SUMMARY

[0012] ~~In one aspect, p~~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.

[0012a] In one 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 is to be administered with an OX40 binding agonist.

[0012b] In another aspect, 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 is to be administered with an anti-angiogenesis agent.

[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~~ In yet another aspect, 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~~ In still yet another aspect, 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~~ In yet a further aspect, 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~~In another aspect, 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

[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~~disclosure. These and other aspects of the invention will become apparent to one of skill in the art. These and other embodiments of the ~~invention~~ disclosure 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).

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 40°C 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.

CLAIMS

WHAT IS CLAIMED IS:

1. 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 is to be administered with an OX40 binding agonist.

2. 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 is to be administered with an anti-angiogenesis agent.

3. The use of claim 1 or 2, 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.

4. The use of claim 3, 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.

5. The use of claim 1 or 2, wherein the anti-angiogenesis agent is an anti-angiogenesis antibody.

6. The use of claim 5, wherein the anti-angiogenesis antibody is a monoclonal antibody.

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

8. The use of claim 1 or 2, wherein the anti-angiogenesis agent is a VEGF antagonist.

9. The use of claim 8, 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%.

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

11. The method of claim 8, 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.

12. The use of claim 8, 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.

13. The use of claim 11 or claim 12, wherein the dendritic cells are myeloid dendritic cells.

14. The use of claim 11 or claim 12, wherein the dendritic cells are non-myeloid dendritic cells.

15. The use of claim 8, wherein the VEGF antagonist comprises a soluble VEGF receptor or a soluble VEGF receptor fragment that specifically binds to VEGF.

16. The use of claim 8, wherein the VEGF antagonist is a chimeric VEGF receptor protein.

17. The use of claim 8, wherein the VEGF antagonist is to be administered by gene therapy.

18. The use of claim 8, wherein the VEGF antagonist is an anti-VEGF antibody.

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

20. The use of claim 18, wherein the anti-VEGF antibody binds to the A4.6.1 epitope.

21. The use of claim 18, wherein the anti-VEGF antibody binds to a functional epitope comprising residues F17, M18, D19, Y21, Y25, Q89, 191, K101, E103, and C104 of human VEGF.

22. The use of claim 18, wherein the anti-VEGF antibody binds to a functional epitope comprising residues F17, Y21, Q22, Y25, D63, 183, and Q89 of human VEGF.

23. The use of claim 18, wherein the anti-VEGF antibody is a G6 series antibody.

24. The use of claim 18, wherein the anti-VEGF antibody is a B20 series antibody.

25. The use of claim 18, wherein the anti-VEGF antibody is a monoclonal anti-VEGF antibody.

26. The use of claim 25, wherein the monoclonal anti-VEGF antibody is bevacizumab.

27. The use of claim 18, 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).

28. The use of claim 18, 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).

29. The use of claim 18, 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).

30. The use of claim 18, wherein the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of bevacizumab.

31. The use of any one of claims 1-30, 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.

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

33. The use of any one of claims 1-31, wherein the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L.

34. The use of any one of claims 1-31, wherein the OX40 binding agonist is an OX40 agonist antibody that binds human OX40.

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

36. The use of claim 34, wherein the OX40 agonist antibody depletes cells that express human OX40.

37. The use of claim 36, wherein the cells are CD4+ effector T cells.

38. The use of claim 36, wherein the cells are Treg cells.

39. The use of any one of claims 36-38, wherein the depleting is by ADCC and/or phagocytosis.

40. The use of claim 39, wherein the depleting is by ADCC.

41. The use of claim 34, wherein the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM.

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

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

44. The use of claim 34, wherein binding to human OX40 has an EC50 of less than or equal to 0.2 ug/ml.

45. The use of claim 34, wherein binding to human OX40 has an EC50 of less than or equal to 0.3 ug/ml.

46. The use of any one of claims 34-45, 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.

47. The use of claim 46, wherein the cytokine is gamma interferon.

48. The use of any one of claims 34-47, wherein the OX40 agonist antibody increases memory T cell proliferation and/or increasing cytokine production by the memory cell.

49. The use of claim 48, wherein the cytokine is gamma interferon.

50. The use of any one of claims 34-49, wherein the OX40 agonist antibody inhibits Treg function.

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

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

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

54. The use of any one of claims 34-53, wherein the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40.

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

56. The use of any one of claims 34-55, wherein the OX40 agonist antibody is stable after treatment at 40°C for two weeks.

57. The use of any one of claims 34-56, 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.

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

59. The use of any one of claims 34-58, wherein OX40 agonist antibody cross-linking is required for anti-human OX40 agonist antibody function.

60. The use of any one of claims 34-59, 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.

61. The use of claim 60, 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.

62. The use of claim 60, 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.

63. The use of claim 60, 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.

64. The use of any one of claims 34-63, 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.

65. The method of any one of claims 34-64, 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.

66. The use of any one of claims 34-65, 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.

67. The use of claim 66, 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.

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

69. The use of any one of claims 66-68, 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.

70. The use of any one of claims 34-69, 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.

71. The use of claim 70, 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.

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

73. The use of any one of claims 70-72, 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.

74. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 56.

75. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 57.

76. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO:56 and a VL sequence of SEQ ID NO: 57.

77. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 94.

78. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 95.

79. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO: 95.

80. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 96.

81. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 97.

82. The use of any one of claims 34-73, wherein the OX40 agonist antibody comprises a VH sequence of SEQ ID NO:96 and a VL sequence of SEQ ID NO: 97.

83. The use of claim 34, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

84. The use of any one of claims 1-83, 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.

85. The use of any one of claims 1-83, wherein the cancer is a gynecologic cancer.

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

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

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

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

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

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

92. The use of any one of claims 1-91, wherein the medicament is to be administered with a chemotherapeutic agent for treating or delaying progression of cancer.

93. 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.

94. 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.

95. 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.

96. 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.

97. 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.

98. 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.

99. The kit of claim 98, 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.

100. 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.