[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] In one aspect, provided herein is use of a human PDL1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the human PDL1 binding antagonist is to be administered with an agonist anti-human OX40 antibody, and wherein the cancer is colon cancer or colorectal cancer. 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 PDL1 binding antagonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the PDL1 binding antagonist is to be administered with an agonist anti-human OX40 antibody, and wherein the cancer is colon cancer or colorectal cancer. 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] 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] 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 PDL1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the human PDL1 binding antagonist and an optional

pharmaceutically acceptable carrier, wherein the medicament is to be used in combination with a composition comprising an agonist anti-human OX40 antibody and an optional pharmaceutically acceptable carrier, and wherein the cancer is colon cancer or colorectal cancer.

[0015] 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 agonist anti-human OX40 antibody in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the OX40 agonist antibody and an optional pharmaceutically acceptable carrier, wherein the medicament is to be used in combination with a composition comprising a human PDL1 binding antagonist and an optional pharmaceutically acceptable carrier, and wherein the cancer is colon cancer or colorectal cancer.

[0016] 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 PDL1 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 used in combination with a second composition, wherein the second composition comprises an agonist anti-human OX40 antibody and an optional pharmaceutically acceptable carrier, and wherein the cancer is colon cancer or colorectal cancer.

[0017] 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 agonist anti-human OX40 antibody and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein said composition is to be used in combination with a second composition, wherein the second composition comprises a human PDL1 binding antagonist and an optional pharmaceutically acceptable carrier, and wherein the cancer is colon cancer or colorectal cancer.

[0018] 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 PDL1 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 agonist anti-human OX40 antibody and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual, wherein the cancer is colon cancer or colorectal cancer.

[0019] 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 PDL1 binding antagonist and an optional pharmaceutically acceptable carrier, and a second medicament comprising an agonist anti-human OX40 antibody 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, and wherein the cancer is colon cancer or colorectal cancer.

[0020] 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 agonist anti-human OX40 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 PDL1 binding antagonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual, wherein the cancer is colon cancer or colorectal cancer.

[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).

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a human PDL1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the human PDL1 binding antagonist is to be administered with an agonist anti-human OX40 antibody, and wherein the cancer is colon cancer or colorectal cancer.

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

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

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

5. The use of any one of claims 1-4, wherein the PDL1 binding antagonist is an anti-PDL1 antibody.

6. The use of claim 5, wherein the anti-PDL1 antibody is a monoclonal antibody.

7. The use of claim 5, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

8. The use of claim 5, wherein the anti-PDL1 antibody is a humanized antibody or a human antibody.

9. The use of claim 1, wherein the PDL1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

10. The use of claim 5, 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).

11. The use of claim 5, wherein the anti- PDL1 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).

12. The use of any one of claims 5-11, wherein the anti- PDL1 antibody is a human IgG1 having Asn to Ala substitution at position 297 according to EU numbering.

13. The use of any one of claims 1-12, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

14. The use of any one of claims 1-12, wherein the OX40 agonist antibody is a full-length human IgG1 antibody.

15. The use of any one of claims 1-14, wherein the individual has cancer or has been diagnosed with cancer.

16. The use of any one of claims 1-15, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

17. The use of any one of claims 1-16, wherein the OX40 agonist antibody is to be administered before the PDL1 binding antagonist, simultaneous with the PDL1 binding antagonist, or after the PDL1 binding antagonist.

18. The use of any one of claims 1-17, wherein the individual is a human.

19. Use of a PDL1 binding antagonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the PDL1 binding antagonist is to be administered with an agonist anti-human OX40 antibody, and wherein the cancer is colon cancer or colorectal cancer.

20. The use of claim 19, wherein CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the administration of the PDL1 binding antagonist and the OX40 agonist antibody.

21. The use of claim 19, wherein the number of CD8 T cells is elevated relative to prior to administration of the combination.

22. The use of claim 21, wherein the CD8 T cell is an antigen-specific CD8 T cell.

23. The use of claim 19, wherein Treg function is suppressed relative to prior to the administration of the combination.

24. The use of claim 19, wherein T cell exhaustion is decreased relative to prior to the

administration of the combination.

25. The use of any one of claims 19-24, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to PD-1.

26. The use of any one of claims 19-24, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to B7-1.

27. The use of any one of claims 19-24, wherein the PDL1 binding antagonist inhibits the binding of PDL1 to both PD-1 and B7-1.

28. The use of any one of claims 19-27, wherein the PDL1 binding antagonist is an anti-PDL1 antibody.

29. The use of claim 28, wherein the anti-PDL1 antibody is a monoclonal antibody.

30. The use of claim 28, wherein the anti-PDL1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

31. The use of claim 28, wherein the anti-PDL1 antibody is a humanized antibody or a human antibody.

32. The use of any one of claims 19-24, wherein the PDL1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

33. The use of claim 28, 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).

34. The use of claim 28, 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).

35. The use of claim any one of claims 28-31, 33, and 34, wherein the antibody is a human IgG1 having Asn to Ala substitution at position 297 according to EU numbering.

36. The use of any one of claims 19-35, wherein the OX40 agonist antibody is MEDI6469, MEDI0562, or MEDI6383.

37. The use of any one of claims 19-35, wherein the OX40 agonist antibody is a full-length IgG1 antibody.

38. The use of any one of claims 19-37, wherein the individual has been diagnosed with cancer.

39. The use of any one of claims 19-38, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

40. The use of any one of claims 19-39, wherein the OX40 agonist antibody is to be administered before the PDL1 binding antagonist, simultaneous with the PDL1 binding antagonist, or after the PDL1 binding antagonist.

41. The use of any one of claims 19-40, wherein the individual is a human.

42. The use of any one of claims 1-41, wherein the PDL1 binding antagonist and/or the OX40 agonist antibody are to be administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

43. The use of any one of claims 1-42, wherein the medicament is to be administered with a chemotherapeutic agent for treating or delaying progression of cancer.

44. Use of a human PDL1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the human PDL1 binding antagonist and an optional pharmaceutically acceptable carrier, wherein the medicament is to be used in combination with a composition comprising an agonist anti-human OX40 antibody and an optional pharmaceutically acceptable carrier, and wherein the cancer is colon cancer or colorectal cancer.

45. Use of an agonist anti-human OX40 antibody in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the OX40 agonist antibody and an optional pharmaceutically acceptable carrier, wherein the medicament is to be used in combination with a composition comprising a human PDL1 binding antagonist and an optional pharmaceutically acceptable carrier, and wherein the cancer is colon cancer or colorectal cancer.

46. A composition comprising a human PDL1 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 used in combination with a

second composition, wherein the second composition comprises an agonist anti-human OX40 antibody and an optional pharmaceutically acceptable carrier, and wherein the cancer is colon cancer or colorectal cancer.

47. A composition comprising an agonist anti-human OX40 antibody and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein said composition is to be used in combination with a second composition, wherein the second composition comprises a human PDL1 binding antagonist and an optional pharmaceutically acceptable carrier, and wherein the cancer is colon cancer or colorectal cancer.

48. A kit comprising a medicament comprising a PDL1 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 agonist anti-human OX40 antibody and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual, wherein the cancer is colon cancer or colorectal cancer.

49. A kit comprising a first medicament comprising a PDL1 binding antagonist and an optional pharmaceutically acceptable carrier, and a second medicament comprising an agonist anti-human OX40 antibody 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, and wherein the cancer is colon cancer or colorectal cancer.

50. A kit comprising a medicament comprising an agonist anti-human OX40 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 PDL1 binding antagonist and an optional pharmaceutically acceptable carrier for treating or delaying progression of cancer in an individual, wherein the cancer is colon cancer or colorectal cancer.