

SUMMARY

[0012] 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, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40.

[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, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40.

[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 medicament is to be administered in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40. 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 medicament is to be administered in combination with a composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40.

[0014] Also 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] Also 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. In yet a further aspect, provided herein 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, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40. 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. Also 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

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, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40.
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, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40.
3. The use of claim 1 or claim 2, wherein the anti-angiogenesis agent is selected from the group consisting of MP-0250, vanucizumab, sevacizumab, and VGX-100.
4. The use of claim 1 or claim 2, wherein the anti-VEGF antibody reduces the expression level or biological activity of VEGF by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.
5. The use of claim 4, wherein the VEGF is VEGF (8-109), VEGF (1-109), or VEGF₁₆₅.
6. The use of claim 1 or claim 2, wherein the anti-VEGF antibody increases MHC class II expression on dendritic cells as compared to MHC class II expression on dendritic cells prior to treatment with the anti-VEGF antibody.
7. The use of claim 1 or claim 2, wherein the anti-VEGF antibody increases OX40L expression on dendritic

cells as compared to OX40L expression on dendritic cells prior to treatment with the anti-VEGF antibody.

8. The use of claim 6 or claim 7, wherein the dendritic cells are myeloid dendritic cells.
9. The use of claim 6 or claim 7, wherein the dendritic cells are non-myeloid dendritic cells.
10. The use of claim 1 or claim 2, wherein the anti-VEGF antibody is a human or humanized antibody.
11. The use of claim 1 or claim 2, 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.
12. The use of claim 1 or claim 2, wherein the anti-VEGF antibody binds to a functional epitope comprising residues F17, Y21, Q22, Y25, D63, 183, and Q89 of human VEGF.
13. The use of claim 1 or claim 2, wherein the anti-VEGF antibody is a G6 series antibody.
14. The use of claim 1 or claim 2, wherein the anti-VEGF antibody is a B20 series antibody.
15. The use of claim 1 or claim 2, wherein the anti-VEGF antibody is a monoclonal anti-VEGF antibody.
16. The use of claim 15, wherein the monoclonal anti-VEGF antibody is bevacizumab.
17. The use of claim 1 or claim 2, wherein the anti-VEGF antibody comprises a light chain variable region comprising the amino acid sequence of DIQMTQSPSS LSASVGDRVITCSASQDIS NYLNWYQQKP GKAPKVLIIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQPEDFATYYCQQ YSTVPWTFGQ GTKVEIKR. (SEQ ID NO:214).
18. The use of claim 1 or claim 2, wherein the anti-VEGF antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTFSLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWFY DVWGQGTLLVTVSS (SEQ ID NO:215).
19. The use of claim 1 or claim 2, wherein the anti-VEGF antibody comprises a light chain variable region comprising the amino acid sequence of DIQMTQSPSS LSASVGDRVITCSASQDIS NYLNWYQQKP GKAPKVLIIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQPEDFATYYCQQ 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).

20. The use of claim 1 or claim 2, wherein the anti-VEGF antibody comprises one, two, three, four, five, or six hypervariable region (HVR) sequences of bevacizumab.
21. The use of any one of claims 1-20, wherein the anti-OX40 agonist antibody is a full-length human IgG1 antibody.
22. The use of any one of claims 1-21, wherein the cells are Treg cells.
23. The use of any one of claims 1-22, wherein the depleting is by ADCC and/or phagocytosis.
24. The use of claim 23, wherein the depleting is by ADCC.
25. The use of any one of claims 1-24, wherein the anti-OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM.
26. The use of claim 25, wherein the anti-OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM.
27. The use of claim 25 or claim 26, wherein anti-OX40 agonist antibody binding affinity is determined using radioimmunoassay.
28. The use of any one of claims 1-24, wherein binding to human OX40 has an EC50 of less than or equal to 0.2 ug/ml.
29. The use of any one of claims 1-24, wherein binding to human OX40 has an EC50 of less than or equal to 0.3 ug/ml.

30. The use of any one of claims 1-29, wherein the anti-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-OX40 agonist antibody.
31. The use of claim 30, wherein the cytokine is gamma interferon.
32. The use of any one of claims 1-31, wherein the anti-OX40 agonist antibody increases memory T cell proliferation and/or increasing cytokine production by the memory cell.
33. The use of claim 32, wherein the cytokine is gamma interferon.
34. The use of any one of claims 1-33, wherein the anti-OX40 agonist antibody inhibits Treg function.
35. The use of claim 34, wherein the anti-OX40 agonist antibody inhibits Treg suppression of effector T cell function.
36. The use of claim 35, wherein effector T cell function is effector T cell proliferation and/or cytokine production.
37. The use of claim 35 or claim 36, wherein the effector T cell is a CD4+ effector T cell.
38. The use of any one of claims 1-37, wherein the anti-OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40.
39. The use of claim 38, wherein OX40 signal transduction is detected by monitoring NFkB downstream signaling.
40. The use of any one of claims 1-39, wherein the anti-OX40 agonist antibody is stable after treatment at 40°C for two weeks.
41. The use of any one of claims 1-40, wherein anti-OX40 agonist antibody cross-linking is required for anti-OX40 agonist antibody function.
42. The use of any one of claims 1-41, wherein the anti-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.

43. The use of claim 42, wherein the anti-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.

44. The use of claim 42, wherein the anti-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.

45. The use of claim 42, wherein the anti-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.

46. The use of any one of claims 42-45, wherein the anti-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.

47. The use of any one of claims 42-46, wherein the anti-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.

48. The use of any one of claims 42-47, wherein the anti-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.

49. The use of claim 48, wherein the VH sequence of the anti-OX40 agonist antibody 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.

50. The use of claim 48 or claim 49, wherein a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO:56.
51. The use of any one of claims 48-50, wherein the VH domain of the anti-OX40 agonist antibody 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.
52. The use of any one of claims 42-51, wherein the anti-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.
53. The use of claim 52, wherein the VL sequence of the anti-OX40 agonist antibody 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.
54. The use of claim 52 or 53, wherein a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 57.
55. The use of any one of claims 52-54, wherein the VL domain of the anti-OX40 agonist antibody 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.
56. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 56.
57. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 57.
58. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VH sequence of SEQ ID NO:56 and a VL sequence of SEQ ID NO: 57.
59. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 94.
60. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 95.
61. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VH sequence of SEQ ID NO:94 and a VL sequence of SEQ ID NO: 95.
62. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VH sequence of SEQ ID NO: 96.

63. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VL sequence of SEQ ID NO: 97.
64. The use of any one of claims 42-55, wherein the anti-OX40 agonist antibody comprises a VH sequence of SEQ ID NO:96 and a VL sequence of SEQ ID NO: 97.
65. The use of any one of claims 1-64, 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.
66. The use of any one of claims 1-64, wherein the cancer is a gynecologic cancer.
67. The use of any one of claims 1-66, wherein the cancer is advanced, refractory, recurrent, chemotherapy-resistant, and/or platinum-resistant.
68. The use of any one of claims 1-67, wherein the individual has cancer or has been diagnosed with cancer.
69. The use of any one of claims 1-68, wherein the treatment results in a sustained response in the individual after cessation of the treatment.
70. The use of any one of claims 1-69, 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.
71. The use of any one of claims 1-70, wherein the individual is a human.
72. The use of any one of claims 1-71, wherein the anti-angiogenesis agent and/or the OX40 binding agonist are to be administered intravenously, intramuscularly, subcutaneously, intracerebrospinally, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, intra-articularly, intrasynovially, or intranasally.
73. The use of any one of claims 1-72, wherein the medicament is to be administered with a chemotherapeutic agent for treating or delaying progression of cancer.
74. 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 medicament is to be administered in combination with a composition comprising an OX40 binding

agonist and an optional pharmaceutically acceptable carrier, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40.

75. 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 medicament is to be administered in combination with a composition comprising an anti-angiogenesis agent and an optional pharmaceutically acceptable carrier, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40.

76. 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, wherein the anti-angiogenesis agent is an anti-VEGF antibody, and wherein the OX40 binding agonist is an anti-OX40 agonist antibody that binds human OX40 and depletes cells that express human OX40.