An optimal therapeutic treatment may combine blockade of PD-1 receptor/ligand interaction with an agent that directly inhibits tumor growth. There remains a need for an optimal therapy for treating, stabilizing, preventing, and/or delaying development of various cancers.

SUMMARY

This disclosure relates to methods of treating cancers and for enhancing immune function in an individual having cancer by administering a PD-1 axis binding antagonist and a taxane.

In one aspect, the invention features use of a human PD-L1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the human PD-L1 binding antagonist is to be administered with a taxane and a platinum-based chemotherapeutic agent, wherein the taxane is nab-paclitaxel or paclitaxel. This disclosure also features 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 a taxane. In some embodiments, the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist, and a PD-L2 binding antagonist.

In some embodiments of the above aspect, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2. In some embodiments, the PD-1 binding antagonist is an antibody. In some embodiments, the PD-1 binding antagonist is selected from the group consisting of MDX-1106 (nivolumab), MK-3475 (lambrolizumab), CT-011 (pidilizumab), and AMP-224.

In other embodiments of the above aspect, the PD-1 axis binding antagonist is a PD-L1 binding antagonist. In some embodiments, the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In some embodiments, the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In some embodiments, the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1. In some embodiments, the PD-L1 binding antagonist is an antibody. In some embodiments, the antibody is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736. In some embodiments, the antibody comprises a heavy chain comprising an HVR-H1 sequence of SEQ ID NO:19, HVR-H2 sequence of SEQ ID NO:20, and HVR-H3 sequence of SEQ ID NO:21; and a light chain comprising an HVR-L1 sequence of SEQ ID NO:22, HVR-L2 sequence of SEQ ID NO:23, and HVR-L3 sequence of SEQ ID NO:24. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:26 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4.

In some embodiments of the above aspect, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In some embodiments, the PD-L2 binding antagonist is an antibody. In some embodiments, the PD-L2 binding antagonist is an immunoadhesin.

In any of the preceding embodiments of the above aspect, the cancer may be, without limitation, breast cancer (including triple-negative breast cancer (TNBC)), bladder cancer (including urothelial bladder cancer (UBC), muscle invasive bladder cancer, and BCG-refractory non-muscle invasive bladder cancer), colorectal cancer, rectal cancer, lung cancer (including non-small cell lung cancer that can be squamous or non-squamous), glioblastoma, non-Hodgkins lymphoma (NHL), renal cell cancer (including

renal cell carcinoma), prostate cancer, liver cancer, pancreatic cancer, soft-tissue sarcoma, kaposi's sarcoma, carcinoid carcinoma, head and neck cancer, gastric cancer, esophageal cancer, prostate cancer, endometrial cancer, kidney cancer, ovarian cancer, mesothelioma, and a heme malignancy (including a myelodysplastic syndrome (MDS) and multiple myeloma). In particular embodiments, the cancer may be lung cancer (including non-small cell lung cancer that can be squamous or non-squamous), bladder cancer (including UBC), breast cancer (including TNBC), renal cell carcinoma, melanoma, colorectal cancer, and a heme malignancy (including a myelodysplastic syndrome (MDS) and multiple myeloma). In some embodiments, the lung cancer is non-small cell lung cancer that can be squamous or non-squamous. In some embodiments, the bladder cancer is UBC. In some embodiments, the breast cancer is TNBC. In some embodiments, the heme malignancy is a MDS or multiple myeloma.

In any of the preceding embodiments of the above aspect, the individual has cancer or has been diagnosed with cancer. In some embodiments, the cancer cells in the individual express PD-L1.

In any of the preceding embodiments of the above aspect, the treatment may result in a response in the individual. In some embodiments, the response is a complete response. In some embodiments, the response is a sustained response after cessation of the treatment. In some embodiments, the response is a complete response that is sustained after cessation of the treatment.

In any of the preceding embodiments of the above aspect, the taxane 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. In some embodiments, the taxane is nab-paclitaxel (ABRAXANE®), paclitaxel, or docetaxel. In some embodiments, the taxane is nab-paclitaxel (ABRAXANE®). In some embodiments, the taxane is paclitaxel.

In another aspect, the invention features use of a PD-L1 binding antagonist in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the PD-L1 binding antagonist is to be administered in combination with a taxane and a platinum-based chemotherapeutic agent, wherein the taxane is nab-paclitaxel or paclitaxel. This disclosure also features a method of enhancing immune function in an individual having cancer, the method comprising administering an effective amount of a PD-1 axis binding antagonist and a taxane. In some embodiments, 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 taxane. In some embodiments, the number of CD8+ T cells is elevated relative to prior to administration of the combination. In some embodiments, the CD8+ T cell is an antigen-specific CD8+ T cell. In some embodiments, Treg function is suppressed relative to prior to the administration of the combination. In some embodiments, T cell exhaustion is decreased relative to prior to the administration of the combination. In some embodiments, the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist and a PD-L2 binding antagonist.

In some embodiments of the above aspect, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2. In some embodiments, the PD-1 binding antagonist is an antibody. In some embodiments, the PD-1 binding antagonist is selected from the group consisting of MDX-1106 (nivolumab), MK-3475 (lambrolizumab), CT-011 (pidilizumab), and AMP-224.

platinum-based chemotherapeutic agent is carboplatin.

In another aspect, the invention features a use of a human PD-L1 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-L1 binding antagonist and an optional pharmaceutically acceptable carrier, and wherein the medicament is to be administered in combination with (i) a composition comprising a taxane and an optional pharmaceutically acceptable carrier, wherein the taxane is nab-paclitaxel or paclitaxel, and (ii) a composition comprising a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier.

In another aspect, the invention features a use of a taxane in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the taxane and an optional pharmaceutically acceptable carrier, wherein the taxane is nab-paclitaxel or paclitaxel, and wherein the medicament is to be administered in combination with (i) a composition comprising a human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier and (ii) a composition comprising a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier.

In another aspect, the invention features a use of an anti-PD-L1 antibody in the manufacture of a medicament for treating or delaying progression of NSCLC in an individual, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4, and wherein the anti-PD-L1 antibody is to be administered in combination with a taxane and carboplatin, wherein the taxane is nab-paclitaxel or paclitaxel, and wherein the NSCLC is non-squamous NSCLC or squamous NSCLC.

In another aspect, the invention features a use of an anti-PD-L1 antibody in the manufacture of a medicament for treating or delaying progression of NSCLC in an individual, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4, and wherein the anti-PD-L1 antibody is to be administered in combination with a taxane, carboplatin, and bevacizumab, wherein the taxane is nab-paclitaxel or paclitaxel, and wherein the NSCLC is non-squamous NSCLC.

In another aspect, the invention features a use of an anti-PD-L1 antibody in the manufacture of a medicament for treating or delaying progression of ovarian cancer in an individual, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4, wherein the anti-PD-L1 antibody is to be administered in combination with a taxane, carboplatin, and bevacizumab, and wherein the taxane is nab-paclitaxel or paclitaxel.

The disclosure also features 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 and a third composition, wherein the second composition comprises a taxane and an optional pharmaceutically acceptable carrier, wherein the taxane is nab-paclitaxel or paclitaxel, and the third composition comprises a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier.

The disclosure further features a composition comprising a taxane and an optional pharmaceutically acceptable carrier for use in treating or delaying progression of cancer in an individual, wherein the taxane is nab-paclitaxel or paclitaxel, wherein the treatment comprises administration of said composition in combination with a second composition and a third composition, wherein the second composition comprises a human PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and the third composition comprises a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier.

Also featured 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 (i) a composition comprising a taxane and an optional pharmaceutically acceptable carrier, wherein the taxane is nab-paclitaxel or paclitaxel, and (ii) a composition comprising a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier, for treating or delaying progression of cancer in an individual.

Further featured is a kit comprising a first medicament comprising a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, a second medicament comprising a taxane and an optional pharmaceutically acceptable carrier, and a third medicament comprising a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier, wherein the taxane is nab-paclitaxel or paclitaxel. In some embodiments, the kit further comprises a package insert comprising instructions for administration of the first medicament and the second medicament for treating or delaying progression of cancer in an individual.

Yet further featured is a kit comprising a medicament comprising a taxane and an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration of the medicament in combination with (i) a composition comprising a PD-1 axis binding antagonist and an optional pharmaceutically acceptable carrier, and (ii) a composition comprising a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier, for treating or delaying progression of cancer in an individual, wherein the taxane is nab-paclitaxel or paclitaxel.

In any one of the preceding aspects, the PD-1 axis binding antagonist may be selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist, and a PD-L2 binding antagonist. In some embodiments, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some embodiments, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

WHAT IS CLAIMED IS:

1. Use of a human PD-L1 binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the human PD-L1 binding antagonist is to be administered with a taxane and a platinum-based chemotherapeutic agent, wherein the taxane is nab-paclitaxel or paclitaxel.

2. The use of claim 1, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

3. The use of claim 1, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

4. The use of claim 1, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

5. The use of any one of claims 1-4, wherein the PD-L1 binding antagonist is an antibody.

6. The use of claim 5, wherein the antibody is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

7. The use of claim 5, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:19, HVR-H2 sequence of SEQ ID NO:20, and HVR-H3 sequence of SEQ ID NO:21; and a light chain comprising HVR-L1 sequence of SEQ ID NO:22, HVR-L2 sequence of SEQ ID NO:23, and HVR-L3 sequence of SEQ ID NO:24.

8. The use of claim 5, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4.

9. The use of any one of claims 1-8, wherein the cancer is lung cancer, bladder cancer, breast cancer, renal cell carcinoma, melanoma, colorectal cancer, ovarian cancer, or a heme malignancy.

10. The use of claim 9, wherein the cancer is lung cancer.

11. The use of claim 10, wherein the lung cancer is non-small cell lung cancer (NSCLC).

12. The use of claim 11, wherein the NSCLC is non-squamous NSCLC.

13. The use of claim 11, wherein the NSCLC is squamous NSCLC.

14. The use of claim 9, wherein the cancer is ovarian cancer.

15. The use of any one of claims 1-14, wherein the cancer cells in the individual express PD-L1.

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

17. The use of claim 16, wherein the response is a complete response.

18. The use of claim 16 or claim 17, wherein the response is a sustained response after cessation of the treatment.

19. The use of any one of claims 1-18, wherein the taxane and/or the platinum-based chemotherapeutic agent 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.

20. The use of claim 19, wherein the taxane and/or the platinum-based chemotherapeutic agent is to be administered before the PD-1 axis binding antagonist.

21. The use of claim 19, wherein the taxane and/or the platinum-based chemotherapeutic agent is to be administered simultaneous with the PD-1 axis binding antagonist.

22. The use of claim 19, wherein the taxane and/or the platinum-based chemotherapeutic agent is to be administered after the PD-1 axis binding antagonist.

23. Use of a PD-L1 binding antagonist in the manufacture of a medicament for enhancing immune

function in an individual having cancer, wherein the PD-L1 binding antagonist is to be administered in combination with a taxane and a platinum-based chemotherapeutic agent, wherein the taxane is nab-paclitaxel or paclitaxel.

24. The use of claim 23, 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 taxane.

25. The use of claim 23, wherein the number of CD8+ T cells is elevated relative to prior to administration of the combination.

26. The use of claim 25, wherein the CD8+ T cell is an antigen-specific CD8+ T cell.

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

28. The use of claim 23, wherein T cell exhaustion is decreased relative to prior to the administration of the combination.

29. The use of any one of claims 23-28, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

30. The use of any one of claims 23-28, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

31. The use of any one of claims 23-28, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

32. The use of any one of claims 23-31, wherein the PD-L1 binding antagonist is an antibody.

33. The use of claim 32, wherein antibody is selected from the group consisting of: YW243.55.S70, MPDL3280A, MDX-1105, and MEDI4736.

34. The use of claim 32, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:19, HVR-H2 sequence of SEQ ID NO:20, and HVR-H3 sequence of SEQ ID NO:21; and a light chain comprising HVR-L1 sequence of SEQ ID NO:22, HVR-L2 sequence of SEQ ID NO:23, and HVR-L3 sequence of SEQ ID NO:24.

35. The use of claim 32, wherein the antibody comprises a heavy chain variable region comprising

the amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4.

36. The use of any one of claims 23-35, wherein the cancer is lung cancer, bladder cancer, breast cancer, renal cell carcinoma, melanoma, colorectal cancer, ovarian cancer, or a heme malignancy.

37. The use of claim 36, wherein the cancer is lung cancer.

38. The use of claim 37, wherein the lung cancer is NSCLC.

39. The use of claim 38, wherein the NSCLC is non-squamous NSCLC.

40. The use of claim 38, wherein the NSCLC is squamous NSCLC.

41. The use of claim 36, wherein the cancer is ovarian cancer.

42. The use of any one of claims 23-41, wherein the cancer cells in the individual express PD-L1.

43. The use of any one of claims 1-42, wherein the PD-L1 binding antagonist, taxane, and/or the platinum-based chemotherapeutic agent are to be administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally,

intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

44. The use of any one of claims 1-43, wherein the platinum-based chemotherapeutic agent is carboplatin, cisplatin, or oxaliplatin.

45. The use of claim 44, wherein the platinum-based chemotherapeutic agent is carboplatin.

46. The use of any one of claims 1-45, wherein the taxane is nab-paclitaxel.

47. The use of any one of claims 1-45, wherein the taxane is paclitaxel.

48. The use of any one of claims 1-47, wherein the medicament is to be further administered with an angiogenesis inhibitor.

49. The use of claim 48, wherein the angiogenesis inhibitor is an anti-VEGF antibody.

50. The use of claim 49, wherein the anti-VEGF antibody is bevacizumab.

51. Use of a human PD-L1 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-L1 binding antagonist and an optional pharmaceutically acceptable carrier, and wherein the medicament is to be administered in combination with (i) a composition comprising a taxane and an optional pharmaceutically acceptable carrier, wherein the taxane is nab-paclitaxel or paclitaxel, and (ii) a composition comprising a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier.

52. Use of a taxane in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament comprises the taxane and an optional pharmaceutically acceptable carrier, wherein the taxane is nab-paclitaxel or paclitaxel, and wherein the medicament is to be administered in combination with (i) a composition comprising a human PD-L1 binding antagonist and an optional pharmaceutically acceptable carrier and (ii) a composition comprising a platinum-based chemotherapeutic agent and an optional pharmaceutically acceptable carrier.

53. The use of claim 51 or 52, wherein the taxane is nab-paclitaxel.

54. The use of claim 51 or 52, wherein the taxane is paclitaxel.

55. The use of any one of claims 51-54, wherein the cancer is lung cancer, bladder cancer, breast cancer, renal cell carcinoma, melanoma, colorectal cancer, ovarian cancer, or a heme malignancy.

56. The use of claim 55, wherein the cancer is lung cancer.

57. The use of claim 56, wherein the lung cancer is non-small cell lung cancer (NSCLC).

58. The use of claim 57, wherein the NSCLC is non-squamous NSCLC.

59. The use of claim 57, wherein the NSCLC is squamous NSCLC.

60. The use of claim 55, wherein the cancer is ovarian cancer.

61. Use of an anti-PD-L1 antibody in the manufacture of a medicament for treating or delaying progression of NSCLC in an individual, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4, and wherein the anti-PD-L1 antibody is to be administered in combination with a taxane and carboplatin, wherein the taxane is nab-paclitaxel or paclitaxel, and wherein the NSCLC is non-squamous NSCLC or squamous NSCLC.

62. The use of claim 61, wherein the NSCLC is non-squamous NSCLC, and the taxane is nab-paclitaxel.

63. The use of claim 61, wherein the NSCLC is squamous NSCLC.

64. Use of an anti-PD-L1 antibody in the manufacture of a medicament for treating or delaying progression of NSCLC in an individual, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4, and wherein the anti-PD-L1 antibody is to be administered in combination with a taxane, carboplatin, and bevacizumab, wherein the taxane is nab-paclitaxel or paclitaxel, and wherein the NSCLC is non-squamous NSCLC.

65. The use of claim 64, wherein the taxane is paclitaxel.

66. Use of an anti-PD-L1 antibody in the manufacture of a medicament for treating or delaying progression of ovarian cancer in an individual, wherein the anti-PD-L1 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4, wherein the anti-PD-L1 antibody is to be administered in combination with a taxane, carboplatin, and bevacizumab, and wherein the taxane is nab-paclitaxel or paclitaxel.

67. The use of claim 66, wherein the taxane is paclitaxel.