[0009] Combining OX40 signaling with other signaling pathways that are deregulated in tumor cells 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.

[0010] All references cited herein, including patent applications, patent publications, and UniProtKB/Swiss-Prot Accession numbers are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY ~~OF THE INVENTION~~

[0011] In one aspect, provided herein is use of a human PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the human PD-1 axis binding antagonist is to be administered with an OX40 binding agonist. Also provided is a method for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a human PD-1 axis binding antagonist and an OX40 binding agonist (e.g., an anti- human OX40 agonist antibody).

[0012] In another aspect, provided herein is use of a PD-1 axis binding antagonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the PD-1 axis binding antagonist is to be administered with an OX40 binding agonist. Also provided is a method of enhancing immune function in an individual having cancer comprising administering an effective amount of a PD-1 axis binding antagonist and an OX40 binding agonist (e.g., an anti- human OX40 agonist antibody).

[0013] ~~In further aspects,~~Further provided herein are methods of treating infection (e.g., with a bacteria or virus or other pathogen). In some embodiments, the infection is with virus and/or bacteria. In some embodiments, the infection is with a pathogen. In some embodiments, the infection is an acute infection. In some embodiments, the infection is a chronic infection.

[0014] ~~In another aspect, p~~Provided herein is use of a human PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual (or, in some embodiments, treating infection), wherein the medicament comprises the human PD-1 axis binding antagonist 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 (e.g., an anti- human OX40 agonist antibody) and an optional pharmaceutically acceptable carrier. In one aspect, provided here in is use of a human PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the human PD-1 axis binding antagonist 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.

[0015] ~~In another aspect, p~~Provided herein is use of an OX40 binding agonist (e.g., an anti- human OX40 agonist antibody) in the manufacture of a medicament for treating or delaying progression of cancer in an individual (or, in some embodiments, treating infection), 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 a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier. In one aspect, provided herein is 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 a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier.

[0016] ~~In another aspect, p~~Provided herein is a composition comprising a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer (or, in some embodiments, treating infection) in an individual, wherein the

treatment comprises administration of said composition in combination with a second composition, wherein the second composition comprises an OX40 binding agonist (e.g., an anti- human OX40 agonist antibody) and an optional pharmaceutically acceptable carrier. In one aspect, provided herein is a composition comprising a human PD-1 axis binding antagonist 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.

[0017] ~~In another aspect, p~~Provided herein is a composition comprising an OX40 binding agonist (e.g., an anti- human OX40 agonist antibody) and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual (or in some embodiments, treating infection), wherein the treatment comprises administration of said composition in combination with a second composition, wherein the second composition comprises a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier. In one 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 a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier.

[0018] ~~In another aspect, p~~Provided herein is a kit comprising a medicament comprising a PD-1 axis binding antagonist 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 (e.g., an anti- human OX40 agonist antibody) and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer (or, in some embodiments, treating infection) in an individual. In one aspect, provided herein is a kit comprising a medicament comprising a PD-1 axis binding antagonist 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.

[0019] ~~In another aspect, p~~Provided herein is a kit comprising a first medicament comprising a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and a second medicament comprising an OX40 binding agonist (e.g., an anti- human OX40 agonist antibody) 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 (or in some embodiments, treating infection) in an

individual. In one aspect, provided herein is a kit comprising a first medicament comprising a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and a second medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier.

[0020] ~~In another aspect, p~~Provided herein is a kit comprising a medicament comprising an OX40 binding agonist (e.g., an anti- human OX40 agonist antibody) and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration of the medicament in combination with a composition comprising a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer (or, in some embodiments, treating infection) in an individual. In one 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 in combination with a composition comprising a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.

[0021] In some embodiments, the cancer is breast cancer, lung cancer, ovarian cancer, gastric cancer, bladder cancer, pancreatic cancer, endometrial cancer, colon cancer, kidney cancer, esophageal cancer, prostate cancer, colorectal cancer, glioblastoma, neuroblastoma, or hepatocellular carcinoma.

[0022] In some embodiments, the individual has cancer or has been diagnosed with cancer.

[0023] In some embodiments, cancer cells (in a sample of the cancer from the individual) do not express PD-L1. In some embodiments, the PD-L1 biomarker is absent from the sample when it comprises 0% of the sample. In some embodiments, the PD-L1 biomarker expression is determined by protein expression (e.g., by immunohistochemistry (IHC) method).

proliferating CD8+ T cells in the sample as compared to a reference (e.g., a level prior to combination treatment) indicates phamacodynamic activity to the combination treatment. In some embodiments, provided herein are methods for monitoring pharmacodynamic activity of an OX40 agonist treatment and a PD-1 axis binding antagonist combination treatment, comprising measuring the level of activated CD8+ T cells (e.g., percentage of CXCR3 +/total CD8+ T cells) in a sample (e.g., a peripheral blood sample) from an individual, wherein an increased level of activated CD8+ T cells in the sample as compared to a reference (e.g., a level prior to combination treatment) indicates pharmacodynamic activity to the combination treatment.

[0035] Provided herein are methods for monitoring responsiveness of a subject to an OX40 agonist treatment by measuring the expression level of one or more marker genes, protein(s) (e.g., a cytokine, e.g., gamma interferon) and/or cellular composition (e.g., percentage of Treg and/or absolute number of Treg; e.g., number of CD8+ effector T cells in peripheral blood samples) in a sample (e.g., peripheral blood) comprising leukocytes obtained from the subject, where the subject has been treated with a PD-1 axis binding antagonist and an OX40 binding agonist (e.g., anti-human OX40 agonist antibody), and where the one or more marker genes are selected from a T cell marker gene, or a memory T cell marker gene (e.g., a marker of T effector memory cells); and classifying the subject as responsive or non-responsive to the treatment based on the expression level of the one or more marker genes, protein(s) and/or cellular composition in the sample obtained from the subject, as compared with a reference, where an increased expression level of the one or more marker genes as compared with the reference indicates responsiveness or lack of reponsiveness to the OX40 agonist treatment. Expression level of a marker gene, protein and/or cellular composition may be measured by one or more methods as described herein. In some embodiments, provided herein are methods for monitoring responsiveness of an OX40 agonist treatment and a PD-1 axis binding antagonist combination treatment, comprising measuring the level of proliferating CD8+ T cells (e.g., percentage of Ki67+/total CD8+ T cells) in a sample (e.g., a peripheral blood sample) from an individual, wherein an increased level of proliferating CD8+ T cells in the sample as compared to a reference (e.g., a level prior to combination treatment) indicates responsiveness to the combination treatment. In some embodiments, provided herein are methods for monitoring responsiveness of an OX40 agonist treatment and a PD-1 axis binding antagonist combination treatment, comprising measuring the level of activated CD8+ T cells (e.g., percentage of CXCR3 +/total CD8+ T cells) in a sample (e.g., a peripheral blood sample) from an individual, wherein an increased level of activated CD8+ T cells in the sample as compared to a reference (e.g., a level prior to combination treatment) indicates responsiveness to the combination treatment.

[0036] 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 SEVERAL VIEWS OF THE DRAWINGS

[0037] FIG. 1: Tumor infiltrating CD8+T cells express high levels of PD-1 inhibitory receptors in the CT26 colorectal syngeneic tumor model (control treated mice). Approximately half of PD-1 expressing CD8+ TILs also express OX40. Representative flow cytometry dot plots from one of 5 mice, day 2 after start of treatment with control antibody.

[0038] FIGS. 2A and B: (FIG. 2A) Treatment with anti-OX40 agonist antibody alone and anti-OX40 agonist antibody in combination with anti-PDL1 antagonist antibody significantly reduced proportion of intratumoral Foxp3+ Tregulatory cells (relative to total number of CD45+ cells). (FIG. 2B) Treatment with anti-OX40 agonist antibody alone and anti-OX40 agonist antibody in combination with anti-PDL1 antagonist antibody significantly reduced absolute number of intratumoral Foxp3+ T regulatory cells in the CT26 colorectal tumor model. For both (FIG. 2A) and (FIG. 2B): data are from day 9 after start of treatment, each symbol represents an individual mouse. Mice were dosed with control antibody or anti-PDL1 antibody at 10mg/kg IV for first dose on day 1, followed by 5mg/kg IP BIW (twice a week). Anti-OX40 agonist antibody was dosed at 0.1mg/kg IV for the first dose on day 1, followed by 0.1mg/kg IP TIW (three times a week).

[0039] FIGS. 3A and B: Treatment with anti-OX40 agonist antibody augmented PDL1 expression on (FIG. 3A) intratumoral myeloid (CD11b+ Gr-1low/intermediate) cells and on (FIG. 3B) tumor cells in the CT26 colorectal syngeneic tumor model. Data are from day 9 after start of treatment. Each dot/square represents one individual mouse. PDL1 expression measured by geometric mean fluorescence intensity (geo MFI) by flow cytometry. $**p<0.01$, $*p<0.05$, as calculated by unpaired t-test. Dosing in this experiment was 10mg/kg IV first dose on day 1, followed by 5mg/kg IP BIW for control antibody. Anti-OX40 agonist antibody was dosed at 0.1mg/kg IV for first dose on day 1, followed by 0.1mg/kg IP TIW.

[0040] FIGS. 4A, 4B: Treatment with anti-OX40 agonist antibody and anti-PDL1 antagonist antibody demonstrated synergistic combination efficacy in the MC38 colorectal cancer syngeneic tumor model in C57BL/6 mice. (FIG. 4A) Average tumor volume (mm3) measurements over time (days) by treatment group, n=10/group. (FIG. 4B) Individual tumor volume measurements over time by treatment group. Black lines indicate average of the group. Blue dashed line indicates average of control group. Gray lines are individual animals. Red lines indicate individual animals dropped from study due to ulcerated tumor or excessive tumor size. Control antibody, anti-PDL1 antibody, or anti-OX40 agonist antibody were dosed at 10mg/kg IV for first dose on day 1, followed by 10mg/kg IP TIW for 3 weeks.

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 a human PD-1 axis binding antagonist and an OX40 binding agonist.

2. The method of claim 1, wherein the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PDL1 binding antagonist and a PDL2 binding antagonist.

3. The method of claim 2, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

4. The method of claim 3, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

5. The method of claim 3, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL1.

6. The method of claim 3, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL2.

7. The method of claim 3, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PDL1 and PDL2.

8. The method of any one of claims 3-7, wherein the PD-1 binding antagonist is an antibody.

9. The method of claim 3, wherein the PD-1 binding antagonist is nivolumab.

10. The method of claim 3, wherein the PD-1 binding antagonist is pembrolizumab.

11. The method of claim 3, wherein the PD-1 binding antagonist is CT-011.

12. The method of claim 3, wherein the PD-1 binding antagonist is AMP-224.

13. The method of claim 2, wherein the PD-1 axis binding antagonist is a PDL1 binding antagonist.

14. The method of claim 13, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to PD-1.

15. The method of claim 13, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to B7-1.

16. The method of claim 13, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to both PD-1 and B7-1.

17. The method of any one of claims 13-16, wherein the PDL1 binding antagonist is an anti-PDL1 antibody.

18. The method of claim 17, wherein the anti-PDL1 antibody is a monoclonal antibody.

19. The method of claim 17, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

20. The method of claim 17, wherein the anti-PDL1 antibody is a humanized antibody or a human antibody.

21. The method of claim 13, wherein the PDL1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

22. The method of claim 17, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO:1), HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO:2), and HVR-H3 sequence of RHWPGGFDY (SEQ ID NO:3); and a light chain comprising HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO:4), HVR-L2 sequence of SASFLYS (SEQ ID NO:5), and HVR-L3 sequence of QQYLYHPAT (SEQ ID NO:6).

23. The method of claim 17, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS (SEQ ID NO:7) or EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSASTK (SEQ ID NO:8) and a light chain variable region comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:9).

24. The method of claim 2, wherein the PD-1 axis binding antagonist is a PDL2 binding antagonist.

25. The method of claim 24, wherein the PDL2 binding antagonist is an antibody.

26. The method of claim 24, wherein the PDL2 binding antagonist is an immunoadhesin.

27. The method of any one of claims 8, 17-23, and 25, wherein the antibody is a human IgG1 having Asn to Ala substitution at position 297 according to EU numbering.

28. The method of any one of claims 1-27, 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.

29. The method of any one of claims 1-28, wherein the OX40 binding agonist is an OX40 agonist antibody that binds human OX40.

30. The method of claim 29, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

31. The method of claim 29, wherein the OX40 agonist antibody is a full-length human IgG1 antibody.

32. The method of any one of claims 1-28, wherein the OX40 binding agonist is a trimeric OX40L-Fc protein.

33. The method of any one of claims 1-28, wherein the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L.

34. The method of any one of claims 1-33, wherein the cancer is breast cancer, lung cancer, ovarian cancer, gastric cancer, bladder cancer, pancreatic cancer, endometrial cancer, colon cancer, kidney cancer, esophageal cancer, prostate cancer, colorectal cancer, glioblastoma, neuroblastoma, or hepatocellular carcinoma.

35. The method of any one of claims 1-34, wherein the individual has cancer or has been diagnosed with cancer.

36. The method of any one of claims 1-35, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

37. The method of any one of claims 1-36, wherein the OX40 binding agonist is administered before the PD-1 axis binding antagonist, simultaneous with the PD-1 axis binding antagonist, or after the PD-1 axis binding antagonist.

38. The method of any one of claims 1-37, wherein the individual is a human.

39. A method of enhancing immune function in an individual having cancer comprising administering an effective amount of a PD-1 axis binding antagonist and an OX40 binding agonist.

40. The method of claim 39, wherein CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the administration of the PD-1 axis binding antagonist and the OX40 binding agonist.

41. The method of claim 39, wherein the number of CD8 T cells is elevated relative to prior to administration of the combination.

42. The method of claim 41, wherein the CD8 T cell is an antigen-specific CD8 T cell.

43. The method of claim 39, wherein Treg function is suppressed relative to prior to the administration of the combination.

44. The method of claim 39, wherein T cell exhaustion is decreased relative to prior to the administration of the combination.

45. The method of any one of claims 39-44, wherein the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PDL1 binding antagonist and a PDL2 binding antagonist.

46. The method of claim 45, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

47. The method of claim 46, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

48. The method of claim 46, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL1.

49. The method of claim 46, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL2.

50. The method of claim 46, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PDL1 and PDL2.

51. The method of any one of claims 46-50, wherein the PD-1 binding antagonist is an antibody.

52. The method of claim 46, wherein the PD-1 binding antagonist is nivolumab.

53. The method of claim 46, wherein the PD-1 binding antagonist is pembrolizumab.

54. The method of claim 46, wherein the PD-1 binding antagonist is CT-011.

55. The method of claim 46, wherein the PD-1 binding antagonist is AMP-224.

56. The method of claim 45, wherein the PD-1 axis binding antagonist is a PDL1 binding antagonist.

57. The method of claim 56, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to PD-1.

58. The method of claim 56, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to B7-1.

59. The method of claim 56, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to both PD-1 and B7-1.

60. The method of any one of claims 56-59, wherein the PDL1 binding antagonist is an anti-PDL1 antibody.

61. The method of claim 60, wherein the anti-PDL1 antibody is a monoclonal antibody.

62. The method of claim 60, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

63. The method of claim 60, wherein the anti-PDL1 antibody is a humanized antibody or a human antibody.

64. The method of claim 56, wherein the PDL1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

65. The method of claim 60, wherein the anti-PDL1 antibody comprises a heavy chain comprising HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO:1), HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO:2), and HVR-H3 sequence of RHWPGGFDY (SEQ ID NO:3); and a light chain comprising HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO:4), HVR-L2 sequence of SASFLYS (SEQ ID NO:5), and HVR-L3 sequence of QQYLYHPAT (SEQ ID NO:6).

66. The method of claim 60, wherein the anti-PDL1 antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS (SEQ ID NO:7) or EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSASTK (SEQ ID NO:8) and a light chain variable region comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIY SASFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:9).

67. The method of claim any one of claims 51, 60-63, 65 and 66, wherein the antibody is a human IgG1 having Asn to Ala substitution at position 297 according to EU numbering.

68. The method of claim 45, wherein the PD-1 axis binding antagonist is a PDL2 binding antagonist.

69. The method of claim 68, wherein the PDL2 binding antagonist is an antibody.

70. The method of claim 68, wherein the PDL2 binding antagonist is an immunoadhesin.

71. The method of any one of claims 39-70, 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.

72. The method of claim 71, wherein the OX40 binding agonist is an OX40 agonist antibody that binds human OX40.

73. The method of claim 72, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

74. The method of claim 72, wherein the OX40 agonist antibody is a full-length IgG1 antibody.

75. The method of any one of claims 39-70, wherein the OX40 binding agonist is a trimeric OX40L-Fc protein.

76. The method of any one of claims 39-70, wherein the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L.

77. The method of any one of claims 39-76, wherein the cancer is breast cancer, lung cancer, ovarian cancer, gastric cancer, bladder cancer, pancreatic cancer, endometrial cancer, colon cancer, kidney cancer, esophageal cancer, prostate cancer, colorectal cancer, glioblastoma, neuroblastoma, or hepatocellular carcinoma.

78. The method of any one of claims 39-77, wherein the individual has been diagnosed with cancer.

79. The method of any one of claims 39-78, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

80. The method of any one of claims 39-79, wherein the OX40 binding agonist is administered before the PD-1 axis binding antagonist, simultaneous with the PD-1 axis binding antagonist, or after the PD-1 axis binding antagonist.

81. The method of any one of claims 39-80, wherein the individual is a human.

82. The method of any one of claims 1-81, wherein the PD-1 axis binding antagonist and/or the OX40 binding agonist are administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

83. The method of any one of claims 1-82, further comprising administering a chemotherapeutic agent for treating or delaying progression of cancer.

84. Use of a human PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the human PD-1 axis binding antagonist 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.

85. 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 a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier.

86. A composition comprising a human PD-1 axis binding antagonist 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.

87. 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 a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier.

88. A kit comprising a medicament comprising a PD-1 axis binding antagonist 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.

89. A kit comprising a first medicament comprising a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and a second medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier.

90. The kit of claim 89, 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.

91. 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 a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a human PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the human PD-1 axis binding antagonist is to be administered with an OX40 binding agonist.

2. The use of claim 1, wherein the PD-1 axis binding antagonist is selected from the group consisting of a PDL1 binding antagonist, a PD-1 binding antagonist and a PDL2 binding antagonist.

3. The use of claim 2, wherein the PD-1 axis binding antagonist is a PDL1 binding antagonist.

4. The use of claim 3, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to PD-1.

5. The use of claim 3, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to B7-1.

6. The use of claim 3, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to both PD-1 and B7-1.

7. The use of any one of claims 3-6, wherein the PDL1 binding antagonist is an anti-PDL1 antibody.

8. The use of claim 7, wherein the anti-PDL1 antibody is a monoclonal antibody.

9. The use of claim 7, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

10. The use of claim 7, wherein the anti-PDL1 antibody is a humanized antibody or a human antibody.

11. The use of claim 3, wherein the PDL1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

12. The use of claim 7, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO:1), HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO:2), and HVR-H3 sequence of RHWPGGFDY (SEQ ID NO:3); and a light chain comprising HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO:4), HVR-L2 sequence of SASFLYS (SEQ ID NO:5), and HVR-L3 sequence of QQYLYHPAT (SEQ ID NO:6).

13. The use of claim7, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA

DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS (SEQ ID NO:7) or EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWI SPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG TLVTVSSASTK (SEQ ID NO:8) and a light chain variable region comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIY SASF LYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:9).

14. The use of claim 2, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

15. The use of claim 14, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

16. The use of claim 14, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL1.

17. The use of claim 14, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL2.

18. The use of claim 14, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PDL1 and PDL2.

19. The use of any one of claims 14-18, wherein the PD-1 binding antagonist is an antibody.

20. The use of claim 14, wherein the PD-1 binding antagonist is nivolumab.

21. The use of claim 14, wherein the PD-1 binding antagonist is pembrolizumab.

22. The use of claim 14, wherein the PD-1 binding antagonist is CT-011.

23. The use of claim 14, wherein the PD-1 binding antagonist is AMP-224.

24. The use of claim 2, wherein the PD-1 axis binding antagonist is a PDL2 binding antagonist.

25. The use of claim 24, wherein the PDL2 binding antagonist is an antibody.

26. The use of claim 24, wherein the PDL2 binding antagonist is an immunoadhesin.

27. The use of any one of claims 7-13, 19, and 25, wherein the antibody is a human IgG1 having Asn to Ala substitution at position 297 according to EU numbering.

28. The use of any one of claims 1-27, 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.

29. The use of any one of claims 1-28, wherein the OX40 binding agonist is an OX40 agonist antibody that binds human OX40.

30. The use of claim 29, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

31. The use of claim 29, wherein the OX40 agonist antibody is a full-length human IgG1 antibody.

32. The use of any one of claims 1-28, wherein the OX40 binding agonist is a trimeric OX40L-Fc protein.

33. The use of any one of claims 1-28, 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 1-33, wherein the cancer is breast cancer, lung cancer, ovarian cancer, gastric cancer, bladder cancer, pancreatic cancer, endometrial cancer, colon cancer, kidney cancer, esophageal cancer, prostate cancer, colorectal cancer, glioblastoma, neuroblastoma, or hepatocellular carcinoma.

35. The use of any one of claims 1-34, wherein the individual has cancer or has been diagnosed with cancer.

36. The use of any one of claims 1-35, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

37. The use of any one of claims 1-36, wherein the OX40 binding agonist is to be administered before the PD-1 axis binding antagonist, simultaneous with the PD-1 axis binding antagonist, or after the PD-1 axis binding antagonist.

38. The use of any one of claims 1-37, wherein the individual is a human.

39. Use of a PD-1 axis binding antagonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the PD-1 axis binding antagonist is to be administered with an OX40 binding agonist.

40. The use of claim 39, wherein CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the administration of the PD-1 axis binding antagonist and the OX40 binding agonist.

41. The use of claim 39, wherein the number of CD8 T cells is elevated relative to prior to administration of the combination.

42. The use of claim 41, wherein the CD8 T cell is an antigen-specific CD8 T cell.

43. The use of claim 39, wherein Treg function is suppressed relative to prior to the administration of the combination.

44. The use of claim 39, wherein T cell exhaustion is decreased relative to prior to the

administration of the combination.

45. The use of any one of claims 39-44, wherein the PD-1 axis binding antagonist is selected from the group consisting of a PDL1 binding antagonist, a PD-1 binding antagonist and a PDL2 binding antagonist.

46. The use of claim 45, wherein the PD-1 axis binding antagonist is a PDL1 binding antagonist.

47. The use of claim 46, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to PD-1.

48. The use of claim 46, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to B7-1.

49. The use of claim 46, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to both PD-1 and B7-1.

50. The use of any one of claims 46-49, wherein the PDL1 binding antagonist is an anti-PDL1 antibody.

51. The use of claim 50, wherein the anti-PDL1 antibody is a monoclonal antibody.

52. The use of claim 50, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

53. The use of claim 50, wherein the anti-PDL1 antibody is a humanized antibody or a human antibody.

54. The use of claim 46, wherein the PDL1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

55. The use of claim 50, wherein the anti-PDL1 antibody comprises a heavy chain comprising HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO:1), HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO:2), and HVR-H3 sequence of RHWPGGFDY (SEQ ID NO:3); and a light chain comprising HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO:4), HVR-L2 sequence of SASFLYS (SEQ ID NO:5), and HVR-L3 sequence of QQYLYHPAT (SEQ ID NO:6).

56. The use of claim 50, wherein the anti-PDL1 antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS (SEQ ID NO:7) or EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSASTK (SEQ ID NO:8) and a light chain variable region comprising the amino acid

sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIY SASF LYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:9).

57. The use of claim 45, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

58. The use of claim 57, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

59. The use of claim 57, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL1.

60. The use of claim 57, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL2.

61. The use of claim 57, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PDL1 and PDL2.

62. The use of any one of claims 57-61, wherein the PD-1 binding antagonist is an antibody.

63. The use of claim 57, wherein the PD-1 binding antagonist is nivolumab.

64. The use of claim 57, wherein the PD-1 binding antagonist is pembrolizumab.

65. The use of claim 57, wherein the PD-1 binding antagonist is CT-011.

66. The use of claim 57, wherein the PD-1 binding antagonist is AMP-224.

67. The use of claim any one of claims 50-53, 55,56 and 62, wherein the antibody is a human IgG1 having Asn to Ala substitution at position 297 according to EU numbering.

68. The use of claim 45, wherein the PD-1 axis binding antagonist is a PDL2 binding antagonist.

69. The use of claim 68, wherein the PDL2 binding antagonist is an antibody.

70. The use of claim 68, wherein the PDL2 binding antagonist is an immunoadhesin.

71. The use of any one of claims 39-70, 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.

72. The use of claim 71, wherein the OX40 binding agonist is an OX40 agonist antibody that binds human OX40.

73. The use of claim 72, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

74. The use of claim 72, wherein the OX40 agonist antibody is a full-length IgG1 antibody.

75. The use of any one of claims 39-70, wherein the OX40 binding agonist is a trimeric OX40L-

Fc protein.

76. The use of any one of claims 39-70, wherein the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L.

77. The use of any one of claims 39-76, wherein the cancer is breast cancer, lung cancer, ovarian cancer, gastric cancer, bladder cancer, pancreatic cancer, endometrial cancer, colon cancer, kidney cancer, esophageal cancer, prostate cancer, colorectal cancer, glioblastoma, neuroblastoma, or hepatocellular carcinoma.

78. The use of any one of claims 39-77, wherein the individual has been diagnosed with cancer.

79. The use of any one of claims 39-78, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

80. The use of any one of claims 39-79, wherein the OX40 binding agonist is to be administered before the PD-1 axis binding antagonist, simultaneous with the PD-1 axis binding antagonist, or after the PD-1 axis binding antagonist.

81. The use of any one of claims 39-80, wherein the individual is a human.

82. The use of any one of claims 1-81, wherein the PD-1 axis binding antagonist and/or the OX40 binding agonist are to be administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

83. The used of any one of claims 1-82, wherein the medicament is to be administered with a chemotherapeutic agent for treating or delaying progression of cancer.

84. Use of a human PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the human PD-1 axis binding antagonist 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.

85. 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 a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier.

86. A composition comprising a human PD-1 axis binding antagonist 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.

87. 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 a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier.

88. A kit comprising a medicament comprising a PD-1 axis binding antagonist 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.

89. A kit comprising a first medicament comprising a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and a second medicament comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier.

90. The kit of claim 89, 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.

91. 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 a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual.