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 example, 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.

[006a] In one aspect, the present disclosure refers to a method for identifying an individual with a cancer who is more likely to respond to treatment with an anti-PD-L1 antagonist antibody, the method comprising:

a. determining the presence or level of PD-L1 and IFN-g in a tumor tissue sample from the individual, wherein the tumor tissue sample is obtained prior to treatment with the anti-PD-L1 antagonist antibody, and wherein the presence or an increased level ofPD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample indicates that the individual is more likely to respond to treatment with the anti-PD-L1 antagonist antibody, and

b. providing a recommendation that the individual will be more likely to respond to treatment with an anti-PD-L1 antagonist antibody,

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);
(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);
(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);
(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);
(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and
(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

[007] In another example, 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.

[007a] In one aspect, the present disclosure refers to a method for predicting responsiveness of an individual with a cancer to treatment with an anti-PD-L1 antagonist antibody, the method comprising:

a. determining the presence or level of PD-L1 and IFN-g in a tumor tissue sample from the individual, wherein the tumor tissue sample is obtained prior to treatment with the anti-PD-L1 antagonist antibody, and wherein the presence or an increased level of PD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample indicates that the individual is more likely to be responsive to treatment with the anti-PD-L1 antagonist antibody, and

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

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);
(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);
(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);
(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);
(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and
(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

[008] In another example, 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.

[008a] In one aspect, the present disclosure refers to a method for determining likelihood that an individual with a cancer will exhibit benefit from treatment with an anti-PD-L1 antagonist antibody, the method comprising:

a. determining the presence or level of PD-L1 and IFN-g in a tumor tissue sample from the individual, wherein the tumor tissue sample is obtained prior to treatment with the anti-PD-L1 antagonist antibody, and wherein the presence or an increased level of PD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample indicates that the individual has an increased likelihood of benefit from treatment with the anti-PD-L1 antagonist antibody, and

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

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);
(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);
(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);
(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);
(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and
(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

[009] In another example, 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.

[009a] In one aspect, the present disclosure refers to a method for selecting a therapy for an individual with a cancer, the method comprising:

a. determining the presence or level of PD-L1 and IFN-g in a tumor tissue sample from the individual, wherein the tumor tissue sample is obtained prior to treatment with an anti-PD-L1 antagonist antibody, and

b. providing a recommendation that the therapy selected for the individual comprise treatment with the anti-PD-L1 antagonist antibody based on the presence or an increased level of PD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample, wherein the presence or an increased level of PD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample indicates that the individual is more likely to respond to treatment with the anti-PD-L1 antagonist antibody,

and wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);
(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);
(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);
(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);
(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and
(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

[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 an anti-PD-L1 antagonist antibody in the manufacture of a medicament for treating a cancer in an individual, wherein the presence or an increased level of PD-L1 and IFN-g has been determined in a tumor tissue sample from the individual, thereby indicating that the individual is likely to have an increased clinical benefit from treatment with the anti-PD-L1 antibody, wherein the tumor tissue sample is obtained prior to treatment with the anti-PD-L1 antagonist antibody, and

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);

(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);

(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);

(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);

(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and

(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

[0010b] In one aspect, the present disclosure refers to use of an anti-PD-L1 antagonist antibody in the manufacture of a medicament for treating a cancer in an individual, wherein treatment comprises:

(a) determining the presence of a PD-L1 protein in a sample from the individual, wherein the sample is a tumor tissue sample comprising tumor infiltrating immune cells; and

(b) administering an effective amount of an anti-PD-L1 antibody to the individual, wherein the sample from the individual has a detectable expression level of the PD-L1 protein in tumor infiltrating immune cells covering at least 10% of tumor area in the tumor tissue sample, thereby indicating that the individual is likely to have an increased clinical benefit from treatment with the anti-PD-L1 antibody,

wherein the sample from the individual is obtained prior to treatment with the anti-PD-L1 antibody, and wherein the anti-PD-L1 antibody is atezolizumab (MPDL3280A).

[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 example, 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 example, 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 example, 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 example, 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.

[0016a] In one aspect, the present disclosure refers to an article of manufacture comprising:

a. an anti-PD-L1 antagonist antibody, and

b. a package insert indicating that the anti-PD-L1 antagonist antibody is for treating an individual having a cancer based a tumor tissue sample obtained from the individual having PD-L1 and IFN-g that is present or at an increased level compared to the level of PD-L1 and IFN-g in a reference sample, wherein the presence or increased level of PD-L1 and IFN-g indicates that the individual is likely to have an increased clinical benefit from treatment with the anti-PD-L1 antagonist antibody, and

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);
(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);
(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);
(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);
(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and
(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

[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

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

[0035] In another example, 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 example, 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.

WHAT IS CLAIMED IS:

1. A method for identifying an individual with a cancer who is more likely to respond to treatment with an anti-PD-L1 antagonist antibody, the method comprising:

a. determining the presence or level of PD-L1 and IFN-g in a tumor tissue sample from the individual, wherein the tumor tissue sample is obtained prior to treatment with the anti-PD-L1 antagonist antibody, and wherein the presence or an increased level ofPD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample indicates that the individual is more likely to respond to treatment with the anti-PD-L1 antagonist antibody, and

b. providing a recommendation that the individual will be more likely to respond to treatment with an anti-PD-L1 antagonist antibody,

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);

(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);

(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);

(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);

(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and

(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

2. A method for predicting responsiveness of an individual with a cancer to treatment with an anti-PD-L1 antagonist antibody, the method comprising:

a. determining the presence or level of PD-L1 and IFN-g in a tumor tissue sample from the individual, wherein the tumor tissue sample is obtained prior to treatment with the anti-PD-L1 antagonist antibody, and wherein the presence or an increased level of PD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample indicates that the individual is more likely to be responsive to treatment with the anti-PD-L1 antagonist antibody, and

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

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);

(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);

(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);

(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);

(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and

(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

3. A method for determining likelihood that an individual with a cancer will exhibit benefit from treatment with an anti-PD-L1 antagonist antibody, the method comprising:

a. determining the presence or level of PD-L1 and IFN-g in a tumor tissue sample from the individual, wherein the tumor tissue sample is obtained prior to treatment with the anti-PD-L1 antagonist antibody, and wherein the presence or an increased level of PD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample indicates that the individual has an increased likelihood of benefit from treatment with the anti-PD-L1 antagonist antibody, and

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

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);

(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);

(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);

(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);

(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and

(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

4. A method for selecting a therapy for an individual with a cancer, the method comprising:

a. determining the presence or level of PD-L1 and IFN-g in a tumor tissue sample from the individual, wherein the tumor tissue sample is obtained prior to treatment with an anti-PD-L1 antagonist antibody, and

b. providing a recommendation that the therapy selected for the individual comprise treatment with the anti-PD-L1 antagonist antibody based on the presence or an increased level of PD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample, wherein the presence or an increased level of PD-L1 and IFN-g in the tumor tissue sample relative to the presence or level of PD-L1 and IFN-g in a reference sample indicates that the individual is more likely to respond to treatment with the anti-PD-L1 antagonist antibody,

and wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);

(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);

(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);

(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);

(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and

(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

5. Use of an anti-PD-L1 antagonist antibody in the manufacture of a medicament for treating a cancer in an individual, wherein the presence or an increased level of PD-L1 and IFN-g has been determined in a tumor tissue sample from the individual, thereby indicating that the individual is likely to have an increased clinical benefit from treatment with the anti-PD-L1 antibody, wherein the tumor tissue sample is obtained prior to treatment with the anti-PD-L1 antagonist antibody, and

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);

(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);

(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);

(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);

(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and

(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

6. An article of manufacture comprising:

a. an anti-PD-L1 antagonist antibody, and

b. a package insert indicating that the anti-PD-L1 antagonist antibody is for treating an individual having a cancer based a tumor tissue sample obtained from the individual having PD-L1 and IFN-g that is present or at an increased level compared to the level of PD-L1 and IFN-g in a reference sample, wherein the presence or increased level of PD-L1 and IFN-g indicates that the individual is likely to have an increased clinical benefit from treatment with the anti-PD-L1 antagonist antibody, and

wherein the anti-PD-L1 antagonist antibody comprises the following hypervariable regions (HVRs):

(a) an HVR-H1 sequence of GFTFSDSWIH (SEQ ID NO: 15);

(b) an HVR-H2 sequence of AWISPYGGSTYYADSVKG (SEQ ID NO: 16);

(c) an HVR-H3 sequence of RHWPGGFDY (SEQ ID NO: 3);

(d) an HVR-L1 sequence of RASQDVSTAVA (SEQ ID NO: 17);

(e) an HVR-L2 sequence of SASFLYS (SEQ ID NO: 18); and

(f) an HVR-L3 sequence of QQYLYHPAT (SEQ ID NO: 19).

7. The method, use, and/or article of manufacture of any one of claims 1-6, wherein the anti-PD-L1 antagonist antibody comprises a heavy chain variable (VH) domain comprising an amino acid sequence having the amino acid sequence of SEQ ID NO: 20 and a light chain variable (VL) domain comprising an amino acid sequence having the amino acid sequence of SEQ ID NO: 21.

8. The method, use, and/or article of manufacture of any one of claims 1-7, further comprising determining the presence or level of PD-1, PD-L2, or both PD-1 and PD-L2.

9. The method, use, and/or article of manufacture of any one of claims 1-8, further comprising determining the presence or level of CD8A, EOMES, Granzyme A, Granzyme B, CXCL9 and any combinations thereof.

10. The method, use, and/or article of manufacture of any one of claims 1-9, further comprising determining the presence or level of CX3CL1, CD45RO, IDO1, Galectin 9, MIC-A, MIC-B, CTLA-4 and any combinations thereof.

11. The method, use, and/or article of manufacture of any one of claims 1-10, 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, melanoma, head and neck cancer, sarcoma, prostate cancer, cervical cancer, thymic carcinoma, lymphomas, myelomas, mycoses fungoides, Merkel cell cancer, and other hematologic malignancies.

12. The method, use, and/or article of manufacture of any one of claims 1-11, wherein the tumor tissue sample comprises tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof.

13. The method, use, and/or article of manufacture of any one of claims 1-12, wherein the tissue sample is formalin fixed and paraffin embedded, archival, fresh or frozen.

14. The method, use, and/or article of manufacture of any one of claims 1-13, wherein the individual treated with the anti-PD-L1 antagonist antibody is likely to have 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.

15. The method, use, and/or article of manufacture of any one of claims 1-14, wherein PD-L1 is present in the tumor tissue sample when it comprises more than 0% of the tumor tissue sample.

16. The method, use, and/or article of manufacture of claim 15, wherein PD-L1 is present in at least 1% of the tumor tissue sample.

17. The method, use, and/or article of manufacture of claim 15, wherein PD-L1 is present in at least 5% of the tumor tissue sample.

18. The method, use, and/or article of manufacture of claim 15, wherein PD-L1 is present in at least 10% of the tumor tissue sample.

19. The method, use, and/or article of manufacture of any one of claims 1-18, wherein PD-L1 is detected in the tumor tissue 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 spectrometry, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, and FISH, and combinations thereof.

20. The method, use, and/or article of manufacture of any one of claims 1-19, wherein PD-L1 is detected in the tumor tissue sample by protein expression.

21. The method, use, and/or article of manufacture of claim 20, wherein protein expression is determined by immunohistochemistry (IHC).

22. The method, use, and/or article of manufacture of claim 21, wherein PD-L1 is detected using an anti-PD-L1 antibody.

23. The method, use, and/or article of manufacture of any one of claims 20-22, wherein PD-L1 is detected as a weak staining intensity by IHC.

24. The method, use, and/or article of manufacture of any one of claims 20-22, wherein PD-L1 is detected as a moderate staining intensity by IHC.

25. The method, use, and/or article of manufacture of any one of claims 20-22, wherein PD-L1 is detected as a strong staining intensity by IHC.

26. The method, use, and/or article of manufacture of any one of claims 15-25, wherein PD-L1 is detected on tumor cells, tumor infiltrating immune cells, stromal cells, and any combinations thereof.

27. The method, use, and/or article of manufacture of any one of claims 15-26, wherein staining is membrane staining, cytoplasmic staining and combinations thereof.

28. The method, use, and/or article of manufacture of any one of claims 15-27, wherein the presence of PD-L1 is detected as any staining in the tumor tissue sample.

29. The method, use, and/or article of manufacture of any one of claims 1-19, wherein PD-L1 is detected in the tumor tissue sample by nucleic acid expression.

30. The method, use, and/or article of manufacture of claim 29, 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.

31. The method, use, and/or article of manufacture of claim 29 or 30, wherein PD-L1 is detected on tumor cells, tumor infiltrating immune cells, stromal cells and any combinations thereof.

32. The method, use, and/or article of manufacture of any one of claims 1-31, wherein the anti-PD-L1 antagonist antibody inhibits the binding of PD-L1 to its ligand binding partners.

33. The method, use, and/or article of manufacture of claim 32, wherein the anti-PD-L1 antagonist antibody inhibits the binding of PD-L1 to PD-1.

34. The method, use, and/or article of manufacture of claim 32, wherein the anti-PD-L1 antagonist antibody inhibits the binding of PD-L1 to B7-1.

35. The method, use, and/or article of manufacture of claim 32, wherein the anti-PD-L1 antagonist antibody inhibits the binding of PD-L1 to both PD-1 and B7-1.

36. The method, use, and/or article of manufacture of any one of claims 1-35, wherein the anti-PD-L1 antagonist antibody is a monoclonal antibody.

37. The method, use, and/or article of manufacture of claim 36, wherein the anti-PD-L1 antagonist antibody is a human, humanized or chimeric antibody.

38. The method, use, and/or article of manufacture of any one of claims 1-37, wherein the anti-PD-L1 antagonist antibody is atezolizumab (MPDL3280A).

39. The method, use, and/or article of manufacture of any one of claims 1-38, wherein the reference sample is:

(a) a sample from one or more individuals with the cancer who is not the individual undergoing treatment;

(b) a sample from one or more healthy individuals who is not the individual undergoing treatment; or

(c) a pre-assigned level for PD-L1 and IFN-g.

40. The method, use, and/or article of manufacture of any one of claims 1-39, wherein the reference sample is a tissue sample, a plasma sample, or a serum sample.

41. The method or use of any one of claims 1-5 or 7-40, wherein the treatment further comprises a second therapeutic agent 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.

42. The article of manufacture of any one of claims 6-40, wherein the article of manufacture further comprises a second therapeutic agent 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.

43. Use of an anti-PD-L1 antagonist antibody in the manufacture of a medicament for treating a cancer in an individual, wherein treatment comprises:

(a) determining the presence of a PD-L1 protein in a sample from the individual, wherein the sample is a tumor tissue sample comprising tumor infiltrating immune cells; and

(b) administering an effective amount of an anti-PD-L1 antibody to the individual, wherein the sample from the individual has a detectable expression level of the PD-L1 protein in tumor infiltrating immune cells covering at least 10% of tumor area in the tumor tissue sample, thereby indicating that the individual is likely to have an increased clinical benefit from treatment with the anti-PD-L1 antibody,

wherein the sample from the individual is obtained prior to treatment with the anti-PD-L1 antibody, and wherein the anti-PD-L1 antibody is atezolizumab (MPDL3280A).

44. The use of claim 43, wherein the cancer is a metastatic non-small cell lung cancer.