

predominantly expressed on antigen presenting cells. OX40 is highly expressed by activated CD4⁺ T cells, activated CD8⁺ T cells, memory T cells, and regulatory T (Treg) cells.

[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

[0011] Provided herein 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] Also provided herein 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, wherein the individual has cancer or has been diagnosed with cancer, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[0012a] In one aspect, provided herein is a use of a human PD-1 axis binding antagonist and an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the individual has cancer or has been diagnosed with cancer, and wherein the cancer cells in a tumor sample of the cancer from the individual do not express PD-L1.

[0013] Also provided herein 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, wherein the individual has cancer or has been diagnosed with cancer, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[0013a] In another aspect, provided herein is a use of a human PD-1 axis binding antagonist and an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the individual has cancer or has been diagnosed with cancer, and wherein the cancer cells in a tumor sample of the cancer from the individual express PD-L1.

[00014] Also provided herein 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).

[00015] Also provided herein is a method for enhancing immune function in an individual having cancer comprising administering to the individual an effective amount of a human PD-1 axis binding antagonist and an OX40 binding agonist, wherein the individual has been diagnosed with cancer, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00015a] In another aspect, provided herein is a use of a PD-1 axis binding antagonist and an OX40 binding agonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the individual has been diagnosed with cancer, and wherein the cancer cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00016] In another aspect, provided herein is a method for enhancing immune function in an individual having cancer comprising administering to the individual an effective amount of a human

PD-1 axis binding antagonist and an OX40 binding agonist, wherein the individual has been diagnosed with cancer, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[00016a] In another aspect, provided herein is a use of a PD-1 axis binding antagonist and an OX40 binding agonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the individual has been diagnosed with cancer, and wherein the cancer cells in a tumor sample of the cancer from the individual express PD-L1.

[00017] Also 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.

[00018] Also 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.

[00018a] In another aspect, provided herein is a 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, wherein the medicament is to be administered in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00018b] In another aspect, provided herein is a 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, wherein the medicament is to be administered in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[00019] Also 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.

[00019a] 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 comprises the OX40 binding agonist and an optional pharmaceutically acceptable carrier, wherein the medicament is to be administered in combination with a composition comprising a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00019b] 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 comprises the OX40 binding agonist and an optional pharmaceutically acceptable carrier, wherein the medicament is to be administered in combination with a composition comprising a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[00020] Also 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.

[00020a] In another 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 said composition is to be administered in combination with a second composition, wherein the second composition comprises OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00020b] In another 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 said composition is to be administered in combination with a second composition, wherein the second composition comprises OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[00021] Also 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.

[00021a] In 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 said composition is to be administered in combination with a second composition, wherein the second composition comprises a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00021b] In 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 said composition is to be administered in combination with a second composition, wherein the second composition comprises a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[00022] Also 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.

[00023] Also 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.

[00024] Also 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.

[00024a] In another 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, wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00024b] In another 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, wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[00024c] In another 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, 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, wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00024d] In another 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, 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, wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[00024e] 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 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, wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

[00024f] 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 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, wherein cells in a tumor sample of the cancer from the individual express PD-L1.

[00025] 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.

[00026] In some embodiments, the individual has cancer or has been diagnosed with cancer.

[00027] 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).

[00028] In some embodiments, cancer cells (from a sample of the cancer from the individual) express PD-L1. In some embodiments, the PD-L1 biomarker is present in the sample when it comprises more than 0% of the sample. In some embodiments, the PD-L1 biomarker is detected in the sample by protein expression. In some embodiments, the protein expression is determined by immunohistochemistry (IHC). In some embodiments, the PD-L1 biomarker is detected using an anti-PD-L1 antibody. In some embodiments, the PD-L1 biomarker is detected as a weak staining intensity by IHC, a moderate staining intensity by IHC, or a strong staining intensity by IHC. In some embodiments, the PD-L1 biomarker is detected using an anti-PD-L1 antibody, and wherein the PD-L1 biomarker is detected as a moderate staining intensity by IHC, or a strong staining intensity by IHC.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a human PD-1 axis binding antagonist and an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the individual has cancer or has been diagnosed with cancer, and wherein the cancer cells in a tumor sample of the cancer from the individual do not express PD-L1.
2. The use of claim 1, wherein the PD-L1 biomarker is absent from the sample when it comprises 0% of the sample.
3. The use of claim 2, wherein the PD-L1 biomarker is determined by protein expression measured by immunohistochemistry (IHC) method.
4. Use of a human PD-1 axis binding antagonist and an OX40 binding agonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the individual has cancer or has been diagnosed with cancer, and wherein the cancer cells in a tumor sample of the cancer from the individual express PD-L1.
5. The use of claim 4, wherein the PD-L1 biomarker is present in the sample when it comprises more than 0% of the sample.
6. The use of claim 4 or claim 5, wherein the PD-L1 biomarker is detected in between 0% and 1% of the sample.
7. The use of claim 4 or claim 5, wherein the PD-L1 biomarker is detected in between 0% and 5% of the sample.
8. The use of any one of claims 5-7, wherein the PD-L1 biomarker is detected in the sample by protein expression determined by immunohistochemistry (IHC) method.
9. The use of claim 8, wherein the PD-L1 biomarker is detected using an anti-PDL1 antibody, and wherein the PD-L1 biomarker is detected as a weak staining intensity by IHC, a moderate staining intensity by IHC, or a strong staining intensity by IHC.
10. The use of claim 8, wherein the PD-L1 biomarker is detected is detected using an anti-PDL1 antibody, and wherein the PD-L1 biomarker is detected as a moderate staining intensity by IHC or a strong staining intensity by IHC.
11. The use of any one of claims 8-10, wherein the sample has an IHC score of IHC 0 or IHC1.

12. The use of any one of claims 1-11, wherein the individual has cancer that is resistant to a PD-1 axis binding antagonist.
13. The use of any one of claims 1-12, wherein the individual is refractory to a PD-1 axis binding antagonist.
14. The use of any one of claims 1-13, 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.
15. The use of claim 14, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.
16. The use of claim 15, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.
17. The use of claim 15, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL1.
18. The use of claim 15, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL2.
19. The use of claim 15, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PDL1 and PDL2.
20. The use of any one of claims 15-19, wherein the PD-1 binding antagonist is an antibody.
21. The use of claim 15, wherein the PD-1 binding antagonist is nivolumab.
22. The use of claim 15, wherein the PD-1 binding antagonist is pembrolizumab.
23. The use of claim 15, wherein the PD-1 binding antagonist is CT-011.
24. The use of claim 15, wherein the PD-1 binding antagonist is AMP-224.
25. The use of claim 14, wherein the PD-1 axis binding antagonist is a PDL1 binding antagonist.
26. The use of claim 25, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to PD-1.
27. The use of claim 25, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to B7-1.
28. The use of claim 25, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to both PD-1 and B7-1.

29. The use of any one of claims 25-28, wherein the PDL1 binding antagonist is an anti-PDL1 antibody.
30. The use of claim 29, wherein the anti-PDL1 antibody is a monoclonal antibody.
31. The use of claim 29, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
32. The use of claim 29, wherein the anti-PDL1 antibody is a humanized antibody or a human antibody.
33. The use of claim 25, wherein the PDL1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.
34. The use of claim 25, 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).
35. The use of claim 29, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLLTVSS (SEQ
ID NO:7) or EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWI
SPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG
TLTVSSASTK (SEQ ID NO:8) and a light chain variable region comprising the amino acid
sequence of DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIY SASF
LYSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLYHPATFGQGGTKVEIKR (SEQ ID
NO:9).
36. The use of claim 14, wherein the PD-1 axis binding antagonist is a PDL2 binding antagonist.
37. The use of claim 36, wherein the PDL2 binding antagonist is an antibody.
38. The use of claim 36, wherein the PDL2 binding antagonist is an immunoadhesin.
39. The use of any one of claims 20, 29-35, and 37, wherein the antibody is a human IgG1 having Asn to Ala substitution at position 297 according to EU numbering.
40. The use of any one of claims 1-39, 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.

41. The use of any one of claims 1-40, wherein the OX40 binding agonist is an OX40 agonist antibody that binds human OX40.
42. The use of claim 41, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.
43. The use of claim 41, wherein the OX40 agonist antibody is a full-length human IgG1 antibody.
44. The use of any one of claims 1-40, wherein the OX40 binding agonist is a trimeric OX40L-Fc protein.
45. The use of any one of claims 1-40, wherein the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L.
46. The use of any one of claims 1-45, 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.
47. The use of any one of claims 1-46, wherein the treatment results in a sustained response in the individual after cessation of the treatment.
48. The use of any one of claims 1-47, 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.
49. The use of any one of claims 1-48, wherein the individual is a human.
50. Use of a PD-1 axis binding antagonist and an OX40 binding agonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the individual has been diagnosed with cancer, and wherein the cancer cells in a tumor sample of the cancer from the individual do not express PD-L1.
51. The use of claim 50, wherein the PD-L1 biomarker is absent from the sample when it comprises 0% of the sample.
52. The use of claim 51, wherein the PD-L1 biomarker is determined by protein expression measured by immunohistochemistry (IHC) method.
53. Use of a PD-1 axis binding antagonist and an OX40 binding agonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the individual has been diagnosed with cancer, and wherein the cancer cells in a tumor sample of the cancer from the individual express PD-L1.

54. The use of claim 53, wherein the PD-L1 biomarker is present in the sample when it comprises more than 0% of the sample.
55. The use of claim 53 or claim 54, wherein the PD-L1 biomarker is detected in between 0% and 1% of the sample.
56. The use of claim 53 or claim 54, wherein the PD-L1 biomarker is detected in between 0% and 5% of the sample.
57. The use of claim 54, wherein the PD-L1 biomarker is detected in the sample by protein expression determined by immunohistochemistry (IHC) method.
58. The use of claim 57, wherein the PD-L1 biomarker is detected using an anti-PDL1 antibody, and wherein the PD-L1 biomarker is detected as a weak staining intensity by IHC, a moderate staining intensity by IHC, or a strong staining intensity by IHC.
59. The use of claim 57, wherein the PD-L1 biomarker is detected using an anti-PD-L1 antibody, and wherein the PD-L1 biomarker is detected as a moderate staining intensity by IHC or a strong staining intensity by IHC.
60. The use of any one of claims 57-59, wherein the sample has an IHC score of IHC 0 or IHC1.
61. The use of any one of claims 50-60, wherein the individual has cancer that is resistant to a PD-1 axis binding antagonist.
62. The use of any one of claims 50-61, wherein the individual is refractory to a PD-1 axis binding antagonist.
63. The use of any one of claims 50-62, 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.
64. The use of any one of claims 50-62, wherein the number of CD8 T cells is elevated relative to prior to administration of the combination.
65. The use of claim 64, wherein the CD8 T cell is an antigen-specific CD8 T cell.
66. The use of any one of claims 50-62, wherein Treg function is suppressed relative to prior to the administration of the combination.
67. The use of any one of claims 50-62, wherein T cell exhaustion is decreased relative to prior to the administration of the combination.
68. The use of any one of claims 50-62, wherein number of Treg is decreased relative to prior to the administration of the combination.

69. The use of any one of claims 50-62, wherein plasma interferon gamma is increased relative to prior to the administration of the combination.
70. The use of any one of claims 50-62, wherein level of memory T effector cells is increased relative to prior to the administration of the combination.
71. The use of claim 70, wherein the increase of the level of memory T effector cells is detected in peripheral blood.
72. The use of claim 71, wherein detection of increase of the level of memory T effector cells is by detection of CXCR3 expressing cells.
73. The use of any one of claims 50-72, 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.
74. The use of claim 73, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.
75. The use of claim 74, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.
76. The use of claim 74, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL1.
77. The use of claim 74, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PDL2.
78. The use of claim 74, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PDL1 and PDL2.
79. The use of any one of claims 74-78, wherein the PD-1 binding antagonist is an antibody.
80. The use of claim 74, wherein the PD-1 binding antagonist is nivolumab.
81. The use of claim 74, wherein the PD-1 binding antagonist is pembrolizumab.
82. The use of claim 74, wherein the PD-1 binding antagonist is CT-011.
83. The use of claim 74, wherein the PD-1 binding antagonist is AMP-224.
84. The use of claim 73, wherein the PD-1 axis binding antagonist is a PDL1 binding antagonist.
85. The use of claim 84, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to PD-1.

86. The use of claim 84, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to B7-1.
87. The use of claim 84, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to both PD-1 and B7-1.
88. The use of any one of claims 84-87, wherein the PDL1 binding antagonist is an anti-PDL1 antibody.
89. The use of claim 88, wherein the anti-PDL1 antibody is a monoclonal antibody.
90. The use of claim 88, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and (Fab')₂ fragments.
91. The use of claim 88, wherein the anti-PDL1 antibody is a humanized antibody or a human antibody.
92. The use of claim 84, wherein the PDL1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.
93. The use of claim 88, 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).
94. The use of claim 88, wherein the anti-PDL1 antibody comprises a heavy chain variable region comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLLTVSS (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 LYSQVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLYHPATFGQGTKVEIKR (SEQ ID NO:9).
95. The use of any one of claims 79, 88-91, 93 and 94, wherein the antibody is a human IgG1 having Asn to Ala substitution at position 297 according to EU numbering.
96. The use of claim 73, wherein the PD-1 axis binding antagonist is a PDL2 binding antagonist.

97. The use of claim 96, wherein the PDL2 binding antagonist is an antibody.
98. The use of claim 96, wherein the PDL2 binding antagonist is an immunoadhesin.
99. The use of any one of claims 50-98, 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.
100. The use of claim 99, wherein the OX40 binding agonist is an OX40 agonist antibody that binds human OX40.
101. The use of claim 100, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.
102. The use of claim 100, wherein the OX40 agonist antibody is a full-length IgG1 antibody.
103. The use of any one of claims 50-98, wherein the OX40 binding agonist is a trimeric OX40L-Fc protein.
104. The use of any one of claims 50-98, wherein the OX40 binding agonist is an OX40L agonist fragment comprising one or more extracellular domains of OX40L.
105. The use of any one of claims 50-104, 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.
106. The use of any one of claims 50-105, wherein the treatment results in a sustained response in the individual after cessation of the treatment.
107. The use of any one of claims 50-106, 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.
108. The use of any one of claims 50-107, wherein the individual is a human.
109. The use of any one of claims 1-108, 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.
110. The use of any one of claims 1-109, wherein a chemotherapeutic agent for treating or delaying progression of cancer is to be further administered.
111. 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, wherein the medicament is to be administered in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

112. 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, wherein the medicament is to be administered in combination with a composition comprising an OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

113. 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, wherein the medicament is to be administered in combination with a composition comprising a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

114. 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, wherein the medicament is to be administered in combination with a composition comprising a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

115. 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 said composition is to be administered in combination with a second composition, wherein the second composition comprises OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

116. 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 said composition is to be administered in combination with a second composition, wherein the second composition comprises OX40 binding agonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

117. 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 said composition is to be administered in combination with a second composition, wherein the second composition comprises a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

118. 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 said composition is to be administered in combination with a second composition, wherein the second composition comprises a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and wherein cells in a tumor sample of the cancer from the individual express PD-L1.

119. 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, wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

120. 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, wherein cells in a tumor sample of the cancer from the individual express PD-L1.

121. 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, 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, wherein cells in a tumor sample of the cancer from the individual do not express PD-L1.

122. 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, 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, wherein cells in a tumor sample of the cancer from the individual express PD-L1.