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, the present disclosure refers to a method 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: a. 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 b. 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, the present disclosure refers to a method for predicting responsiveness of an individual with a disease or disorder to treatment with a PD-L1 axis binding antagonist, the method comprising: a. 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 b. 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, the present disclosure refers to a method 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: a. 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 b. 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, the present disclosure refers to a method for selecting a therapy for an individual with a disease or disorder, the method comprising: a. determining the presence of a PD-L1 biomarker in a sample from the individual, and b. 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 examples, the methods further comprise administering an effective amount of the PD-L1 axis binding antagonist to the individual.

[0010a] In another aspect, the present disclosure refers to 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, the present disclosure refers to 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, the present disclosure refers to 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.

[0014] In another aspect, the present disclosure refers to an assay 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, the present disclosure refers to 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.

[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 examples 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 examples of any of the methods, uses, assays and/or kits, the PD-L1 biomarker is an immune-related marker. In some examples, the immune-related marker is a T-cell related marker. In some examples, 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 examples, 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 examples of any of the methods, uses, assays and/or kits, the disease or disorder is a proliferative disease or disorder. In some examples of any of the methods, uses, assays and/or kits, the disease or disorder is an immune-related disease or disorder. In some examples of any of the methods, uses, assays and/or kits, the disease or disorder is cancer. In some examples, 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 examples 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 examples, the tissue sample is a tumor tissue sample. In some examples, the tumor tissue sample comprises tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof. In some examples, the

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

[0021] In some examples 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 examples 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 examples, 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 examples 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 examples 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 examples, the PD-L1 biomarker is present in at least 1% of the sample. In some examples, the PD-L1 biomarker is present in at least 5% of the sample. In some examples, the PD-L1 biomarker is present in at least 10% of the sample.

[0025] In some examples 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 examples of any of the methods, uses, assays and/or kits, the PD-L1 biomarker is detected in the sample by protein expression. In some examples, protein expression is determined by immunohistochemistry (IHC). In some examples, the PD-L1 biomarker is detected using an anti-PD-L1 antibody. In some examples, the PD-L1 biomarker is detected as a weak staining intensity by IHC. In some examples, the PD-L1 biomarker is detected as a moderate staining intensity by IHC. In some examples, the PD-L1 biomarker is detected as a strong staining intensity by IHC. In some examples, the PD-L1 biomarker is detected on tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof. In some examples, the staining is membrane staining, cytoplasmic staining or combinations thereof.

[0027] In some examples 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 examples 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 examples 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 examples, 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 examples, the PD-L1 biomarker is detected on tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof.

[0029] In some examples 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 examples of any of the methods, uses, assays and/or kits, the PD-L1 axis binding antagonist is a PD-L1 binding antagonist. In some examples 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 examples 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 examples 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 examples 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 examples of any of the methods, uses, assays and/or kits, the PD-L1 binding antagonist is an antibody. In some examples of any of the methods, uses, assays and/or kits, the antibody is a monoclonal antibody. In some examples of any of the methods, uses, assays and/or kits, the antibody is a human, humanized or chimeric antibody.

[0032] In some examples of any of the methods, uses, assays and/or kits, the PD-L1 axis binding antagonist is a PD-1 binding antagonist. In some examples 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 examples 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 examples 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 examples 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 examples of any of the methods, uses, assays and/or kits, the PD-1 binding antagonist is an antibody. In some examples of any of the methods, uses, assays and/or kits, the antibody is a monoclonal antibody. In some examples of any of the methods, uses, assays and/or kits, the antibody is a human, humanized or chimeric antibody.

[0034] In some examples 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, the present disclosure refers to 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.

[0036] In another aspect, the present disclosure refers to 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.

[0037] In some examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the one or more biomarkers is an immune related marker. In some examples, the one or more biomarkers is a T-cell related marker.

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

[0044] In some examples, the T-cell activation marker is increased in the biological sample compared to the reference levels.

[0045] In some examples, the T-cell activation marker is selected from the group consisting of an CD8, IFN-g, Granzyme-A, TNF-a, perforin and any combinations thereof. In some examples, an increase in the T-cell activation marker selected from the group consisting of CD8, IFN-g, Granzyme-A, TNF-a, perforin and any combinations thereof in the biological sample compared to the reference levels is indicative of a positive response to treatment.

[0046] In some examples, the one or more biomarkers is an activated proliferating T cell.

[0047] In some examples, the activated proliferating T cell is increased in the biological sample compared to the reference levels.

[0048] In some examples, the activated proliferating T cell is a CD8+/Ki67+ cell, CD8+/HLA-DR+/Ki67+ cell and any combinations thereof.

[0049] In some examples, the one or more biomarkers is IL-6. In some examples, the IL-6 level is decreased in the biological sample compared to the reference levels. In some examples, a decrease in the IL-6 level in the biological sample compared to the reference levels is indicative of a positive response to treatment. In some examples, the IL-6 level is increased in the biological sample compared to the reference levels. In some examples, an increase in the IL-6 level in the biological sample compared to the reference levels is indicative of a negative response to treatment.

[0050] In some examples, the biological sample derived from the individual is selected from the group consisting of a cell, a tissue, a tissue culture, a tumor, a biological fluid and combinations thereof.

[0051] In some examples, the biological fluid is selected from the group consisting of plasma, serum, whole blood, PBMCs and combinations thereof.

[0052] In some examples, the tissue is a tumor tissue. In some examples, the tumor tissue is selected from the group consisting of tumor cells, tumor infiltrating cells, stromal cells and any combinations thereof.

[0053] In some examples, the cell is a circulating tumor cell (CTC).

[0054] In some examples, the individual suffers from a proliferative disease or disorder.

[0055] In some examples, the individual suffers from cancer or malignancy. In some examples, the cancer or malignancy is selected from 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.

[0056] In some examples, the individual suffers from an immune-related disease or disorder.

[0057] In some examples, the PD-L1 axis binding antagonist is a PD-L1 binding antagonist.

[0058] In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to its ligand binding partners.

[0059] In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

[0060] In some examples, the PD-L1 binding antagonist is an antibody. In some examples, the antibody is a monoclonal antibody. In some examples, the antibody is a human, humanized or chimeric antibody.

[0061] In some examples, the PD-L1 axis binding antagonist is a PD-1 binding antagonist.

[0062] In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

[0063] In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.

[0064] In some examples, the PD-1 binding antagonist is an antibody. In some examples, the antibody is a monoclonal antibody. In some examples, the antibody is a human, humanized or chimeric antibody.

BRIEF DESCRIPTION OF THE FIGURES

[0065] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0066] **Figure 1** shows exemplary IHC analysis of control cell samples. (A) Negative control IHC staining of parental HEK-293 cells; (B) IHC staining of HEK-293 cells transfected with recombinant human PD-L1 with weak staining intensity; (C) IHC staining of HEK-293 cells transfected with recombinant human PD-L1 with moderate staining intensity; (D) IHC staining of HEK-293 cells transfected with recombinant human PD-L1 with strong staining intensity; (E) Positive tissue control IHC staining of placental tissue sample; (F) Positive tissue control IHC staining of tonsil tissue sample. All IHC staining were performed using a proprietary anti-PD-L1 antibody.

WHAT IS CLAIMED IS:

1. A method 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:

a. 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

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

2. A method for predicting responsiveness of an individual with a disease or disorder to treatment with a PD-L1 axis binding antagonist, the method comprising:

a. 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

b. providing a recommendation that the individual will have an increased likelihood of being responsive to treatment with a PD-L1 axis binding antagonist.

3. A method 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:

a. 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

b. providing a recommendation that the individual will have an increased likelihood of benefit from treatment with a PD-L1 axis binding antagonist.

4. A method for selecting a therapy for an individual with a disease or disorder, the method comprising:

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

b. 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.

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 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.

7. 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.

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.

70. 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 a decrease in the levels.

71. The method of any of claims 66-70, wherein the one or more biomarkers is selected from the group consisting of PD-L1, PD-1, PD-L2 and any combinations thereof.

72. The method of any of claims 66-71, wherein the one or more biomarkers is an immune related marker.

73. The method of any of claims 66-71, wherein the one or more biomarkers is a T-cell related marker.

74. The method of any of claims 66-71, wherein the one or more biomarkers is a T-cell activation marker.

75. The method of claim 74, wherein the T-cell activation marker is increased in the biological sample compared to the reference levels.

76. The method of claim 75, wherein the T-cell activation marker is selected from the group consisting of CD8, IFN-g, Granzyme-A, TNF-a, perforin and any combinations thereof.

77. The method of any of claims 66-71, wherein the one or more biomarkers is an activated proliferating T cell.

78. The method of claim 77, wherein the activated proliferating T cell is increased in the biological sample compared to the reference levels.

79. The method of claim 78, wherein the activated proliferating T cell is a CD8+/Ki67+ cell, CD8+/HLA-DR+/Ki67+ cell and any combinations thereof.

80. The method of any of claims 66-71, wherein the one or more biomarkers is IL-6.

81. The method of claim 80, wherein the IL-6 level is decreased in the biological sample compared to the reference levels.

82. The method of any of claims 66-81, wherein the biological sample derived from the individual is selected from the group consisting of a cell, a tissue, a tissue culture, a tumor, a biological fluid and combinations thereof.

83. The method of claim 82, wherein the biological fluid is selected from the group consisting of plasma, serum, whole blood, PBMCs and combinations thereof.

84. The method of claim 82, wherein the tissue is a tumor tissue.

85. The method of claim 84, wherein the tumor tissue is selected from the group consisting of tumor cells, tumor infiltrating cells, stromal cells and any combinations thereof.

86. The method of claim 82, wherein the cell is a circulating tumor cell (CTC).

87. The method of any of claims 66-86, wherein the individual suffers from a proliferative disease or disorder.

88. The method of any of claims 66-86, wherein the individual suffers from cancer or malignancy.

89. The method of claim 88, wherein the cancer or malignancy is selected from 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.

90. The method of any of claims 66-86, wherein the individual suffers from an immune-related disease or disorder.

91. The method of any of claims 66-90, wherein the PD-L1 axis binding antagonist is a PD-L1 binding antagonist.

92. The method of claim 91, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to its ligand binding partners.

93. The method of claim 92, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

94. The method of claim 92, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

95. The method of claim 92, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

96. The method of claim 91, wherein the PD-L1 binding antagonist is an antibody.

97. The method of claim 96, wherein the antibody is a monoclonal antibody.

98. The method of claim 96, wherein the antibody is a human, humanized or chimeric antibody.

99. The method of any of claims 66-90, wherein the PD-L1 axis binding antagonist is a PD-1 binding antagonist.

100. The method of claim 99, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

101. The method of claim 100, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1.

102. The method of claim 100, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2.

103. The method of claim 100, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.

104. The method of claim 99, wherein the PD-1 binding antagonist is an antibody.

105. The method of claim 104, wherein the antibody is a monoclonal antibody.

106. The method of claim 104, wherein the antibody is a human, humanized or chimeric antibody.