 93/25673 and the references cited therein.

Anti-VEGF Antibodies

[0132] In some embodiments, the anti-angiogenesis agent is a VEGF antagonist. In some embodiments, the VEGF antagonist is an anti-VEGF antibody. In some embodiments, the anti-VEGF antibody may be a human or humanized antibody. In some embodiments, the anti-VEGF antibody may be a monoclonal antibody.

[0133] The VEGF antigen to be used for production of VEGF antibodies may be, e.g., the $VEGF_{165}$ molecule as well as other isoforms of VEGF or a fragment thereof containing the desired epitope. In one embodiment, the desired epitope is the one recognized by bevacizumab, which binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709 (known as "epitope A.4.6.1" defined herein). Other forms of VEGF useful for generating anti-VEGF antibodies of the invention will be apparent to those skilled in the art.

[0134] Human VEGF was obtained by first screening a cDNA library prepared from human cells, using bovine VEGF cDNA as a hybridization probe. Leung et al. (1989) Science, 246:1306. One cDNA identified thereby encodes a 165-amino acid protein having greater than 95% homology to bovine VEGF; this 165-amino acid protein is typically referred to as human VEGF (hVEGF) or $VEGF_{165}$. The mitogenic activity of human VEGF was confirmed by expressing the human VEGF cDNA in mammalian host cells. Media conditioned by cells transfected with the human VEGF cDNA promoted the proliferation of capillary endothelial cells, whereas control cells did not. Leung et al. (1989) Science, supra. Further efforts were undertaken to clone and express VEGF via recombinant DNA techniques. (See, e.g., Ferrara, Laboratory Investigation 72:615-618 (1995), and the references cited therein).

[0135] VEGF is expressed in a variety of tissues as multiple homodimeric forms (121, 145, 165, 189, and 206 amino acids per monomer) resulting from alternative RNA splicing. $VEGF_{121}$ is a soluble mitogen that does not bind heparin; the longer forms of VEGF bind heparin with progressively higher affinity. The heparin-binding forms of VEGF can be cleaved in the carboxy terminus by plasmin to release a diffusible form(s) of VEGF. Amino acid sequencing of the carboxy terminal peptide identified after plasmin cleavage is Arg_{110}-Ala_{111}. Amino terminal "core" protein, VEGF (1-110) isolated as a homodimer, binds neutralizing monoclonal antibodies (such as the antibodies referred to as 4.6.1 and 3.2E3.1.1) and soluble forms of VEGF receptors with similar affinity compared to the intact $VEGF_{165}$ homodimer.

[0136] Several molecules structurally related to VEGF have also been identified recently, including placenta growth factor (PIGF), VEGF-B, VEGF-C, VEGF-D and VEGF-E. Ferrara and Davis-Smyth

(1987) Endocr. Rev., supra; Ogawa et al. J. Biological Chem. 273:31273-31281 (1998); Meyer et al. EMBO J., 18:363-374 (1999). A receptor tyrosine kinase, Flt-4 (VEGFR-3), has been identified as the receptor for VEGF-C and VEGF-D. Joukov et al. EMBO. J. 15:1751 (1996); Lee et al. PNAS USA 93:1988-1992 (1996); Achen et al. (1998) PNAS USA 95:548-553. VEGF-C has been shown to be involved in the regulation of lymphatic angiogenesis. Jeltsch et al. Science 276:1423-1425 (1997).

[0137] Two VEGF receptors have been identified, Flt-1 (also called VEGFR-1) and KDR (also called VEGFR-2). Shibuya et al. (1990) Oncogene 8:519-527; de Vries et al. (1992) Science 255:989-991; Terman et al. (1992) Biochem. Biophys. Res. Commun. 187:1579-1586. Neuropilin-1 has been shown to be a selective VEGF receptor, able to bind the heparin-binding VEGF isoforms (Soker et al. (1998) Cell 92:735-45).

[0138] Anti-VEGF antibodies that are useful in the methods of the invention include any antibody, or antigen binding fragment thereof, that bind with sufficient affinity and specificity to VEGF and can reduce or inhibit the biological activity of VEGF. An anti-VEGF antibody will usually not bind to other VEGF homologues such as VEGF-B or VEGF-C, nor other growth factors such as PlGF, PDGF, or bFGF.

[0139] In certain embodiments of the invention, the anti-VEGF antibodies include, but are not limited to, a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709; a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta et al. (1997) Cancer Res. 57:4593-4599. In one embodiment, the anti-VEGF antibody is "bevacizumab (BV)", also known as "rhuMAb VEGF" or "AVASTIN®". It comprises mutated human IgG1 framework regions and antigen-binding complementarity-determining regions from the murine anti-hVEGF monoclonal antibody A.4.6.1 that blocks binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence of bevacizumab, including most of the framework regions, is derived from human IgG1, and about 7% of the sequence is derived from the murine antibody A4.6.1.

[0140] Bevacizumab (AVASTIN®) was the first anti-angiogenesis therapy approved by the FDA and is approved for the treatment metastatic colorectal cancer (first- and second-line treatment in combination with intravenous 5-FU-based chemotherapy), advanced non-squamous, non-small cell lung cancer (NSCLC) (first-line treatment of unresectable, locally advanced, recurrent or metastatic NSCLC in combination with carboplatin and paclitaxel) and metastatic HER2-negative breast cancer (previously untreated, metastatic HER2-negative breast cancer in combination with paclitaxel).

[0141] Bevacizumab and other humanized anti-VEGF antibodies are further described in U.S. Pat. No. 6,884,879 issued Feb. 26, 2005. Additional antibodies include the G6 or B20 series antibodies (e.g., G6-31, B20-4.1), as described in PCT Publication No. WO2005/012359, PCT Publication No. WO2005/044853, and U.S. Patent Application 60/991,302, the content of these patent applications are expressly incorporated herein by reference. For additional antibodies see U.S. Pat. Nos. 7,060,269, 6,582,959, 6,703,020; 6,054,297; WO98/45332; WO 96/30046; WO94/10202; EP 0666868B1; U.S.

Patent Application Publication Nos. 2006009360, 20050186208, 20030206899, 20030190317, 20030203409, and 20050112126; and Popkov et al., Journal of Immunological Methods 288:149-164 (2004). Other antibodies include those that bind to a functional epitope on human VEGF comprising of residues F17, M18, D19, Y21, Y25, Q89, I191, K101, E103, and C104 or, alternatively, comprising residues F17, Y21, Q22, Y25, D63, I83 and Q89.

[0142] In one embodiment of the invention, the anti-VEGF antibody has a light chain variable region comprising the following amino acid sequence: DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR. (SEQ ID NO:214); and/or a heavy chain variable region comprising the following amino acid sequence: EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:215).

[0143] In some embodiments, the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of bevacizumab. In some embodiments, the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of selected from (a) HVR-H1 comprising the amino acid sequence of GYTFTNYGMN (SEQ ID NO:216); (b) HVR-H2 comprising the amino acid sequence of WINTYTGEPTYAADFKR (SEQ ID NO:217); (c) HVR-H3 comprising the amino acid sequence of YPHYYGSSHWYFDV (SEQ ID NO:218); (d) HVR-L1 comprising the amino acid sequence of SASQDISNYLN (SEQ ID NO:219); (e) HVR-L2 comprising the amino acid sequence of FTSSLHS (SEQ ID NO:220); and (f) HVR-L3 comprising the amino acid sequence of QQYSTVPWT (SEQ ID NO:221). In some embodiments, the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of an antibody described in U.S. Pat. No. 6,884,879. In some embodiments, the anti-VEGF antibody comprises one, two, or three hypervariable region (HVR) sequences of a light chain variable region comprising the following amino acid sequence: DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR. (SEQ ID NO:214) and/or one, two, or three hypervariable region (HVR) sequences of a heavy chain variable region comprising the following amino acid sequence: EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:215).

[0144] A "G6 series antibody" according to this invention, is an anti-VEGF antibody that is derived from a sequence of a G6 antibody or G6-derived antibody according to any one of FIGS. 7, 24-26, and 34-35 of PCT Publication No. WO2005/012359, the entire disclosure of which is expressly incorporated herein by reference. See also PCT Publication No. WO2005/044853, the entire disclosure of which is expressly incorporated herein by reference. In one embodiment, the G6 series

antibody binds to a functional epitope on human VEGF comprising residues F17, Y21, Q22, Y25, D63, I83 and Q89.

[0145] A "B20 series antibody" according to this invention is an anti-VEGF antibody that is derived from a sequence of the B20 antibody or a B20-derived antibody according to any one of FIGS. 27-29 of PCT Publication No. WO2005/012359, the entire disclosure of which is expressly incorporated herein by reference. See also PCT Publication No. WO2005/044853, and U.S. Patent Application 60/991,302, the content of these patent applications are expressly incorporated herein by reference. In one embodiment, the B20 series antibody binds to a functional epitope on human VEGF comprising residues F17, M18, D19, Y21, Y25, Q89, I91, K101, E103, and C104.

[0146] A "functional epitope" according to this invention refers to amino acid residues of an antigen that contribute energetically to the binding of an antibody. Mutation of any one of the energetically contributing residues of the antigen (for example, mutation of wild-type VEGF by alanine or homolog mutation) will disrupt the binding of the antibody such that the relative affinity ratio (IC50mutant VEGF/IC50wild-type VEGF) of the antibody will be greater than 5 (see Example 2 of WO2005/012359). In one embodiment, the relative affinity ratio is determined by a solution binding phage displaying ELISA. Briefly, 96-well Maxisorp immunoplates (NUNC) are coated overnight at 4°C with an Fab form of the antibody to be tested at a concentration of 2 μg/ml in PBS, and blocked with PBS, 0.5% BSA, and 0.05% Tween20 (PBT) for 2 h at room temperature. Serial dilutions of phage displaying hVEGF alanine point mutants (residues 8-109 form) or wild type hVEGF (8-109) in PBT are first incubated on the Fab-coated plates for 15 min at room temperature, and the plates are washed with PBS, 0.05% Tween20 (PBST). The bound phage is detected with an anti-M13 monoclonal antibody horseradish peroxidase (Amersham Pharmacia) conjugate diluted 1:5000 in PBT, developed with 3,3',5,5'-tetramethylbenzidine (TMB, Kirkegaard & Perry Labs, Gaithersburg, Md.) substrate for approximately 5 min, quenched with 1.0 M H3PO4, and read spectrophotometrically at 450 nm. The ratio of IC50 values (IC50,ala/IC50,wt) represents the fold of reduction in binding affinity (the relative binding affinity).

III. OX40 binding agonists

[0147] Provided herein are methods treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of an anti-angiogenesis agent and an OX40 binding agonist.

[0148] An OX40 binding agonist includes, for example, an OX40 agonist antibody (e.g., an anti-human OX40 agonist antibody), an OX40L agonist fragment, an OX40 oligomeric receptor, and an OX40 immunoadhesin. In some embodiments, the OX40 binding agonist is a trimeric OX40L-Fc protein. In some embodiments, the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L. In some embodiments, the OX40 agonist antibody is a

full-length human IgG1 antibody. Any of the OX40 binding agonists (*e.g.,* anti-human OX40 agonist antibodies) described herein may be used in any of the methods, uses, and/or kits described herein.

[0149] In some embodiments, the OX40 agonist antibody increases CD4+ effector T cell proliferation and/or increases cytokine production by the CD4+ effector T cell as compared to proliferation and/or cytokine production prior to treatment with the OX40 agonist antibody. In some embodiments, the cytokine is IFN-γ.

[0150] In some embodiments, the OX40 agonist antibody increases memory T cell proliferation and/or increasing cytokine production by the memory cell. In some embodiments, the cytokine is IFN-γ.

[0151] In some embodiments, the OX40 agonist antibody inhibits Treg suppression of effector T cell function. In some embodiments, effector T cell function is effector T cell proliferation and/or cytokine production. In some embodiments, the effector T cell is a CD4+ effector T cell.

[0152] In some embodiments, the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40. In some embodiments, OX40 signal transduction is detected by monitoring NFkB downstream signaling.

[0153] In some embodiments, the anti-human OX40 agonist antibody is a depleting anti-human OX40 antibody (e.g., depletes cells that express human OX40). In some embodiments, the OX40 agonist antibody depletes cells that express human OX40 *in vitro*. In some embodiments, the human OX40 expressing cells are CD4+ effector T cells. In some embodiments, the human OX40 expressing cells are Treg cells. In some embodiments, depleting is by ADCC and/or phagocytosis. In some embodiments, the antibody mediates ADCC by binding FcγR expressed by a human effector cell and activating the human effector cell function. In some embodiments, the antibody mediates phagocytosis by binding FcγR expressed by a human effector cell and activating the human effector cell function. Exemplary human effector cells include, e.g., macrophage, natural killer (NK) cells, monocytes, neutrophils. In some embodiments, the human effector cell is macrophage.

[0154] In some embodiments, the anti-human OX40 agonist antibody has a functional Fc region. In some embodiments, effector function of a functional Fc region is ADCC. In some embodiments, effector function of a functional Fc region is phagocytosis. In some embodiments, effector function of a functional Fc region is ADCC and phagocytosis. In some embodiments, the Fc region is human IgG1. In some embodiments, the Fc region is human IgG4.

[0155] In some embodiments, the anti-human OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM. In some embodiments, the anti-human OX40 antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM. In some embodiments, the anti-human OX40 antibody binds human OX40 with an affinity of less than or equal to about 0.5nM. In some embodiments, the binding affinity is determined using radioimmunoassay.

[0156] In some embodiments, the OX40 binding agonist is an OX40 agonist antibody that binds human OX40. In some embodiments, the OX40 agonist antibody binds human OX40 with an affinity

of less than or equal to about 1 nM. In some embodiments, the anti-human OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM. In some embodiments, the anti-human OX40 antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM. In some embodiments, the anti-human OX40 antibody binds human OX40 with an affinity of less than or equal to about 0.5nM. In some embodiments, the binding affinity is determined using radioimmunoassay.

[0157] In some embodiments, the anti-human OX40 agonist antibody binds human OX40 and cynomolgus OX40. In some embodiments, binding is determined using a FACS assay. In some embodiments, binding to human OX40 has an EC50 of about 0.2 ug/ml. In some embodiments, binding to human OX40 has an EC50 of about 0.3 ug/ml or lower. In some embodiments, binding to cynomolgus OX40 has an EC50 of about 1.5 ug/ml. In some embodiments, binding to cynomolgus OX40 has an EC50 of about 1.4 ug/ml.

[0158] In some embodiments, the anti-human OX40 agonist antibody does not bind to rat OX40 or mouse OX40.

[0159] In some embodiments, the anti-human OX40 agonist antibody is a depleting anti-human OX40 antibody (e.g., depletes cells that express human OX40). In some embodiments, the human OX40 expressing cells are CD4+ effector T cells. In some embodiments, the human OX40 expressing cells are Treg cells. In some embodiments, depleting is by ADCC and/or phagocytosis. In some embodiments, the antibody mediates ADCC by binding FcγR expressed by a human effector cell and activating the human effector cell function. In some embodiments, the antibody mediates phagocytosis by binding FcγR expressed by a human effector cell and activating the human effector cell function. Exemplary human effector cells include, e.g., macrophage, natural killer (NK) cells, monocytes, neutrophils. In some embodiments, the human effector cell is macrophage. In some embodiments, the human effector cell is NK cells. In some embodiments, depletion is not by apoptosis.

[0160] In some embodiments, the anti-human OX40 agonist antibody has a functional Fc region. In some embodiments, effector function of a functional Fc region is ADCC. In some embodiments, effector function of a functional Fc region is phagocytosis. In some embodiments, effector function of a functional Fc region is ADCC and phagocytosis. In some embodiments, the Fc region is human IgG1. In some embodiments, the Fc region is human IgG4.

[0161] In some embodiments, the anti-human OX40 agonist antibody does not induce apoptosis in OX40-expressing cells (e.g., Treg). In some embodiments, apoptosis is assayed using an antibody concentration of 30ug/ml, e.g., by determining whether apoptosis has occurred using annexin V and proprodium iodide stained Treg.

[0162] In some embodiments, the anti-human OX40 agonist antibody enhances CD4+ effector T cell function, for example, by increasing CD4+ effector T cell proliferation and/or increasing gamma interferon production by the CD4+ effector T cell (for example, as compared to proliferation and/or

cytokine production prior to treatment with anti-human OX40 agonist antibody). In some embodiments, the cytokine is gamma interferon. In some embodiments, the anti-human OX40 agonist antibody increases number of intratumoral (infiltrating) CD4+ effector T cells (e.g., total number of CD4+ effector T cells, or e.g., percentage of CD4+ cells in CD45+ cells), e.g., as compared to number of intratumoral (infiltrating) CD4+ T cells prior to treatment with anti-human OX40 agonist antibody. In some embodiments, the anti-human OX40 agonist antibody increases number of intratumoral (infiltrating) CD4+ effector T cells that express gamma interferon (e.g., total gamma interferon expressing CD4+ cells, or e.g., percentage of gamma interferon expressing CD4+ cells in total CD4+ cells), e.g., as compared to number of intratumoral (infiltrating) CD4+ T cells that express gamma interferon prior to treatment with anti-human OX40 agonist antibody.

[0163] In some embodiments, the anti-human OX40 agonist antibody increases number of intratumoral (infiltrating) CD8+ effector T cells (e.g., total number of CD8+ effector T cells, or e.g., percentage of CD8+ in CD45+ cells), e.g., as compared to number of intratumoral (infiltrating) CD8+ T effector cells prior to treatment with anti-human OX40 agonist antibody. In some embodiments, the anti-human OX40 agonist antibody increases number of intratumoral (infiltrating) CD8+ effector T cells that express gamma interferon (e.g., percentage of CD8+ cells that express gamma interferon in total CD8+ cells), e.g., compared to number of intratumoral (infiltrating) CD8+ T cells that express gamma interferon prior to treatment with anti-human OX40 agonist antibody.

[0164] In some embodiments, the anti-human OX40 agonist antibody enhances memory T cell function, for example by increasing memory T cell proliferation and/or increasing cytokine production by the memory cell. In some embodiments, the cytokine is gamma interferon.

[0165] In some embodiments, the anti-human OX40 agonist antibody inhibits Treg function, for example, by decreasing Treg suppression of effector T cell function (e.g., effector T cell proliferation and/or effector T cell cytokine secretion). In some embodiments, the effector T cell is a CD4+ effector T cell. In some embodiments, the anti-human OX40 agonist antibody reduces the number of intratumoral (infiltrating) Treg (e.g., total number of Treg or e.g., percentage of Fox3p+ cells in CD4+ cells).

[0166] In some embodiments, the anti-human OX40 agonist antibody is engineered to increase effector function (e.g., compared to effector function in a wild-type IgG1). In some embodiments, the antibody has increased binding to a Fc receptor. In some embodiments, the antibody lacks fucose attached (directly or indirectly) to the Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. In some embodiments, the Fc region comprises bisected oligosaccharides, e.g., in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. In some embodiments, the antibody comprises an Fc region with one or more amino acid substitutions which improve ADCC, e.g., substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

[0167] In some embodiments, the anti-human OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40. In some embodiments, OX40 signal transduction is detected by monitoring NFkB downstream signaling.

[0168] In some embodiments, the anti-human OX40 agonist antibody is stable after treatment at 40ºC for two weeks.

[0169] In some embodiments, the anti-human OX40 agonist antibody binds human effector cells, e.g., binds FcγR (e.g., an activating FcγR) expressed by human effector cells. In some embodiments, the human effector cell performs (is capable of performing) ADCC effector function. In some embodiments, the human effector cell performs (is capable of performing) phagocytosis effector function.

[0170] In some embodiments, the anti-human OX40 agonist antibody comprising a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells (e.g., a DANA mutation) has diminished activity (e.g., CD4+ effector T cell function, e.g., proliferation), relative to anti-human OX40 agonist antibody comprising native sequence IgG1 Fc portion. In some embodiment, the anti-human OX40 agonist antibody comprising a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells (e.g., a DANA mutation) does not possess substantial activity (e.g., CD4+ effector T cell function, e.g., proliferation).

[0171] In some embodiments, antibody cross-linking is required for anti-human OX40 agonist antibody function. In some embodiments, function is stimulation of CD4+ effector T cell proliferation. In some embodiments, antibody cross-linking is determined by providing anti-human OX40 agonist antibody adhered on a solid surface (e.g., a cell culture plate). In some embodiments, antibody cross-linking is determined by introducing a mutation in the antibody's IgG1 Fc portion (e.g., a DANA mutation) and testing function of the mutant antibody.

[0172] In some embodiments, the anti-human OX40 agonist antibody competes for binding to human OX40 with OX40L. In some embodiments, addition of OX40L does not enhance anti-human OX40 antibody function in an in vitro assay.

[0173] According to another embodiment, the anti-human OX40 agonist antibodies include any one, any combination, or all of the following properties: (1) binds human OX40 with an affinity of less than or equal to about 0.45 nM, in some embodiments, binds human OX40 with an affinity of less than or equal to about 0.4 nM, in some embodiments, binds human OX40 with an affinity of less than or equal to about 0.5nM, in some embodiments, the binding affinity is determined using radioimmunoassay; (2) binds human OX40 and cynomolgus OX40, in some embodiments, binding is determined using a FACS assay, (3) binds human OX40 with an EC50 of about 0.2 ug/ml, in some embodiments, binds to human OX40 has an EC50 of about 0.3 ug/ml or lower, in some embodiments, binds to cynomolgus OX40 with an EC50 of about 1.5 ug/ml, in some embodiments, binds to cynomolgus OX40 has an EC50 of about 1.4 ug/ml, (4) does not substantially bind to rat OX40 or mouse OX40, (6) is a depleting anti-human OX40 antibody (e.g., depletes cells that express human

OX40), in some embodiments, the cells are CD4+ effector T cells and/or Treg cells, (7) enhances CD4+ effector T cell function, for example, by increasing CD4+ effector T cell proliferation and/or increasing gamma interferon production by the CD4+ effector T cell (for example, as compared to proliferation and/or cytokine production prior to treatment with anti-human OX40 agonist antibody), (8) enhances memory T cell function, for example by increasing memory T cell proliferation and/or increasing cytokine production by the memory cell, (9) inhibits Treg function, for example, by decreasing Treg suppression of effector T cell function (e.g., effector T cell proliferation and/or effector T cell cytokine secretion). In some embodiments, the effector T cell is a CD4+ effector T cell, (10) increases OX40 signal transduction in a target cell that expresses OX40 (in some embodiments, OX40 signal transduction is detected by monitoring NFkB downstream signaling), (11) is stable after treatment at 40ºC for two weeks, (12) binds human effector cells, e.g., binds FcγR expressed by human effector cells, (13) anti-human OX40 agonist antibody comprising a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells (e.g., N297G) has diminished activity (e.g., CD4+ effector T cell function, e.g., proliferation), relative to anti-human OX40 agonist antibody comprising native sequence IgG1 Fc portion, in some embodiment, the anti-human OX40 agonist antibody comprising a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells (e.g., N297G) does not possess substantial activity (e.g., CD4+ effector T cell function, e.g., proliferation), (14) antibody cross-linking (e.g., by Fc receptor binding) is required for anti-human OX40 agonist antibody function.

[0174] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7.

[0175] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4. In one embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:4. In another embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:4 and HVR-L3 comprising the amino acid sequence of SEQ ID NO:7. In a further embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:4, HVR-L3 comprising the amino acid sequence of SEQ ID NO:7, and HVR-H2 comprising the amino acid sequence of SEQ ID NO:3. In a further embodiment, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4.

[0176] In another aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7. In one embodiment, the antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7.

[0177] In another aspect, an anti-human OX40 agonist antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:4; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7.

[0178] In another aspect, the invention provides an anti-human OX40 agonist antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:7.

[0179] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:26.

[0180] In another embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:4 and HVR-L3 comprising the amino acid sequence of SEQ ID NO:26. In a further embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:4, HVR-L3 comprising the amino acid sequence of SEQ ID NO:26, and HVR-H2 comprising the amino acid sequence of SEQ ID NO:3.

[0181] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:4; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i)

HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:26.

[0182] In another aspect, the invention provides an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:26.

[0183] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:27.

[0184] In another embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:4 and HVR-L3 comprising the amino acid sequence of SEQ ID NO:27. In a further embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:4, HVR-L3 comprising the amino acid sequence of SEQ ID NO:27, and HVR-H2 comprising the amino acid sequence of SEQ ID NO:3.

[0185] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:4; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:27.

[0186] In another aspect, the invention provides an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:27.

[0187] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, 8 or 9; (b) HVR-H2 comprising the amino acid sequence of SEQ ID

NO:3, 10, 11, 12, 13 or 14; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4, 15, or 19; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7, 22, 23, 24, 25, 26, 27, or 28.

[0188] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 2, 8 or 9; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 4, 15, or 19. In one embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO: 4, 15, or 19. In another embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:4, 15, or 19 and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28. In a further embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO: 4, 15, or 19, HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28, and HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14. In a further embodiment, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 2, 8 or 9; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 4, 15, or 19.

[0189] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28. In one embodiment, the antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28.

[0190] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 2, 8 or 9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 4, 15, or 19; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28.

[0191] In another aspect, the invention provides an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 2, 8 or 9; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 4, 15, or 19; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2

comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28.

[0192] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:172; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:173; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:174; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:175. In some embodiment, HVR-H2 is not DMYPDAAAASYNQKFRE (SEQ ID NO:230).In some embodiments, HVR-H3 is not APRWAAAA (SEQ ID NO:231). In some embodiments, HVR-L3 is not QAAAAAAAT (SEQ ID NO:232).

[0193] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:172; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:173; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:174. In one embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:174. In another embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:174 and HVR-L3 comprising the amino acid sequence of SEQ ID NO:175. In a further embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:174, HVR-L3 comprising the amino acid sequence of SEQ ID NO:175, and HVR-H2 comprising the amino acid sequence of SEQ ID NO:173. In a further embodiment, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:172; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:173; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:174. In some embodiment, HVR-H2 is not DMYPDAAAASYNQKFRE (SEQ ID NO:230).In some embodiments, HVR-H3 is not APRWAAAA (SEQ ID NO:231). In some embodiments, HVR-L3 is not QAAAAAAAT (SEQ ID NO:232).

[0194] In another aspect, the invention provides an antibody comprising (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:175. In some embodiments, HVR-L3 is not QAAAAAAAT (SEQ ID NO:232).

[0195] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:172, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:173, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:174; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, (ii) HVR-L2 comprising the

amino acid sequence of SEQ ID NO:6, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:175.

[0196] In another aspect, the invention provides an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:172; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:173; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:174; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:175. In some embodiment, HVR-H2 is not DMYPDAAAASYNQKFRE (SEQ ID NO:230).In some embodiments, HVR-H3 is not APRWAAAA (SEQ ID NO:231). In some embodiments, HVR-L3 is not QAAAAAAAT (SEQ ID NO:232).

[0197] All possible combinations of the above substitutions are encompassed by the consensus sequences of SEQ ID NO:172, 173, 174 and 175.

[0198] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:39; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42.

[0199] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33. In one embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:33. In another embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:33 and HVR-L3 comprising the amino acid sequence of SEQ ID NO:42. In a further embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:33, HVR-L3 comprising the amino acid sequence of SEQ ID NO:42, and HVR-H2 comprising the amino acid sequence of SEQ ID NO:30. In a further embodiment, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33.

[0200] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:39; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42. In one embodiment, the antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:39; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42.

[0201] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:33; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:39, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42.

[0202] In another aspect, the invention provides an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:39; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:42.

[0203] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:40; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42.

[0204] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:40; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42. In one embodiment, the antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:40; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42.

[0205] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:33; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:40, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42.

[0206] In another aspect, the invention provides an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ

ID NO:30; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:40; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:42.

[0207] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30, 31, or 32; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:39, 40 or 41; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42, 43, or 44.

[0208] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 30, 31, or 32; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33. In another embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:33 and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 42, 43, or 44. In a further embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:33, HVR-L3 comprising the amino acid sequence of SEQ ID NO: 42, 43, or 44, and HVR-H2 comprising the amino acid sequence of SEQ ID NO: 39, 40 or 41. In a further embodiment, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30, 31, or 32; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33.

[0209] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39, 40 or 41; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 42, 43, or 44. In one embodiment, the antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39, 40 or 41; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 42, 43, or 44.

[0210] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 30, 31, or 32, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:33; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37, (ii) HVR-L2

comprising the amino acid sequence of SEQ ID NO: 39, 40 or 41, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 42, 43, or 44.

[0211] In another aspect, the invention provides an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 30, 31, or 32; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 39, 40 or 41; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO: 42, 43, or 44.

[0212] In one aspect, the invention provides an anti-human OX40 agonist antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:175; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:177; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:178.

[0213] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:175; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33. In another embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:33 and HVR-L3 comprising the amino acid sequence of SEQ ID NO:177. In a further embodiment, the antibody comprises HVR-H3 comprising the amino acid sequence of SEQ ID NO:33, HVR-L3 comprising the amino acid sequence of SEQ ID NO:178, and HVR-H2 comprising the amino acid sequence of SEQ ID NO:176. In a further embodiment, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:176; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33.

[0214] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:177; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:177. In one embodiment, the antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:177; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:178.

[0215] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:176, and (iii) HVR-H3 comprising an amino acid sequence selected from SEQ ID NO:33; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i)

HVR-L1 comprising the amino acid sequence of SEQ ID NO:37, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:177, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:178.

[0216] In another aspect, the invention provides an antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:176; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:177; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO:178.

[0217] In any of the above embodiments, an anti-OX40 agonist antibody is humanized. In one embodiment, an anti-OX40 antibody comprises HVRs as in any of the above embodiments or for any of the embodiments in Figure 11, and further comprises an acceptor human framework, e.g. a human immunoglobulin framework or a human consensus framework. In another embodiment, an anti-OX40 antibody comprises HVRs as in any of the above embodiments, and further comprises a VH and/or VL comprising an FR sequence shown in Figure 11.

[0218] In another aspect, an anti-human OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 108, 114, 116, 233, or 234. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 108, 114, 116, 233, or 234. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VH sequence in SEQ ID NO: SEQ ID NO:56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 108, 114, 116, 233, or 234, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4.

[0219] In another aspect, an anti-human OX40 agonist antibody is provided, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 109, 115 or 117. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or

99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 109, 115 or 117. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VL sequence in SEQ ID NO: 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 109, 115 or 117, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7.

[0220] In another aspect, an anti-human OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:56. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VH sequence in SEQ ID NO:56, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4.

[0221] In another aspect, an anti-human OX40 agonist antibody is provided, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 57. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VL sequence in SEQ ID NO: 57, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two

or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7.

[0222] In another aspect, an anti-human OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:179. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:179. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VH sequence in SEQ ID NO:179, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4.

[0223] In another aspect, an anti-human OX40 agonist antibody is provided, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:180. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 180. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VL sequence in SEQ ID NO: 180, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7.

[0224] In another aspect, an anti-human OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:94. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to

bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:94. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VH sequence in SEQ ID NO:94, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4.

[0225] In another aspect, an anti-human OX40 agonist antibody is provided, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:95. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:95. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VL sequence in SEQ ID NO:95, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:26.

[0226] In another aspect, an anti-human OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:96. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:96. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VH sequence in SEQ ID NO:96, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4.

[0227] In another aspect, an anti-human OX40 agonist antibody is provided, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:97. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:97. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VL sequence in SEQ ID NO:97, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:27.

[0228] In another aspect, an anti-human OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VH sequence in SEQ ID NO: 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 29, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:30, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:33.

[0229] In another aspect, an anti-human OX40 agonist antibody is provided, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to

bind to OX40. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-human OX40 agonist antibody comprises the VL sequence in SEQ ID NO: 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:37; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:39; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:42.

[0230] In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:56 and SEQ ID NO:57, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:58 and SEQ ID NO:59, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:60 and SEQ ID NO:61, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:62 and SEQ ID NO:63, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:64 and SEQ ID NO:65, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:66 and SEQ ID NO:67, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:68 and SEQ ID NO:69, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:70 and SEQ ID NO:71, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:72 and SEQ ID NO:73, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:74 and SEQ ID NO:75, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:76 and SEQ ID NO:77, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:78 and SEQ ID NO:79, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:80 and SEQ ID NO:81, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:82 and SEQ ID NO:83, respectively, including post-translational modifications of those sequences. In one

embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:84 and SEQ ID NO:85, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:86 and SEQ ID NO:87, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:88 and SEQ ID NO:89, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:90 and SEQ ID NO:91, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:92 and SEQ ID NO:93, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:94 and SEQ ID NO:95, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:96 and SEQ ID NO:97, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:98 and SEQ ID NO:99, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:100 and SEQ ID NO:101, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:108 and SEQ ID NO:109, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:114 and SEQ ID NO:115, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:116 and SEQ ID NO:117, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:233 and SEQ ID NO:65, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:234 and SEQ ID NO:69, respectively, including post-translational modifications of those sequences.

[0231] In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:118 and SEQ ID NO:119, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:120 and SEQ ID NO:121, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:122 and SEQ ID NO:123, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:124 and SEQ ID NO:125, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:126 and SEQ ID

NO:127, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:128 and SEQ ID NO:129, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:130 and SEQ ID NO:131, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:132 and SEQ ID NO:133, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:134 and SEQ ID NO:135, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:136 and SEQ ID NO:137, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:138 and SEQ ID NO:139, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:140 and SEQ ID NO:141, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:142 and SEQ ID NO:143, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:144 and SEQ ID NO:145, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO:146 and SEQ ID NO:147, respectively, including post-translational modifications of those sequences.

[0232] In another aspect, an anti-human OX40 agonist antibody is provided, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above.

[0233] In a further aspect, the invention provides an antibody that binds to the same epitope as an anti-human OX40 antibody provided herein. In some embodiments, the antibody is an anti-human OX40 agonist antibody.

[0234] In some embodiments, the anti-human OX40 agonist antibody is a human or humanized antibody. In some embodiments, the OX40 binding agonist (e.g., an OX40 agonist antibody) is not MEDI6383. In some embodiments, the OX40 binding agonist (e.g., an OX40 agonist antibody) is not MEDI0562.

[0235] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in U.S. Patent No. 7,550,140, which is incorporated herein by reference in its entirety. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain comprising the sequence of

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYTMNWVRQAPGKGLEWVSAISGSGGSTYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRYSQVHYALDYWGQGTLVTVSS

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO:183) and/or a light chain comprising the sequence of DIVMTQSPDSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKAGQSPQLLIYLGSNRASGV PDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQYYNHPTTFGQGTKLEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:184). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody 008 as described in U.S. Patent No. 7,550,140. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody 008 as described in U.S. Patent No. 7,550,140.

[0236] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in U.S. Patent No. 7,550,140. In some embodiments, the anti-human OX40 agonist antibody comprises the sequence of DIQMTQSPDSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKAGQSPQLLIYLGSNRASGV PDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQYYNHPTTFGQGTKLEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:185). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody SC02008 as described in U.S. Patent No. 7,550,140. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody SC02008 as described in U.S. Patent No. 7,550,140.

[0237] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in U.S. Patent No. 7,550,140. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain comprising the sequence of EVQLVESGGGLVHPGGSLRLSCAGSGFTFSSYAMHWVRQAPGKGLEWVSAIGTGGGTYYA DSVMGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYDNVMGLYWFDYWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO:186) and/or a light chain comprising the sequence of EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSG

SGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:187). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody 023 as described in U.S. Patent No. 7,550,140. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody 023 as described in U.S. Patent No. 7,550,140.

[0238] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in U.S. Patent No. 7,960,515, which is incorporated herein by reference in its entirety. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSSTIDYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARESGWYLFDYWGQGTLVTVSS (SEQ ID NO:188) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQYNSYPPTFGGGTKVEIK (SEQ ID NO:189). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody 11D4 as described in U.S. Patent No. 7,960,515. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody 11D4 as described in U.S. Patent No. 7,960,515.

[0239] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in U.S. Patent No. 7,960,515. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGSIGYA DSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDQSTADYYFYYGMDVWGQGTTVT VSS (SEQ ID NO:190) and/or a light chain variable region comprising the sequence of EIVVTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSG SGSGTDFTLTISSLEPEDFAVYYCQQRSNWPTFGQGTKVEIK (SEQ ID NO:191). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody 18D8 as described in U.S. Patent No. 7,960,515. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody 18D8 as described in U.S. Patent No. 7,960,515.

[0240] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2012/027328, which is incorporated herein by reference in its entirety. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGSELKKPGASVKVSCKASGYTFTDYSMHWVRQAPGQGLKWMGWINTETGEPTY

ADDFKGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCANPYYDYVSYYAMDYWGQGTTVTVS
S (SEQ ID NO:192) and/or a light chain variable region comprising the sequence of
DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYLYTGVPSRFS
GSGSGTDFTFTISSLQPEDIATYYCQQHYSTPRTFGQGTKLEIK (SEQ ID NO:193). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody hu106-222 as described in WO 2012/027328. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody hu106-222 as described in WO 2012/027328.

[0241] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2012/027328. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of
EVQLVESGGGLVQPGGSLRLSCAASEYEFPSHDMSWVRQAPGKGLELVAAINSDGGSTYYP
DTMERRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARHYDDYYAWFAYWGQGTMVTVSS
(SEQ ID NO:194) and/or a light chain variable region comprising the sequence of
EIVLTQSPATLSLSPGERATLSCRASKSVSTSGYSYMHWYQQKPGQAPRLLIYLASNLESGVP
ARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRELPLTFGGGTKVEIK (SEQ ID NO:195). In some embodiments, the antibody comprises at least one, two, three, four, five or six hypervariable region (HVR) sequences of antibody Hu119-122 as described in WO 2012/027328. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody Hu119-122 as described in WO 2012/027328.

[0242] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2013/028231, which is incorporated herein by reference in its entirety. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain comprising the sequence of
MYLGLNYVFIVFLLNGVQSEVKLEESGGGLVQPGGSMKLSCAASGFTFSDAWMDWVRQSPE
KGLEWVAEIRSKANNHATYYAESVNGRFTISRDDSKSSVYLQMNSLRAEDTGIYYCTWGEV
FYFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYITCNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:196) and/or a light chain comprising the sequence of
MRPSIQFLGLLLFWLHGAQCDIQMTQSPSSLSASLGGKVTITCKSSQDINKYIAWYQHKPGKG
PRLLIHYTSTLQPGIPSRFSGSGSGRDYSFSISNLEPEDIATYYCLQYDNLLTFGAGTKLELKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:197). In some

embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of MYLGLNYVFIVFLLNGVQSEVKLEESGGGLVQPGGSMKLSCAASGFTFSDAWMDWVRQSPE KGLEWVAEIRSKANNHATYYAESVNGRFTISRDDSKSSVYLQMNSLRAEDTGIYYCTWGEV FYFDYWGQGTTLTVSS (SEQ ID NO:198) and/or a light chain variable region comprising the sequence of MRPSIQFLGLLLFWLHGAQCDIQMTQSPSSLSASLGGKVTITCKSSQDINKYIAWYQHKPGKG PRLLIHYTSTLQPGIPSRFSGSGSGRDYSFSISNLEPEDIATYYCLQYDNLLTFGAGTKLELK (SEQ ID NO:199). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody Mab CH 119-43-1 as described in WO 2013/028231. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody Mab CH 119-43-1 as described in WO 2013/028231.

[0243] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2013/038191, which is incorporated herein by reference in its entirety. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of EVQLQQSGPELVKPGASVKMSCKASGYTFTSYVMHWVKQKPGQGLEWIGYINPYNDGTKY NEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCANYYGSSLSMDYWGQGTSVTVSS (SEQ ID NO:200) and/or a light chain variable region comprising the sequence of DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGTVKLLIYYTSRLHSGVPSRFS GSGSGTDYSLTISNLEQEDIATYFCQQGNTLPWTFGGGTKLEIKR (SEQ ID NO:201). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 20E5 as described in WO 2013/038191. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 20E5 as described in WO 2013/038191.

[0244] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2013/038191. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of EVQLQQSGPELVKPGASVKISCKTSGYTFKDYTMHWVKQSHGKSLEWIGGIYPNNGGSTYN QNFKDKATLTVDKSSSTAYMEFRSLTSEDSAVYYCARMGYHGPHLDFDVWGAGTTVTVSP (SEQ ID NO:202) and/or a light chain variable region comprising the sequence of DIVMTQSHKFMSTSLGDRVSITCKASQDVGAAVAWYQQKPGQSPKLLIYWASTRHTGVPDR FTGGGSGTDFTLTISNVQSEDLTDYFCQQYINYPLTFGGGTKLEIKR (SEQ ID NO:203). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 12H3 as described in WO 2013/038191. In some

embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 12H3 as described in WO 2013/038191.

[0245] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1, which is incorporated herein by reference in its entirety. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNDGTK YNEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS (SEQ ID NO:204) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKLLIYYTSRLHSGVPSRFS GSGSGTDYTLTISSLQPEDFATYYCQQGNTLPWTFGQGTKVEIKR (SEQ ID NO:205). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 20E5 as described in WO 2014/148895A1. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 20E5 as described in WO 2014/148895A1.

[0246] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWMGYINPYNDGTK YNEKFKGRVTITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS (SEQ ID NO:204) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAVKLLIYYTSRLHSGVPSRFS GSGSGTDYTLTISSLQPEDFATYFCQQGNTLPWTFGQGTKVEIKR (SEQ ID NO:206). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 20E5 as described in WO 2014/148895A1. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 20E5 as described in WO 2014/148895A1.

[0247] In some embodiments the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS (SEQ ID NO:207) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKLLIYYTSRLHSGVPSRFS GSGSGTDYTLTISSLQPEDFATYYCQQGNTLPWTFGQGTKVEIKR (SEQ ID NO:205). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 20E5 as described in WO 2014/148895A1. In some

embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 20E5 as described in WO 2014/148895A1.

[0248] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY NEKFKGRATITSDTSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS (SEQ ID NO:207) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAVKLLIYYTSRLHSGVPSRFS GSGSGTDYTLTISSLQPEDFATYFCQQGNTLPWTFGQGTKVEIKR (SEQ ID NO:206). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 20E5 as described in WO 2014/148895A1. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 20E5 as described in WO 2014/148895A1.

[0249] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS (SEQ ID NO:208) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKLLIYYTSRLHSGVPSRFS GSGSGTDYTLTISSLQPEDFATYYCQQGNTLPWTFGQGTKVEIKR (SEQ ID NO:205). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 20E5 as described in WO 2014/148895A1. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 20E5 as described in WO 2014/148895A1.

[0250] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYINPYNDGTKY NEKFKGRATLTSDKSASTAYMELSSLRSEDTAVYYCANYYGSSLSMDYWGQGTLVTVSS (SEQ ID NO:208) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAVKLLIYYTSRLHSGVPSRFS GSGSGTDYTLTISSLQPEDFATYFCQQGNTLPWTFGQGTKVEIKR (SEQ ID NO:206). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 20E5 as described in WO 2014/148895A1. In some

embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 20E5 as described in WO 2014/148895A1.

[0251] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNNGGST YNQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTV SS (SEQ ID NO:209) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCKASQDVGAAVAWYQQKPGKAPKLLIYWASTRHTGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQYINYPLTFGGGTKVEIKR (SEQ ID NO:210). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 12H3 as described in WO 2014/148895A1. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 12H3 as described in WO 2014/148895A1.

[0252] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWMGGIYPNNGGST YNQNFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTV SS (SEQ ID NO:209) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCKASQDVGAAVAWYQQKPGKAPKLLIYWASTRHTGVPDR FSGGGSGTDFTLTISSLQPEDFATYYCQQYINYPLTFGGGTKVEIKR (SEQ ID NO:211). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 12H3 as described in WO 2014/148895A1. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 12H3 as described in WO 2014/148895A1.

[0253] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVS S (SEQ ID NO:212) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCKASQDVGAAVAWYQQKPGKAPKLLIYWASTRHTGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQYINYPLTFGGGTKVEIKR (SEQ ID NO:210). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 12H3 as described in WO 2014/148895A1. In some

embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 12H3 as described in WO 2014/148895A1.

[0254] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY NQNFKDRVTLTADKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVS S (SEQ ID NO:212) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCKASQDVGAAVAWYQQKPGKAPKLLIYWASTRHTGVPDR FSGGGSGTDFTLTISSLQPEDFATYYCQQYINYPLTFGGGTKVEIKR (SEQ ID NO:211). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 12H3 as described in WO 2014/148895A1. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 12H3 as described in WO 2014/148895A1.

[0255] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVS S (SEQ ID NO:213) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCKASQDVGAAVAWYQQKPGKAPKLLIYWASTRHTGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQYINYPLTFGGGTKVEIKR (SEQ ID NO:210). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 12H3 as described in WO 2014/148895A1. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 12H3 as described in WO 2014/148895A1.

[0256] In some embodiments, the OX40 agonist antibody is an anti-human OX40 agonist antibody described in WO 2014/148895A1. In some embodiments, the anti-human OX40 agonist antibody comprises a heavy chain variable region comprising the sequence of QVQLVQSGAEVKKPGSSVKVSCKASGYTFKDYTMHWVRQAPGQGLEWIGGIYPNNGGSTY NQNFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARMGYHGPHLDFDVWGQGTTVTVS S (SEQ ID NO:213) and/or a light chain variable region comprising the sequence of DIQMTQSPSSLSASVGDRVTITCKASQDVGAAVAWYQQKPGKAPKLLIYWASTRHTGVPDR FSGGGSGTDFTLTISSLQPEDFATYYCQQYINYPLTFGGGTKVEIKR (SEQ ID NO:211). In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody clone 12H3 as described in WO 2014/148895A1. In some

embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody clone 12H3 as described in WO 2014/148895A1.

[0257] In some embodiments, the agonist anti-human OX40 antibody is L106 BD (Pharmingen Product # 340420). In some embodiments, the antibody comprises at least one, two, three, four, five or six hypervariable region (HVR) sequences of antibody L106 (BD Pharmingen Product # 340420). In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody L106 (BD Pharmingen Product # 340420).

[0258] In some embodiments, the agonist anti-human OX40 antibody is ACT35 (Santa Cruz Biotechnology, Catalog # 20073). In some embodiments, the antibody comprises at least one, two, three, four, five or six hypervariable region (HVR) sequences of antibody ACT35 (Santa Cruz Biotechnology, Catalog # 20073). In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody ACT35 (Santa Cruz Biotechnology, Catalog # 20073).

[0259] In some embodiments, the OX40 agonist antibody is MEDI6469. In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody MEDI6469. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody MEDI6469.

[0260] In some embodiments, the OX40 agonist antibody is MEDI0562. In some embodiments, the antibody comprises at least one, two, three, four, five, or six hypervariable region (HVR) sequences of antibody MEDI0562. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody MEDI0562.

[0261] In some embodiments, the OX40 agonist antibody is an agonist antibody that binds to the same epitope as any one of the OX40 agonist antibodies set forth above.

[0262] In some embodiments, the anti-human OX40 agonist antibody has a functional Fc region. In some embodiments, the Fc region is human IgG1. In some embodiments, the Fc region is human IgG4. In some embodiments, the anti-human OX40 agonist antibody is engineered to increase effector function (e.g., compared to effector function in a wild-type IgG1). In some embodiments, the antibody has increased binding to a Fc receptor. In some embodiments, the antibody lacks fucose attached (directly or indirectly) to the Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. In some embodiments, the Fc region comprises bisected oligosaccharides, e.g., in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. In some embodiments, the antibody comprises an Fc region with one or more amino acid substitutions which improve ADCC, e.g., substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

[0263] OX40 agonists useful for the methods described herein are in no way intended to be limited to antibodies. Non-antibody OX40 agonists are contemplated and well known in the art.

[0264] As described above, OX40L (also known as CD134L) serves as a ligand for OX40. As such, agonists that present part or all of OX40L may serve as OX40 agonists. In some embodiments, an OX40 agonist may include one or more extracellular domains of OX40L. Examples of extracellular domains of OX40L may include OX40-binding domains. In some embodiments, an OX40 agonist may be a soluble form of OX40L that includes one or more extracellular domains of OX40L but lacks other, insoluble domains of the protein, e.g., transmembrane domains. In some embodiments, an OX40 agonist is a soluble protein that includes one or more extracellular domains of OX40L able to bind OX40L. In some embodiments, an OX40 agonist may be linked to another protein domain, e.g., to increase its effectiveness, half-life, or other desired characteristics. In some embodiments, an OX40 agonist may include one or more extracellular domains of OX40L linked to an immunoglobulin Fc domain.

[0265] In some embodiments, an OX40 agonist may be any one of the OX40 agonists described in U.S. Patent No. 7,696,175.

[0266] In some embodiments, an OX40 agonist may be an oligomeric or multimeric molecule. For example, an OX40 agonist may contain one or more domains (e.g., a leucine zipper domain) that allows proteins to oligomerize. In some embodiments, an OX40 agonist may include one or more extracellular domains of OX40L linked to one or more leucine zipper domains.

[0267] In some embodiments, an OX40 agonist may be any one of the OX40 agonists described in European Patent No. EP0672141 B1.

[0268] In some embodiments, an OX40 agonist may be a trimeric OX40L fusion protein. For example, an OX40 agonist may include one or more extracellular domains of OX40L linked to an immunoglobulin Fc domain and a trimerization domain (including without limitation an isoleucine zipper domain).

[0269] In some embodiments, an OX40 agonist may be any one of the OX40 agonists described in International Publication No. WO2006/121810, such as an OX40 immunoadhesin. In some embodiments, the OX40 immunoadhesin may be a trimeric OX40-Fc protein. In some embodiments, the OX40 agonist is MEDI6383.

[0270] In a further aspect of the invention, an anti-OX40 antibody according to any of the above embodiments is a monoclonal antibody, including a chimeric, humanized or human antibody. In one embodiment, an anti-OX40 antibody is an antibody fragment, e.g., a Fv, Fab, Fab', scFv, diabody, or $F(ab')_2$ fragment. In another embodiment, the antibody is a full length antibody, e.g., an intact IgG1 antibody or other antibody class or isotype as defined herein. In some embodiments, the antibody is a full length intact IgG4 antibody.

IV. Antibody Preparation

[0271] An anti-angiogenesis antibody (*e.g.,* an anti-VEGF antibody) and/or an anti-OX40 antibody according to any of the above embodiments may incorporate any of the features, singly or in combination, as described in Sections 1-7 below:

1. Antibody Affinity

[0272] In certain embodiments, an antibody provided herein has a dissociation constant (Kd) of ≤ 1μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 0.1 nM, ≤ 0.01 nM, or ≤ 0.001 nM (e.g. 10^{-8} M or less, e.g. from 10^{-8} M to 10^{-13} M, e.g., from 10^{-9} M to 10^{-13} M).

[0273] In one embodiment, Kd is measured by a radiolabeled antigen binding assay (RIA). In one embodiment, an RIA is performed with the Fab version of an antibody of interest and its antigen. For example, solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (^{125}I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, e.g., Chen et al., *J. Mol. Biol.* 293:865-881(1999)). To establish conditions for the assay, MICROTITER® multi-well plates (Thermo Scientific) are coated overnight with 5 μg/ml of a capturing anti-Fab antibody (Cappel Labs) in 50 mM sodium carbonate (pH 9.6), and subsequently blocked with 2% (w/v) bovine serum albumin in PBS for two to five hours at room temperature (approximately 23°C). In a non-adsorbent plate (Nunc #269620), 100 pM or 26 pM [^{125}I]-antigen are mixed with serial dilutions of a Fab of interest (e.g., consistent with assessment of the anti-VEGF antibody, Fab-12, in Presta et al., *Cancer Res.* 57:4593-4599 (1997)). The Fab of interest is then incubated overnight; however, the incubation may continue for a longer period (e.g., about 65 hours) to ensure that equilibrium is reached. Thereafter, the mixtures are transferred to the capture plate for incubation at room temperature (e.g., for one hour). The solution is then removed and the plate washed eight times with 0.1% polysorbate 20 (TWEEN-20®) in PBS. When the plates have dried, 150 μl/well of scintillant (MICROSCINT-20 ™; Packard) is added, and the plates are counted on a TOPCOUNT ™ gamma counter (Packard) for ten minutes. Concentrations of each Fab that give less than or equal to 20% of maximal binding are chosen for use in competitive binding assays.

[0274] According to another embodiment, Kd is measured using a BIACORE® surface plasmon resonance assay. For example, an assay using a BIACORE®-2000 or a BIACORE ®-3000 (BIAcore, Inc., Piscataway, NJ) is performed at 25°C with immobilized antigen CM5 chips at ~10 response units (RU). In one embodiment, carboxymethylated dextran biosensor chips (CM5, BIACORE, Inc.) are activated with *N*-ethyl-*N'*- (3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS) according to the supplier's instructions. Antigen is diluted with 10 mM sodium acetate, pH 4.8, to 5 μg/ml (~0.2 μM) before injection at a flow rate of 5 μl/minute to achieve approximately 10 response units (RU) of coupled protein. Following the injection of antigen, 1 M ethanolamine is injected to block unreacted groups. For kinetics measurements, two-fold serial

dilutions of Fab (0.78 nM to 500 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20™) surfactant (PBST) at 25°C at a flow rate of approximately 25 μl/min. Association rates (k_{on}) and dissociation rates (k_{off}) are calculated using a simple one-to-one Langmuir binding model (BIACORE® Evaluation Software version 3.2) by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (Kd) is calculated as the ratio k_{off}/k_{on}. See, e.g., Chen et al., *J. Mol. Biol.* 293:865-881 (1999). If the on-rate exceeds 106 M-1 s-1 by the surface plasmon resonance assay above, then the on-rate can be determined by using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation = 295 nm; emission = 340 nm, 16 nm band-pass) at 25oC of a 20 nM anti-antigen antibody (Fab form) in PBS, pH 7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophometer (Aviv Instruments) or a 8000-series SLM-AMINCO™ spectrophotometer (ThermoSpectronic) with a stirred cuvette.

2. Antibody Fragments

[0275] In certain embodiments, an antibody provided herein is an antibody fragment. Antibody fragments include, but are not limited to, Fab, Fab', Fab'-SH, $F(ab')_2$, Fv, and scFv fragments, and other fragments described below. For a review of certain antibody fragments, see Hudson et al. *Nat. Med.* 9:129-134 (2003). For a review of scFv fragments, see, e.g., Pluckthün, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); see also WO 93/16185; and U.S. Patent Nos. 5,571,894 and 5,587,458. For discussion of Fab and $F(ab')_2$ fragments comprising salvage receptor binding epitope residues and having increased in vivo half-life, see U.S. Patent No. 5,869,046.

[0276] Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, for example, EP 404,097; WO 1993/01161; Hudson et al., *Nat. Med.* 9:129-134 (2003); and Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., *Nat. Med.* 9:129-134 (2003).

[0277] Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, MA; *see,* e.g., U.S. Patent No. 6,248,516 B1).

[0278] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (e.g. *E. coli* or phage), as described herein.

3. Chimeric and Humanized Antibodies

[0279] In certain embodiments, an antibody provided herein is a chimeric antibody. Certain chimeric antibodies are described, e.g., in U.S. Patent No. 4,816,567; and Morrison et al., *Proc. Natl.*

Acad. Sci. USA, 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (e.g., a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a "class switched" antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-binding fragments thereof.

[0280] In certain embodiments, a chimeric antibody is a humanized antibody. Typically, a non-human antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized antibody comprises one or more variable domains in which HVRs, e.g., CDRs, (or portions thereof) are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody optionally will also comprise at least a portion of a human constant region. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (e.g., the antibody from which the HVR residues are derived), e.g., to restore or improve antibody specificity or affinity.

[0281] Humanized antibodies and methods of making them are reviewed, e.g., in Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008), and are further described, e.g., in Riechmann et al., *Nature* 332:323-329 (1988); Queen et al., *Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); US Patent Nos. 5, 821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri *et al.*, *Methods* 36:25-34 (2005) (describing specificity determining region (SDR) grafting); Padlan, *Mol. Immunol.* 28:489-498 (1991) (describing "resurfacing"); Dall'Acqua et al., *Methods* 36:43-60 (2005) (describing "FR shuffling"); and Osbourn et al., *Methods* 36:61-68 (2005) and Klimka et al., *Br. J. Cancer*, 83:252-260 (2000) (describing the "guided selection" approach to FR shuffling).

[0282] Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (see, e.g., Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al. *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); and Presta et al. *J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, e.g., Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)).

4. Human Antibodies

[0283] In certain embodiments, an antibody provided herein is a human antibody. Human antibodies can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5: 368-74 (2001) and Lonberg, *Curr. Opin. Immunol.* 20:450-459 (2008).

[0284] Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, see Lonberg, *Nat. Biotech.* 23:1117-1125 (2005). See also, e.g., U.S. Patent Nos. 6,075,181 and 6,150,584 describing XENOMOUSE™ technology; U.S. Patent No. 5,770,429 describing HUMAB® technology; U.S. Patent No. 7,041,870 describing K-M MOUSE® technology, and U.S. Patent Application Publication No. US 2007/0061900, describing VELOCIMOUSE® technology). Human variable regions from intact antibodies generated by such animals may be further modified, e.g., by combining with a different human constant region.

[0285] Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (See, e.g., Kozbor *J. Immunol.*, 133: 3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner et al., *J. Immunol.*, 147: 86 (1991).) Human antibodies generated via human B-cell hybridoma technology are also described in Li et al., *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006). Additional methods include those described, for example, in U.S. Patent No. 7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, *Xiandai Mianyixue*, 26(4):265-268 (2006) (describing human-human hybridomas). Human hybridoma technology (Trioma technology) is also described in Vollmers and Brandlein, *Histology and Histopathology*, 20(3):927-937 (2005) and Vollmers and Brandlein, *Methods and Findings in Experimental and Clinical Pharmacology*, 27(3):185-91 (2005).

[0286] Human antibodies may also be generated by isolating Fv clone variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain. Techniques for selecting human antibodies from antibody libraries are described below.

5. Library-Derived Antibodies

[0287] Antibodies of the invention may be isolated by screening combinatorial libraries for antibodies with the desired activity or activities. For example, a variety of methods are known in the art for generating phage display libraries and screening such libraries for antibodies possessing the desired binding characteristics. Such methods are reviewed, e.g., in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, 2001) and further

described, e.g., in the McCafferty et al., *Nature* 348:552-554; Clackson et al., *Nature* 352: 624-628 (1991); Marks et al., *J. Mol. Biol.* 222: 581-597 (1992); Marks and Bradbury, in *Methods in Molecular Biology* 248:161-175 (Lo, ed., Human Press, Totowa, NJ, 2003); Sidhu et al., *J. Mol. Biol.* 338(2): 299-310 (2004); Lee et al., *J. Mol. Biol.* 340(5): 1073-1093 (2004); Fellouse, *Proc. Natl. Acad. Sci. USA* 101(34): 12467-12472 (2004); and Lee et al., *J. Immunol. Methods* 284(1-2): 119-132(2004).

[0288] In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter et al., *Ann. Rev. Immunol.*, 12: 433-455 (1994). Phage typically display antibody fragments, either as single-chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (e.g., from human) to provide a single source of antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths et al., *EMBO J,* 12: 725-734 (1993). Finally, naive libraries can also be made synthetically by cloning unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement *in vitro*, as described by Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: US Patent No. 5,750,373, and US Patent Publication Nos. 2005/0079574, 2005/0119455, 2005/0266000, 2007/0117126, 2007/0160598, 2007/0237764, 2007/0292936, and 2009/0002360.

[0289] Antibodies or antibody fragments isolated from human antibody libraries are considered human antibodies or human antibody fragments herein.

6. Multispecific Antibodies

[0290] In certain embodiments, an antibody provided herein is a multispecific antibody, e.g. a bispecific antibody. Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. In certain embodiments, one of the binding specificities is for OX40 and the other is for any other antigen. In certain embodiments, bispecific antibodies may bind to two different epitopes of OX40. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express OX40. Bispecific antibodies can be prepared as full length antibodies or antibody fragments.

[0291] Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having different specificities (see Milstein and Cuello, *Nature* 305: 537 (1983)), WO 93/08829, and Traunecker et al., *EMBO J.* 10: 3655 (1991)), and "knob-in-hole" engineering (see, e.g., U.S. Patent No. 5,731,168). Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-

heterodimeric molecules (WO 2009/089004A1); cross-linking two or more antibodies or fragments (see, e.g., US Patent No. 4,676,980, and Brennan et al., *Science*, 229: 81 (1985)); using leucine zippers to produce bi-specific antibodies (see, e.g., Kostelny et al., *J. Immunol.*, 148(5):1547-1553 (1992)); using "diabody" technology for making bispecific antibody fragments (see, e.g., Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (see,e.g. Gruber et al., *J. Immunol.*, 152:5368 (1994)); and preparing trispecific antibodies as described, e.g., in Tutt et al. *J. Immunol.* 147: 60 (1991).

[0292] Engineered antibodies with three or more functional antigen binding sites, including "Octopus antibodies," are also included herein (see, e.g. US 2006/0025576A1).

[0293] The antibody or fragment herein also includes a "Dual Acting FAb" or "DAF" comprising an antigen binding site that binds to OX40 as well as another, different antigen (see, US 2008/0069820, for example).

7. Antibody Variants

[0294] In certain embodiments, amino acid sequence variants of the antibodies provided herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, e.g., antigen-binding.

a) Substitution, Insertion, and Deletion Variants

[0295] In certain embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the HVRs and FRs. Conservative substitutions are shown in Table A under the heading of "preferred substitutions." More substantial changes are provided in Table A under the heading of "exemplary substitutions," and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, e.g., retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

TABLE A

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

[0296] Amino acids may be grouped according to common side-chain properties:

(1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

(2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

(3) acidic: Asp, Glu;

(4) basic: His, Lys, Arg;

(5) residues that influence chain orientation: Gly, Pro;

(6) aromatic: Trp, Tyr, Phe.

[0297] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[0298] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (*e.g.* a humanized or human antibody). Generally, the resulting

variant(s) selected for further study will have modifications (e.g., improvements) in certain biological properties (e.g., increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, e.g., using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more HVR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (e.g. binding affinity).

[0299] Alterations (e.g., substitutions) may be made in HVRs, e.g., to improve antibody affinity. Such alterations may be made in HVR "hotspots," i.e., residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (see, e.g., Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and/or residues that contact antigen, with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, e.g., in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (e.g., error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves HVR-directed approaches, in which several HVR residues (e.g., 4-6 residues at a time) are randomized. HVR residues involved in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[0300] In certain embodiments, substitutions, insertions, or deletions may occur within one or more HVRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (e.g., conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in HVRs. Such alterations may, for example, be outside of antigen contacting residues in the HVRs. In certain embodiments of the variant VH and VL sequences provided above, each HVR either is unaltered, or contains no more than one, two or three amino acid substitutions.

[0301] A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells (1989) *Science*, 244:1081-1085. In this method, a residue or group of target residues (e.g., charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated

as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[0302] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (e.g. for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

b) Glycosylation variants

[0303] In certain embodiments, an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0304] Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al. *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

[0305] In one embodiment, antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e. g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (Eu numbering of Fc region residues); however, Asn297 may also be located about ± 3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. See, e.g., US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to "defucosylated" or "fucose-deficient" antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US

2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki et al. *J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. *Arch. Biochem. Biophys.* 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams *et al.*, especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, *FUT8,* knockout CHO cells (see, e.g., Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004); Kanda, Y. et al., *Biotechnol. Bioeng.*, 94(4):680-688 (2006); and WO2003/085107).

[0306] Antibodies variants are further provided with bisected oligosaccharides, e.g., in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, e.g., in WO 2003/011878 (Jean-Mairet et al.); US Patent No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana *et al.*). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, e.g., in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

c) Fc region variants

[0307] In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of an antibody provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (*e.g.*, a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (*e.g.* a substitution) at one or more amino acid positions.

[0308] In certain embodiments, the invention contemplates an antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half life of the antibody *in vivo* is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express Fc(RIII only, whereas monocytes express Fc(RI, Fc(RII and Fc(RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is described in U.S. Patent No. 5,500,362 (see, e.g. Hellstrom, I. et al. *Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I et al., *Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985);

5,821,337 (see Bruggemann, M. et al., *J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTI™ non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.*, in a animal model such as that disclosed in Clynes et al. *Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. See, e.g., C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996); Cragg, M.S. et al., *Blood* 101:1045-1052 (2003); and Cragg, M.S. and M.J. Glennie, *Blood* 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half life determinations can also be performed using methods known in the art (see, e.g., Petkova, S.B. et al., *Int'l. Immunol.* 18(12):1759-1769 (2006)).

[0309] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581).

[0310] Certain antibody variants with improved or diminished binding to FcRs are described. (See, e.g., U.S. Patent No. 6,737,056; WO 2004/056312, and Shields et al., *J. Biol. Chem.* 9(2): 6591-6604 (2001).)

[0311] In certain embodiments, an antibody variant comprises an Fc region with one or more amino acid substitutions which improve ADCC, e.g., substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

[0312] In some embodiments, alterations are made in the Fc region that result in altered (*i.e.*, either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), e.g., as described in US Patent No. 6,194,551, WO 99/51642, and Idusogie et al. *J. Immunol.* 164: 4178-4184 (2000).

[0313] Antibodies with increased half lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976) and Kim et al., *J. Immunol.* 24:249 (1994)), are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, e.g., substitution of Fc region residue 434 (US Patent No. 7,371,826).

[0314] See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

d) Cysteine engineered antibody variants

[0315] In certain embodiments, it may be desirable to create cysteine engineered antibodies, e.g., "thioMAbs," in which one or more residues of an antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, e.g., in U.S. Patent No. 7,521,541.

e) Antibody Derivatives

[0316] In certain embodiments, an antibody provided herein may be further modified to contain additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propropylene glycol homopolymers, prolypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, etc.

[0317] In another embodiment, conjugates of an antibody and nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In one embodiment, the nonproteinaceous moiety is a carbon nanotube (Kam et al., *Proc. Natl. Acad. Sci. USA* 102: 11600-

11605 (2005)). The radiation may be of any wavelength, and includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody-nonproteinaceous moiety are killed.

A. Recombinant Methods and Compositions

[0318] Antibodies may be produced using recombinant methods and compositions, e.g., as described in U.S. Patent No. 4,816,567. In one embodiment, isolated nucleic acid encoding an anti-OX40 antibody described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chains of the antibody). In a further embodiment, one or more vectors (e.g., expression vectors) comprising such nucleic acid are provided. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In one embodiment, the host cell is eukaryotic, e.g. a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., Y0, NS0, Sp20 cell). In one embodiment, a method of making an anti-OX40 antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[0319] For recombinant production of an anti-OX40 antibody, nucleic acid encoding an antibody, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0320] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology, Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0321] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0322] Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[0323] Plant cell cultures can also be utilized as hosts. *See,* e.g., US Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0324] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including $DHFR^-$ CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology, Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

B. Assays

[0325] Anti-OX40 antibodies provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

1. Binding assays and other assays

[0326] In one aspect, an antibody of the invention is tested for its antigen binding activity, e.g., by known methods such as ELISA, Western blot, etc. OX40 binding may be determined using methods known in the art and exemplary methods are disclosed herein. In one embodiment, binding is

measured using radioimmunoassay. An exemplary radioimmunassay is exemplified in the Examples. OX40 antibody is iodinated, and competition reaction mixtures are prepared containing a fixed concentration of iodinated antibody and decreasing concentrations of serially diluted, unlabeled OZ X40 antibody. Cells expressing OX40 (e.g., BT474 cells stably transfected with human OX40) are added to the reaction mixture. Following an incubation, cells are washed to separate the free iodinated OX40 antibody from the OX40 antibody bound to the cells. Level of bound iodinated OX40 antibody is determined, e.g., by counting radioactivity associated with cells, and binding affinity determined using standard methods. In another embodiment, ability of OX40 antibody to bind to surface-expressed OX40 (e.g., on T cell subsets) is assessed using flow cytometry. Peripheral white blood cells are obtained (e.g., from human, cynomolgus monkey, rat or mouse) and cells are blocked with serum. Labeled OX40 antibody is added in serial dilutions, and T cells are also stained to identify T cell subsets (using methods known in the art). Following incubation of the samples and washing, the cells are sorted using flow cytometer, and data analyzed using methods well known in the art. In another embodiment, OX40 binding may be analyzed using surface plasmon resonance. An exemplary surface plasmon resonance method is exemplified in the Examples.

[0327] In another aspect, competition assays may be used to identify an antibody that competes with any of the anti-OX40 antibodies disclosed herein for binding to OX40, or to identify an antibody that competes with any of the anti-VEGF antibodies disclosed herein for binding to VEGF. In certain embodiments, such a competing antibody binds to the same epitope (e.g., a linear or a conformational epitope) that is bound by any of the anti-OX40 antibodies disclosed herein. In certain embodiments, such a competing antibody binds to the same epitope (e.g., a linear or a conformational epitope, or the A4.6.1 epitope) that is bound by any of the anti-VEGF antibodies disclosed herein. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ). A competition assay is exemplified in the Examples.

[0328] In an exemplary competition assay, immobilized OX40 or VEGF is incubated in a solution comprising a first labeled antibody that binds to OX40 or VEGF, respectively (e.g., mab 1A7.gr.1 or mab 3C8.gr5 for OX40, or A4.6.1 for VEGF) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to OX40 or VEGF, respectively. The second antibody may be present in a hybridoma supernatant. As a control, immobilized OX40 or VEGF, respectively, is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to OX40 or VEGF, respectively, excess unbound antibody is removed, and the amount of label associated with immobilized OX40 or VEGF, respectively, is measured. If the amount of label associated with immobilized OX40 or VEGF, respectively, is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first

antibody for binding to OX40 or VEGF, respectively. See Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

2. Activity assays

[0329] In one aspect, assays are provided for identifying anti-OX40 antibodies thereof having biological activity. Biological activity may include, e.g., binding OX40 (e.g., binding human and/or cynomolgus OX40), increasing OX40-mediated signal transduction (e.g., increasing NFkB-mediated transcription), depleting cells that express human OX40 (e.g., T cells), depleting cells that express human OX40 by ADCC and/or phagocytosis, enhancing T effector cell function (e.g., CD4+ effector T cell), e.g., by increasing effector T cell proliferation and/or increasing cytokine production (e.g., gamma interferon) by effector T cells, enhancing memory T cell function (e.g., CD4+ memory T cell), e.g., by increasing memory T cell proliferation and/or increasing cytokine production by memory T cells (e.g., gamma interferon), inhibiting regulatory T cell function (e.g., by decreasing Treg suppression of effector T cell function (e.g., CD4+ effector T cell function), binding human effector cells. Antibodies having such biological activity in vivo and/or in vitro are also provided.

[0330] In certain embodiments, an antibody of the invention is tested for such biological activity.

[0331] T cell costimulation may be assayed using methods known in the art and exemplary methods are disclosed herein. For example, T cells (e.g., memory or effector T cells) may be obtained from peripheral white blood cells (e.g., isolated from human whole blood using Ficoll gradient centrifugation). Memory T cells (e.g., CD4+ memory T cells) or effector T cells (e.g. CD4+ Teff cells) may be isolated from PBMC using methods known in the art. For example, the Miltenyi CD4+ memory T cell isolation kit or Miltenyi naïve CD4+ T cell isolation kit may be used. Isolated T cells are cultured in the presence of antigen presenting cells (e.g., irradiated L cells that express CD32 and CD80), and activated by addition of anti-CD3 antibody in the presence or absence of OX40 agonist antibody. Effect of agonist OX40 antibody of T cell proliferation may be measured using methods well known in the art. For example, the CellTiter Glo kit (Promega) may be used, and results read on a Multilabel Reader (Perkin Elmer). Effect of agonist OX40 antibody on T cell function may also be determined by analysis of cytokines produced by the T cell. In one embodiment, production of interferon gamma by CD4+ T cells is determined, e.g., by measurement of interferon gamma in cell culture supernatant. Methods for measuring interferon gamma are well-known in the art.

[0332] Treg cell function may be assayed using methods known in the art and exemplary methods are disclosed herein. In one example, the ability of Treg to suppress effector T cell proliferation is assayed. T cells are isolated from human whole blood using methods known in the art (e.g., isolating memory T cells or naïve T cells). Purified CD4+ naïve T cells are labeled (e.g., with CFSE) and purified Treg cells are labeled with a different reagent. Irradiated antigen presenting cells (e.g., L cells expressing CD32 and CD80) are co-cultured with the labeled purified naïve CD4+ T cells and purified Tregs. The co-cultures are activated using anti-CD3 antibody and tested in the presence or

absence of agonist OX40 antibody. Following a suitable time (e.g., 6 days of coculture), level of CD4+ naïve T cell proliferation is tracked by dye dilution in reduced label staining (e.g., reduced CFSE label staining) using FACS analysis.

[0333] OX40 signaling may be assayed using methods well known in the art and exemplary methods are disclosed herein. In one embodiment, transgenic cells are generated that express human OX40 and a reporter gene comprising the NFkB promoter fused to a reporter gene (e.g., beta luciferase). Addition of OX40 agonist antibody to the cells results in increased NFkB transcription, which is detected using an assay for the reporter gene.

[0334] Phagocytosis may be assayed, e.g., by using monocyte-derived macrophages, or U937 cells (a human histiocytic lymphoma cells line with the morphology and characteristics of mature macrophages). OX40 expressing cells are added to the monocyte-derived macrophages or U937 cells in the presence or absence of anti-OX40 agonist antibody. Following culturing of the cells for a suitable period of time, the percentage of phagocytosis is determined by examining percentage of cells that double stain for markers of 1) the macrophage or U937 cell and 2) the OX40 expressing cell, and dividing this by the total number of cells that show markers of the OX40 expressing cell (e.g., GFP). Analysis may be done by flow cytometry. In another embodiment, analysis may be done by fluorescent microscopy analysis.

[0335] ADCC may be assayed, e.g., using methods well known in the art. Exemplary methods are described in the definition section and an exemplary assay is disclosed in the Examples. In some embodiments, level of OX40 is characterized on an OX40 expressing cell that is used for testing in an ADCC assay. The cell may be stained with a detectably labeled anti-OX40 antibody (e.g., PE labeled), then level of fluorescence determined using flow cytometry, and results presented as median fluorescence intensity (MFI). In another embodiment, ADCC may be analyzed by CellTiter Glo assay kit and cell viability/cytotoxicity may be determined by chemioluminescence.

[0336] The binding affinities of various antibodies to FcγRIA, FcγRIIA, FcγRIIB, and two allotypes of FcγRIIIA (F158 and V158) may be measured in ELISA-based ligand-binding assays using the respective recombinant Fcγ receptors. Purified human Fcγ receptors are expressed as fusion proteins containing the extracellular domain of the receptor γ chain linked to a Gly/6xHis/glutathione S-transferase (GST) polypeptide tag at the C-terminus. The binding affinities of antibodies to those human Fcγ receptors are assayed as follows. For the low-affinity receptors, i.e. FcγRIIA (CD32A), FcγRIIB (CD32B), and the two allotypes of FcγRIIIA (CD16), F-158 and V-158, antibodies may be tested as multimers by cross-linking with a F(ab')2 fragment of goat anti-human kappa chain (ICN Biomedical; Irvine, CA) at an approximate molar ratio of 1:3 antibody:cross-linking $F(ab')_2$. Plates are coated with an anti-GST antibody (Genentech) and blocked with bovine serum albumin (BSA). After washing with phosphate-buffered saline (PBS) containing 0.05% Tween-20 with an ELx405™ plate washer (Biotek Instruments; Winooski, VT), Fcγ receptors are added to the plate at 25 ng/well and incubated at room temperature for 1 hour. After the plates are washed, serial dilutions of test

antibodies are added as multimeric complexes and the plates were incubated at room temperature for 2 hours. Following plate washing to remove unbound antibodies, the antibodies bound to the Fcγ receptor are detected with horseradish peroxidase (HRP)–conjugated $F(ab')_2$ fragment of goat anti-human $F(ab')_2$ (Jackson ImmunoResearch Laboratories; West Grove, PA) followed by the addition of substrate, tetramethylbenzidine (TMB) (Kirkegaard & Perry Laboratories; Gaithersburg, MD). The plates are incubated at room temperature for 5–20 minutes, depending on the Fcγ receptors tested, to allow color development. The reaction is terminated with 1 M H_3PO_4 and absorbance at 450 nm was measured with a microplate reader (SpectraMax®190, Molecular Devices; Sunnyvale, CA). Dose-response binding curves are generated by plotting the mean absorbance values from the duplicates of antibody dilutions against the concentrations of the antibody. Values for the effective concentration of the antibody at which 50% of the maximum response from binding to the Fcγ receptor is detected (EC_{50}) were determined after fitting the binding curve with a four-parameter equation using SoftMax Pro (Molecular Devices).

[0337] To select for antibodies which induce cell death, loss of membrane integrity as indicated by, *e.g.*, propidium iodide (PI), trypan blue or 7AAD uptake may be assessed relative to control. A PI uptake assay can be performed in the absence of complement and immune effector cells. OX40 expressing cells are incubated with medium alone or medium containing of the appropriate monoclonal antibody at e.g., about 10μg/ml. The cells are incubated for a time period (e.g., 1 or 3 days). Following each treatment, cells are washed and aliquoted. In some embodiments, cells are aliquoted into 35 mm strainer-capped 12 x 75 tubes (1ml per tube, 3 tubes per treatment group) for removal of cell clumps. Tubes then receive PI (10μg/ml). Samples may be analyzed using a FACSCAN™ flow cytometer and FACSCONVERT™ CellQuest software (Becton Dickinson).

[0338] Cells for use in any of the above in vitro assays include cells or cell lines that naturally express OX40 or that have been engineered to express OX40. Such cells include activated T cells, Treg cells and activated memory T cells that naturally express OX40. Such cells also include cell lines that express OX40 and cell lines that do not normally express OX40 but have been transfected with nucleic acid encoding OX40. Exemplary cell lines provided herein for use in any of the above in vitro assays include transgenic BT474 cells (a human breast cancer cell line) that express human OX40

[0339] It is understood that any of the above assays may be carried out using an immunoconjugate of the invention in place of or in addition to an anti-OX40 antibody.

[0340] It is understood that any of the above assays may be carried out using anti-OX40 antibody and an additional therapeutic agent.

[0341] Assays for identifying anti-VEGF antibodies are known in the art. For example, antibody affinities may be determined by a surface plasmon resonance based assay (such as the BIAcore assay as described in PCT Application Publication No. WO2005/012359); enzyme-linked immunoabsorbent assay (ELISA); and competition assays (e.g. RIA's), for example. In certain embodiments, the anti-VEGF antibody of the invention can be used as a therapeutic agent in targeting and interfering with

diseases or conditions wherein the VEGF activity is involved. Also, the antibody may be subjected to other biological activity assays, e.g., in order to evaluate its effectiveness as a therapeutic. Such assays are known in the art and depend on the target antigen and intended use for the antibody. Examples include the HUVEC inhibition assay; tumor cell growth inhibition assays (as described in WO 89/06692, for example); antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity (CDC) assays (US Patent 5,500,362); and agonistic activity or hematopoiesis assays (see WO 95/27062).

C. Immunoconjugates

[0342] The invention also provides immunoconjugates comprising an anti-OX40 antibody herein conjugated to one or more cytotoxic agents, such as chemotherapeutic agents or drugs, growth inhibitory agents, toxins (e.g., protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), or radioactive isotopes.

[0343] In one embodiment, an immunoconjugate is an antibody-drug conjugate (ADC) in which an antibody is conjugated to one or more drugs, including but not limited to a maytansinoid (see U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP 0 425 235 B1); an auristatin such as monomethylauristatin drug moieties DE and DF (MMAE and MMAF) (see U.S. Patent Nos. 5,635,483 and 5,780,588, and 7,498,298); a dolastatin; a calicheamicin or derivative thereof (see U.S. Patent Nos. 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, and 5,877,296; Hinman et al., *Cancer Res.* 53:3336-3342 (1993); and Lode et al., *Cancer Res.* 58:2925-2928 (1998)); an anthracycline such as daunomycin or doxorubicin (see Kratz et al., *Current Med. Chem.* 13:477-523 (2006); Jeffrey et al., *Bioorganic & Med. Chem. Letters* 16:358-362 (2006); Torgov et al., *Bioconj. Chem.* 16:717-721 (2005); Nagy et al., *Proc. Natl. Acad. Sci. USA* 97:829-834 (2000); Dubowchik et al., *Bioorg. & Med. Chem. Letters* 12:1529-1532 (2002); King et al., *J. Med. Chem.* 45:4336-4343 (2002); and U.S. Patent No. 6,630,579); methotrexate; vindesine; a taxane such as docetaxel, paclitaxel, larotaxel, tesetaxel, and ortataxel; a trichothecene; and CC1065.

[0344] In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to an enzymatically active toxin or fragment thereof, including but not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes.

[0345] In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples include At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu. When the radioconjugate is used for detection,

it may comprise a radioactive atom for scintigraphic studies, for example tc99m or I123, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[0346] Conjugates of an antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science* 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of a cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., *Cancer Res.* 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

[0347] The immunuoconjugates or ADCs herein expressly contemplate, but are not limited to such conjugates prepared with cross-linker reagents including, but not limited to, BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate) which are commercially available (e.g., from Pierce Biotechnology, Inc., Rockford, IL., U.S.A).

OX40 Agonist Antibody Sequences

Name	SEQUENCE	SEQ ID NO:
Human OX40 (lacking the signal peptide)	LHCVGDTYPSNDRCCHECRPGNGMVSRCSRSQNTVCRPCGPG FYNDVVSSKPCKPCTWCNLRSGSERKQLCTATQDTVCRCRAG TQPLDSYKPGVDCAPCPPGHFSPGDNQACKPWTNCTLAGKHT LQPASNSSDAICEDRDPPATQPQETQGPPARPITVQPTEAWPRT SQGPSTRPVEVPGGRAVAAILGLGLVLGLLGPLAILLALYLLRR DQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI	1
HVR-H1- 1A7.gr.1 1A7.gr.2 1A7.gr.3 1A7.gr.4 1A7.gr.5 1A7.gr.5' 1A7.gr.6 1A7.gr.7	 DSYMS	2

1A7.gr.7' 1A7.gr.NADS 1A7.gr.NADA 1A7.gr.NGDA 1A7.gr.SGDS 1A7.gr.NGSS 1A7.Ala.1 1A7.Ala.2 1A7.Ala.3 1A7.Ala.4 1A7.Ala.5 1A7.Ala.6 1A7.Ala.7 1A7.Ala.8 1A7.Ala.9 1A7.Ala.10 1A7.Ala.11 1A7.Ala.12 1A7.Ala.13 1A7.Ala.14 1A7.Ala.15 1A7.Ala.16		
HVR-H2- 1A7.gr.1 1A7.gr.2 1A7.gr.3 1A7.gr.4 1A7.gr.5 1A7.gr.5' 1A7.gr.6 1A7.gr.7 1A7.gr.7' 1A7.gr.DA 1A7.gr.ES 1A7.Ala.1 1A7.Ala.2 1A7.Ala.3 1A7.Ala.4 1A7.Ala.5 1A7.Ala.6 1A7.Ala.7 1A7.Ala.8 1A7.Ala.9 1A7.Ala.10 1A7.Ala.11 1A7.Ala.12 1A7.Ala.13 1A7.Ala.14 1A7.Ala.15 1A7.Ala.16	DMYPDNGDSSYNQKFRE	3
HVR-H3- 1A7.gr.1 1A7.gr.2	APRWYFSV	4

1A7.gr.3 1A7.gr.4 1A7.gr.5 1A7.gr.5' 1A7.gr.6 1A7.gr.7 1A7.gr.7' 1A7.gr.DA 1A7.gr.ES 1A7.gr.NADS 1A7.gr.NADA 1A7.gr.NGDA 1A7.gr.SGDS 1A7.gr.NGSS 1A7.gr.DANADA 1A7.Ala.1 1A7.Ala.2 1A7.Ala.3 1A7.Ala.4 1A7.Ala.5 1A7.Ala.6 1A7.Ala.7 1A7-Ala.15 1A7.Ala.16		
HVR-L1- 1A7.gr.1 1A7.gr.2 1A7.gr.3 1A7.gr.4 1A7.gr.5 1A7.gr.5' 1A7.gr.6 1A7.gr.7 1A7.gr.7' 1A7.gr.DA 1A7.gr.ES 1A7.gr.NADS 1A7.gr.NADA 1A7.gr.NGDA 1A7.gr.SGDS 1A7.gr.NGSS 1A7.gr.DANADA 1A7.Ala.1 1A7.Ala.2 1A7.Ala.3 1A7.Ala.4 1A7.Ala.5 1A7.Ala.6 1A7.Ala.7 1A7.Ala.8 1A7.Ala.9 1A7.Ala.10 1A7.Ala.11	RASQDISNYLN	5

1A7.Ala.12 1A7.Ala.13 1A7.Ala.14 1A7.Ala.15 1A7.Ala.16		
HVR-L2- 1A7.gr.1 1A7.gr.2 1A7.gr.3 1A7.gr.4 1A7.gr.5 1A7.gr.5' 1A7.gr.6 1A7.gr.7 1A7.gr.7' 1A7.gr.DA 1A7.gr.ES 1A7.gr.NADS 1A7.gr.NADA 1A7.gr.NGDA 1A7.gr.SGDS 1A7.gr.NGSS 1A7.gr.DANADA 1A7.Ala.1 1A7.Ala.2 1A7.Ala.3 1A7.Ala.4 1A7.Ala.5 1A7.Ala.6 1A7.Ala.7 1A7.Ala.8 1A7.Ala.9 1A7.Ala.10 1A7.Ala.11 1A7.Ala.12 1A7.Ala.13 1A7.Ala.14 1A7.Ala.15 1A7.Ala.16	YTSRLRS	6
HVR-L3- 1A7.gr.1 1A7.gr.2 1A7.gr.3 1A7.gr.4 1A7.gr.5 1A7.gr.5' 1A7.gr.6 1A7.gr.7 1A7.gr.7' 1A7.gr.DA 1A7.gr.ES 1A7.gr.NADS	QQGHTLPPT	7

1A7.gr.NADA 1A7.gr.NGDA 1A7.gr.SGDS 1A7.gr.NGSS 1A7.gr.DANADA 1A7.Ala.8 1A7.Ala.9 1A7.Ala.10 1A7.Ala.11 1A7.Ala.12 1A7.Ala.13 1A7.Ala.14 1A7.Ala.15 1A7.Ala.16		
HVR-H1-1A7.gr.DA	DAYMS	8
HVR-H1-1A7.gr.ES 1A7.gr.DANADA	ESYMS	9
HVR-H2-1A7.gr.NADS	DMYPDNADSSYNQKFRE	10
HVR-H2-1A7.gr.NADA 1A7.gr.DANADA	DMYPDNADASYNQKFRE	11
HVR-H2-1A7.gr.NGDA	DMYPDNGDASYNQKFRE	12
HVR-H2-1A7.gr.SGDS	DMYPDSGDSSYNQKFRE	13
HVR-H2-1A7.gr.NGSS	DMYPDNGSSSYNQKFRE	14
HVR-H3-1A7.Ala.8	APRWYFSA	15
HVR-H3-1A7.Ala.9	APRWYASV	16
HVR-H3-1A7.Ala.10	APRWAFSV	17
HVR-H3-1A7.Ala.11	APAWYFSV	18
HVR-H3-1A7.Ala.12	APRWYFAV	19
HVR-H3-	APRAYFSV	20

1A7.Ala.13		
HVR-H3-1A7.Ala.14	AARWYFSV	21
HVR-L3-1A7.Ala.1	QQGHTLPAT	22
HVR-L3-1A7.Ala.2	QQGHTAPPT	23
HVR-L3-1A7.Ala.3	QQGATLPPT	24
HVR-L3-1A7.Ala.4	QQGHALPPT	25
HVR-L3-1A7.Ala.5	QQAHTLPPT	26
HVR-L3-1A7.Ala.6	QQGHTLAPT	27
HVR-L3-1A7.Ala.7	QAGHTLPPT	28
HVR-H1-3C8.gr.1 3C8.gr.2 3C8.gr.3 3C8.gr.4 3C8.gr.5 3C8.gr.5.SG 3C8.gr.5.EG 3C8.gr.5.QG 3C9.gr.5.DQ 3C8.gr.5.DA 3C8.gr.6 3C8.gr.7 3C8.gr.8 3C8.gr.9 3C8.gr.10 3C8.gr.11 3C8.A.1 3C8.A.2 3C8.A.3 3C8.A.4 3C8.A.5 3C8.A.6 3C8.A.7 3C8.A.8	NYLIE	29

3C8.A.9 3C8.A.10		
HVR-H2- 3C8.gr.1 3C8.gr.2 3C8.gr.3 3C8.gr.4 3C8.gr.5 3C8.gr.5.SG 3C8.gr.5.EG 3C8.gr.5.QG 3C8.gr.6 3C8.gr.7 3C8.gr.8 3C8.gr.9 3C8.gr.10 3C8.gr.11 3C8.A.1 3C8.A.2 3C8.A.3 3C8.A.4 3C8.A.5 3C8.A.6 3C8.A.7 3C8.A.8 3C8.A.9 3C8.A.10	VINPGSGDTYYSEKFKG	30
HVR-H2- 3C8.gr.5.DA	VINPGSGDAYYSEKFKG	31
HVR-H2- 3C8.gr.5.DQ	VINPGSGDQYYSEKFKG	32
HVR-H3- 3C8.gr.1 3C8.gr.2 3C8.gr.3 3C8.gr.4 3C8.gr.5 3C8.gr.5.SG 3C8.gr.5.EG 3C8.gr.5.QG 3C8.gr.5.DA 3C8.gr.5.DQ 3C8.gr.6 3C8.gr.7 3C8.gr.8 3C8.gr.9 3C8.gr.10 3C8.gr.11 3C8.A.1 3C8.A.2 3C8.A.3 3C8.A.4	DRLDY	33

3C8.A.5 3C8.A.6 3C8.A.7		
HVR-H3- 3C8.A.8	ARLDY	34
HVR-H3- 3C8.A.9	DALDY	35
HVR-H3- 3C8.A.10	DRADY	36
HVR-L1- 3C8.gr.1 3C8.gr.2 3C8.gr.3 3C8.gr.4 3C8.gr.5 3C8.gr.5.SG 3C8.gr.5.EG 3C8.gr.5.QG 3C8.gr.5.DA 3C8.gr.5.DQ 3C8.gr.6 3C8.gr.7 3C8.gr.8 3C8.gr.9 3C8.gr.10 3C8.gr.11 3C8.A.1 3C8.A.2 3C8.A.3 3C8.A.4 3C8.A.5 3C8.A.6 3C8.A.7 3C8.A.8 3C8.A.9 3C8.A.10	HASQDISSYIV	37
HVR-L2- 3C8.gr.1 3C8.gr.2 3C8.gr.3 3C8.gr.4 3C8.gr.5 3C8.gr.5.DA 3C8.gr.5.DQ 3C8.gr.6 3C8.gr.7 3C8.gr.8 3C8.gr.9 3C8.gr.10 3C8.gr.11	HGTNLED	38

3C8.A.1 3C8.A.2 3C8.A.3 3C8.A.4 3C8.A.5 3C8.A.6 3C8.A.7 3C8.A.8 3C8.A.9 3C8.A.10		
HVR-L2- 3C8.gr5.SG	HGTNLES	39
HVR-L2- 3C8.gr.5.EG	HGTNLEE	40
HVR-L2- 3C8.gr.5.QG	HGTNLEQ	41
HVR-L3 3C8.gr.1 3C8.gr.2 3C8.gr.3 3C8.gr.4 3C8.gr.5 3C8.gr.5.SG 3C8.gr.5.EG 3C8.gr.5.QG 3C8.gr.5.DA 3C8.gr.5.DQ 3C8.gr.6 3C8.gr.7 3C8.gr.8 3C8.gr.9 3C8.gr.10 3C8.gr.11 3C8.A.8 3C8.A.9 3C8.A.10	VHYAQFPYT	42
HVR-L3- 3C8.A.1	AHYAQFPYT	43
HVR-L3- 3C8.A.2	VAYAQFPYT	44
HVR-L3- 3C8.A.3	VHAAQFPYT	45
HVR-L3- 3C8.A.4	VHYAAFPYT	46
HVR-L3-	VHYAQAPYT	47

3C8.A.5		
HVR-L3-3C8.A.6	VHYAQFAYT	48
HVR-L3-3C8.A.7	VHYAQFPAT	49
HVR-H1-1D2.gr.1 1D2.gr.2 1D2.gr.3	DYGVL	50
HVR-H2-1D2.gr.1 1D2.gr.2 1D2.gr.3	MIWSGGTTDYNAAFIS	51
HVR-H3-1D2.gr.1 1D2.gr.2 1D2.gr.3	EEMDY	52
HVR-L1-1D2.gr.1 1D2.gr.2 1D2.gr.3	RASQDISNFLN	53
HVR-L2-1D2.gr.1 1D2.gr.2 1D2.gr.3	YTSRLHS	54
HVR-L3-1D2.gr.1 1D2.gr.2 1D2.gr.3	QQGNTLPWT	55
1A7.gr.1 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	56
1A7.gr.1 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	57
1A7.gr.2 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITVDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	58
1A7.gr.2 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	59
1A7.gr.3 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTLTVDTSTSTAYLEL SSLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	60
1A7.gr.3 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	61
1A7.gr.4 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITVDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	62
1A7.gr.4	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKT	63

V_L	VKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	
1A7.gr.5 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITVDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	64
1A7.gr.5 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKT VKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	65
1A7.gr.6 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITVDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	66
1A7.gr.6 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKT VKLLIYYTSRLRSGVPSRFSGSGSGKDYTLTISSLQPEDFATYFC QQGHTLPPTFGQGTKVEIK	67
1A7.gr.7 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITVDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	68
1A7.gr.7 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKT VKLLIYYTSRLRSGVPSRFSGSGSGKDYTLTISSLQPEDFATYFC QQGHTLPPTFGQGTKVEIK	69
1A7.gr.DA V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDAYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	70
1A7.gr.DA V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	71
1A7.gr.ES V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTESYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	72
1A7.gr.ES V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	73
1A7.gr.NADS V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNADSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	74
1A7.gr.NADS V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	75
1A7.gr.NADA V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNADASYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	76
1A7.gr.NADA V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	77
1A7.gr.NGDA V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDASYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	78
1A7.gr.NGDA V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	79
1A7.gr.SGDS V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDSGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	80
1A7.gr.SGDS	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA	81

V_L	PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	
1A7.gr.NGSS V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGSSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	82
1A7.gr.NGSS V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	83
1A7.gr.DANADA V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDAYMSWVRQAP GQGLEWIGDMYPDNADASYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	84
1A7.gr.DANADA V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	85
1A7.Ala.1 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	86
1A7.Ala.1 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPATFGQGTKVEIK	87
1A7.Ala.2 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	88
1A7.Ala.2 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTAPPTFGQGTKVEIK	89
1A7.Ala.3 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	90
1A7.Ala.3 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGATLPPTFGQGTKVEIK	91
1A7.Ala.4 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	92
1A7.Ala.4 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHALPPTFGQGTKVEIK	93
1A7.Ala.5 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	94
1A7.Ala.5 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQAHTLPPTFGQGTKVEIK	95
1A7.Ala.6 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	96
1A7.Ala.6 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLAPTFGQGTKVEIK	97
1A7.Ala.7 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	98
1A7.Ala.7	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA	99

V_L	PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QAGHTLPPTFGQGTKVEIK	
1A7.Ala.8 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFSAWGQGTLVTVSS	100
1A7.Ala.8 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	101
1A7.Ala.9 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYASVWGQGTLVTVSS	102
1A7.Ala.9 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	103
1A7.Ala.10 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWAFSVWGQGTLVTVSS	104
1A7.Ala.10 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	105
1A7.Ala.11 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPAWYFSVWGQGTLVTVSS	106
1A7.Ala.11 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	107
1A7.Ala.12 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRWYFAVWGQGTLVTVSS	108
1A7.Ala.12 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	109
1A7.Ala.13 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAPRAYFSVWGQGTLVTVSS	110
1A7.Ala.13 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	111
1A7.Ala.14 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVLAARWYFSVWGQGTLVTVSS	112
1A7.Ala.14 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	113
1A7.Ala.15 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCALAPRWYFSVWGQGTLVTVSS	114
1A7.Ala.15 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	115
1A7.Ala.16 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTITRDTSTSTAYLELS SLRSEDTAVYYCVAAPRWYFSVWGQGTLVTVSS	116
1A7.Ala.16	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKA	117

V_L	PKLLIYYTSRLRSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPPTFGQGTKVEIK	
3C8.gr.1 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTITRDTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	118
3C8.gr.1 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKAP KLLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	119
3C8.gr.2 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTITADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	120
3C8.gr.2 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKAP KLLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	121
3C8.gr.3 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	122
3C8.gr.3 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKAP KLLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	123
3C8.gr.4 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTITADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	124
3C8.gr.4 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	125
3C8.gr.5 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	126
3C8.gr.5 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	127
3C8.gr.5.SG V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	128
3C8.gr.5.SG V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCV HYAQFPYTFGQGTKVEIK	129
3C8.gr.5.EG V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	130
3C8.gr.5.EG V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEEGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	131
3C8.gr.5.QG V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	132
3C8.gr.5.QG V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEQGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	133
3C8.gr.6 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTITADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	134

3C8.gr.6 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGADYTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	135
3C8.gr.7 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	136
3C8.gr.7 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGADYTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	137
3C8.gr.8 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTRDTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	138
3C8.gr.8 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	139
3C8.gr.9 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTRDTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	140
3C8.gr.9 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSP KLLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	141
3C8.gr.10 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTRDTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	142
3C8.gr.10 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKAF KLLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	143
3C8.gr.11 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTRDTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	144
3C8.gr.11 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKAP KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	145
3C8.A.1 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	146
3C8.A.1 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC AHYAQFPYTFGQGTKVEIK	147
3C8.A.2 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	148
3C8.A.2 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VAYAQFPYTFGQGTKVEIK	149
3C8.A.3 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	150
3C8.A.3 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHAAQFPYTFGQGTKVEIK	151
3C8.A.4 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL	152

	RSEDTAVYYCARDRLDYWGQGTLVTVSS	
3C8.A.4 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAAFPYTFGQGTKVEIK	153
3C8.A.5 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	154
3C8.A.5 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQAPYTFGQGTKVEIK	155
3C8.A.6 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	156
3C8.A.6 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFAYTFGQGTKVEIK	157
3C8.A.7 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRLDYWGQGTLVTVSS	158
3C8.A.7 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPATFGQGTKVEIK	159
3C8.A.8 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARARLDYWGQGTLVTVSS	160
3C8.A.8 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	161
3C8.A.9 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDALDYWGQGTLVTVSS	162
3C8.A.9 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	163
3C8.A.10 V_H	EVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPG QGLEWIGVINPGSGDTYYSEKFKGRVTLTADTSTSTAYLELSSL RSEDTAVYYCARDRADYWGQGTLVTVSS	164
3C8.A.10 V_L	DIQMTQSPSSLSASVGDRVTITCHASQDISSYIVWYQQKPGKSF KGLIYHGTNLEDGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC VHYAQFPYTFGQGTKVEIK	165
1D2.gr.1 V_H	EVQLVESGPGLVKPSETLSLTCTVSGFSLTDYGVLWIRQPPGKG LEWIGMIWSGGTTDYNAAFISRVTISVDTSKNQFSLKLSSVTAA DTAVYYCVREEMDYWGQGTLVTVSS	166
1D2.gr.1 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNFLNWYQQKPGKA PKLLIYYTSRLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGNTLPWTFGQGTKVEIK	167
1D2.gr.2 V_H	EVQLVESGPGLVKPSETLSLTCTVSGFSLTDYGVLWIRQPPGKG LEWIGMIWSGGTTDYNAAFISRVTISKDTSKNQVSLKLSSVTA ADTAVYYCVREEMDYWGQGTLVTVSS	168
1D2.gr.2 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNFLNWYQQKPGKA PKLLIYYTSRLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGNTLPWTFGQGTKVEIK	169

1D2.gr.3 V_H	EVQLVESGPGLVKPSETLSLTCTVSGFSLTDYGVLWVRQPPGK GLEWLGMIWSGGTTDYNAAFISRLTISKDTSKNQVSLKLSSVT AADTAVYYCVREEMDYWGQGTLVTVSS	170
1D2.gr.3 V_L	DIQMTQSPSSLSASVGDRVTITCRASQDISNFLNWYQQKPGKA PKLLIYYTSRLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQGNTLPWTFGQGTKVEIK	171
CON1 (1A7)HVR-H1	X_1X_2YMS, wherein X_1 is D or E, and X_2 is S or A	172
CON1 (1A7) HVR-H2	DMYPD$X_1X_2X_3X_4$SYNQKFRE, wherein X_1 is N or S, X_1 is A or G, X_3 is D or S, and X_4 is A or S	173
CON1 (1A7) HVR-H3	APRW$X_1X_2X_3X_4$, wherein X_1 is Y or A, X_2 is A or F, X_3 is S or A, and X_4 is A or V.	174
CON1 (1A7) HVR-L3	Q$X_1X_2X_3X_4X_5X_6X_7$T, wherein X_1 is A or Q, X_2 is A or G, X_3 is A or H, X_4 is A or T, X_5 is A or L, X_6 is A or P, and X_7 is A or P.	175
CON2 (3C8) HVR-H2	VINPGSGDX_1YYSEKFKG, wherein X_1 is T, A or Q.	176
CON2 (3C8) HVR-L2	HGTNLEX_1, wherein X_1 is S, E, or Q.	177
CON2 (3C8) HVR-L3	X_1X_2YAQFPYX_3, wherein X_1 is V or A, X_2 is H or A, and X_3 is Y or A.	178
1A7 V_L	DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGT VKLLIYYTSRLRSGVPSRFSGSGSGKDYFLTISNLEQEDVAAYF CQQGHTLPPTFGGGTKLEIK	179
1A7 V_H	EVQLQQSGPELVKPGASVKISCKASGYTFTDSYMSWVKQSHG KTLEWIGDMYPDNGDSSYNQKFREKVTLTVDKSSTTAYMEFR SLTSEDSAVYYCVLAPRWYFSVWGTGTTVTVSS	180
3C8 V_L	DILMTQSPSSMSVSLGDTVSITCHASQDISSYIVWLQQKPGKSF RGLIYHGTNLEDGIPSRFSGSGSGADYSLTISSLESEDFADYYCV HYAQFPYTFGGGTKLEIK	181
3C8 V_H	QVQLQQSGAELVRPGTSVKVSCKASGYAFTNYLIEWVKQRPG QGLEWIGVINPGSGDTYYSEKFKGKVTLTADKSSSTAYMQLSS LTSEDSAVYFCARDRLDYWGQGTTLTVSS	182
1A7.gr.5' V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTLTVDTSTSTAYLEL SSLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	233
1A7.gr.7' V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDSYMSWVRQAP GQGLEWIGDMYPDNGDSSYNQKFRERVTLTVDTSTSTAYLEL SSLRSEDTAVYYCVLAPRWYFSVWGQGTLVTVSS	234

IV. Methods of Treatment

[0348] Certain aspects of the present disclosure relate to method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of an anti-angiogenesis agent described herein and an OX40 binding agonist described herein. For example, any of the anti-angiogenesis agents (*e.g.,* anti-VEGF antibodies) and OX40 binding agonists (*e.g.,* anti-human OX40 antibodies) provided herein may be used in therapeutic methods. In some embodiments, the individual has cancer or has been diagnosed with cancer. In some embodiments,

the treatment results in a sustained response in the individual after cessation of the treatment. In some embodiments, the individual is a human.

[0349] In some embodiments, the OX40 binding agonist is administered before the anti-angiogenesis agent, simultaneous with the anti-angiogenesis agent, or after the anti-angiogenesis agent.

[0350] Examples of various cancer types that can be treated with an anti-angiogenesis agent (*e.g.*, a VEGF antagonist such as an anti-VEGF antibody like bevacizumab) and an OX40 binding agonist are described above. Preferred cancer types include gynecologic cancers (e.g., ovarian, peritoneal, fallopian tube, cervical, endometrial, vaginal, and vulvar cancer). Additional cancers include epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer (including platinum sensitive and platinum resistant ovarian cancer), liver cancer, bladder cancer, hepatoma, neuroblastoma, melanoma, breast cancer, colon cancer, colorectal cancer, fallopian tube, peritoneal, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, soft-tissue sarcoma, kaposi's sarcoma, carcinoid carcinoma, mesothelioma, multiple myeloma, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome. In various embodiments, the cancer that is treated is advanced, refractory, recurrent, chemotherapy-resistant, and/or platinum-resistant cancer.

[0351] In some embodiments, examples of cancer further include, but are not limited to, B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), B-cell proliferative disorders, and Meigs' syndrome. More specific examples include, but are

not limited to, relapsed or refractory NHL, front line low grade NHL, Stage III/IV NHL, chemotherapy resistant NHL, precursor B lymphoblastic leukemia and/or lymphoma, small lymphocytic lymphoma, B-cell chronic lymphocytic leukemia and/or prolymphocytic leukemia and/or small lymphocytic lymphoma, B-cell prolymphocytic lymphoma, immunocytoma and/or lymphoplasmacytic lymphoma, lymphoplasmacytic lymphoma, marginal zone B-cell lymphoma, splenic marginal zone lymphoma, extranodal marginal zone—MALT lymphoma, nodal marginal zone lymphoma, hairy cell leukemia, plasmacytoma and/or plasma cell myeloma, low grade/follicular lymphoma, intermediate grade/follicular NHL, mantle cell lymphoma, follicle center lymphoma (follicular), intermediate grade diffuse NHL, diffuse large B-cell lymphoma, aggressive NHL (including aggressive front-line NHL and aggressive relapsed NHL), NHL relapsing after or refractory to autologous stem cell transplantation, primary mediastinal large B-cell lymphoma, primary effusion lymphoma, high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small non-cleaved cell NHL, bulky disease NHL, Burkitt's lymphoma, precursor (peripheral) large granular lymphocytic leukemia, mycosis fungoides and/or Sezary syndrome, skin (cutaneous) lymphomas, anaplastic large cell lymphoma, angiocentric lymphoma.

[0352] In some embodiments, examples of cancer further include, but are not limited to, B-cell proliferative disorders, which further include, but are not limited to, lymphomas (e.g., B-Cell Non-Hodgkin's lymphomas (NHL)) and lymphocytic leukemias. Such lymphomas and lymphocytic leukemias include e.g. a) follicular lymphomas, b) Small Non-Cleaved Cell Lymphomas/ Burkitt's lymphoma (including endemic Burkitt's lymphoma, sporadic Burkitt's lymphoma and Non-Burkitt's lymphoma), c) marginal zone lymphomas (including extranodal marginal zone B-cell lymphoma (Mucosa-associated lymphatic tissue lymphomas, MALT), nodal marginal zone B-cell lymphoma and splenic marginal zone lymphoma), d) Mantle cell lymphoma (MCL), e) Large Cell Lymphoma (including B-cell diffuse large cell lymphoma (DLCL), Diffuse Mixed Cell Lymphoma, Immunoblastic Lymphoma, Primary Mediastinal B-Cell Lymphoma, Angiocentric Lymphoma-Pulmonary B-Cell Lymphoma), f) hairy cell leukemia, g) lymphocytic lymphoma, Waldenstrom's macroglobulinemia, h) acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia, i) plasma cell neoplasms, plasma cell myeloma, multiple myeloma, plasmacytoma, and/or j) Hodgkin's disease.

[0353] In some embodiments of any of the methods, the cancer is a B-cell proliferative disorder. In some embodiments, the B-cell proliferative disorder is lymphoma, non-Hodgkins lymphoma (NHL), aggressive NHL, relapsed aggressive NHL, relapsed indolent NHL, refractory NHL, refractory indolent NHL, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma, leukemia, hairy cell leukemia (HCL), acute lymphocytic leukemia (ALL), or mantle cell lymphoma. In some embodiments, the B-cell proliferative disorder is NHL, such as indolent NHL and/or aggressive NHL. In some embodiments, the B-cell proliferative disorder is indolent follicular lymphoma or diffuse large B-cell lymphoma.

[0354] In some embodiments, the anti-angiogenesis agent and/or the OX40 binding agonist are administered intravenously, intramuscularly, subcutaneously, intracerobrospinally, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, intra-articularly, intrasynovially, or intranasally. The VEGF antagonist and/or the OX40 binding agonist (e.g., an anti-VEGF antibody, such as bevacizumab), optionally in combination with one or more chemotherapeutic agents (e.g., carboplatin and/or paclitaxel), are administered to a human patient in accordance with known methods, such as intravenous administration, e.g., as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous administration of the antibody is preferred.

[0355] Pharmaceutical formulations of an anti-OX40 antibody and/or anti-angiogenesis agent as described herein are prepared by mixing such antibody or other agent having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.* Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include insterstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[0356] In some embodiments, a "histidine buffer" is a buffer comprising histidine ions. Examples of histidine buffers include histidine chloride, histidine acetate, histidine phosphate, histidine sulfate. The preferred histidine buffer identified in the examples herein was found to be histidine acetate. In the preferred embodiment, the histidine acetate buffer is prepared by titrating L-histidine (free base,

solid) with acetic acid (liquid). In some embodiments, the histidine buffer or histidine-acetate buffer is at pH 5.0 to 6.0, in some embodiments, pH 5.3 to 5.8.

[0357] In some embodiments, a "saccharide" herein comprises the general composition (CH2O)n and derivatives thereof, including monosaccharides, disaccharides, trisaccharides, polysaccharides, sugar alcohols, reducing sugars, nonreducing sugars, etc. Examples of saccharides herein include glucose, sucrose, trehalose, lactose, fructose, maltose, dextran, glycerin, dextran, erythritol, glycerol, arabitol, sylitol, sorbitol, mannitol, mellibiose, melezitose, raffinose, mannotriose, stachyose, maltose, lactulose, maltulose, glucitol, maltitol, lactitol, iso-maltulose, etc. In some embodiments, the saccharide is a nonreducing disaccharide, such as trehalose or sucrose.

[0358] In some embodiments herein, a "surfactant" refers to a surface-active agent, preferably a nonionic surfactant. Examples of surfactants herein include polysorbate (for example, polysorbate 20 and polysorbate 80); poloxamer (*e.g.* poloxamer 188); Triton; sodium dodecyl sulfate (SDS); sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (*e.g.* lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; and the MONAQUAT™ series (Mona Industries, Inc., Paterson, New Jersey); polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (*e.g.* Pluronics, PF68 etc); etc. In some embodiments, the surfactant is polysorbate 20. In some embodiments, the surfactant is polysorbate 80.

[0359] Exemplary lyophilized antibody formulations are described in US Patent No. 6,267,958. Aqueous antibody formulations include those described in US Patent No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

[0360] The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide an additional medicament (examples of which are provided herein). Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

[0361] Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

[0362] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.* films, or microcapsules.

[0363] The formulations to be used for *in vivo* administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

[0364] In some embodiments, provided herein are pharmaceutical formulations comprising: (a) any of the anti-human OX40 agonist antibodies described herein; (b) a histidine buffer at pH 5.0-6.0.

[0365] In some embodiments, provided herein are pharmaceutical formulations comprising: (a) any of the anti-human OX40 agonist antibodies described herein; (b) a histidine buffer at pH 5.0-6.0; (c) a saccharide; and (d) a surfactant.

[0366] In some embodiments of any of the formulations, the anti-human OX40 agonist antibody is present at a concentration between about 10 mg/mL and about 100 mg/mL (*e.g.* about 15 mg/mL, 18 mg/mL, 20 mg/mL, 60 mg/mL, and 75 mg/mL). In some embodiments, the anti-human OX40 agonist antibody is present at a concentration of about 20 mg/mL. In some embodiments, the anti-human OX40 agonist antibody is present at a concentration of about 50 mg/mL. In some embodiments, the anti-human OX40 agonist antibody is present at a concentration of about 60 mg/mL. In some embodiments, the anti-human OX40 agonist antibody is present at a concentration of about 70 mg/mL.

[0367] In some embodiments of any of the formulations, the saccharide is present at a concentration of about 75 mM to about 360 mM (*e.g.*, about 100 mM, about 120 mM, about 240 mM, about 320 mM to about 360 mM). In some embodiments, the saccharide is present at a concentration of about 120 mM. In some embodiments, the saccharide is present at a concentration of about 240 mM. In some embodiments, the saccharide is present at a concentration of about 320 mM. In some embodiments, the saccharide is a disaccharide. In some embodiments, the disaccharide is trehalose. In some embodiments, the disaccharide is sucrose.

[0368] In some embodiments of any of the formulations, the histidine buffer is at a concentration of about 1 mM to about 50 mM (*e.g.* about 1 mM to about 25 mM). In some embodiments, the histidine buffer is at a concentration of about 10 mM. In some embodiments, the histidine buffer is at a concentration of about 20 mM. In some embodiments, the histidine buffer is at a concentration of about 30 mM. In some embodiments, the histidine buffer is histidine acetate.

[0369] In some embodiments of any of the formulations, the surfactant is polysorbate (e.g., polysorbate 20 or polysorbate 40), poloxamer (*e.g.* poloxamer 188); Triton; sodium dodecyl sulfate (SDS); sodium laurel sulfate; or sodium octyl glycoside.

[0370] In some embodiments of any of the formulations, the surfactant is polysorbate. In some embodiments, the polysorbate is present at a concentration of about 0.005% to about 0.1%. In some embodiments, the polysorbate is present at a concentration of about 0.005%. In some embodiments, the polysorbate is present at a concentration of about 0.02%. In some embodiments, the polysorbate is present at a concentration of about 0.04%. In some embodiments, the polysorbate is present at a concentration of about 0.06%. In some embodiments, the polysorbate is polysorbate 20. In some embodiments, the polysorbate is polysorbate 80.

[0371] In some embodiments of any of the formulations, the formulation is diluted with a diluent (*e.g.*, 0.9% NaCl). In some embodiments, the anti-human OX40 agonist antibody is present at a concentration of about 1 mg/mL.

[0372] In particular, provided herein are pharmaceutical formulations comprising (a) any of the anti-human OX40 agonist antibodies described herein, (b) a polysorbate, wherein the polysorbate concentration is about 0.005% to about 0.1%.; and (c) a histidine buffer (*e.g.*, a histidine buffer at a pH between 5.0 and 6.0).

[0373] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) a polysorbate, wherein the polysorbate concentration is about 0.02% to about 0.06%; (c) a histidine buffer (*e.g.*, a histidine buffer at a pH between 5.0 and 6.0); and a saccharide, wherein the saccharide concentration is about 120mM to about 320 mM. In some embodiments, the saccharide is sucrose.

[0374] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) a polysorbate, wherein the polysorbate concentration is about 0.02% to about 0.06%, wherein the polysorbate is polysorbate 20 or polysorbate 40; (c) a histidine acetate buffer (*e.g.*, a histidine acetate buffer at a pH between 5.0 and 6.0); and a saccharide (e.g., sucrose) at a concentration of about 120mM to about 320 mM.

[0375] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.02% to about 0.06%; (c) a histidine acetate buffer (*e.g.*, a histidine acetate buffer at a pH between 5.0 and 6.0); and (d) sucrose, wherein the sucrose concentration is about 120 mM to about 320 mM.

[0376] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 40, wherein the polysorbate concentration is about 0.02% to about 0.06%; (c) a histidine acetate buffer (*e.g.*, a histidine acetate buffer at a pH between 5.0 and 6.0); and sucrose, wherein the sucrose concentration is about 120 mM to about 320 mM.

[0377] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.02%; (c) a histidine acetate buffer at pH 6.0; and (d) sucrose, wherein the sucrose concentration is about 320 mM.

[0378] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration is about 0.02%; (c) a histidine acetate buffer at pH 5.5; and (d) sucrose, wherein the sucrose concentration is about 240 mM.

[0379] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 20, wherein the polysorbate concentration

is about 0.04%; (c) a histidine acetate buffer at pH 6.0; and (d) sucrose, wherein the sucrose concentration is about 120 mM.

[0380] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 40, wherein the polysorbate concentration is about 0.04%; (c) a histidine acetate buffer at pH 5.0; and (d) sucrose, wherein the sucrose concentration is about 240 mM.

[0381] In some embodiments, the pharmaceutical formulation comprises (a) any of the anti-human OX40 agonist antibodies described herein, (b) polysorbate 40, wherein the polysorbate concentration is about 0.04%; (c) a histidine acetate buffer at pH 6.0; and (d) sucrose, wherein the sucrose concentration is about 120 mM.

[0382] In some embodiments, the pharmaceutical formulation is a liquid pharmaceutical formulation. In some embodiments, the pharmaceutical formulation is a stable pharmaceutical formulation. In some embodiments, the pharmaceutical formulation is a stable liquid pharmaceutical formulation.

[0383] In some embodiments of any of the pharmaceutical formulations described herein, the anti-human OX40 agonist antibody of the pharmaceutical formulation is present at a concentration between about 10 mg/mL and about 100 mg/mL. In some embodiments, the concentration of the human OX40 agonist antibody is between about any of 10 mg/mL to 50 mg/mL, 10 mg/mL to 75 mg/mL, 25 mg/mL to 75 mg/mL, 50 mg/mL to 100 mg/mL, 50 mg/mL to 75 mg/mL, and/or 75 mg/mL to 100 mg/mL. In some embodiments, the concentration of the human OX40 agonist antibody is greater than about any of 20 mg/mL, 30 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, 70 mg/mL, or 100 mg/mL.

[0384] The pharmaceutical formulation preferably comprises a polysorbate. The polysorbate is generally included in an amount which reduces aggregate formation (such as that which occurs upon shaking or shipping). Examples of polysorbate include, but are not limited to, polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), and/or polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In some embodiments, the polysorbate is polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate). In some embodiments of any of the pharmaceutical formulations described herein, the polysorbate concentration is sufficient to minimize aggregation and/or maintain stability upon long term storage and/or during administration (*e.g.*, after dilution in an IV bag). In some embodiments, the polysorbate concentration is about 0.005% w/v, about 0.02% w/v, about 0.04% w/v and less than about 0.1% w/v. In some embodiments, the polysorbate concentration is greater than 0.01% w/v and less than about 0.1% w/v. In some embodiments, the polysorbate concentration is about any of 0.005% w/v, about 0.02% w/v, 0.03% w/v, 0.04% w/v, or 0.05% w/v. In some embodiments, the polysorbate is present at a concentration of about 0.04% w/v. In some embodiments, the polysorbate is present at a concentration of about 0.02% w/v.

[0385] The pharmaceutical formulation preferably comprises a saccharide. Saccharides include monosaccharides, disaccharides, trisaccharides, polysaccharides, sugar alcohols, reducing sugars, nonreducing sugars, etc. Further examples of saccharides include, but are not limited to, glucose, sucrose, trehalose, lactose, fructose, maltose, dextran, glycerin, dextran, erythritol, glycerol, arabitol, sylitol, sorbitol, mannitol, mellibiose, melezitose, raffinose, mannotriose, stachyose, maltose, lactulose, maltulose, glucitol, maltitol, lactitol, iso-maltulose, etc. In some embodiments, the saccharide is a disaccharide. In some embodiments, the saccharide is a nonreducing disaccharide. In some embodiments, the saccharide is trehalose.

[0386] The saccharide is generally included in an amount which reduces aggregate formation. In some embodiments of any of the pharmaceutical formulations described herein, the saccharide is present at a concentration of between about any of 50 mM to 250 mM, 75 mM to 200 mM, 75 mM to 150 mM, 100 mM to 150 mM, or 110 mM to 130 mM, or 100mM to 320 mM, or 240 mM to 320 mM, or 240 mM to 400mM. In some embodiments, the saccharide is present at a concentration greater than about any of 50 mM, 75 mM, 100 mM, 110 mM, or 115 mM. In some embodiments, the saccharide is present at a concentration of about any of 100 mM, 110 mM, 120 mM, 130 mM, or 140 mM. In some embodiments, the saccharide is present at a concentration of about 120 mM. In some embodiments of any of the formulations, the saccharide is present at a concentration of about 75 mM to about 360 mM (*e.g.*, about 100 mM, about 120 mM, about 240 mM, about 320 mM to about 360 mM). In some embodiments, the saccharide is present at a concentration of about 240 mM. In some embodiments, the saccharide is present at a concentration of about 320 mM.

[0387] The pharmaceutical formulation preferably comprises a histidine buffer. Examples of histidine buffers include, but are not limited to, histidine chloride, histidine succinate, histidine acetate, histidine phosphate, histidine sulfate. In some embodiments, the histidine buffer is histidine acetate. In some embodiments of any of the pharmaceutical formulations described herein, the histidine buffer concentration is between about any of 1 mM to 50 mM, 1 mM to 35 mM, 1 mM to 25 mM, 1 mM to 20 mM, 7.5 mM to 12.5 mM, or 5 mM to 15 mM, 20mM to 30mM, 25 mM to 35 mM. In some embodiments, the histidine buffer concentration is about any of 5 mM, 7.5 mM, 10 mM, 12.5 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM or 40 mM. In some embodiments, the histidine buffer concentration is about 10 mM. In some embodiments, the histidine buffer concentration is about 20 mM. In some embodiments, the histidine buffer concentration is about 30 mM. In some embodiments, the histidine buffer concentration is about 40 mM. In some embodiments of any of the pharmaceutical formulations described herein, the histidine buffer is at a pH of between pH 5.0 and 6.0, for example, about any of pH 5.0, pH 5.1, pH 5.2, pH 5.3, pH 5.4, pH 5.5, pH 5.6, pH 5.7, pH 5.8, pH 5.9 or pH 6.0.. In some embodiments, the pH is between pH 4.9 to pH 6.3.

[0388] The pharmaceutical formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities

that do not adversely affect each other. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0389] Further, provided herein are vials and methods of filing a vial comprising a pharmaceutical formulation described herein. In some embodiments, the pharmaceutical formulation is provided inside a vial with a stopper pierceable by a syringe, preferably in aqueous form. The vial is desirably stored at about 2-8°C as well as up to 30°C for 24 hours until it is administered to a subject in need thereof. The vial may for example be a 15 cc vial (for example for a 200 mg dose).

[0390] The pharmaceutical formulation for administration is preferably a liquid formulation (not lyophilized) and has not been subjected to prior lyophilization. While the pharmaceutical formulation may be lyophilized, preferably it is not. In some embodiments of any of the pharmaceutical formulations, the pharmaceutical formulation, the pharmaceutical formulation is a lyophilized pharmaceutical formulation. In some embodiments, the pharmaceutical formulation is a liquid formulation. In some embodiments, the pharmaceutical formulation does not contain a tonicifying amount of a salt such as sodium chloride. In some embodiments of any of the pharmaceutical formulations, the pharmaceutical formulation is diluted.

[0391] Exemplary lyophilized antibody formulations are described in US Patent No. 6,267,958. Aqueous antibody formulations include those described in US Patent No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

[0392] The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide an additional medicament (examples of which are provided herein). Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

[0393] Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

[0394] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.* films, or microcapsules.

[0395] The formulations to be used for *in vivo* administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

[0396] In one aspect, an OX40 binding agonist (*e.g.,* an anti-human OX40 agonist antibody) and/or anti-angiogenesis agent (*e.g.,* an anti-VEGF antibody) for use as a medicament is provided. In some embodiments, an anti-angiogenesis agent (*e.g.,* an anti-VEGF antibody) for use as a medicament is

provided for treating or delaying progression of cancer in an individual, where the medicament comprises the anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and where the treatment comprises administration of the medicament in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier. In other embodiments, an OX40 binding agonist (*e.g.,* an anti-human OX40 agonist antibody) for use as a medicament is provided for treating or delaying progression of cancer in an individual, where the medicament comprises the anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and where the treatment comprises administration of the medicament in combination with a composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier. In some embodiments, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, e.g., as described below.

[0397] In one aspect that may be combined with an anti-angiogenesis agent as described herein, provided is an anti-human OX40 agonist antibody for use in enhancing immune function (e.g., by upregulating cell-mediated immune responses) in an individual having cancer comprising administering to the individual an effective amount of the anti-human agonist OX40 antibody. In one aspect, provided is an anti-human OX40 agonist antibody for use in enhancing T cell function in an individual having cancer comprising administering to the individual an effective amount of the anti-human agonist OX40 antibody. In one aspect, provided are an anti-human OX40 agonist antibody for use in depleting human OX40-expressing cells (e.g., OX40 expressing T cells, e.g., OX40 expressing Treg) comprising administering to the individual an effective amount of the anti-human agonist OX40 antibody. In some embodiments, depletion is by ADCC. In some embodiments, depletion is by phagocytosis. Provided is an anti-human OX40 agonist antibody for treating an individual having tumor immunity.

[0398] In a further aspect, the invention provides for the use of an anti-OX40 antibody in the manufacture or preparation of a medicament. In a further aspect, the invention provides for the use of an anti-VEGF antibody in the manufacture or preparation of a medicament. In one embodiment, the medicament is for treatment of cancer. In a further embodiment, the medicament is for use in a method of treating cancer comprising administering to an individual having cancer an effective amount of the medicament. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, e.g., as described below.

[0399] In one aspect, the medicament is for use in enhancing immune function (e.g., by upregulating cell-mediated immune responses) in an individual having cancer comprising administering to the individual an effective amount of the medicament. In one aspect, the medicament is for use in enhancing T cell function in an individual having cancer comprising administering to the individual an effective amount of the medicament. In some embodiments, the T cell dysfunctional disorder is cancer. In one aspect, the medicament is for use in depleting human OX40-expressing cells

(e.g., cell expressing high OX40, e.g., OX40 expressing T cells) comprising administering to the individual an effective amount of the medicament. In some embodiments, depletion is by ADCC. In some embodiments, depletion is by phagocytosis. In one aspect, the medicament is for treating an individual having tumor immunity.

[0400] In a further aspect, the invention provides pharmaceutical formulations comprising any of the OX40 binding agonists (*e.g.,* anti-OX40 antibodies) and/or anti-angiogenesis agents (*e.g.,* anti-VEGF antibodies) provided herein, e.g., for use in any of the above therapeutic methods. In one embodiment, a pharmaceutical formulation comprises any of the anti-OX40 antibodies and/or anti-angiogenesis agents (*e.g.,* anti-VEGF antibodies) provided herein and a pharmaceutically acceptable carrier. In another embodiment, a pharmaceutical formulation comprises any of the anti-OX40 antibodies provided herein and/or anti-angiogenesis agents (*e.g.,* anti-VEGF antibodies) and at least one additional therapeutic agent, e.g., as described below.

[0401] In some embodiments of any of the methods of the invention, the anti-human OX40 agonist antibodies inhibits tumor immunity by inhibiting Treg function (e.g., inhibiting the suppressive function of Tregs), killing OX40 expressing cells (e.g., cells that express high levels of OX40), increasing effector T cell function and/or increasing memory T cell function. In some embodiments of any of the methods of the invention, the anti-human OX40 agonist antibodies treat cancer by inhibiting Treg function (e.g., inhibiting the suppressive function of Tregs), killing OX40 expressing cells (e.g., cells that express high levels of OX40), increasing effector T cell function and/or increasing memory T cell function. In some embodiments of any of the methods of the invention, the anti-human OX40 agonist antibodies enhance immune function by inhibiting Treg function (e.g., inhibiting the suppressive function of Tregs), killing OX40 expressing cells (e.g., cells that express high levels of OX40), increasing effector T cell function and/or increasing memory T cell function. In some embodiments of any of the methods of the invention, the anti-human OX40 agonist antibodies enhance T cell function by inhibiting Treg function (e.g., inhibiting the suppressive function of Tregs), killing OX40 expressing cells (e.g., cells that express high levels of OX40), increasing effector T cell function and/or increasing memory T cell function.

[0402] In some embodiments of any of the methods, the anti-human OX40 agonist antibody is a depleting anti-human agonist antibody. In some embodiments, treatment with the anti-human OX40 agonist antibody results in cell depletion (e.g., depletion of OX40-expressing cells, e.g., depletion of cells that express high levels of OX40). In some embodiments, depletion is by ADCC. In some embodiments, depletion is by phagocytosis.

[0403] In some embodiments of any of the methods, the anti-human OX40 agonist antibody inhibits Treg function, e.g., by inhibiting Treg suppression of effector and/or memory T cell function (in some embodiments, effector T cell and/or memory T cell proliferation and/or cytokine secretion), relative to Treg function prior to administration of the OX40 agonist antibody. In some embodiments of any of the methods, the anti-human OX40 agonist antibody increases effector T cell proliferation,

relative to effector T cell proliferation prior to administration of the OX40 agonist antibody. In some embodiments of any of the methods, the anti-human OX40 agonist antibody increases memory T cell proliferation, relative to memory T cell proliferation prior to administration of the OX40 agonist antibody. In some embodiments of any of the methods, the anti-human OX40 agonist antibody increases effector T cell cytokine production (e.g., gamma interferon production), relative to effector T cell cytokine production prior to administration of the OX40 agonist antibody. In some embodiments of any of the methods, the anti-human OX40 agonist antibody increases memory T cell cytokine production (e.g., gamma interferon production), relative to memory T cell cytokine production prior to administration of the OX40 agonist antibody. In some embodiments of any of the methods, the anti-human OX40 agonist antibody increases CD4+ effector T cell proliferation and/or CD8+ effector T cell proliferation relative to CD4+ effector T cell proliferation and/or CD8+ effector T cell proliferation prior to administration of the OX40 agonist antibody. In some embodiments of any of the methods, the anti-human OX40 agonist antibody increases memory T cell proliferation (e.g., CD4+ memory T cell proliferation), relative to memory T cell proliferation prior to administration of the OX40 agonist antibody. In some embodiments, the CD4+ effector T cells in the individual have enhanced proliferation, cytokine secretion and/or cytolytic activity relative to proliferation, cytokine secretion and/or cytolytic activity prior to the administration of the anti-human OX40 agonist antibody.

[0404] In some embodiments of any of the methods of the invention, the number of CD4+ effector T cells is elevated relative to prior to administration of the anti-human OX40 agonist antibody. In some embodiments, CD4+ effector T cell cytokine secretion is elevated relative to prior to administration of the anti-human OX40 agonist antibody. In some embodiments of any of the methods, the CD8+ effector T cells in the individual have enhanced proliferation, cytokine secretion and/or cytolytic activity relative to prior to the administration of the anti-human OX40 agonist antibody. In some embodiments, the number of CD8+ effector T cells is elevated relative to prior to administration of the anti-human OX40 agonist antibody. In some embodiments, CD8+ effector T cell cytokine secretion is elevated relative to prior to administration of the anti-human OX40 agonist antibody.

[0405] In some embodiments of any of the methods of the invention, the anti-human OX40 agonist antibody binds human effector cells, e.g., binds FcγR expressed by human effector cells. In some embodiments, the human effector cell performs ADCC effector function. In some embodiments, the human effector cell performs phagocytosis effector function.

[0406] In some embodiments of any of the methods of the invention, the anti-human OX40 agonist antibody comprising a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells (e.g., a DANA or N297G mutation) has diminished activity (e.g., CD4+ effector T cell function, e.g., proliferation), relative to anti-human OX40 agonist antibody comprising native sequence IgG1 Fc portion. In some embodiment, the anti-human OX40 agonist antibody comprising

a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells (e.g., a DANA or N297G mutation) does not possess substantial activity (e.g., CD4+ effector T cell function, e.g., proliferation).

[0407] In some embodiments of any of the methods of the invention, antibody cross-linking is required for anti-human OX40 agonist antibody function. In some embodiments, function is stimulation of CD4+ effector T cell proliferation. In some embodiments, antibody cross-linking is determined by providing anti-human OX40 agonist antibody adhered on a solid surface (e.g., a cell culture plate). In some embodiments, antibody cross-linking is determined by introducing a mutation in the antibody's IgG1 Fc portion (e.g., a DANA or N297S mutation) and testing function of the mutant antibody.

[0408] In some embodiments of any of the methods, the memory T cells in the individual have enhanced proliferation and/or cytokine secretion relative to prior to the administration of the anti-human OX40 agonist antibody. In some embodiments, the number of memory T cells is elevated relative to prior to administration of the anti-human OX40 agonist antibody. In some embodiments, memory T cell cytokine secretion (level) is elevated relative to prior to administration of the anti-human OX40 agonist antibody. In some embodiments of any of the methods, the Treg in the individual have decreased inhibition of effector T cell function (e.g., proliferation and/or cytokine secretion) relative to prior to the administration of the anti-human OX40 agonist antibody. In some embodiments, the number of effector T cells is elevated relative to prior to administration of the anti-human OX40 agonist antibody. In some embodiments, effector T cell cytokine secretion (level) is elevated relative to prior to administration of the anti-human OX40 agonist antibody.

[0409] In some embodiments of any of the methods of the invention, the number of intratumoral (infiltrating) CD4+ effector T cells (e.g., total number of CD4+ effector T cells, or e.g., percentage of CD4+ cells in CD45+ cells) is elevated relative to prior to administration of the anti-human OX40 agonist antibody. In some embodiments of any of the methods of the invention, number of intratumoral (infiltrating) CD4+ effector T cells that express gamma interferon (e.g., total gamma interferon expressing CD4+ cells, or e.g., percentage of gamma interferon expressing CD4+ cells in total CD4+ cells) is elevated relative to prior to administration anti-human OX40 agonist antibody.

[0410] In some embodiments of any of the methods of the invention, the number of intratumoral (infiltrating) CD8+ effector T cells (e.g., total number of CD8+ effector T cells, or e.g., percentage of CD8+ in CD45+ cells) is elevated relative to prior to administration of anti-human OX40 agonist antibody. In some embodiments of any of the methods of the invention, number of intratumoral (infiltrating) CD8+ effector T cells that express gamma interferon (e.g., percentage of CD8+ cells that express gamma interferon in total CD8+ cells) is increased relative to prior to administration of anti-human OX40 agonist antibody.

[0411] In some embodiments of any of the methods of the invention, the number of intratumoral (infiltrating) Treg (e.g., total number of Treg or e.g., percentage of Fox3p+ cells in CD4+ cells) is reduced relative to prior to administration of anti-human OX40 agonist antibody.

[0412] In some embodiments of any of the methods of the invention, administration of anti-human OX40 agonist antibody is in combination with administration of a tumor antigen. In some embodiments, the tumor antigen comprises protein. In some embodiments, the tumor antigen comprises nucleic acid. In some embodiments, the tumor antigen is a tumor cell.

[0413] In some embodiments of any of the methods of the invention, the cancer displays human effector cells (e.g., is infiltrated by human effector cells). Methods for detecting human effector cells are well known in the art, including, e.g., by IHC. In some embodiments, the cancer display high levels of human effector cells. In some embodiments, human effector cells are one or more of NK cells, macrophages, monocytes. In some embodiments, the cancer is any cancer described herein.

[0414] In some embodiments of any of the methods of the invention, the cancer displays cells expressing FcR (e.g., is infiltrated by cells expressing FcR). Methods for detecting FcR are well known in the art, including, e.g., by IHC. In some embodiments, the cancer display high levels of cells expressing FcR. In some embodiments, FcR is FcγR. In some embodiments, FcR is activating FcγR.

[0415] An "individual" according to any of the above embodiments is preferably a human.

[0416] Antibodies of the invention can be used either alone or in combination with other agents in a therapy. For instance, a combination therapy of the invention (*e.g.,* including an OX40 binding agonist and an anti-angiogenesis agent) may be co-administered with at least one additional therapeutic agent.

[0417] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of the antibody of the invention can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent or agents. In one embodiment, administration of the anti-OX40 antibody and anti-angiogenesis agent (*e.g.,* anti-VEGF antibodies) and administration of an additional therapeutic agent occur within about one month, or within about one, two or three weeks, or within about one, two, three, four, five, or six days, of each other. Antibodies of the invention can also be used in combination with radiation therapy.

[0418] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (*e.g.,* anti-VEGF antibody) may be administered in conjunction with a chemotherapy or chemotherapeutic agent. In some embodiments, an anti-human OX40 agonist antibody may be administered in conjunction with a radiation therapy or radiotherapeutic agent. In some embodiments, an anti-human OX40 agonist antibody may be administered in conjunction with a targeted therapy or targeted therapeutic agent. In some embodiments, an anti-human OX40 agonist antibody may be

administered in conjunction with an immunotherapy or immunotherapeutic agent, for example a monoclonal antibody.

[0419] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (*e.g.,* anti-VEGF antibody) may be administered in conjunction with a PARP inhibitor (e.g., Olaparanib, Rucaparib, Niraparib, Cediranib, BMN673, Veliparib), Trabectedin, nab-paclitaxel (albumen-bound paclitaxel, ABRAXANE), Trebananib, Pazopanib, Cediranib, Palbociclib, everolimus, fluoropyrimidine (e.g., FOLFOX, FOLFIRI), IFL, regorafenib, Reolysin, Alimta, Zykadia, Sutent, Torisel (temsirolimus), Inlyta (axitinib, Pfizer), Afinitor (everolimus, Novartis), Nexavar (sorafenib, Onyx / Bayer), Votrient, Pazopanib, axitinib, IMA-901, AGS-003, cabozantinib, Vinflunine, Hsp90 inhibitor (e.g., apatorsin), Ad-GM-CSF (CT-0070), Temazolomide, IL-2, IFNa, vinblastine, Thalomid, dacarbazine, cyclophosphamide, lenalidomide, azacytidine, lenalidomide, bortezomid (VELCADE), amrubicine, carfilzomib, pralatrexate, and/or enzastaurin.

[0420] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (*e.g.,* anti-VEGF antibody) may be administered in conjunction with a PD-1 axis binding antagonist. A PD-1 axis binding antagonist includes but is not limited to a PD-1 binding antagonist, a PD-L1 binding antagonist and a PD-L2 binding antagonist. Alternative names for "PD-1" include CD279 and SLEB2. Alternative names for "PD-L1" include B7-H1, B7-4, CD274, and B7-H. Alternative names for "PD-L2" include B7-DC, Btdc, and CD273. In some embodiments, PD-1, PD-Ll , and PD-L2 are human PD-1 , PD-Ll and PD-L2. In some embodiments, the PD-1 binding antagonist is a molecule that inhibits the binding of PD-1 to its ligand binding partners. In a specific aspect the PD-1 ligand binding partners are PD-Ll and/or PD-L2. In another embodiment, a PD-Ll binding antagonist is a molecule that inhibits the binding of PD-Ll to its binding partners. In a specific aspect, PD-Ll binding partners are PD-1 and/or B7- 1. In another embodiment, the PD-L2 binding antagonist is a molecule that inhibits the binding of PD-L2 to its binding partners. In a specific aspect, a PD-L2 binding partner is PD-1. The antagonist may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide. In some embodiments, the PD-1 binding antagonist is an anti-PD-1 antibody (e.g., a human antibody, a humanized antibody, or a chimeric antibody). In some embodiments, the anti-PD-1 antibody is selected from the group consisting of MDX-1106 (nivolumab, OPDIVO), Merck 3475 (MK-3475, pembrolizumab, KEYTRUDA) and CT-011 (Pidilizumab). In some embodiments, the PD-1 binding antagonist is an immunoadhesin (e.g., an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (e.g., an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 binding antagonist is AMP-224. In some embodiments, the PD-Ll binding antagonist is anti-PD-Ll antibody. In some embodiments, the anti-PD-Ll binding antagonist is selected from the group consisting of YW243.55.S70, MPDL3280A, MEDI4736 and MDX-1105. MDX-1105, also known as BMS-936559, is an anti-PD-Ll antibody described in WO2007/005874. Antibody YW243.55.S70 (heavy and light chain variable region sequences shown in SEQ ID Nos. 20 and 21, respectively) is an

anti-PD-Ll described in WO 2010/077634 Al . MDX-1106, also known as MDX-1106-04, ONO-4538, BMS-936558 or nivolumab, is an anti-PD-1 antibody described in WO2006/121168. Merck 3475, also known as MK-3475, SCH-900475 or pembrolizumab, is an anti-PD-1 antibody described in WO2009/114335. CT-011, also known as hBAT, hBAT-1 or pidilizumab, is an anti- PD-1 antibody described in WO2009/101611. AMP-224, also known as B7-DCIg, is a PD-L2- Fc fusion soluble receptor described in WO2010/027827 and WO201 1/066342. In some embodiments, the anti-PD-1 antibody is MDX- 1106. Alternative names for "MDX- 1106" include MDX-1 106-04, ONO-4538, BMS-936558 or nivolumab. In some embodiments, the anti-PD-1 antibody is nivolumab (CAS Registry Number: 946414-94-4).

[0421] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (*e.g.,* anti-VEGF antibody) may be administered in conjunction with an agonist directed against an activating co-stimulatory molecule. In some embodiments, an activating co-stimulatory molecule may include CD40, CD226, CD28, GITR, CD137, CD27, HVEM, or CD127. In some embodiments, the agonist directed against an activating co-stimulatory molecule is an agonist antibody that binds to CD40, CD226, CD28, OX40, GITR, CD137, CD27, HVEM, or CD127. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antagonist directed against an inhibitory co-stimulatory molecule. In some embodiments, an inhibitory co-stimulatory molecule may include CTLA-4 (also known as CD152), PD-1, TIM-3, BTLA, VISTA, LAG-3, B7-H3, B7-H4, IDO, TIGIT, MICA/B, or arginase. In some embodiments, the antagonist directed against an inhibitory co-stimulatory molecule is an antagonist antibody that binds to CTLA-4, PD-1, TIM-3, BTLA, VISTA, LAG-3 (e.g., LAG-3-IgG fusion protein (IMP321)), B7-H3, B7-H4, IDO, TIGIT, MICA/B, or arginase.

[0422] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antagonist directed against CTLA-4 (also known as CD152), *e.g.,* a blocking antibody. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ipilimumab (also known as MDX-010, MDX-101, or Yervoy®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with tremelimumab (also known as ticilimumab or CP-675,206). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antagonist directed against B7-H3 (also known as CD276), *e.g.,* a blocking antibody. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with MGA271. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antagonist directed against a TGF beta, *e.g.,* metelimumab (also known as CAT-192), fresolimumab (also known as GC1008), or LY2157299.

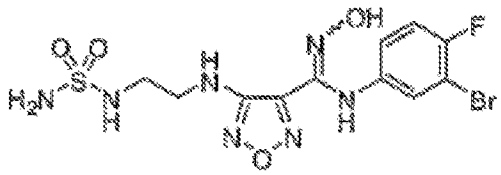
[0423] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a treatment comprising adoptive transfer of a T cell (*e.g.,* a cytotoxic T cell or CTL) expressing a chimeric antigen receptor (CAR). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with UCART19. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with WT128z. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with KTE-C19 (Kite). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with CTL019 (Novartis). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a treatment comprising adoptive transfer of a T cell comprising a dominant-negative TGF beta receptor, *e.g,* a dominant-negative TGF beta type II receptor. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a treatment comprising a HERCREEM protocol (see, e.g., ClinicalTrials.gov Identifier NCT00889954).

[0424] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antagonist directed against CD19. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with MOR00208. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antagonist directed against CD38. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with daratumumab.

[0425] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agonist directed against CD137 (also known as TNFRSF9, 4-1BB, or ILA), *e.g.,* an activating antibody. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with urelumab (also known as BMS-663513). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agonist directed against CD40, *e.g.,* an activating antibody. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with CP-870893. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agonist directed against OX40 (also known as CD134), *e.g.,* an activating antibody. In some embodiments, an anti-human OX40 agonist

antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a different anti-OX40 antibody (e.g., AgonOX). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agonist directed against CD27, *e.g.,* an activating antibody. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with CDX-1127. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antagonist directed against indoleamine-2,3-dioxygenase (IDO). In some embodiments, with the IDO antagonist is 1-methyl-D-tryptophan (also known as 1-D-MT).

[0426] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agonist directed against CD137 (also known as TNFRSF9, 4-1BB, or ILA), *e.g.,* an activating antibody. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with urelumab (also known as BMS-663513). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agonist directed against CD40, *e.g.,* an activating antibody. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with CP-870893 or RO7009789. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agonist directed against OX40 (also known as CD134), *e.g.,* an activating antibody.). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agonist directed against CD27, *e.g.,* an activating antibody. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with CDX-1127 (also known as varlilumab). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antagonist directed against indoleamine-2,3-dioxygenase (IDO). In some embodiments, with the IDO antagonist is 1-methyl-D-tryptophan (also known as 1-D-MT). In some embodiments, the IDO antagonist is an IDO antagonist shown in WO2010/005958 (the contents of which are expressly incorporated by record herein). In some embodiments the IDO antagonist is 4-({2-[(Aminosulfonyl)amino]ethyl}amino)-*N*-(3-bromo-4-fluorophenyl)-*N'*-hydroxy-1,2,5-oxadiazole-3-carboximidamide (*e.g.,* as described in Example 23 of WO2010/005958). In some embodiments the IDO antagonist is



In some embodiments, the IDO antagonist is INCB24360. In some embodiments, the IDO antagonist is Indoximod (the D isomer of 1-methyl-tryptophan). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody-drug conjugate. In some embodiments, the antibody-drug conjugate comprises mertansine or monomethyl auristatin E (MMAE). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an anti-NaPi2b antibody-MMAE conjugate (also known as DNIB0600A, RG7599 or lifastuzumab vedotin). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with trastuzumab emtansine (also known as T-DM1, ado-trastuzumab emtansine, or KADCYLA®, Genentech). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an anti-MUC16 antibody-MMAE conjugate, DMUC5754A. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an anti-MUC16 antibody-MMAE conjugate, DMUC4064A. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody-drug conjugate targeting the endothelin B receptor (EDNBR), *e.g.,* an antibody directed against EDNBR conjugated with MMAE. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody-drug conjugate targeting the lymphocyte antigen 6 complex, locus E (Ly6E), *e.g.,* an antibody directed against Ly6E conjugated with MMAE, (also known as DLYE5953A). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with polatuzumab vedotin. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody-drug conjugate targeting CD30. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ADCETRIS (also known as brentuximab vedotin). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with polatuzumab vedotin.

[0427] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an angiogenesis inhibitor. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody directed against a VEGF, *e.g.,* VEGF-A. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab (also known as AVASTIN®, Genentech). In some embodiments, an anti-human OX40 agonist

antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody directed against angiopoietin 2 (also known as Ang2). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with MEDI3617. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody directed against VEGFR2. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ramucirumab. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a VEGF Receptor fusion protein. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with aflibercept. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ziv-aflibercept (also known as VEGF Trap or Zaltrap®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a bispecific antibody directed against VEGF and Ang2. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with RG7221 (also known as vanucizumab). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an angiogenesis inhibitor and in conjunction with a PD-1 axis binding antagonist (e.g., a PD-1 binding antagonist such as an anti-PD-1 antibody, a PD-L1 binding antagonist such as an anti-PD-L1 antibody, and a PD-L2 binding antagonist such as an anti-PD-L2 antibody). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab and a PD-1 axis binding antagonist (e.g., a PD-1 binding antagonist such as an anti-PD-1 antibody, a PD-L1 binding antagonist such as an anti-PD-L1 antibody, and a PD-L2 binding antagonist such as an anti-PD-L2 antibody). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab and MDX-1106 (nivolumab, OPDIVO). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab and Merck 3475 (MK-3475, pembrolizumab, KEYTRUDA). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab and CT- 011 (Pidilizumab). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab and YW243.55.S70. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab and MPDL3280A. In some

embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab and MEDI4736. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with bevacizumab and MDX-1105.

[0428] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antineoplastic agent. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agent targeting CSF-1R (also known as M-CSFR or CD115). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with anti-CSF-1R antibody (also known as IMC-CS4 or LY3022855) In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with anti-CSF-1R antibody, RG7155 (also known as RO5509554 or emactuzumab). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an interferon, for example interferon alpha or interferon gamma. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with Roferon-A (also known as recombinant Interferon alpha-2a). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with GM-CSF (also known as recombinant human granulocyte macrophage colony stimulating factor, rhu GM-CSF, sargramostim, or Leukine®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with IL-2 (also known as aldesleukin or Proleukin®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with IL-12. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with IL27. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with IL-15. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ALT-803. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody targeting CD20. In some embodiments, the antibody targeting CD20 is obinutuzumab (also known as GA101 or Gazyva®) or rituximab. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody targeting GITR. In some embodiments, the antibody targeting GITR is TRX518. In some embodiments, the antibody targeting GITR is MK04166 (Merck).

[0429] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of Bruton's tyrosine kinase (BTK). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ibrutinib. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of Isocitrate dehydrogenase 1 (IDH1) and/or Isocitrate dehydrogenase 2 (IDH2). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with AG-120 (Agios).

[0430] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with obinutuzumab and a PD-1 axis binding antagonist (e.g., a PD-1 binding antagonist such as an anti-PD-1 antibody, a PD-L1 binding antagonist such as an anti-PD-L1 antibody, and a PD-L2 binding antagonist such as an anti-PD-L2 antibody).

[0431] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a cancer vaccine. In some embodiments, the cancer vaccine is a peptide cancer vaccine, which in some embodiments is a personalized peptide vaccine. In some embodiments the peptide cancer vaccine is a multivalent long peptide, a multi-peptide, a peptide cocktail, a hybrid peptide, or a peptide-pulsed dendritic cell vaccine (see, e.g., Yamada et al., Cancer Sci, 104:14-21, 2013). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an adjuvant. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a treatment comprising a TLR agonist, *e.g.,* Poly-ICLC (also known as Hiltonol®), LPS, MPL, or CpG ODN. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with tumor necrosis factor (TNF) alpha. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with IL-1. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with HMGB1. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an IL-10 antagonist. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an IL-4 antagonist. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an IL-13 antagonist. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an IL-17

antagonist. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an HVEM antagonist. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an ICOS agonist, *e.g.,* by administration of ICOS-L, or an agonistic antibody directed against ICOS. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a treatment targeting CX3CL1. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a treatment targeting CXCL9. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a treatment targeting CXCL10. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a treatment targeting CCL5. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an LFA-1 or ICAM1 agonist. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a Selectin agonist.

[0432] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of B-Raf. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with vemurafenib (also known as Zelboraf®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with dabrafenib (also known as Tafinlar®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with encorafenib (LGX818).

[0433] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an EGFR inhibitor. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with erlotinib (also known as Tarceva®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of EGFR-T790M. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with gefitinib. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with afatinib. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with cetuximab (also known as Erbitux®). In some embodiments, an anti-human OX40

agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with panitumumab (also known as Vectibix®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with rociletinib. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with AZD9291. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of a MEK, such as MEK1 (also known as MAP2K1) and/or MEK2 (also known as MAP2K2). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with cobimetinib (also known as GDC-0973 or XL-518). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with trametinib (also known as Mekinist®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with binimetinib.

[0434] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction an inhibitor of B-Raf (e.g., vemurafenib or dabrafenib) and an inhibitor of MEK (e.g., MEK1 and/or MEK2 (e.g., cobimetinib or trametinib). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of ERK (e.g., ERK1/2). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with GDC-0994). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of B-Raf, an inhibitor of MEK, and an inhibitor of ERK1/2. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of EGFR, an inhibitor of MEK, and an inhibitor of ERK1/2. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with one or more MAP kinase pathway inhibitor. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with CK127. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of K-Ras.

[0435] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of c-Met. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with onartuzumab (also known as MetMAb). In

some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of anaplatic lymphoma kinase (ALK). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with AF802 (also known as CH5424802 or alectinib). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with crizotinib. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ceritinib. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of a phosphatidylinositol 3-kinase (PI3K). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjuction with buparlisib (BKM-120). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with pictilisib (also known as GDC-0941). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with buparlisib (also known as BKM-120). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with perifosine (also known as KRX-0401). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a delta-selective inhibitor of a phosphatidylinositol 3-kinase (PI3K). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with idelalisib (also known as GS-1101 or CAL-101). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with taselisib (also known as GDC-0032). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with BYL-719. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of an Akt. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with MK2206. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with GSK690693. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ipatasertib (also known as GDC-0068). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of mTOR. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with sirolimus

(also known as rapamycin). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with temsirolimus (also known as CCI-779 or Torisel®). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with everolimus (also known as RAD001). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ridaforolimus (also known as AP-23573, MK-8669, or deforolimus). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with OSI-027. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with AZD8055. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with INK128. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with a dual PI3K/mTOR inhibitor. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with XL765. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with GDC-0980. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with BEZ235 (also known as NVP-BEZ235). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with BGT226. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with GSK2126458. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with PF-04691502. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with PF-05212384 (also known as PKI-587).

[0436] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agent that selectively degrades the estrogen receptor. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with GDC-0927. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of HER3. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with duligotuzumab. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be

administered in conjunction with an inhibitor of LSD1. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of MDM2. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of BCL2. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with venetoclax. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of CHK1. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with GDC-0575. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an inhibitor of activated hedgehog signaling pathway. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with ERIVEDGE.

[0437] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with radiation therapy. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with gemcitabine. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with nab-paclitaxel (ABRAXANE). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with trastuzumab. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with TVEC. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with IL27. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with cyclophosphamide. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an agent that recruits T cells to the tumor. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with lirilumab (IPH2102/BMS-986015). In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with Idelalisib. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody that targets CD3 and CD20. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with REGN1979. In some embodiments, an anti-human OX40 agonist

antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an antibody that targets CD3 and CD19. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with blinatumomab.

[0438] In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with an oncolytic virus. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with carboplatin and nab-paclitaxel. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with carboplatin and paclitaxel. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with cisplatin and pemetrexed. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with cisplatin and gemcitabine. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with FOLFOX. In some embodiments, an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (e.g., anti-VEGF antibody) may be administered in conjunction with FOLFIRI.

[0439] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of the anti-human OX40 agonist antibody and/or anti-angiogenesis agent can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent and/or adjuvant. Anti-human OX40 agonist antibodies and/or anti-angiogenesis agents can also be used in combination with radiation therapy.

[0440] An anti-human OX40 agonist antibody and/or anti-angiogenesis agent (and any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g. by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

[0441] Anti-human OX40 agonist antibodies and anti-angiogenesis agents would be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical

practitioners. The antibody need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of antibody present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate. Further, exemplary dosages for an anti-angiogenesis agent (*e.g.,* an anti-VEGF antibody) are provided below.

[0442] For the prevention or treatment of disease, the appropriate dosage of an anti-human OX40 agonist antibody and/or anti-angiogenesis agent (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the type of antibody, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 µg/kg to 40 mg/kg of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 µg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. Such doses may be administered intermittently, e.g. every week or every three weeks (*e.g.* such that the patient receives from about two to about twenty, or *e.g.* about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

[0443] It is understood that any of the above formulations or therapeutic methods may be carried out using an immunoconjugate of the invention in place of or in addition to an anti-human OX40 agonist antibody and/or anti-angiogenesis agent.

[0444] Exemplary doses for anti-VEGF antibodies are provided below. It will be appreciated by one of skill in the art that these doses are merely exemplary and are based on dosing of anti-VEGF antibody alone. Dosing and/or administration practices described herein for anti-VEGF antibody treatment alone may of course be modified when combined with OX40 binding agonist treatment. In some embodiments, the OX40 binding agonist is administered before the anti-angiogenesis agent (*e.g.,* anti-VEGF antibody), simultaneous with the anti-angiogenesis agent, or after the anti-angiogenesis agent.

[0445] For the prevention or treatment of cancer, the dose of VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab), anti-human OX40 agonist antibody, and/or chemotherapeutic agent will depend on the type of cancer to be treated, as defined above, the severity and course of the

cancer, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the drug, and the discretion of the attending physician. In one embodiment, VEGF antagonist (e.g., bevacizumab) is administered at 5 mg/kg of body weight given once every 2 weeks, 10 mg/kg of body weight given once every 2 weeks , 7.5 mg/kg of body weight given once every 3 weeks, or 15 mg/kg of body weight given once every 3 weeks.

[0446] With respect to bevacizumab for the treatment of colorectal cancer, the preferred dosages according to the EMEA are 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks. For the treatment of NSCLC, the preferred dosage is 15 mg/kg given once every 3 weeks by infusion in combination with carboplatin and paclitaxel. For the treatment of renal cell carcinoma, the preferred dosage is 10 mg/kg given once every 2 weeks by infusion with interferon α-2a or as a monotherapy. For the treatment of cervical cancer, the preferred dosage is 15 mg/kg given once every three weeks by infusion and administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan. For the treatment of glioblastoma, the preferred dosage is 10 mg/kg given once every two weeks by infusion.

[0447] In one embodiment, a fixed dose of the VEGF antagonist is administered. A "fixed" or "flat" dose of a therapeutic agent herein refers to a dose that is administered to a human patient without regard for the weight (WT) or body surface area (BSA) of the patient. The fixed or flat dose is therefore not provided as a mg/kg dose or a mg/m^2 dose, but rather as an absolute amount of the therapeutic agent. The fixed dose may suitably be administered to the patient at one time or over a series of treatments. Where a fixed dose is administered, preferably it is in the range from about 20 mg to about 2000 mg of the inhibitor. For example, the fixed dose may be approximately 420 mg, approximately 525 mg, approximately 840 mg, or approximately 1050 mg of the inhibitor (e.g., an anti-VEGF antibody, such as bevacizumab). Where a series of doses are administered, these may, for example, be administered approximately every week, approximately every 2 weeks, approximately every 3 weeks, or approximately every 4 weeks, but preferably approximately every 3 weeks. The fixed doses may, for example, continue to be administered until disease progression, adverse event, or other time as determined by the physician. For example, from about two, three, or four, up to about 17 or more fixed doses may be administered.

[0448] Administration of an angiogenesis inhibitor, e.g., an anti-VEGF antibody, such as bevacizumab, and/or a pharmaceutical composition/treatment regimen comprising an angiogenesis inhibitor, e.g., an anti-VEGF antibody, such as bevacizumab, to a patient in need of such treatment or medical intervention may be by any suitable means known in the art for administration of a therapeutic antibody. Nonlimiting routes of administration include by oral, intravenous, intraperitoneal, subcutaneous, intramuscular, topical, intradermal, intranasal or intrabronchial administration (for example as effected by inhalation). Particularly preferred in context of this invention is parenteral administration, e.g., intravenous administration. Where a VEGF antagonist is

administered as a "single anti-tumor agent" it is the only anti-tumor agent administered to treat the cancer, i.e., it is not administered in combination with another anti-tumor agent, such as chemotherapy or an OX40 binding agonist.

[0449] In one embodiment, one or more loading dose(s) of the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) are administered, followed by one or more maintenance dose(s). A "loading" dose herein generally comprises an initial dose of a therapeutic agent administered to a patient, and is followed by one or more maintenance dose(s) thereof. Generally, a single loading dose is administered, but multiple loading doses are contemplated herein. Usually, the amount of loading dose(s) administered exceeds the amount of the maintenance dose(s) administered and/or the loading dose(s) are administered more frequently than the maintenance dose(s), so as to achieve the desired steady-state concentration of the therapeutic agent earlier than can be achieved with the maintenance dose(s). A "maintenance" dose or "extended" dose herein refers to one or more doses of a therapeutic agent administered to the patient over a treatment period. Usually, the maintenance doses are administered at spaced treatment intervals, such as approximately every week, approximately every 2 weeks, approximately every 3 weeks, or approximately every 4 weeks. In another embodiment, a plurality of the same dose is administered to the patient. According to one preferred embodiment of the invention, a fixed dose of a VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) of approximately 840 mg (loading dose) is administered, followed by one or more doses of approximately 420 mg (maintenance dose(s)) of the antagonist. The maintenance doses are preferably administered about every 3 weeks, for a total of at least two doses, up to 17 or more doses.

[0450] According to another preferred embodiment of the invention, one or more fixed dose(s) of approximately 1050 mg of the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) are administered, for example every 3 weeks. According to this embodiment, one, two or more of the fixed doses are administered, e.g., for up to one year (17 cycles), and longer as desired.

[0451] In another embodiment, a fixed dose of approximately 1050 mg of the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) is administered as a loading dose, followed by one or more maintenance dose(s) of approximately 525 mg. About one, two, or more maintenance doses may be administered to the patient every 3 weeks according to this embodiment.

[0452] While the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) and/or anti-human OX40 agonist antibody or chemotherapeutic agent may be administered in conjunction, the patient is optionally treated with a combination of the inhibitor (or chemotherapeutic agent), and one or more (additional) chemotherapeutic agent(s). Exemplary chemotherapeutic agents herein include: gemcitabine, carboplatin, oxaliplatin, irinotecan, fluoropyrimidine (e.g., 5-FU), paclitaxel (e.g., nab-paclitaxel), docetaxel, topotecan, capecitabine, temozolomide, interferon-alpha, and/or liposomal doxorubicin (e.g., pegylated liposomal doxorubicin). In some embodiments, at least one of the chemotherapeutic agents is carboplatin or paclitaxel. In some embodiments, at least one of the

chemotherapeutic agents is carboplatin or gemcitabine. The combined administration includes co-administration or concurrent administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Thus, the chemotherapeutic agent may be administered prior to, or following, administration of the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab). In this embodiment, the timing between at least one administration of the chemotherapeutic agent and at least one administration of the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) is preferably approximately 1 month or less, and most preferably approximately 2 weeks or less. Alternatively, the chemotherapeutic agent and the inhibitor are administered concurrently to the patient, in a single formulation or separate formulations. Treatment with the combination of the chemotherapeutic agent (e.g., carboplatin and/or paclitaxel) and the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) may result in a synergistic, or greater than additive, therapeutic benefit to the patient.

[0453] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g. for therapy of ovarian cancer, include: a chemotherapeutic agent such as a platinum compound (e.g., carboplatin), a taxol such as paclitaxel or docetaxel, topotecan, or liposomal doxorubicin.

[0454] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g., for therapy of advanced stage epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer include: chemotherapeutic agents such as carboplatin, paclitaxel, and/or gemcitabine.

[0455] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g., for therapy of platinum-sensitive epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer include: chemotherapeutic agents such as carboplatin and gemcitabine.

[0456] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g., for therapy of platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer include: a chemotherapeutic agent such as paclitaxel, topotecan, or pegylated liposomal doxorubicin.

[0457] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g., for therapy of breast cancer, include: chemotherapeutic agents such as capecitabine, and a taxol such as paclitaxel (e.g., nab-paclitaxel) or docetaxel.

[0458] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g., for

therapy of glioblastoma, include: chemotherapeutic agents such as temozolomide, optionally in combination with radiotherapy.

[0459] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g., for therapy of colorectal cancer, include: chemotherapeutic agents such as a fluoropyrimidine (e.g., 5-FU), paclitaxel, cisplatin, topotecan, irinotecan, fluoropyrimidine-oxaliplatin, fluoropyrimidine-irinotecan, FOLFOX4 (5-FU, lecovorin, oxaliplatin), and IFL (ironotecan, 5-FU, leucovorin).

[0460] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g., for therapy of renal cell carcinoma, include: chemotherapeutic agents such as interferon-alpha2a.

[0461] Particularly desired chemotherapeutic agents for combining with the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) and/or anti-human OX40 agonist antibody, e.g., for therapy of cervical cancer, include: chemotherapeutic agents such as paclitaxel, cisplatin, topotecan, paclitaxel in combination with cisplatin, and paclitaxel in combination with topotecan.

[0462] A chemotherapeutic agent, if administered, is usually administered at dosages known therefore, or optionally lowered due to combined action of the drugs or negative side effects attributable to administration of the chemotherapeutic agent. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Where the chemotherapeutic agent is paclitaxel, preferably, it is administered at a dose between about 130 mg/m^2 to 200 mg/m^2 (for example approximately 175 mg/m^2), for instance, over 3 hours, once every 3 weeks. Where the chemotherapeutic agent is carboplatin, preferably it is administered by calculating the dose of carboplatin using the Calvert formula which is based on a patient's preexisting renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. The use of this dosing formula, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function). The target AUC of 4-6 mg/mL/min using single agent carboplatin appears to provide the most appropriate dose range in previously treated patients.

[0463] Aside from the VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab), anti-human OX40 agonist antibody, and chemotherapeutic agent, other therapeutic regimens may be combined therewith. For example, a second (third, fourth, etc.) chemotherapeutic agent(s) may be administered, wherein the second chemotherapeutic agent is an antimetabolite chemotherapeutic agent, or a chemotherapeutic agent that is not an antimetabolite. For example, the second chemotherapeutic agent may be a taxane (such as paclitaxel or docetaxel), capecitabine, or platinum-based chemotherapeutic agent (such as carboplatin, cisplatin, or oxaliplatin), anthracycline (such as

doxorubicin, including, liposomal doxorubicin), topotecan, pemetrexed, vinca alkaloid (such as vinorelbine), and TLK 286. "Cocktails" of different chemotherapeutic agents may be administered.

[0464] Suitable dosages for any of the above-noted co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the agent and inhibitor. In addition to the above therapeutic regimes, the patient may be subjected to surgical removal of tumors and/or cancer cells, and/or radiation therapy.

[0465] Where the VEGF antagonist is an antibody (e.g., bevacizumab), preferably the administered antibody is a naked antibody. The VEGF antagonist (e.g., an anti-VEGF antibody, such as bevacizumab) administered may be conjugated with a cytotoxic agent. Preferably, the conjugated and/or antigen to which it is bound is/are internalized by the cell, resulting in increased therapeutic efficacy of the conjugate in killing the cancer cell to which it binds. In a preferred embodiment, the cytotoxic agent targets or interferes with nucleic acid in the cancer cell. Examples of such cytotoxic agents include maytansinoids, calicheamicins, ribonucleases, and DNA endonucleases.

VI. Articles of Manufacture or Kits

[0466] In another aspect of the invention, an article of manufacture or kit containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture or kit comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an antibody of the invention (*e.g.,* an anti-human OX40 agonist antibody of the present disclosure or an anti-angiogenic antibody of the present disclosure, such as an anti-VEGF antibody). The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture or kit may comprise (a) a first container with a composition contained therein, wherein the composition comprises an antibody of the invention; and (b) a second container with a composition contained therein, wherein the composition comprises a further cytotoxic or otherwise therapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture or kit may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other

materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0467] In some embodiments, provided herein is a kit comprising a medicament comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration of the medicament in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual. Further provided here is a kit comprising a first medicament comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and a second medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier. In some embodiments, the kit further comprises a package insert comprising instructions for administration of the first medicament and the second medicament for treating or delaying progression of cancer in an individual. Still further provided herein is a kit comprising a medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration of the medicament in combination with a composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.

[0468] It is understood that any of the above articles of manufacture may include an immunoconjugate of the invention in place of or in addition to an anti-OX40 antibody and/or anti-angiogenesis agent.

[0469] The specification is considered to be sufficient to enable one skilled in the art to practice the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

EXAMPLES

[0470] The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

Example 1: Combinatorial anti-VEGF + anti-OX40 treatment exhibited greater efficacy than single agent treatment

[0471] Combining different modalities for cancer treatment may result in beneficial effects on tumor growth. As described below, anti-VEGF treatment resulted in reduced tumor growth when compared to anti-GP120 (control) treated mice. Anti-OX40 treatment exhibited little activity alone. Surprisingly, despite little anti-tumor activity on its own, anti-OX40 treatment in combination with anti-VEGF treatment demonstrated superior tumor growth inhibition when compared to single agent administration or anti-GP120 treatment. Without wishing to be bound to theory, it is hypothesized that the synergistic enhancement of activity observed with combinatorial anti-VEGF + anti-OX40 treatment may be due to increased intratumoral dendritic cell activation induced by anti-VEGF treatment.

[0472] The results described herein suggest that sequencing anti-OX40 treatment with anti-VEGF administration may augment therapy. For instance, without wishing to be bound to theory, administering anti-VEGF first (thereby enhancing dendritic cell activation), followed by anti-OX40 therapy, may be more effective than co-administration of treatments. However, it is possible that the anti-angiogenic effects of anti-VEGF treatment may deplete vasculature, thereby limiting leukocyte infiltration. Therefore, without wishing to be bound to theory, it may be more beneficial to administer anti-OX40 prior to anti-VEGF treatment.

Materials and Methods

CT26 Mouse Tumor Model

[0473] 6 week old female Balb/C mice were inoculated subcutaneously in the right hind flank with 100 µl of HBSS + matrigel (according to manufacturer's specifications) containing $1X10^5$ CT26 tumor cells. Tumors were allowed to grow for ~2 weeks. Mice were grouped into four different experimental arms of 10 mice per arm. Groups were selected to have similar tumor volume averages with a tumor volume range from 100-300 mm^3.

[0474] Mice received 0.1 mg/kg of anti-OX40 or isotype control anti-GP120 (negative control). The anti-OX40 antibody was clone OX-86 mouse-IgG2a (generated by cloning rat anti-mouse OX40 agonist antibody OX-86 onto a murine IgG2a backbone). Antibody was administered intravenously on day 1 followed by 0.1 mg/kg of the same antibody intraperitoneally (i.p.) 3 times a week for a total treatment duration of three weeks. These same treatment groups also received 5 mg/kg of anti-VEGFA (B20) or isotype control anti-GP120 (negative control) i.p. twice a week for three weeks starting on day 1.

[0475] Antibodies were diluted to the desired concentration with sterile PBS and administered in volumes of 100 or 200 µl. Tumor volume was measured by calipers periodically over the duration of the experiment. Mice were euthanized and removed from the experiment when: 1) Mice became moribund, 2) Tumor became ulcerated, or 3) Tumor volume exceeded 2000 mm^3.

Flow cytometry

[0476] CT26 tumors harvested from mice treated with anti-VEGF or anti-GP120 (control) were subjected to enzymatic digestion for retrieval of a suspension of single cells. Subsequently, these cells were stained for flow cytometry using a cocktail of antibodies against CD45, CD11b, CD11c, F4/80 (used for exclusion of macrophages), Gr1 (used for exclusion of neutrophils and granulocytic myeloid cells), MHC-II, OX40L, and PD-L1. Fixable Viability Dye eFluor® 780 was used for exclusion of dead cells from flow cytometric analysis. Myeloid dendritic cells were defined and gated as $CD45^+CD11b^+Gr1^-$ $F4/80^-CD11c^+MHCII^+$. Non-myeloid dendritic cells were defined and gated as $CD45^+CD11b^-Gr1^-$ $F4/80^-CD11c^+MHCII^+$. Expression of the functional markers MHCII, PD-L1, and OX40L was quantified by means of flow cytometric Mean Fluorescence Intensity using the following antibodies: PeCy7-conjugated anti-MHC-II (Biolegend), BV421-conjugated anti-PD-L1 (Biolegend), and PE-conjugated OX-40L.

Results

[0477] To determine the effect of combination treatment with anti-OX40 and anti-VEGF on tumor growth, a mouse CT26 tumor model was used. **FIG. 1** shows that anti-VEGF treatment plus isotype control inhibited tumor growth when compared to anti-GP120 negative control administration. In contrast, anti-OX40 plus isotype control afforded no inhibition of tumor growth when compared to anti-GP120 negative control administration this experiment. This is inconsistent with other experiments utilizing the same antibody and experimental tumor model where tumor growth inhibition was observed. Without wishing to be bound to theory, an explanation for why anti-OX40 treatment did not work in this experiment is that the average starting tumor volume was larger in this group and anti-OX40 efficacy in the CT26 tumor model is dramatically affected by tumor size especially when tumors are larger than 200 mm^3. It is thought that anti-OX40 efficacy in the CT26 tumor model may be negatively affected by tumor size. **FIG. 1** also shows that combinatorial anti-VEGF and anti-OX40 treatment showed superior efficacy over anti-VEGF or anti-OX40 alone.

[0478] **FIG. 2** provides tumor volume measurements for individual mice. These data further demonstrate the superior efficacy of combinatorial anti-VEGF and anti-OX40 treatment over anti-VEGF or anti-OX40 alone. Compared to tumor growth in mice receiving control treatment, mice receiving VEGF treatment experienced 53% tumor growth inhibition. Anti-OX40 treatment alone

resulted in tumor growth 30% above control treatment. In contrast, combination anti-VEGF plus anti-OX40 treatment resulted in a remarkable 94% tumor growth inhibition compared to control treatment. In this treatment group, 9 out of 10 mice exhibited tumor stasis or regression. These results demonstrate the superior and synergistic effects of combination anti-VEGF and anti-OX40 treatment, as compared to each single treatment or control treatment.

[0479] Next, the effect of anti-VEGF treatment on intratumoral dendritic cell activation was tested in the CT26 tumor model. First, in **FIG. 3A**, intratumoral myeloid dendritic cells were assayed. Among $CD45^+CD11b^+Gr1^-F4/80^-CD11c^+MHCII^+$ myeloid dendritic cells, abundance of expression of MHC class II, OX40L, and PD-L1 was determined by quantifying the mean fluorescence intensity of each molecule. Myeloid dendritic cells from anti-VEGF-treated mice were found to have higher MHC II ($p=0.002$) and OX40L ($p=0.003$) expression, as compared to cells from anti-GP120 (control)-treated mice. PD-L1 expression, a negative regulator of T cell responses, was statistically undistinguishable between the two groups ($p=0.81$). These results suggest that treatment with anti-VEGF promoted maturation of tumoral dendritic cells as opposed to control treatment. Improved expression of MHC Class II and OX40L enables dendritic cells to present antigens and prime T cells more effectively.

[0480] **FIG. 3B** shows the effect of anti-VEGF treatment on non-myeloid intratumoral dendritic cell activation. Among $CD45^+CD11b^-Gr1^-F4/80^-CD11c^+MHCII^+$ non-myeloid dendritic cells, expression of MHC class II, as well as PD-L1 and OX40L was determined by quantifying the mean fluorescence intensity of each molecule. Similar to myeloid dendritic cells, non-myeloid dendritic cells also expressed significantly higher levels of MHC II ($p=0.03$) and OX40L ($p=0.002$) when treated with anti-VEGF, as compared to control treatment.

[0481] These results suggest that anti-VEGF treatment can improve the functional phenotype of tumoral dendritic cells, a phenomenon that can result in enhanced anti-tumoral T cell responses. Hence, combining anti-VEGF treatment with immunotherapeutics targeting T cells (e.g., anti-OX40) may synergistically potentiate anti-tumor responses.

CLAIMS

WHAT IS CLAIMED IS:

1. A method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of an anti-angiogenesis agent and an OX40 binding agonist.

2. The method of claim 1, wherein the anti-angiogenesis agent is selected from the group consisting of an anti-VEGFR2 antibody; an anti-VEGFR1 antibody; a VEGF-trap; a bispecific VEGF antibody; a bispecific antibody comprising a combination of two arms selected from the group consisting of an anti-VEGF arm, an anti-VEGFR1 arm, and an anti-VEGFR2 arm; an anti-VEGF-A antibody; an anti-VEGFB antibody; an anti-VEGFC antibody; an anti-VEGFD antibody; a nonpeptide small molecule VEGF antagonist; an anti-PDGFR inhibitor; and a native angiogenesis inhibitor.

3. The method of claim 2, wherein the anti-angiogenesis agent is selected from the group consisting of ramucirumab, tanibirumab, aflibercept, icrucumab, ziv-aflibercept, MP-0250, vanucizumab, sevacizumab, VGX-100, pazopanib, axitinib, vandetanib, stivarga, cabozantinib, lenvatinib, nintedanib, orantinib, telatinib, dovitinig, cediranib, motesanib, sulfatinib, apatinib, foretinib, famitinib, imatinib, and tivozanib.

4. The method of claim 1, wherein the anti-angiogenesis agent is an anti-angiogenesis antibody.

5. The method of claim 4, wherein the anti-angiogenesis antibody is a monoclonal antibody.

6. The method of claim 4 or claim 5, wherein the anti-angiogenesis antibody is a human or humanized antibody.

7. The method of claim 1, wherein the anti-angiogenesis agent is a VEGF antagonist.

8. The method of claim 7, wherein the VEGF antagonist reduces the expression level or biological activity of VEGF by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

9. The method of claim 8, wherein the VEGF is VEGF (8-109), VEGF (1-109), or $VEGF_{165}$.

10. The method of claim 7, wherein the VEGF antagonist increases MHC class II expression on dendritic cells as compared to MHC class II expression on dendritic cells prior to treatment with the VEGF antagonist.

11. The method of claim 7, wherein the VEGF antagonist increases OX40L expression on dendritic cells as compared to OX40L expression on dendritic cells prior to treatment with the VEGF antagonist.

12. The method of claim 10 or claim 11, wherein the dendritic cells are myeloid dendritic cells.

13. The method of claim 10 or claim 11, wherein the dendritic cells are non-myeloid dendritic cells.

14. The method of claim 7, wherein the VEGF antagonist comprises a soluble VEGF receptor or a soluble VEGF receptor fragment that specifically binds to VEGF.

15. The method of claim 7, wherein the VEGF antagonist is a chimeric VEGF receptor protein.

16. The method of claim 7, wherein the VEGF antagonist is administered by gene therapy.

17. The method of claim 7, wherein the VEGF antagonist is an anti-VEGF antibody.

18. The method of claim 17, wherein the anti-VEGF antibody is a human or humanized antibody.

19. The method of claim 17, wherein the anti-VEGF antibody binds to the A4.6.1 epitope.

20. The method of claim 17, wherein the anti-VEGF antibody binds to a functional epitope comprising residues F17, M18, D19, Y21, Y25, Q89, I91, K101, E103, and C104 of human VEGF.

21. The method of claim 17, wherein the anti-VEGF antibody binds to a functional epitope comprising residues F17, Y21, Q22, Y25, D63, I83, and Q89 of human VEGF.

22. The method of claim 17, wherein the anti-VEGF antibody is a G6 series antibody.

23. The method of claim 17, wherein the anti-VEGF antibody is a B20 series antibody.

24. The method of claim 17, wherein the anti-VEGF antibody is a monoclonal anti-VEGF antibody.

25. The method of claim 24, wherein the monoclonal anti-VEGF antibody is bevacizumab.

26. The method of claim 17, wherein the anti-VEGF antibody comprises a light chain variable region comprising the amino acid sequence of DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR. (SEQ ID NO:214).

27. The method of claim 17, wherein the anti-VEGF antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:215).

28. The method of claim 17, wherein the anti-VEGF antibody comprises a light chain variable region comprising the amino acid sequence of DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR. (SEQ ID NO:214) and a heavy chain variable region comprising the amino acid sequence of EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED

TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:215).

29. The method of claim 17, wherein the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of bevacizumab.

30. The method of any one of claims 1-29, wherein the OX40 binding agonist is selected from the group consisting of an OX40 agonist antibody, an OX40L agonist fragment, an OX40 oligomeric receptor, and an OX40 immunoadhesin.

31. The method of any one of claims 1-30, wherein the OX40 binding agonist is a trimeric OX40L-Fc protein.

32. The method of any one of claims 1-30, wherein the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L.

33. The method of any one of claims 1-30, wherein the OX40 binding agonist is an OX40 agonist antibody that binds human OX40.

34. The method of claim 33, wherein the OX40 agonist antibody is a full-length human IgG1 antibody.

35. The method of claim 33, wherein the OX40 agonist antibody depletes cells that express human OX40.

36. The method of claim 35, wherein the cells are CD4+ effector T cells.

37. The method of claim 35, wherein the cells are Treg cells.

38. The method of any one of claims 35-37, wherein the depleting is by ADCC and/or phagocytosis.

39. The method of claim 38, wherein the depleting is by ADCC.

40. The method of claim 33, wherein the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM.

41. The method of claim 40, wherein the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM.

42. The method of claim 40 or claim 41, wherein OX40 agonist antibody binding affinity is determined using radioimmunoassay.

43. The method of claim 33, wherein binding to human OX40 has an EC50 of less than or equal to 0.2 ug/ml.

44. The method of claim 33, wherein binding to human OX40 has an EC50 of less than or equal to 0.3 ug/ml.

45. The method of any one of claims 33-44, wherein the OX40 agonist antibody increases CD4+ effector T cell proliferation and/or increasing cytokine production by the CD4+ effector T cell as compared to proliferation and/or cytokine production prior to treatment with anti-human OX40 agonist antibody.

46. The method of claim 45, wherein the cytokine is gamma interferon.

47. The method of any one of claims 33-46, wherein the OX40 agonist antibody increases memory T cell proliferation and/or increasing cytokine production by the memory cell.

48. The method of claim 47, wherein the cytokine is gamma interferon.

49. The method of any one of claims 33-48, wherein the OX40 agonist antibody inhibits Treg function.

50. The method of claim 49, wherein the OX40 agonist antibody inhibits Treg suppression of effector T cell function.

51. The method of claim 50, wherein effector T cell function is effector T cell proliferation and/or cytokine production.

52. The method of claim 50 or claim 51, wherein the effector T cell is a CD4+ effector T cell.

53. The method of any one of claims 33-52, wherein the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40.

54. The method of claim 53, wherein OX40 signal transduction is detected by monitoring NFkB downstream signaling.

55. The method of any one of claims 33-54, wherein the OX40 agonist antibody is stable after treatment at 40ºC for two weeks.

56. The method of any one of claims 33-55, wherein the OX40 agonist antibody comprises a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells, and wherein the antibody has diminished activity relative to an anti-human OX40 agonist antibody comprising a native sequence IgG1 Fc portion.

57. The method of claim 56, wherein the OX40 agonist antibody comprises a variant Fc portion comprising a DANA mutation.

58. The method of any one of claims 33-57, wherein OX40 agonist antibody cross-linking is required for anti-human OX40 agonist antibody function.

59. The method of any one of claims 33-58, the OX40 agonist antibody comprises (a) a VH domain comprising (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 2, 8 or 9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 3, 10, 11, 12, 13 or 14, and (iii) HVR-

H3 comprising an amino acid sequence selected from SEQ ID NO: 4, 15, or 19; and (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 7, 22, 23, 24, 25, 26, 27, or 28.

60. The method of claim 59, wherein the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:7.

61. The method of claim 59, wherein the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:26.

62. The method of claim 59, wherein the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (f) HVR-L3 comprising an amino acid sequence of SEQ ID NO:27.

63. The method of any one of claims 33-62, wherein the OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 108, 114, 116, 233, or 234.

64. The method of any one of claims 33-63, wherein the OX40 agonist antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 109, 115 or 117.

65. The method of any one of claims 33-64, wherein the OX40 agonist antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:56.

66. The method of claim 65, wherein the OX40 agonist VH sequence having at least 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to human OX40.

67. The method of claim 65 or claim 66, wherein a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:56.

68. The method of any one of claims 65-67, wherein the OX40 agonist VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:2, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:3, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:4.

69. The method of any one of claims 33-68, wherein the OX40 agonist antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:57.

70. The method of claim 69, wherein the OX40 agonist VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-human OX40 agonist antibody comprising that sequence retains the ability to bind to human OX40.

71. The method of claim 69 or 70, wherein a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 57.

72. The method of any one of claims 69-71, wherein the OX40 agonist VL comprises one, two or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:6; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:7.

73. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 56.

74. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 57.

75. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO:56 and a VL sequence of SEQ ID NO: 57.

76. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 94.

77. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 95.

78. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VH

sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO: 95.

79. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 96.

80. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 97.

81. The method of any one of claims 33-72, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO:96 and a VL sequence of SEQ ID NO: 97.

82. The method of claim 33, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

83. The method of any one of claims 1-82, wherein the cancer is lung cancer, glioblastoma, cervical cancer, ovarian cancer, breast cancer, colon cancer, colorectal cancer, fallopian tube cancer, peritoneal cancer, kidney cancer, renal cancer, non-Hodgkins lymphoma, prostate cancer, pancreatic cancer, soft-tissue sarcoma, kaposi's sarcoma, carcinoid carcinoma, head and neck cancer, mesothelioma, multiple myeloma, non-small cell lung cancer, neuroblastoma, melanoma, gastric cancer, or liver cancer.

84. The method of any one of claims 1-82, wherein the cancer is a gynecologic cancer.

85. The method of any one of claims 1-84, wherein the cancer is advanced, refractory, recurrent, chemotherapy-resistant, and/or platinum-resistant.

86. The method of any one of claims 1-85, wherein the individual has cancer or has been diagnosed with cancer.

87. The method of any one of claims 1-86, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

88. The method of any one of claims 1-87, wherein the OX40 binding agonist is administered before the anti-angiogenesis agent, simultaneous with the anti-angiogenesis agent, or after the anti-angiogenesis agent.

89. The method of any one of claims 1-88, wherein the individual is a human.

90. The method of any one of claims 1-89, wherein the anti-angiogenesis agent and/or the OX40 binding agonist are administered intravenously, intramuscularly, subcutaneously, intracerobrospinally, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, intra-articularly, intrasynovially, or intranasally.

91. The method of any one of claims 1-90, further comprising administering a chemotherapeutic agent for treating or delaying progression of cancer.

92. Use of an anti-angiogenesis agent in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and wherein the treatment comprises administration of the medicament in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier.

93. Use of an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein the treatment comprises administration of the medicament in combination with a composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier.

94. A composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the treatment comprises administration of said composition in combination with a second composition, wherein the second composition comprises OX40 binding agonist and an optional pharmaceutically acceptable carrier.

95. A composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the treatment comprises administration of said composition in combination with a second composition, wherein the second composition comprises an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier.

96. A kit comprising a medicament comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration of the medicament in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.

97. A kit comprising a first medicament comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, and a second medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier.

98. The kit of claim 97, wherein the kit further comprises a package insert comprising instructions for administration of the first medicament and the second medicament for treating or delaying progression of cancer in an individual.

99. A kit comprising a medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration of the medicament in combination with a composition comprising an anti-angiogenesis agent and an

optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.

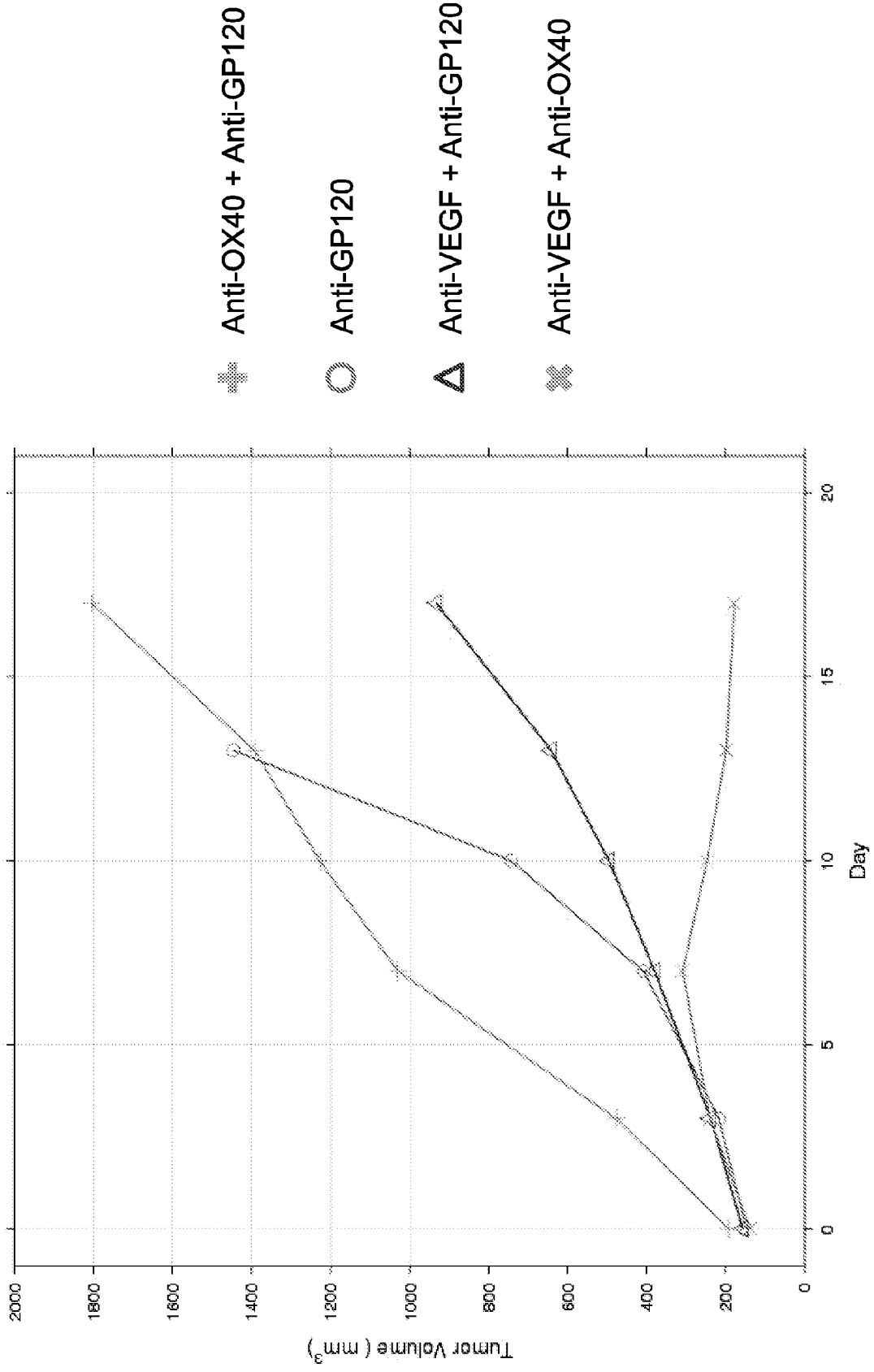

Anti-OX40 + Anti-GP120
Anti-GP120
Anti-VEGF + Anti-GP120
Anti-VEGF + Anti-OX40
Tumor Volume (mm3)
Day
0
200
400
600
800
1000
1200
1400
1600
1800
2000
0
5
10
15
20

FIG. 1

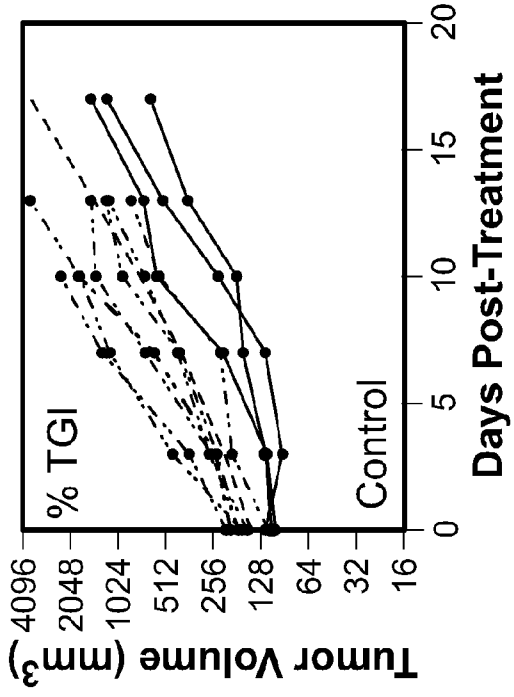


FIG. 2A

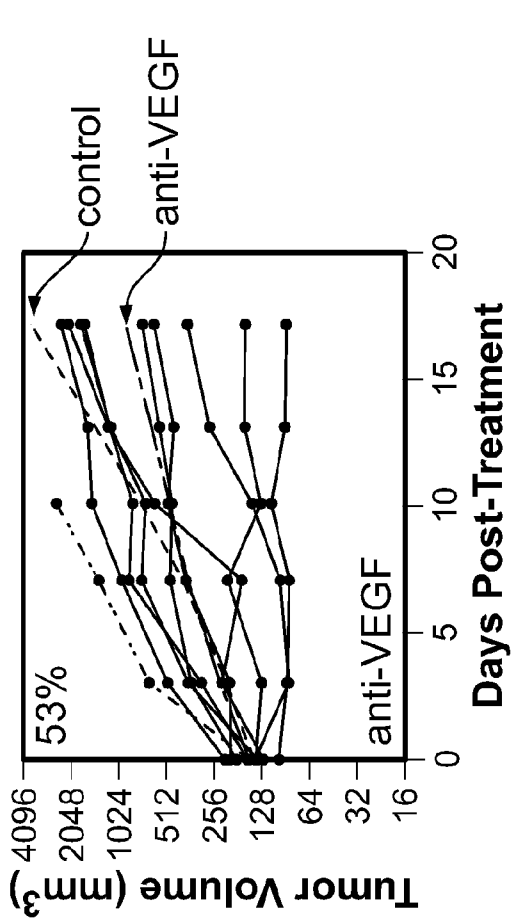


FIG. 2B

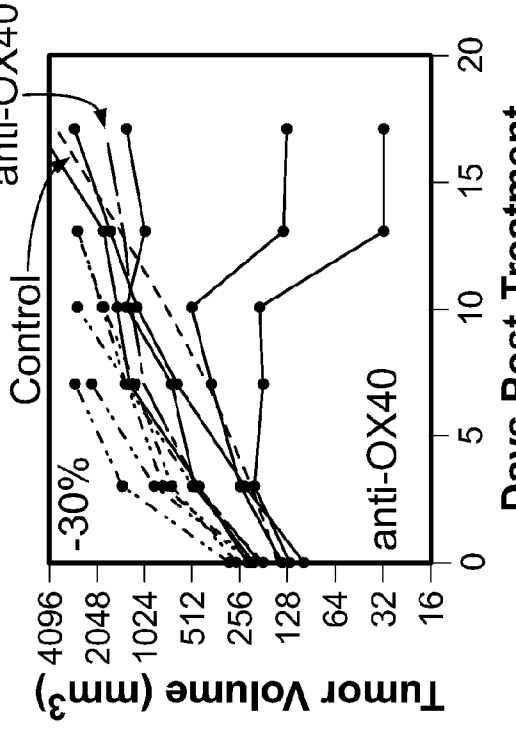


FIG. 2C

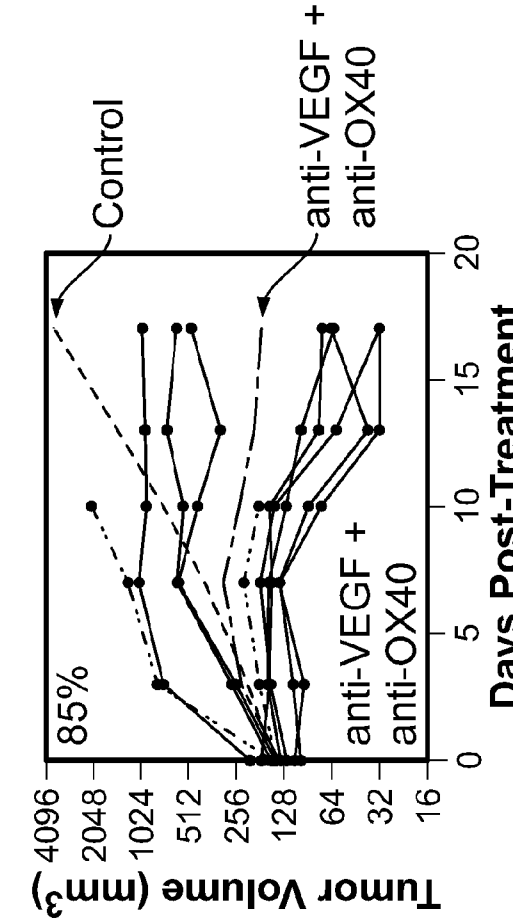
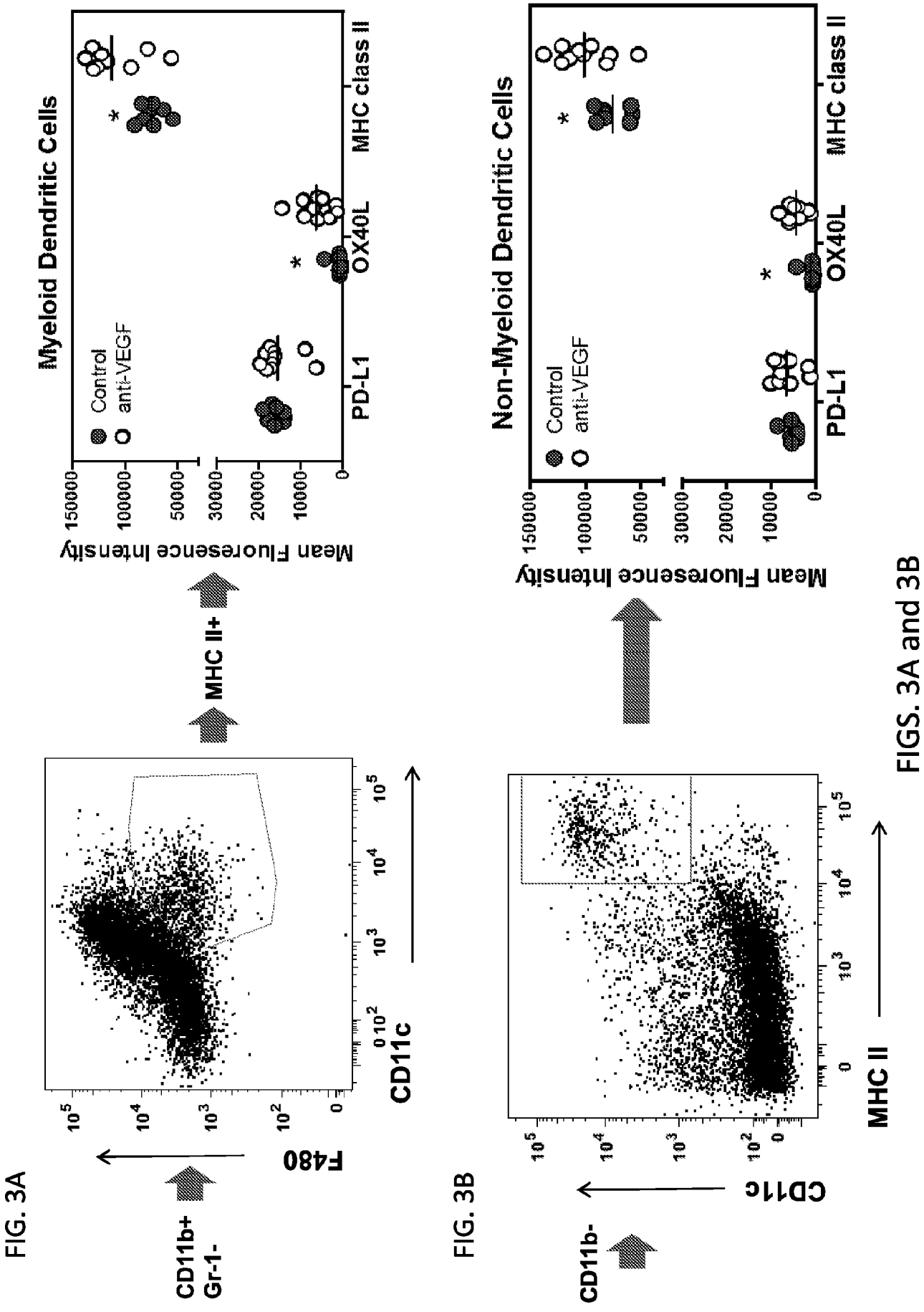


FIG. 2D



FIGS. 3A and 3B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/023434

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. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

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      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/023434

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/22 C07K16/28 A61P35/00 A61K39/395
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/079335 A1 (MEDAREX INC [US]; PFIZER [US]; MIN JING [US]; WU YANLI [US]; FINN RORY) 25 June 2009 (2009-06-25) paragraph [0116] - paragraph [0118]; claims 1-24,30	1-99

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 June 2015	07/07/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Siaterli, Maria

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	D. HIRSCHHORN-CYMERMAN ET AL: "OX40 engagement and chemotherapy combination provides potent antitumor immunity with concomitant regulatory T cell apoptosis", JOURNAL OF EXPERIMENTAL MEDICINE, vol. 188, no. 2, 11 May 2009 (2009-05-11), pages 287-1116, XP055197756, ISSN: 0022-1007, DOI: 10.1084/jem.188.2.287 the whole document	1,30-99
X	WO 2008/051424 A2 (UNIV SOUTHAMPTON [GB]; TESKIN ROBIN L [US]; GLENNIE MARTIN JOHN [GB];) 2 May 2008 (2008-05-02) claims 1,57,100	92-99

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Information on patent family members

International application No
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