BIOMARKERS AND METHODS OF TREATING PD-1 AND PD-L1 RELATED CONDITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of provisional U.S. Application Nos. 61/802,296 filed 15 March 2013; 61/812,678 filed 16 April 2013; 61/829,236 filed 30 May 2013 and 61/883,186 filed 26 September 2013, which are hereby incorporated by reference in their entirety.

FIELD

[0002] Provided herein are biomarkers for the treatment of pathological conditions, such as cancer, and methods of using PD-L1/PD-1 pathway antagonists. In particular, provided biomarkers for patient selection and prognosis in cancer, as well as methods of therapeutic treatment, articles of manufacture and methods for making them, diagnostic kits, methods of detection and methods of advertising related thereto.

BACKGROUND

[0003] Cancer remains to be one of the most deadly threats to human health. In the U.S., cancer affects nearly 1.3 million new patients each year, and is the second leading cause of death after heart disease, accounting for approximately 1 in 4 deaths. For example, lung cancer is the most common form of cancer and the leading cancer killer among American women. It is also predicted that cancer may surpass cardiovascular diseases as the number one cause of death within 5 years. Solid tumors are responsible for most of those deaths. Although there have been significant advances in the medical treatment of certain cancers, the overall 5-year survival rate for all cancers has improved only by about 10% in the past 20 years. Cancers, or malignant tumors, metastasize and grow rapidly in an uncontrolled manner, making timely detection and treatment extremely difficult.

[0004] Despite the significant advancement in the treatment of cancer, improved therapies are still being sought.

[0005] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

SUMMARY

[006] In one aspect, there is Pprovided ~~herein area~~ methods for identifying an individual with a disease or disorder who is more likely to respond to treatment with a PD-L1 axis binding antagonist, the method comprising: determining the presence of a PD-L1 biomarker in a sample from the individual, wherein the presence of a PD-L1 biomarker in the sample indicates that the individual is more likely to respond to treatment with the PD-L1 axis binding antagonist, and providing a

recommendation that the individual will be more likely to respond to treatment with a PD-L1 axis binding antagonist.

[007] In another aspect, there is ~~P~~provided ~~aherein are~~ methods for predicting responsiveness of an individual with a disease or disorder to treatment with a PD-L1 axis binding antagonist, the method comprising: determining the presence of a PD-L1 biomarker in a sample from the individual, wherein the presence of a PD-L1 biomarker in the sample indicates that the individual is more likely to be responsive to treatment with the PD-L1 axis binding antagonist, and providing a recommendation that the individual will have an increased likelihood of being responsive to treatment with a PD-L1 axis binding antagonist.

[008] In another aspect, there is ~~P~~provided ~~aherein are~~ methods for determining likelihood that an individual with a disease or disorder will exhibit benefit from treatment with a PD-L1 axis binding antagonist, the method comprising: determining the presence of a PD-L1 biomarker in a sample from the individual, wherein the presence of a PD-L1 biomarker in the sample indicates that the individual has an increased likelihood of benefit from treatment with the PD-L1 axis binding antagonist, and providing a recommendation that the individual will have an increased likelihood of benefit from treatment with a PD-L1 axis binding antagonist.

[009] In another aspect, there is ~~P~~provided ~~aherein are~~ methods for selecting a therapy for an individual with a disease or disorder, the method comprising: determining the presence of a PD-L1 biomarker in a sample from the individual, and providing a recommendation that the therapy selected for the individual comprise treatment with a PD-L1 axis binding antagonist based on the presence of a PD-L1 biomarker in the sample.

[0010] In some embodiments, the methods further comprise administering an effective amount of the PD-L1 axis binding antagonist to the individual.

[0010a] In another aspect, there is provided use of a PD-L1 axis binding antagonist in the manufacture of a medicament for treating a disease or disorder in an individual wherein the presence of a PD-L1 biomarker has been determined in a sample from the individual.

[0011] Provided herein are methods for treating a disease or disorder in an individual, the method comprising: determining the presence of a PD-L1 biomarker in a sample from the individual, and administering an effective amount of a PD-L1 axis binding antagonist to the individual.

[0011a] In another aspect, there is provided use of a PD-L1 axis binding antagonist in the manufacture of a medicament for treating a disease or disorder in an individual wherein treatment is based upon the presence of a PD-L1 biomarker in a sample from the individual.

[0012] Provided herein are methods of treating a disease or disorder in an individual comprising administering to the individual an effective amount of a PD-L1 axis binding antagonist, wherein treatment is based upon the presence of a PD-L1 biomarker in a sample from the individual.

[0013] In another aspect, there is ~~P~~provided ~~aherein are~~ methods for advertising a PD-L1 axis binding antagonist comprising promoting, to a target audience, the use of the PD-L1 axis binding antagonist for treating an individual with a disease or disorder based on the presence of a PD-L1 biomarker.

[0014] In another aspect, there is ~~P~~provided ~~anherein are~~ assays for identifying an individual with a disease or disorder to receive a PD-L1 axis binding antagonist, the method comprising: determining the presence of a PD-L1 biomarker in a sample from the individual, and recommending a PD-L1 axis binding antagonist based on the presence of a PD-L1 biomarker.

[0015] In another aspect, there is ~~P~~provided ~~herein are~~ diagnostic kits comprising one or more reagent for determining the presence of a PD-L1 biomarker in a sample from an individual with a disease or disorder, wherein the presence of a PD-L1 biomarker means a higher likelihood of efficacy when the individual is treated with a PD-L1 axis binding antagonist, and wherein the absence of a PD-L1 biomarker means a less likelihood of efficacy when the individual with the disease is treated with the PD-L1 axis binding antagonist.

[0016] Provided herein are also articles of manufacture comprising, packaged together, a PD-L1 axis binding antagonist, in a pharmaceutically acceptable carrier and a package insert indicating that the PD-L1 axis binding antagonist is for treating a patient with a disease or disorder based on expression of a PD-L1 biomarker. Treatment methods include any of the treatment methods disclosed herein. Further provided are methods for manufacturing an article of manufacture comprising combining in a package a pharmaceutical composition comprising a PD-L1 axis binding antagonist and a package insert indicating that the pharmaceutical composition is for treating a patient with a disease or disorder based on expression of a PD-L1 biomarker.

[0017] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 biomarker is selected from the group consisting of PD-L1, PD-1, PD-L2 and any combinations thereof.

[0018] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 biomarker is an immune-related marker. In some embodiments, the immune-related marker is a T-cell related marker. In some embodiments, the T-cell related marker is selected from the group consisting of CD8A, IFN-g, EOMES, Granzyme-A, CXCL9 and any combinations thereof. In some embodiments, the immune-related marker is selected from the group consisting of CX3CL1, CD45RO, IDO1, Galectin 9, MIC-A, MIC-B, CTLA-4 and any combinations thereof.

[0019] In some embodiments of any of the methods, uses, assays and/or kits, the disease or disorder is a proliferative disease or disorder. In some embodiments of any of the methods, uses, assays and/or kits, the disease or disorder is an immune-related disease or disorder. In some embodiments of any of the methods, uses, assays and/or kits, the disease or disorder is cancer. In some embodiments, the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, renal cell cancer, colorectal cancer, ovarian cancer, breast cancer, pancreatic cancer, gastric carcinoma, bladder cancer, esophageal cancer, mesothelioma, melanoma, head and neck cancer, thyroid cancer, sarcoma, prostate cancer, glioblastoma, cervical cancer, thymic carcinoma, leukemia, lymphomas, myelomas, mycoses fungoids, merkel cell cancer, and other hematologic malignancies.

[0020] In some embodiments of any of the methods, uses, assays and/or kits, wherein the sample obtained from the individual is selected from the group consisting of tissue, whole blood, plasma, serum and combinations thereof. In some embodiments, the tissue sample is a tumor tissue sample. In some embodiments, the tumor tissue sample comprises tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof. In some embodiments, the

tissue sample is formalin fixed and paraffin embedded, archival, fresh or frozen. In some embodiments, the sample is whole blood. In some embodiments, the whole blood comprises immune cells, circulating tumor cells and any combinations thereof.

[0021] In some embodiments of any of the methods, uses, assays and/or kits, the sample is obtained prior to treatment with a PD-L1 axis binding antagonist.

[0022] In some embodiments of any of the methods, uses, assays and/or kits, the presence of a PD-L1 biomarker indicates that the individual is likely to have increased clinical benefit when the individual is treated with the PD-L1 axis binding antagonist. In some embodiments, the increased clinical benefit comprises a relative increase in one or more of the following: overall survival (OS), progression free survival (PFS), complete response (CR), partial response (PR) and combinations thereof.

[0023] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 biomarker is absent from the sample when it comprises 0% of the sample.

[0024] In some embodiments of any of the methods, uses, assays and/or kits, 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 present in at least 1% of the sample. In some embodiments, the PD-L1 biomarker is present in at least 5% of the sample. In some embodiments, the PD-L1 biomarker is present in at least 10% of the sample.

[0025] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 biomarker is detected in the sample using a method selected from the group consisting of FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometery, HPLC, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, and FISH, and combinations thereof.

[0026] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 biomarker is detected in the sample by protein expression. In some embodiments, 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. In some embodiments, the PD-L1 biomarker is detected as a moderate staining intensity by IHC. In some embodiments, the PD-L1 biomarker is detected as a strong staining intensity by IHC. In some embodiments, the PD-L1 biomarker is detected on tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof. In some embodiments, the staining is membrane staining, cytoplasmic staining or combinations thereof.

[0027] In some embodiments of any of the methods, uses, assays and/or kits, the absence of the PD-L1 biomarker is detected as absent or no staining in the sample. In some embodiments of any of

the methods, uses, assays and/or kits, the presence of the PD-L1 biomarker is detected as any staining in the sample.

[0028] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 biomarker is detected in the sample by nucleic acid expression. In some embodiments, the nucleic acid expression is determined using qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH. . In some embodiments, the PD-L1 biomarker is detected on tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof.

[0029] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 axis binding antagonist is selected from the group consisting of a PD-L1 binding antagonist and a PD-1 binding antagonist.

[0030] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 axis binding antagonist is a PD-L1 binding antagonist. In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 binding antagonist inhibits the binding of PD-L1 to its ligand binding partners. In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

[0031] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 binding antagonist is an antibody. In some embodiments of any of the methods, uses, assays and/or kits, the antibody is a monoclonal antibody. In some embodiments of any of the methods, uses, assays and/or kits, the antibody is a human, humanized or chimeric antibody.

[0032] In some embodiments of any of the methods, uses, assays and/or kits, the PD-L1 axis binding antagonist is a PD-1 binding antagonist. In some embodiments of any of the methods, uses, assays and/or kits, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In some embodiments of any of the methods, uses, assays and/or kits, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In some embodiments of any of the methods, uses, assays and/or kits, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In some embodiments of any of the methods, uses, assays and/or kits, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.

[0033] In some embodiments of any of the methods, uses, assays and/or kits, the PD-1 binding antagonist is an antibody. In some embodiments of any of the methods, uses, assays and/or kits, the antibody is a monoclonal antibody. In some embodiments of any of the methods, uses, assays and/or kits, the antibody is a human, humanized or chimeric antibody.

[0034] In some embodiments of any of the methods, uses, assays and/or kits, further comprising an effective amount of a second therapeutic selected from the group consisting of cytotoxic agent, a

chemotherapeutic agent, a growth inhibitory agent, a radiation therapy agent, and anti-angiogenic agent, and combinations thereof.

[0035] In another aspect, there is ~~P~~provided ~~a~~herein ~~are~~ method~~s~~ for assessing a treatment response of an individual with a PD-L1 axis binding antagonist, the method comprising: (a) determining the level(s) of one or more biomarkers in a biological sample derived from the individual at a time point during or after administration of the PD-L1 axis binding antagonist; and (b) maintaining, adjusting, or stopping the treatment of the individual based on a comparison of the level(s) of one or more biomarkers in the biological sample with reference levels, wherein a change in the level(s) of one or more biomarkers in the biological sample compared to the reference levels is indicative of a response to treatment with the PD-L1 axis binding antagonist.

[0036] In another aspect, there is ~~P~~provided ~~a~~herein ~~are~~ method~~s~~ for monitoring the response of an individual treated with a PD-L1 axis binding antagonist, said method comprising: (a) determining the level(s) of one or more biomarkers in a biological sample derived from the individual at a time point during or after administration of the PD-L1 axis binding antagonist; and (b) comparing the level(s) of one or more biomarkers in the biological sample with reference levels in order to monitor the response in the individuals undergoing treatment with the PD-L1 axis binding antagonist.

[0037] In some embodiments, the reference levels of the one or more biomarkers is selected from the group consisting of (1) the level of the one or more biomarkers from the individual prior to administration of the PD-L1 axis binding antagonist; (2) the level of the one or more biomarkers from a reference population; (3) a pre-assigned level for the one or more biomarkers; and (4) the level of the one or more biomarkers from the individual at a second time point prior to the first time point.

[0038] In some embodiments, the change in the level(s) of one or more biomarkers in the biological sample compared to the reference levels is an increase in the levels.

[0039] In some embodiments, the change in the level(s) of one or more biomarkers in the biological sample compared to the reference levels is a decrease in the levels.

[0040] In some embodiments, the one or more biomarkers is selected from the group consisting of PD-L1, PD-1, PD-L2 and any combinations thereof.

[0041] In some embodiments, the one or more biomarkers selected from the group consisting of PD-L1, PD-1, PD-L2 and any combinations thereof is increased in the biological sample compared to the reference levels. In some embodiments, an increase in one or more biomarkers selected from the group consisting of PD-L1, PD-1, PD-L2 and any combinations thereof in the biological sample compared to the reference levels is indicative of a positive response to treatment.

[0042] In some embodiments, the one or more biomarkers is an immune related marker. In some embodiments, the one or more biomarkers is a T-cell related marker.

[0043] In some embodiments, the one or more biomarkers is a T-cell activation marker.

5. The method of any one of claims 1-4, further comprising administering an effective amount of the PD-L1 axis binding antagonist to the individual.

6. Use of a PD-L1 axis binding antagonist in the manufacture of a medicament ~~A method~~ for treating a disease or disorder in an individual, wherein~~the method comprising:~~

~~determining~~ the presence of a PD-L1 biomarker has been determined in a sample from the individual,~~, and~~

~~administering an effective amount of a PD-L1 axis binding antagonist to the individual.~~

7. Use of a PD-L1 axis binding antagonist in the manufacture of a medicament for~~A method of~~ treating a disease or disorder in an individual ~~comprising administering to the individual an effective amount of a PD-L1 axis binding antagonist,~~ wherein treatment is based upon the presence of a PD-L1 biomarker in a sample from the individual.

8. A method for advertising a PD-L1 axis binding antagonist comprising promoting, to a target audience, the use of the PD-L1 axis binding antagonist for treating an individual with a disease or disorder based on the presence of a PD-L1 biomarker.

9. An assay for identifying an individual with a disease or disorder to receive a PD-L1 axis binding antagonist, the method comprising:

a. determining the presence of a PD-L1 biomarker in a sample from the individual, and

b. recommending a PD-L1 axis binding antagonist based on the presence of a PD-L1 biomarker.

10. A diagnostic kit comprising one or more reagent for determining the presence of a PD-L1 biomarker in a sample from an individual with a disease or disorder, wherein the presence of a PD-L1 biomarker means a higher likelihood of efficacy when the individual is treated with a PD-L1 axis binding antagonist, and wherein the absence of a PD-L1 biomarker means a less likelihood of efficacy when the individual with the disease is treated with the PD-L1 axis binding antagonist.

11. The method, use, assay and/or kit of any of claims 1-10, wherein the PD-L1 biomarker is selected from the group consisting of PD-L1, PD-1, PD-L2 and any combinations thereof.

12. The method, use, assay and/or kit of any of claims 1-10, wherein the PD-L1 biomarker is an immune-related marker.

13. The method, use, assay and/or kit of claim 12, wherein the immune-related marker is a T-cell related marker.

14. The method, use, assay and/or kit of claim 13, wherein the T-cell related marker is selected from the group consisting of CD8A, IFN-g, EOMES, Granzyme-A, CXCL9 and any combinations thereof.

15. The method, use, assay and/or kit of claim 12, wherein the immune-related marker is selected from the group consisting of CX3CL1, CD45RO, IDO1, Galectin 9, MIC-A, MIC-B, CTLA-4 and any combinations thereof.

16. The method, use, assay and/or kit of any of claims 1-15, wherein the disease or disorder is a proliferative disease or disorder.

17. The method, use, assay and/or kit of any of claims 1-15, wherein the disease or disorder is an immune-related disease or disorder.

18. The method, use, assay and/or kit of any of claims 1-15, wherein the disease or disorder is cancer.

19. The method, use, assay and/or kit of claim 18, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, renal cell cancer, colorectal cancer, ovarian cancer, breast cancer, pancreatic cancer, gastric carcinoma, bladder cancer, esophageal cancer, mesothelioma, melanoma, head and neck cancer, thyroid cancer, sarcoma, prostate cancer, glioblastoma, cervical cancer, thymic carcinoma, leukemia, lymphomas, myelomas, mycoses fungoids, merkel cell cancer, and other hematologic malignancies.

20. The method, use, assay and/or kit of any of claims 1-19, wherein the sample obtained from the individual is selected from the group consisting of tissue, whole blood, plasma, serum and combinations thereof.

21. The method, use, assay and/or kit of claim 20 wherein the tissue sample is a tumor tissue sample.

22. The method, use, assay and/or kit of claim 21, wherein the tumor tissue sample comprises tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof.

23. The method, use, assay and/or kit of any of claims 20-22, wherein the tissue sample is formalin fixed and paraffin embedded, archival, fresh or frozen.

24. The method, use, assay and/or kit of claim 20, wherein the sample is whole blood.

25. The method, use, assay and/or kit of claim 24, wherein the whole blood comprises immune cells, circulating tumor cells and any combinations thereof.

26. The method, use, assay and/or kit of any of claims 1-25, wherein the sample is obtained prior to treatment with a PD-L1 axis binding antagonist.

27. The method, use, assay and/or kit of any of claims 1-26, wherein the presence of a PD-L1 biomarker indicates that the individual is likely to have increased clinical benefit when the individual is treated with the PD-L1 axis binding antagonist.

28. The method, use, assay and/or kit of claim 27, wherein the increased clinical benefit comprises a relative increase in one or more of the following: overall survival (OS), progression free survival (PFS), complete response (CR), partial response (PR) and combinations thereof.

29. The method, use, assay and/or kit any of claims 1-28, wherein the PD-L1 biomarker is absent from the sample when it comprises 0% of the sample.

30. The method, use, assay and/or kit of any of claims 1-28, wherein the PD-L1 biomarker is present in the sample when it comprises more than 0% of the sample.

31. The method, use, assay and/or kit of claim 30, wherein the PD-L1 biomarker is present in at least 1% of the sample.

32. The method, use, assay and/or kit of claim 30, wherein the PD-L1 biomarker is present in at least 5% of the sample.

33. The method, use, assay and/or kit of claim 30, wherein the PD-L1 biomarker is present in at least 10% of the sample.

34. The method, use, assay and/or kit of any of claims 1-33, wherein the PD-L1 biomarker is detected in the sample using a method selected from the group consisting of FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometery, HPLC, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, and FISH, and combinations thereof.

35. The method, use, assay and/or kit of any of claims 1-34, wherein the PD-L1 biomarker is detected in the sample by protein expression.

36. The method, use, assay and/or kit of claim 35, wherein protein expression is determined by immunohistochemistry (IHC).

37. The method, use, assay and/or kit of claim 36, wherein the PD-L1 biomarker is detected using an anti-PD-L1 antibody.

38. The method, use, assay and/or kit of any of claims 35-37, wherein the PD-L1 biomarker is detected as a weak staining intensity by IHC.

39. The method, use, assay and/or kit of any of claims 35-37, wherein the PD-L1 biomarker is detected as a moderate staining intensity by IHC.

40. The method, use, assay and/or kit of any of claims 35-37, wherein the PD-L1 biomarker is detected as a strong staining intensity by IHC.

41. The method, use, assay and/or kit of any of claims 30-40, wherein the PD-L1 biomarker is detected on tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof.

42. The method, use, assay and/or kit of any of claims 30-41, wherein staining is membrane staining, cytoplasmic staining and combinations thereof.

43. The method, use, assay and/or kit of any of claims 30-42, wherein absence of the PD-L1 biomarker is detected as absent or no staining in the sample.

44. The method, use, assay and/or kit of any of claims 30-43, wherein the presence of the PD-L1 biomarker is detected as any staining in the sample.

45. The method, use, assay and/or kit of any of claims 1-34, wherein the PD-L1 biomarker is detected in the sample by nucleic acid expression.

46. The method, use, assay and/or kit of claim 45, wherein the nucleic acid expression is determined using qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, or FISH.

47. The method, use, assay and/or kit of claim 45-46, wherein the PD-L1 biomarker is detected on tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof.

48. The method, use, assay and/or kit of any of claims 1-47, wherein the PD-L1 axis binding antagonist is selected from the group consisting of a PD-L1 binding antagonist and a PD-1 binding antagonist.

49. The method, use, assay and/or kit of claim 48, wherein the PD-L1 axis binding antagonist is a PD-L1 binding antagonist.

50. The method, use, assay and/or kit of claim 49, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to its ligand binding partners.

51. The method, use, assay and/or kit of claim 50, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

52. The method, use, assay and/or kit of claim 50, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

53. The method, use, assay and/or kit of claim 50, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

54. The method, use, assay and/or kit of claim 50, wherein the PD-L1 binding antagonist is an antibody.

55. The method, use, assay and/or kit of claim 54, wherein the antibody is a monoclonal antibody.

56. The method, use, assay and/or kit of claim 55, wherein the antibody is a human, humanized or chimeric antibody.

57. The method, use, assay and/or kit of claim 48, wherein the PD-L1 axis binding antagonist is a PD-1 binding antagonist.

58. The method, use, assay and/or kit of claim 57, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

59. The method, use, assay and/or kit of claim 58, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1.

60. The method, use, assay and/or kit of claim 58, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2.

61. The method, use, assay and/or kit of claim 58, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.

62. The method, use, assay and/or kit of claim 58, wherein the PD-1 binding antagonist is an antibody.

63. The method, use, assay and/or kit of claim 62, wherein the antibody is a monoclonal antibody.

64. The method, use, assay and/or kit of claim 63, wherein the antibody is a human, humanized or chimeric antibody.

65. The method, use, assay and/or kit of any of claims 1-64, further comprising an effective amount of a second therapeutic selected from the group consisting of cytotoxic agent, a chemotherapeutic agent, a growth inhibitory agent, a radiation therapy agent, and anti-angiogenic agent, and combinations thereof.

66. A method for assessing a treatment response of an individual with a PD-L1 axis binding antagonist, the method comprising:
(a) determining the level(s) of one or more biomarkers in a biological sample derived from the individual at a time point during or after administration of the PD-L1 axis binding antagonist; and
(b) maintaining, adjusting, or stopping the treatment of the individual based on a comparison of the level(s) of one or more biomarkers in the biological sample with reference levels, wherein a change in the level(s) of one or more biomarkers in the biological sample compared to the reference levels is indicative of a response to treatment with the PD-L1 axis binding antagonist.

67. A method for monitoring the response of an individual treated with a PD-L1 axis binding antagonist, said method comprising:
(a) determining the level(s) of one or more biomarkers in a biological sample derived from the individual at a time point during or after administration of the PD-L1 axis binding antagonist; and
(b) comparing the level(s) of one or more biomarkers in the biological sample with reference levels in order to monitor the response in the individuals undergoing treatment with the PD-L1 axis binding antagonist.

68. The method of any of claims 66-67, wherein the reference levels of the one or more biomarkers is selected from the group consisting of (1) the level of the one or more biomarkers from the individual prior to administration of the PD-L1 axis binding antagonist; (2) the level of the one or more biomarkers from a reference population; (3) a pre-assigned level for the one or more biomarkers; and (4) the level of the one or more biomarkers from the individual at a second time point prior to the first time point.

69. The method of any of claims 66-68, wherein the change in the level(s) of one or more biomarkers in the biological sample compared to the reference levels is an increase in the levels.