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 PD-1 axis binding antagonist and a MEK inhibitor.

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 PD-L1 binding antagonist and a PD-L2 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 4, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1.

6. The method of Claim 4, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2.

7. The method of Claim 4, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.

8. The method of Claim 4, wherein the PD-1 binding antagonist is an antibody.

9. The method of Claim 8, wherein the PD-1 binding antagonist is MDX-1106.

10. The method of Claim 8, wherein the PD-1 binding antagonist is Merck 3745.

11. The method of Claim 8, wherein the PD-1 binding antagonist is CT-011.

12. The method of Claim 4, wherein the PD-1 binding antagonist is AMP-224.

13. The method of Claim 2, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist.

14. The method of Claim 13, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

15. The method of Claim 13, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

16. The method of Claim 13, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

17. The method of Claim 15, wherein the PD-L1 binding antagonist is an antibody.

18. The method of Claim 17, wherein the PD-L1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, and MDX-1105.

19. The method of Claim 17, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:15, HVR-H2 sequence of SEQ ID NO:16, and HVR-H3 sequence of SEQ ID NO:3; and a light chain comprising HVR-L1 sequence of SEQ ID NO:17, HVR-L2 sequence of SEQ ID NO:18, and HVR-L3 sequence of SEQ ID NO:19.

20. The method of Claim 17, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:24 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:21.

21. The method of Claim 2, wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.

22. The method of Claim 21, wherein the PD-L2 binding antagonist is an antibody.

23. The method of Claim 21, wherein the PD-L2 binding antagonist is an immunoadhesin.

24. The method of any one of claims 1-23, wherein the MEK inhibitor is a competitive inhibitor of MEK.

25. The method of any one of claims 1-23, wherein the MEK inhibitor is more selective against an activating KRAS mutation.

26. The method of any one of claims 1-23, wherein the MEK inhibitor is an allosteric inhibitor of MEK.

27. The method of any one of claims 1-23, wherein the MEK inhibitor is more selective against an activating BRAF mutation.

28. The method of any one of claims 1-23, wherein the MEK inhibitor is a compound of the formula (I), (II), (III), (IV), (V), (VI) or (VII), or a pharmaceutically acceptable salt or solvate thereof.

29. The method of any one of claims 1-23, wherein the MEK inhibitor is selected from the group consisting of G02442104, G-38963, G02443714, G00039805 and GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

30. The method of claim 29, wherein the MEK inhibitor is G02443714, G02442104 or G00039805.

31. The method of any one of claims 1-30, wherein the cancer contains a BRAF V600E mutation.

32. The method of any one of claims 1-30, wherein the cancer contains a BRAF wildtype.

33. The method of any one of claims 1-30, wherein the cancer contains a KRAS wildtype.

34. The method of any one of claims 1-30, wherein the cancer contains an activating KRAS mutation.

35. The method of any one of claims 1-34, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

36. The method of any of claims 1-35, wherein the MEK inhibitor is administered continuously.

37. The method of any of claims 1-35, wherein the MEK inhibitor is administered intermittently.

38. The method of any of claims 1-35, wherein the MEK inhibitor is administered before the PD-1 axis binding antagonist.

39. The method of any of claims 1-35, wherein the MEK inhibitor is administered simultaneous with the PD-1 axis binding antagonist.

40. The method of any of claims 1-36, wherein the MEK inhibitor is administered after the PD-1 axis binding antagonist.

41. The method of any one of claims 1-40, wherein the individual has colorectal cancer.

42. The method of any one of claims 1-40, wherein the individual has melanoma.

43. The method of any one of claims 1-40, wherein the individual has non-small cell lung cancer.

44. The method of any one of claims 1-40, wherein the individual has ovarian cancer.

45. The method of any one of claims 1-40, wherein the individual has breast cancer.

46. The method of any one of claims 1-40, wherein the individual has pancreatic cancer.

47. The method of any one claims 1-40, wherein the individual has a hematological malignancy.

48. The method of any one of claims 1-40, wherein the individual has renal cell carcinoma.

49. A method of enhancing immune function in an individual having cancer comprising administering an effective amount of a combination of a PD-1 axis binding antagonist and a MEK inhibitor.

50. The method of claim 49, wherein CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the administration of the combination.

51. The method of claim 50, wherein the CD8 T cell activation is characterized by an elevated frequency of γ-IFN$^+$ CD8 T cells and/or enhanced cytolytic activity relative to prior to administration of the combination.

52. The method of claim 50, wherein the number of CD8 T cells is elevated relative to prior to administration of the combination.

53. The method of any one of claims 50-52, wherein the CD8 T cell is an antigen-specific CD8 T cell.

54. The method of claim 50, wherein the cancer cells in the individual selectively have elevated expression of MHC class I antigen expression relative to prior to the administration of the PD-1 axis binding antagonist and the MEK inhibitor.

55. The method of claim 54, wherein PBMC cells of the individual do not have elevated expression of MHC class I antigen.

56. The method of claim 49, wherein the antigen presenting cells in the individual have enhanced maturation and activation relative prior to the administration of the PD-1 axis binding antagonist and the MEK inhibitor.

57. The method of claim 56, wherein the antigen presenting cells are dendritic cells.

58. The method of claim 56, wherein the maturation of the antigen presenting cells is characterized by increased frequency of CD83$^+$ dendritic cells.

59. The method of claim 56, wherein the activation of the antigen presenting cells is characterized by elevated expression of CD80 and CD86 on dendritic cells.

60. The method of claim 50, wherein the serum levels of IL-10 and/or IL-8 in the individual are reduced relative to prior to the administration of the combination.

61. The method of claim 50, wherein the cancer has elevated levels of T-cell infiltration.

62. The method of any one of claims 49-61, wherein the MEK inhibitor is a compound of the formula (I), (II), (III), (IV), (V), (VI) or (VII), or a pharmaceutically acceptable salt or solvate thereof.

63. The method of any one of claims 49-61, wherein the MEK inhibitor is selected from the group consisting of G02442104, G-38963, G02443714, G00039805 and GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

64. The method of any one of claims 49-61, wherein the PD-1 axis binding antagonist is an anti-PD-L1 antibody.

65. The method of claim 64, wherein PD-L1 on the cancer cell surface is inhibited from transducing a signal to the intracellular pathway.

66. The method of claim 64, wherein the anti-PD-L1 antibody is capable of inhibiting binding between PD-L1 and PD-1 and/or between PD-L1 and B7-1.

67. The method of claim 64, wherein the anti-PD-L1 antibody is a monoclonal antibody.

68. The method of claim 64, wherein the anti-PD-L1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

69. The method of any one of claims 64-68, wherein the anti-PD-L1 antibody is a humanized antibody.

70. The method of any one of claims 64-68, wherein the anti-PD-L1 antibody is a human antibody.

71. The method of Claim 64, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:15, HVR-H2 sequence of SEQ ID NO:16, and HVR-H3 sequence of SEQ ID NO:3; and a light chain comprising HVR-L1 sequence of SEQ ID NO:17, HVR-L2 sequence of SEQ ID NO:18, and HVR-L3 sequence of SEQ ID NO:19.

72. The method of Claim 64, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:24 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:21.

73. The method of any one of claims 1-72, wherein the PD-1 axis binding antagonist is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

74. A kit comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with a MEK inhibitor to treat or delay progression of cancer in an individual.

75. A kit comprising a PD-1 axis binding antagonist and a MEK inhibitor, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the MEK inhibitor to treat or delay progression of cancer in an individual.

76. A kit comprising a MEK inhibitor and a package insert comprising instructions for using the MEK inhibitor in combination with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.

77. The kit of any one of claims 74-76, wherein the PD-1 axis binding antagonist is an anti-PD-L1 antibody.

78. The kit of any one of claims 74-76, wherein the PD-1 axis binding antagonist is an anti-PD-1 antibody.

79. The kit of any one of claims 74-76, wherein the PD-1 axis binding antagonist is an anti-PD-1 immunoadhesin.

CLAIMS

What is claimed is:

1. Use of an effective amount of a PD-1 axis binding antagonist and a MEK inhibitor for the manufacture of a first medicament comprising the PD-1 axis binding antagonist and a second medicament comprising the MEK inhibitor for treating or delaying progression of cancer in an individual.

2. Use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the PD-1 axis binding agent is used in combination with a MEK inhibitor.

3. Use of an effective amount of a MEK inhibitor in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the MEK inhibitor is used in combination with a PD-1 axis binding antagonist.

4. A pharmaceutical composition comprising a PD-1 axis binding antagonist in combination with a MEK inhibitor for use in treating or delaying progression of cancer.

5. A pharmaceutical composition comprising a PD-1 axis binding antagonist for use in treating or delaying progression of cancer in combination with a MEK inhibitor.

6. A pharmaceutical composition comprising a MEK inhibitor for use in treating or delaying progression of cancer in combination with a PD-1 axis binding antagonist.

7. The use or pharmaceutical composition of any one of Claims 1-6, wherein 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.

8. The use or pharmaceutical composition of Claim 7, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

9. The use or pharmaceutical composition of Claim 8, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

10. The use or pharmaceutical composition of Claim 9, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1.

11. The use or pharmaceutical composition of Claim 9, wherein the PD-1 binding antagonist

inhibits the binding of PD-1 to PD-L2.

12. The use or pharmaceutical composition of Claim 9, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.

13. The use or pharmaceutical composition of Claim 9, wherein the PD-1 binding antagonist is an antibody.

14. The use or pharmaceutical composition of Claim 13, wherein the PD-1 binding antagonist is MDX-1106.

15. The use or pharmaceutical composition of Claim 13, wherein the PD-1 binding antagonist is Merck 3745.

16. The use or pharmaceutical composition of Claim 13, wherein the PD-1 binding antagonist is CT-011.

17. The use or pharmaceutical composition of Claim 9, wherein the PD-1 binding antagonist is AMP-224.

18. The use or pharmaceutical composition of Claim 7, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist.

19. The use or pharmaceutical composition of Claim 18, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

20. The use or pharmaceutical composition of Claim 18, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

21. The use or pharmaceutical composition of Claim 18, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

22. The use or pharmaceutical composition of Claim 18, wherein the PD-L1 binding antagonist is an antibody.

23. The use or pharmaceutical composition of Claim 22, wherein the PD-L1 binding antagonist is selected from the group consisting of: YW243.55.S70, MPDL3280A, and MDX-1105.

24. The use or pharmaceutical composition of Claim 22, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:15, HVR-H2 sequence of SEQ ID NO:16, and HVR-H3 sequence of SEQ ID NO:3; and a light chain comprising HVR-L1

sequence of SEQ ID NO:17, HVR-L2 sequence of SEQ ID NO:18, and HVR-L3 sequence of SEQ ID NO:19.

25. The use or pharmaceutical composition of Claim 22, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:24 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:21.

26. The use or pharmaceutical composition of Claim 7, wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.

27. The use or pharmaceutical composition of Claim 26, wherein the PD-L2 binding antagonist is an antibody.

28. The use or pharmaceutical composition of Claim 26, wherein the PD-L2 binding antagonist is an immunoadhesin.

29. The use or pharmaceutical composition of any one of Claims 1-28, wherein the MEK inhibitor is a competitive inhibitor of MEK.

30. The use or pharmaceutical composition of any one of Claims 1-28, wherein the MEK inhibitor is more selective against an activating KRAS mutation.

31. The use or pharmaceutical composition of any one of Claims 1-28, wherein the MEK inhibitor is an allosteric inhibitor of MEK.

32. The use or pharmaceutical composition of any one of Claims 1-28, wherein the MEK inhibitor is more selective against an activating BRAF mutation.

33. The use or pharmaceutical composition of any one of Claims 1-28, wherein the MEK inhibitor is a compound of the formula (I), (II), (III), (IV), (V), (VI) or (VII), or a pharmaceutically acceptable salt or solvate thereof.

34. The use or pharmaceutical composition of any one of Claims 1-28, wherein the MEK inhibitor is selected from the group consisting of G02442104, G-38963, G02443714, G00039805 and GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

35. The use or pharmaceutical composition of Claim 34, wherein the MEK inhibitor is G02443714, G02442104 or G00039805.

36. The use or pharmaceutical composition of any one of Claims 1-35, wherein the cancer contains a BRAF V600E mutation.

37. The use or pharmaceutical composition of any one of Claims 1-35, wherein the cancer contains a BRAF wildtype.

38. The use or pharmaceutical composition of any one of Claims 1-35, wherein the cancer contains a KRAS wildtype.

39. The use or pharmaceutical composition of any one of Claims 1-35, wherein the cancer contains an activating KRAS mutation.

40. The use or pharmaceutical composition of any one of Claims 1-39, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

41. The use or pharmaceutical composition of any one of Claims 1-40, wherein the MEK inhibitor is used continuously.

42. The use or pharmaceutical composition of any one of Claims 1-41, wherein the MEK inhibitor is used intermittently.

43. The use or pharmaceutical composition of any one of Claims 1-41, wherein the MEK inhibitor is used before the PD-1 axis binding antagonist.

44. The use or pharmaceutical composition of any one of Claims 1-41, wherein the MEK inhibitor is used simultaneous with the PD-1 axis binding antagonist.

45. The use or pharmaceutical composition of any one of Claims 1-41, wherein the MEK inhibitor is used after the PD-1 axis binding antagonist.

46. The use or pharmaceutical composition of any one of Claims 1-45, wherein the individual has colorectal cancer.

47. The use or pharmaceutical composition of any one of Claims 1-45, wherein the individual has melanoma.

48. The use or pharmaceutical composition of any one of Claims 1-45, wherein the individual has non-small cell lung cancer.

49. The use or pharmaceutical composition of any one of Claims 1-45, wherein the individual has ovarian cancer.

50. The use or pharmaceutical composition of any one of Claims 1-45, wherein the individual has breast cancer.

51. The use or pharmaceutical composition of any one of Claims 1-45, wherein the individual

has pancreatic cancer.

52. The use or pharmaceutical composition of any one of Claims 1-45, wherein the individual has a hematological malignancy.

53. The use or pharmaceutical composition of any one of Claims 1-45, wherein the individual has renal cell carcinoma.

54. Use of an effective amount of a PD-1 axis binding antagonist and a MEK inhibitor for the manufacture of a first medicament comprising the PD-1 axis binding antagonist and a second medicament comprising the MEK inhibitor for enhancing immune function in an individual having cancer.

55. Use of an effective amount 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 agent is used in combination with a MEK inhibitor.

56. Use of an effective amount of a MEK inhibitor in the manufacture of a medicament for enhancing immune function in an individual having cancer, wherein the MEK inhibitor is used in combination with a PD-1 axis binding antagonist.

57. A pharmaceutical composition comprising a PD-1 axis binding antagonist in combination with a MEK inhibitor for use in enhancing immune function in an individual having cancer.

58. A pharmaceutical composition comprising a PD-1 axis binding antagonist for use in enhancing immune function in an individual having cancer in combination with a MEK inhibitor.

59. A pharmaceutical composition comprising a MEK inhibitor for use in enhancing immune function in an individual having cancer in combination with a PD-1 axis binding antagonist.

60. The use or pharmaceutical composition of any one of Claims 54-59, wherein CD8 T cells in the individual have enhanced priming, activation, proliferation and/or cytolytic activity relative to prior to the use of the medicament or pharmaceutical composition.

61. The use or pharmaceutical composition of Claim 60, wherein the CD8 T cell activation is characterized by an elevated frequency of γ-IFN$^+$ CD8 T cells and/or enhanced cytolytic activity relative to prior to the use of the medicament or pharmaceutical composition.

62. The use or pharmaceutical composition of Claim 60, wherein the number of CD8 T cells

is elevated relative to prior to the use of the medicament or pharmaceutical composition.

63. The use or pharmaceutical composition of any one of claims 60-62, wherein the CD8 T cell is an antigen-specific CD8 T cell.

64. The use or pharmaceutical composition of Claim 60, wherein the cancer cells in the individual selectively have elevated expression of MHC class I antigen expression relative to prior to the use of the PD-1 axis binding antagonist and the MEK inhibitor.

65. The use or pharmaceutical composition of Claim 64, wherein PBMC cells of the individual do not have elevated expression of MHC class I antigen.

66. The use or pharmaceutical composition of any one of Claims 54-59, wherein antigen presenting cells in the individual have enhanced maturation and activation relative prior to the use of the PD-1 axis binding antagonist and the MEK inhibitor.

67. The use or pharmaceutical composition of Claim 66, wherein the antigen presenting cells are dendritic cells.

68. The use or pharmaceutical composition of Claim 66, wherein the maturation of the antigen presenting cells is characterized by increased frequency of $CD83^+$ dendritic cells.

69. The use or pharmaceutical composition of Claim 66, wherein the activation of the antigen presenting cells is characterized by elevated expression of CD80 and CD86 on dendritic cells.

70. The use or pharmaceutical composition of Claim 60, wherein serum levels of IL-10 and/or IL-8 in the individual are reduced relative to prior to the use of the medicament or pharmaceutical composition.

71. The use or pharmaceutical composition of Claim 60, wherein the cancer has elevated levels of T-cell infiltration.

72. The use or pharmaceutical composition of any one of Claims 54-71, wherein the MEK inhibitor is a compound of the formula (I), (II), (III), (IV), (V), (VI) or (VII), or a pharmaceutically acceptable salt or solvate thereof.

73. The use or pharmaceutical composition of any one of Claims 54-71, wherein the MEK inhibitor is selected from the group consisting of G02442104, G-38963, G02443714, G00039805 and GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

74. The use or pharmaceutical composition of any one of Claims 54-71, wherein the PD-1

axis binding antagonist is an antibody.

75. The use or pharmaceutical composition of Claim 74, wherein PD-L1 on the cancer cell surface is inhibited from transducing a signal to the intracellular pathway.

76. The use or pharmaceutical composition of Claim 74, wherein the antibody is capable of inhibiting binding between PD-L1 and PD-1 and/or between PD-L1 and B7-1.

77. The use or pharmaceutical composition of Claim 22 or 74, wherein the antibody is a monoclonal antibody.

78. The use or pharmaceutical composition of Claim 22 or 74, wherein the antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

79. The use or pharmaceutical composition of Claim 22 or 74, wherein the antibody is a humanized antibody.

80. The use or pharmaceutical composition of Claim 22 or 74, wherein the antibody is a human antibody.

81. The use or pharmaceutical composition of Claim 74, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:15, HVR-H2 sequence of SEQ ID NO:16, and HVR-H3 sequence of SEQ ID NO:3; and a light chain comprising HVR-L1 sequence of SEQ ID NO:17, HVR-L2 sequence of SEQ ID NO:18, and HVR-L3 sequence of SEQ ID NO:19.

82. The use or pharmaceutical composition of Claim 74, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:24 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:21.

83. The use or pharmaceutical composition of any one of claims 1-82, wherein the PD-1 axis binding antagonist is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

84. A kit comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with a MEK inhibitor to treat or delay progression of cancer in an individual.

85. A kit comprising a PD-1 axis binding antagonist and a MEK inhibitor, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the MEK inhibitor to treat or delay progression of cancer in an individual.

86. A kit comprising a MEK inhibitor and a package insert comprising instructions for using the MEK inhibitor in combination with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.

87. The kit of any one of Claims 84-86, wherein the PD-1 axis binding antagonist is an anti-PD-L1 antibody.

88. The kit of any one of Claims 84-86, wherein the PD-1 axis binding antagonist is an anti-PD-1 antibody.

89. The kit of any one of Claims 84-86, wherein the PD-1 axis binding antagonist is an anti-PD-1 immunoadhesin.