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(54) Title: COMBINATION OF A PD-1 ANTAGONIST AND AN ALK INHIBITOR FOR TREATING CANCER

(57) Abstract: The present disclosure describes combination therapies comprising an antagonist of Programmed Death 1 receptor (PD-1) and an Anaplastic Lymphoma Kinase (ALK) inhibitor, and the use of the combination therapies for the treatment of cancer, and in particular for treating cancers that test positive for ALK, PD-L 1, or both ALK and PD-L 1.

COMBINATION OF A PD-1 ANTAGONIST AND AN ALK INHIBITOR FOR TREATING CANCER

RELATED APPLICATIONS

[0001]   This application claims the benefit of U.S. provisional application 62/041,288, filed on August 25, 2014, which is incorporated by reference in its entirety.

SEQUENCE LISTING

[0002]   The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 7, 2015, is named PCFC-955-WO1_SL.txt and is 32,533 bytes in size.

FIELD OF THE INVENTION

[0003]   The present invention relates to combination therapies useful for the treatment of cancer. In particular, the invention relates to a combination therapy which comprises an antagonist of a Programmed Death 1 protein (PD-1) and an inhibitor of anaplastic lymphoma kinase (ALK).

BACKGROUND OF THE INVENTION

[0004]   PD-1 is recognized as an important player in immune regulation and the maintenance of peripheral tolerance. PD-1 is moderately expressed on naive T, B and NKT cells and up-regulated by T/B cell receptor signaling on lymphocytes, monocytes and myeloid cells (1).

[0005]   Two known ligands for PD-1, PD-L1 (B7-H1) and PD-L2 (B7-DC) are expressed in human cancers arising in various tissues. In large sample sets of e.g. ovarian, renal, colorectal, pancreatic, liver cancers and melanoma, it was shown that PD-L1 expression correlated with poor prognosis and reduced overall survival irrespective of subsequent treatment (2-13). Similarly, PD-1 expression on tumor infiltrating lymphocytes was found to mark dysfunctional T cells in breast cancer and melanoma (14-15) and to correlate with poor prognosis in renal cancer (16). Thus, it has been proposed that PD-L1 expressing tumor cells interact with PD-1 expressing T cells to attenuate T cell activation and evasion of immune surveillance, thereby contributing to an impaired immune response against the tumor.

[0006]   Several monoclonal antibodies that inhibit the interaction between PD-1 and one or both of its ligands PD-L1 and PD-L2 are in clinical development for treating cancer.

[0007]   Anaplastic lymphoma kinase (ALK) is a member of the receptor tyrosine kinase superfamily, and at an amino acid sequence level is most closely related to members such as c-ros oncogene 1 (Ros1), leucocyte tyrosine kinase, the insulin receptor and c-Met (hepatic growth factor receptor) (Kostich M et al, *Genome Biology* 2002, 3, 1-12). ALK is largely expressed in the developing nervous system (Iwahara T et al, *Oncogene* 1997, 14, 439-449). Its relative abundance does tend to decrease in the adult animal, though its expression is maintained in certain regions of the brain, spinal cord and the eye (Vernersson et al., *Gene Expression Patterns* 2006, 6, 448-461).

[0008]   ALK also has an important role in oncology (Webb TR et al, *Expert Reviews in Anticancer Therapy* 2009 9 331-355). Point mutations in the full length ALK enzyme that lead to activation of the enzyme, and also increase in expression of the full length enzyme, have both been shown to lead to neuroblastoma (Ogawa S et al., *Cancer Sci* 2011 102:302-308). In addition, the fusion of ALK with other proteins due to genetic translocation events has also been shown to lead to activated kinase domain associated with cancer. A number of such ALK translocations leading to gene fusions are seen in lymphomas, the most prevalent being the nucleophosmin (NPM)-ALK fusion seen in anaplastic large cell lymphomas (ALCL). ALK fusion with EML4 leads to a chimeric protein (EML4-ALK) responsible for 2-7% of non-small cell lung carcinomas (NSCLC) (Soda M et al, *Nature* 2007 448 561-567).

[0009]   ALK inhibitors have been approved for the treatment of ALK-positive metastatic non-small cell lung cancer (NSCLC), and continue to be investigated in the clinical setting.

SUMMARY OF THE INVENTION

[0010]   In one embodiment, the invention provides a method for treating a cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and an ALK inhibitor.

[0011]   In another embodiment, the invention provides a medicament comprising a PD-1 antagonist for use in combination with an ALK inhibitor for treating a cancer.

[0012]   In yet another embodiment, the invention provides a medicament comprising an ALK inhibitor for use in combination with a PD-1 antagonist for treating a cancer.

[0013]   Other embodiments provide use of a PD-1 antagonist in the manufacture of medicament for treating a cancer in an individual when administered in combination with an ALK inhibitor and use of an ALK inhibitor in the manufacture of a medicament for treating a cancer in an individual when administered in combination with a PD-1 antagonist.

5   [0014]   In a still further embodiment, the invention provides use of a PD-1 antagonist and an ALK inhibitor in the manufacture of medicaments for treating a cancer in an individual. In some embodiments, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-1 antagonist in combination with an ALK inhibitor to treat a cancer in an individual.

10   [0015]   In all of the above treatment method, medicaments and uses, the PD-1 antagonist inhibits the binding of PD-L1 to PD-1, and preferably also inhibits the binding of PD-L2 to PD-1. In some embodiments of the above treatment method, medicaments and uses, the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to PD-1 or to PD-L1 and blocks the binding of PD-L1 to PD-1. In one embodiment, the

15   PD-1 antagonist is an anti-PD-1 antibody which comprises a heavy chain and a light chain, and wherein the heavy and light chains comprise the amino acid sequences shown in Figure 6 (SEQ ID NO:21 and SEQ ID NO:22).

[0016]   In all of the above embodiments of the treatment method, medicaments and uses herein, the ALK inhibitor is a small molecule inhibitor of ALK kinase. In one embodiment, the

20   ALK inhibitor is 3-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine (crizotinib), or a pharmaceutically acceptable salt thereof.

[0017]   In some embodiments of the above treatment method, medicaments and uses of the invention, the individual is a human and the cancer is a solid tumor and in some embodiments, the solid tumor is bladder cancer, breast cancer, clear cell kidney cancer,

25   head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), neuroblastoma, glioblastoma, or rhabdomycosarcoma. In some embodiments, the cancer is non-small-cell lung cancer (NSCLC).

[0018]   In other embodiments of the above treatment method, medicaments and uses of

30   the invention, the individual is a human and the cancer is a Heme malignancy and in some embodiments, the Heme malignancy is acute lymphoblastic leukemia (ALL), acute myeloid

leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), anaplastic large-cell lymphoma (ALCL), EBV-positive DLBCL, primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

[0019]   In some embodiments of any of the above treatment method, medicaments and uses, the cancer tests positive for the expression of one or both of PD-L1 and PD-L2. In still other embodiments, the cancer has elevated PD-L1 expression.

[0020]   In one embodiment of the above treatment method, medicaments and uses, the individual is a human and the cancer is NSCLC that tests positive for human PD-L1.

[0021]   In some embodiments of any of the above treatment method, medicaments and uses, the cancer tests positive for ALK, in particular human ALK. In still other embodiments, the cancer has elevated ALK expression.

[0022]   In one embodiment of the above treatment method, medicaments and uses, the individual is a human and the cancer is NSCLC that tests positive for human ALK. In some such embodiments, the cancer is advanced non-squamous NSCLC that tests positive for human ALK.

[0023]   In another embodiment of the above treatment method, medicaments and uses, the individual is a human and the cancer is advanced non-squamous NSCLC that tests positive for human ALK and is present in a human who has not been previously treated for NSCLC.

[0024]   In another embodiment of the above treatment method, medicaments and uses, the cancer is advanced non-squamous NSCLC that tests positive for each of human PD-L1 and human ALK and is present in a human who has not been previously treated for NSCLC.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025]   FIGURE 1 shows amino acid sequences of the light chain and heavy chain CDRs for an exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NOs:1-6).

[0026]   FIGURE 2 shows amino acid sequences of the light chain and heavy chain CDRs for another exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NOs:7-12).

[0027]   FIGURE 3 shows amino acid sequences of the heavy chain variable region and full length heavy chain for an exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NO:13 and SEQ ID NO:14).

[0028]   FIGURE 4 shows amino acid sequences of alternative light chain variable regions for an exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NOs:15-17).

[0029]   FIGURES 5A-5B show amino acid sequences of alternative light chains for an exemplary anti-PD-1 monoclonal antibody useful in the present invention, with FIG. 5A showing the amino acid sequences for the K09A-L-11 and K09A-L-16 light chains (SEQ ID NOs:18 and 19, respectively) and FIG. 5B showing the amino acid sequence for the K09A-L-17 light chain (SEQ ID NO:20).

[0030]   FIGURE 6 shows amino acid sequences of the heavy and light chains for MK-3475 (SEQ ID NOs. 21 and 22, respectively).

[0031]   FIGURE 7 shows amino acid sequences of the heavy and light chains for nivolumab (SEQ ID NOs. 23 and 24, respectively).

DETAILED DESCRIPTION

Abbreviations. Throughout the detailed description and examples of the invention the following abbreviations will be used:

[0032]   BID   One dose twice daily

[0033]   CDR   Complementarity determining region

[0034]   CHO   Chinese hamster ovary

[0035]   DFS   Disease free survival

[0036]   DTR   Dose limiting toxicity

[0037]   FFPE   formalin-fixed, paraffin-embedded

[0038]   FR   Framework region

[0039]   IgG   Immunoglobulin G

[0040]   IHC   Immunohistochemistry or immunohistochemical

[0041]   MTD   Maximum tolerated dose

[0042]	NCBI	National Center for Biotechnology Information
[0043]	NCI	National Cancer Institute
[0044]	OR	Overall response
[0045]	OS	Overall survival
[0046]	PD	Progressive disease
[0047]	PFS	Progression free survival
[0048]	PR	Partial response
[0049]	Q2W	One dose every two weeks
[0050]	Q3W	One dose every three weeks
[0051]	QD	One dose per day
[0052]	RECIST	Response Evaluation Criteria in Solid Tumors
[0053]	SD	Stable disease
[0054]	VH	Immunoglobulin heavy chain variable region
[0055]	VK	Immunoglobulin kappa light chain variable region

I. DEFINITIONS

[0056]   So that the invention may be more readily understood, certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0057]   "About" when used to modify a numerically defined parameter (e.g., the dose of a PD-1 antagonist or ALK inhibitor, or the length of treatment time with a combination therapy described herein) means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter. For example, a dose of about 2 mg/kg of the PD-1 antagonist, i.e., MK-3475, may vary between 1.8 mg/kg and 2.2 mg/kg and a dose of about 250 mg of the ALK inhibitor, i.e., crizotinib may vary between 225 mg and 275 mg.

[0058]   As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise.

[0059]   "Administration" and "treatment," as it applies to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, refers to contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as

contact of a reagent to a fluid, where the fluid is in contact with the cell. "Administration" and "treatment" also means *in vitro* and *ex vivo* treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell.

[0060]   "ALK" means anaplastic lymphoma receptor tyrosine kinase. All references to ALK herein will be understood to include references to both ALK and to oncogenic variants thereof, including ALK fusions (including without limitation EML4-ALK, KIF5B-ALK, TFG-ALK, KLC1-ALK and NPM-ALK) and selected oncogenic mutations of ALK.
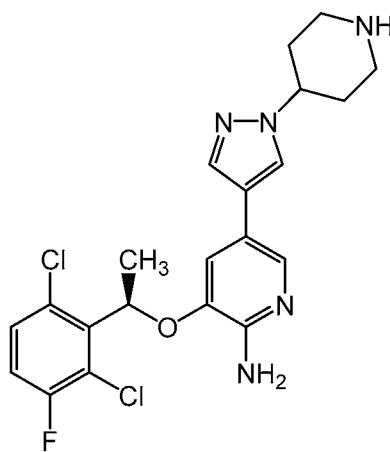
[0061]   "ALK inhibitor" means a small molecule inhibitor of anaplastic lymphoma kinase (ALK) and/or its oncogenic variants, i.e., ALK fusions and selected oncogenic mutations of ALK.

[0062]   Specific ALK inhibitors useful as the ALK inhibitor in the treatment methods, medicaments and uses of the present invention, include crizotinib (Pfizer; Xalkori[®], PF-02341066), with the structure described in *WHO Drug Information*, Vol. 25, No. 1, page 54 (2011); ceritinib (Novartis; Zykadia[™], LDK378), with the structure described in *WHO Drug Information*, Vol. 28, No. 1, page 79 (2014); and alectinib (Roche/Chugai; Alecensa[®], RO542802, CH542802), with the structure described in *WHO Drug Information*, Vol. 27, No. 3, page 70 (2013). In a preferred embodiment, the ALK inhibitor useful in the treatment methods, medicaments and uses of the present invention is crizotinib.

[0063]   Additional examples of ALK inhibitors include, for example, PF-06463922 (Pfizer), NVP-TAE684 (Novartis), AP26113 (Ariad), TSR-011 (Tesaro), X-396 (Xcovery), CEP-37440 (Cephalon/Teva) and RXDX-101 (Igynta; NMS-E628, Nerviano). (Wang et al., *Med. Chem. Commun.* 2014, 5:1266)

[0064]   In an embodiment of the treatment method, medicaments and uses of the present invention, the ALK inhibitor is the compound, 3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine, having the following structure:

,

which is known as crizotinib or PF-02341066, or a pharmaceutically acceptable salt thereof.

[0065]   Crizotinib is an inhibitor of anaplastic lymphoma kinase (ALK) and its oncogenic variants (i.e., ALK fusion events and selected oncogenic ALK mutations), as well as the hepatocyte growth factor receptor (HGFR, c-Met), c-ros oncogene 1 (Ros1) and its oncogenic variants, and Recepteur d'Origine Nantais (RON) receptor tyrosine kinases (RTKs).

[0066]   Xalkori® (crizotinib) has been approved in the United States for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test, and has also been approved for the treatment of ALK-positive NSCLC in Europe, Japan and other jurisdictions.

[0067]   Crizotinib, as well as pharmaceutically acceptable salts thereof, is described in International Publication Nos. WO 2006/021884, WO 2006/021881 and WO 2007/066185, and in U.S. Patent Nos. 7,858,643, 8,217,057 and 8,785,632. The use of crizotinib in treating abnormal cell growth, such as cancers, mediated by ALK or c-MET/HGFR is described in WO 2007/06617 and U.S. Patent No. 7,825,137. The use of crizotinib in treating ROS mediated cancers is described in WO 2013/017989. The contents of each of the foregoing patents and applications are incorporated herein by reference in their entirety.

[0068]   References to crizotinib are understood to include references to the pharmaceutically acceptable salts thereof, unless otherwise indicated. Crizotinib is basic in nature and capable of forming a wide variety of salts with various inorganic and organic acids. The term "salt(s)", as employed herein, denotes acid addition salts formed with inorganic and/or organic acids. Pharmaceutically acceptable salts of crizotinib may be formed, for example, by

reacting crizotinib with an amount of acid, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0069]   Exemplary acid addition salts of crizotinib include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

[0070]   All such acid salts are intended to be pharmaceutically acceptable salts within the scope of crizotinib, as used in the present invention and all acid salts are considered equivalent to the free forms of the corresponding compound for purposes of the invention.

[0071]   Prodrugs of crizotinib are also contemplated for use in the methods, medicaments and uses of the present invention. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield crizotinib or a salt thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

[0072]   As used herein, the term "antibody" refers to any form of antibody that exhibits the desired biological or binding activity. Thus, it is used in the broadest sense and specifically covers, but is not limited to, monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), humanized, fully human antibodies, chimeric antibodies and camelized single domain antibodies. "Parental antibodies" are antibodies obtained by exposure of an immune system to an antigen prior to modification of the antibodies for an intended use, such as humanization of an antibody for use as a human therapeutic.

- 10 -

[0073]   In general, the basic antibody structural unit comprises a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of the heavy chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989).

[0074]   The variable regions of each light/heavy chain pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are, in general, the same.

[0075]   Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), which are located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat, et al.; National Institutes of Health, Bethesda, Md. ; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32:1-75; Kabat, et al., (1977) J. Biol. Chem. 252:6609-6616; Chothia, et al., (1987) J Mol. Biol. 196:901-917 or Chothia, et al., (1989) Nature 342:878-883.

[0076]   As used herein, the term "hypervariable region" refers to the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarity determining region" or "CDR" (i.e. CDRL1, CDRL2 and CDRL3 in the light chain variable domain and CDRH1, CDRH2 and CDRH3 in the heavy chain variable domain). See Kabat et al. (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (defining the CDR regions of an antibody by sequence); see also Chothia and Lesk (1987) J. Mol. Biol. 196: 901-917 (defining the CDR regions of an antibody by structure). As used herein, the term

"framework" or "FR" residues refers to those variable domain residues other than the hypervariable region residues defined herein as CDR residues.

[0077]   As used herein, unless otherwise indicated, "antibody fragment" or "antigen binding fragment" refers to antigen binding fragments of antibodies, i.e. antibody fragments that retain the ability to bind specifically to the antigen bound by the full-length antibody, e.g. fragments that retain one or more CDR regions.   Examples of antibody binding fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules, e.g., sc-Fv; nanobodies and multispecific antibodies formed from antibody fragments.

[0078]   An antibody that "specifically binds to" a specified target protein is an antibody that exhibits preferential binding to that target as compared to other proteins, but this specificity does not require absolute binding specificity. An antibody is considered "specific" for its intended target if its binding is determinative of the presence of the target protein in a sample, e.g. without producing undesired results such as false positives. Antibodies, or binding fragments thereof, useful in the present invention will bind to the target protein with an affinity that is at least two fold greater, preferably at least ten times greater, more preferably at least 20-times greater, and most preferably at least 100-times greater than the affinity with non-target proteins. As used herein, an antibody is said to bind specifically to a polypeptide *comprising* a given amino acid sequence, e.g. the amino acid sequence of a mature human PD-1 or human PD-L1 molecule, if it binds to polypeptides comprising that sequence but does not bind to proteins lacking that sequence.

[0079]   "Chimeric antibody" refers to an antibody in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in an antibody derived from a particular species (e.g., human) or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in an antibody derived from another species (e.g., mouse) or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity.

[0080]   "Human antibody" refers to an antibody that comprises human immunoglobulin protein sequences only. A human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, "mouse antibody" or "rat antibody" refer to an antibody that comprises only mouse or rat immunoglobulin sequences, respectively.

[0081]   "Humanized antibody" refers to forms of antibodies that contain sequences from non-human (*e.g.*, murine) antibodies as well as human antibodies. Such antibodies contain minimal sequence derived from non-human immunoglobulin. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The prefix "hum", "hu" or "h" is added to antibody clone designations when necessary to distinguish humanized antibodies from parental rodent antibodies. The humanized forms of rodent antibodies will generally comprise the same CDR sequences of the parental rodent antibodies, although certain amino acid substitutions may be included to increase affinity, increase stability of the humanized antibody, or for other reasons.

[0082]   The terms "cancer", "cancerous", or "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, leukemia, blastoma, and sarcoma. More particular examples of such cancers include squamous cell carcinoma, myeloma, small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), glioma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute myeloid leukemia (AML), multiple myeloma, gastrointestinal (tract) cancer, renal cancer, ovarian cancer, liver cancer, lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma multiforme, cervical cancer, brain cancer, stomach cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer. Another particular example of cancer includes non-small cell lung cancer (NSCLC). Cancers that may be treated in accordance with the present invention include those that test positive for one or more of ALK, PD-L1 and PD-L2 in tested tissue samples.

[0083]   "Biotherapeutic agent" means a biological molecule, such as an antibody or fusion protein, that blocks ligand / receptor signaling in any biological pathway that supports tumor maintenance and/or growth or suppresses the anti-tumor immune response.

- 13 -

[0084]   "CDR" or "CDRs" as used herein means complementarity determining region(s) in a immunoglobulin variable region, defined using the Kabat numbering system, unless otherwise indicated.

[0085]   "Chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, kinase inhibitors, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topisomerase inhibitors, photosensitizers, anti-estrogens and selective estrogen receptor modulators (SERMs), anti-progesterones, estrogen receptor down-regulators (ERDs), estrogen receptor antagonists, leutinizing hormone-releasing hormone agonists, anti-androgens, aromatase inhibitors, EGFR inhibitors, VEGF inhibitors, and anti-sense oligonucleotides that inhibit expression of genes implicated in abnormal cell proliferation or tumor growth. Chemotherapeutic agents useful in the treatment methods of the present invention include cytostatic and/or cytotoxic agents.

[0086]   "Chothia" as used herein means an antibody numbering system described in Al-Lazikani *et al.*, *JMB* **273:**927-948 (1997).

[0087]   "Conservatively modified variants" or "conservative substitution" refers to substitutions of amino acids in a protein with other amino acids having similar characteristics (e.g. charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.), such that the changes can frequently be made without altering the biological activity or other desired property of the protein, such as antigen affinity and/or specificity. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (*see, e.g.,* Watson *et al.* (1987) *Molecular Biology of the Gene,* The Benjamin/Cummings Pub. Co., p. 224 (4th Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to disrupt biological activity. Exemplary conservative substitutions are set forth in Table 1 below.

[0088]   **TABLE 1. Exemplary Conservative Amino Acid Substitutions**

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys; His
Asn (N)	Gln; His
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn
Glu (E)	Asp; Gln
Gly (G)	Ala

Original residue	Conservative substitution
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; His
Met (M)	Leu; Ile; Tyr
Phe (F)	Tyr; Met; Leu
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

[0089]   "Consists essentially of," and variations such as "consist essentially of" or "consisting essentially of," as used throughout the specification and claims, indicate the inclusion of any recited elements or group of elements, and the optional inclusion of other elements, of similar or different nature than the recited elements, that do not materially change the basic or novel properties of the specified dosage regimen, method, or composition. As a non-limiting example, a PD-1 antagonist that consists essentially of a recited amino acid sequence may also include one or more amino acids, including substitutions of one or more amino acid residues, which do not materially affect the properties of the binding compound.

[0090]   "Diagnostic anti-PD-L monoclonal antibody" means a mAb which specifically binds to the mature form of the designated PD-L (PD-L1 or PDL2) that is expressed on the surface of certain mammalian cells. A mature PD-L lacks the presecretory leader sequence, also referred to as leader peptide The terms "PD-L" and "mature PD-L" are used interchangeably herein, and shall be understood to mean the same molecule unless otherwise indicated or readily apparent from the context.

[0091]   As used herein, a diagnostic anti-human PD-L1 mAb or an anti-hPD-L1 mAb refers to a monoclonal antibody that specifically binds to mature human PD-L1. A mature human PD-L1 molecule consists of amino acids 19-290 of the following sequence:

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNII
QFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKV
NAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTS
TLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFR
LRKGRMMDVKKCGIQDTNSKKQSDTHLEET (SEQ ID NO:25).

[0092] Specific examples of diagnostic anti-human PD-L1 mAbs useful as diagnostic mAbs for immunohistochemistry (IHC) detection of PD-L1 expression in formalin-fixed, paraffin-embedded (FFPE) tumor tissue sections are antibody 20C3 and antibody 22C3, which are described in WO2014/100079. Another anti-human PD-L1 mAb that has been reported to be useful for IHC detection of PD-L1 expression in FFPE tissue sections (Chen, B.J. et al., *Clin Cancer Res* 19: 3462-3473 (2013)) is a rabbit anti-human PD-L1 mAb publicly available from Sino Biological, Inc. (Beijing, P.R. China; Catalog number 10084-R015)..

[0093] "Framework region" or "FR" as used herein means the immunoglobulin variable regions excluding the CDR regions.

[0094] "Homology" refers to sequence similarity between two polypeptide sequences when they are optimally aligned. When a position in both of the two compared sequences is occupied by the same amino acid monomer subunit, e.g., if a position in a light chain CDR of two different Abs is occupied by alanine, then the two Abs are homologous at that position. The percent of homology is the number of homologous positions shared by the two sequences divided by the total number of positions compared ×100. For example, if 8 of 10 of the positions in two sequences are matched or homologous when the sequences are optimally aligned then the two sequences are 80% homologous. Generally, the comparison is made when two sequences are aligned to give maximum percent homology. For example, the comparison can be performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences.

[0095] The following references relate to BLAST algorithms often used for sequence analysis: BLAST ALGORITHMS: Altschul, S.F., *et al.*, (1990) J. Mol. Biol. 215:403-410; Gish, W., *et al.*, (1993) Nature Genet. 3:266-272; Madden, T.L., *et al.*, (1996) Meth. Enzymol. 266:131-141; Altschul, S.F., *et al.*, (1997) Nucleic Acids Res. 25:3389-3402; Zhang, J., *et al.*, (1997) Genome Res. 7:649-656; Wootton, J.C., *et al.*, (1993) Comput. Chem. 17:149-163; Hancock, J.M. *et al.*, (1994) Comput. Appl. Biosci. 10:67-70; ALIGNMENT SCORING SYSTEMS: Dayhoff, M.O., *et al.*, "A model of evolutionary change in proteins." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, Natl. Biomed. Res. Found., Washington, DC; Schwartz, R.M., *et al.*, "Matrices for detecting distant relationships." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3." M.O. Dayhoff (ed.), pp. 353-358, Natl. Biomed. Res. Found., Washington, DC; Altschul, S.F., (1991) J. Mol. Biol. 219:555-565; States, D.J., *et al.*, (1991) Methods 3:66-70; Henikoff, S., *et al.*, (1992) Proc.

Natl. Acad. Sci. USA 89:10915-10919; Altschul, S.F., *et al.*, (1993) J. Mol. Evol. 36:290-300; ALIGNMENT STATISTICS: Karlin, S., *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268; Karlin, S., *et al.*, (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877; Dembo, A., *et al.*, (1994) Ann. Prob. 22:2022-2039; and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in Theoretical and Computational Methods in Genome Research (S. Suhai, ed.), (1997) pp. 1-14, Plenum, New York.

[0096]   "Isolated antibody" and "isolated antibody fragment" refers to the purification status and in such context means the named molecule is substantially free of other biological molecules such as nucleic acids, proteins, lipids, carbohydrates, or other material such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to a complete absence of such material or to an absence of water, buffers, or salts, unless they are present in amounts that substantially interfere with experimental or therapeutic use of the binding compound as described herein.

[0097]   "Kabat" as used herein means an immunoglobulin alignment and numbering system pioneered by Elvin A. Kabat ((1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.).

[0098]   "Monoclonal antibody" or "mAb" or "Mab", as used herein, refers to a population of substantially homogeneous antibodies, *i.e.*, the antibody molecules comprising the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies having different amino acid sequences in their variable domains, particularly their CDRs, which are often specific for different epitopes. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.* (1975) *Nature* 256: 495, or may be made by recombinant DNA methods (*see, e.g.*, U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.* (1991) *Nature* 352: 624-628 and Marks *et al.* (1991) *J. Mol. Biol.* 222: 581-597, for example. *See also* Presta (2005) *J. Allergy Clin. Immunol.* 116:731.

[0099]   "Patient" or "subject" or "individual" refers to any single subject for which therapy is desired or that is participating in a clinical trial, epidemiological study or used as a

control, including humans and mammalian veterinary patients such as cattle, horses, dogs, and cats. Preferably, the subject or individual is an animal, more preferably a mammal, and most preferably a human.

[00100]   "PD-1 antagonist" means any chemical compound or biological molecule that blocks binding of PD-L1 expressed on a cancer cell to PD-1 expressed on an immune cell (T cell, B cell or NKT cell) and preferably also blocks binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279 and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btdc and CD273 for PD-L2. In any of the treatment method, medicaments and uses of the present invention in which a human individual is being treated, the PD-1 antagonist blocks binding of human PD-L1 to human PD-1, and preferably blocks binding of both human PD-L1 and PD-L2 to human PD-1. Human PD-1 amino acid sequences can be found in NCBI Locus No.: NP_005009. Human PD-L1 and PD-L2 amino acid sequences can be found in NCBI Locus No.: NP_054862 and NP_079515, respectively.

[00101]   PD-1 antagonists useful in the any of the treatment method, medicaments and uses of the present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and may include a human constant region. In some embodiments the human constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4 constant regions, and in preferred embodiments, the human constant region is an IgG1 or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')$_2$, scFv and Fv fragments.

[00102]   Examples of mAbs that bind to human PD-1, and useful in the treatment method, medicaments and uses of the present invention, are described in US7488802, US7521051, US8008449, US8354509, US8168757, WO2004/004771, WO2004/072286, WO2004/056875, and US2011/0271358. Specific anti-human PD-1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include: MK-3475, a humanized IgG4 mAb with the structure described in *WHO Drug Information*, Vol. 27, No. 2, pages 161-162 (2013) and which comprises the heavy and light chain amino acid sequences shown in Figure 6, nivolumab (BMS-936558), a human IgG4 mAb with the structure described in *WHO Drug Information*, Vol. 27, No. 1, pages 68-69 (2013) and which comprises

the heavy and light chain amino acid sequences shown in Figure 7; the humanized antibodies h409A11, h409A16 and h409A17, which are described in WO2008/156712, and AMP-514, which is being developed by MedImmune.

[00103]   Examples of mAbs that bind to human PD-L1, and useful in the treatment method, medicaments and uses of the present invention, are described in WO2013/019906, WO2010/077634 A1 and US8383796. Specific anti-human PD-L1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include MPDL3280A, BMS-936559, MEDI4736, MSB0010718C and an antibody which comprises the heavy chain and light chain variable regions of SEQ ID NO:24 and SEQ ID NO:21, respectively, of WO2013/019906.

[00104]   Other PD-1 antagonists useful in the any of the treatment method, medicaments and uses of the present invention include an immunoadhesin that specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1, e.g., a fusion protein containing the extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region such as an Fc region of an immunoglobulin molecule. Examples of immunoadhesion molecules that specifically bind to PD-1 are described in WO2010/027827 and WO2011/066342. Specific fusion proteins useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include AMP-224 (also known as B7-DCIg), which is a PD-L2-FC fusion protein and binds to human PD-1.

[00105]   In some preferred embodiments of the treatment method, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody, or antigen binding fragment thereof, which comprises: (a) light chain CDRs SEQ ID NOs: 1, 2 and 3 and heavy chain CDRs SEQ ID NOs: 4, 5 and 6; or (b) light chain CDRs SEQ ID NOs: 7, 8 and 9 and heavy chain CDRs SEQ ID NOs: 10, 11 and 12.

[00106]   In other preferred embodiments of the treatment method, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody, or antigen binding fragment thereof, which specifically binds to human PD-1 and comprises (a) a heavy chain variable region comprising SEQ ID NO:13 or a variant thereof, and (b) a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:15 or a variant thereof; SEQ ID NO:16 or a variant thereof; and SEQ ID NO: 17 or a variant thereof. A variant of a heavy chain variable region sequence is identical to the reference sequence except having up to 17 conservative amino acid substitutions in the framework region (i.e., outside of the CDRs), and preferably has less than ten, nine, eight, seven, six or five conservative amino acid

substitutions in the framework region. A variant of a light chain variable region sequence is identical to the reference sequence except having up to five conservative amino acid substitutions in the framework region (i.e., outside of the CDRs), and preferably has less than four, three or two conservative amino acid substitution in the framework region.

[00107]   In another preferred embodiment of the treatment method, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody which specifically binds to human PD-1 and comprises (a) a heavy chain comprising SEQ ID NO: 14 and (b) a light chain comprising SEQ ID NO:18, SEQ ID NO:19 or SEQ ID NO:20.

[00108]   In yet another preferred embodiment of the treatment method, medicaments and uses of the present invention, the PD-1 antagonist is a monoclonal antibody which specifically binds to human PD-1 and comprises (a) a heavy chain comprising SEQ ID NO: 14 and (b) a light chain comprising SEQ ID NO:18.

[00109]   Table 2 below provides a list of the amino acid sequences of exemplary anti-PD-1 mAbs for use in the treatment method, medicaments and uses of the present invention, and the sequences are shown in Figures 1-5.

Table 2. EXEMPLARY ANTI-HUMAN PD-1 MONOCLONAL ANTIBODIES	
A. Comprises light and heavy chain CDRs of hPD-1.08A in WO2008/156712	
CDRL1	SEQ ID NO:1
CDRL2	SEQ ID NO:2
CDRL3	SEQ ID NO:3
CDRH1	SEQ ID NO:4
CDRH2	SEQ ID NO:5
CDRH3	SEQ ID NO:6
B. Comprises light and heavy chain CDRs of hPD-1.09A in WO2008/156712	
CDRL1	SEQ ID NO:7
CDRL2	SEQ ID NO:8
CDRL3	SEQ ID NO:9
CDRH1	SEQ ID NO:10
CDRH2	SEQ ID NO:11
CDRH3	SEQ ID NO:12
C. Comprises the mature h109A heavy chain variable region and one of the mature K09A light chain variable regions in WO2008/156712	
Heavy chain VR	SEQ ID NO:13
Light chain VR	SEQ ID NO:15 or SEQ ID NO:16 or SEQ ID NO:17

D. Comprises the mature 409 heavy chain and one of the mature K09A light chains in WO2008/156712	
Heavy chain	SEQ ID NO:14
Light chain	SEQ ID NO:18 or SEQ ID NO:19 or SEQ ID NO:20

[00110]   "PD-L1" or "PD-L2" expression as used herein means any detectable level of expression of the designated PD-L protein on the cell surface or of the designated PD-L mRNA within a cell or tissue. PD-L protein expression may be detected with a diagnostic PD-L antibody in an IHC assay of a tumor tissue section or by flow cytometry. Alternatively, PD-L protein expression by tumor cells may be detected by PET imaging, using a binding agent (e.g., antibody fragment, affibody and the like) that specifically binds to the desired PD-L target, e.g., PD-L1 or PD-L2. Techniques for detecting and measuring PD-L mRNA expression include RT-PCR and realtime quantitative RT-PCR.

[00111]   Several approaches have been described for quantifying PD-L1 protein expression in IHC assays of tumor tissue sections. *See*, e.g., Thompson, R. H., et al., *PNAS* **101** (49); 17174-17179 (2004); Thompson, R. H. et al., *Cancer Res.* **66**:3381-3385 (2006); Gadiot, J., et al., *Cancer* **117**:2192-2201 (2011); Taube, J. M. et al., *Sci Transl Med* **4**, 127ra37 (2012); and Toplian, S. L. et al., *New Eng. J Med.* **366** (26): 2443-2454 (2012).

[00112]   One approach employs a simple binary end-point of positive or negative for PD-L1 expression, with a positive result defined in terms of the percentage of tumor cells that exhibit histologic evidence of cell-surface membrane staining. A tumor tissue section is counted as positive for PD-L1 expression if IHC membrane staining is observed in at least 1%, and preferably 5% of total tumor cells in the tumor tissue section. In an embodiment, a NSCLC tumor sample is designated as having weak PD-L1 expression if 1% to 49% of the total tumor cells in the sample exhibit membrane staining and is designated as having strong PD-L1 expression if at least 50% of the tumor cells in the sample exhibit membrane staining, in each case as determined by IHC assay using the antibody 22C3 described in WO2014/100079.

[00113]   In another approach, PD-L1 expression in the tumor tissue section is quantified in the tumor cells as well as in infiltrating immune cells, which predominantly comprise lymphocytes. The percentage of tumor cells and infiltrating immune cells that exhibit membrane staining are separately quantified as < 5%, 5 to 9%, and then in 10% increments up to 100%. For tumor cells, PD-L1 expression is counted as negative if the score is < 5% score and positive if the score is ≥ 5%. PD-L1 expression in the immune infiltrate is reported as a semi-quantitative measurement called the adjusted inflammation score (AIS), which is determined by multiplying

the percent of membrane staining cells by the intensity of the infiltrate, which is graded as none (0), mild (score of 1, rare lymphocytes), moderate (score of 2, focal infiltration of tumor by lymphohistiocytic aggregates), or severe (score of 3, diffuse infiltration). A tumor tissue section is counted as positive for PD-L1 expression by immune infiltrates if the AIS is ≥ 5.

[00114]   The level of PD-L mRNA expression may be compared to the mRNA expression levels of one or more reference genes that are frequently used in quantitative RT-PCR, such as ubiquitin C.

[00115]   In some embodiments, a level of PD-L1 expression (protein and/or mRNA) by malignant cells and/or by infiltrating immune cells within a tumor is determined to be "overexpressed" or "elevated" based on comparison with the level of PD-L1 expression (protein and/ or mRNA) by an appropriate control. For example, a control PD-L1 protein or mRNA expression level may be the level quantified in nonmalignant cells of the same type or in a section from a matched normal tissue. In some preferred embodiments, PD-L1 expression in a tumor sample is determined to be elevated if PD-L1 protein (and/or PD-L1 mRNA) in the sample is at least 10%, 20%, or 30% greater than in the control.

[00116]   "RECIST 1.1 Response Criteria" as used herein means the definitions set forth in Eisenhauer et al., E.A. et al., *Eur. J Cancer* 45:228-247 (2009) for target lesions or nontarget lesions, as appropriate based on the context in which response is being measured.

[00117]   "Sustained response" means a sustained therapeutic effect after cessation of treatment with a therapeutic agent, or a combination therapy described herein. In some embodiments, the sustained response has a duration that is at least the same as the treatment duration, or at least 1.5, 2.0, 2.5 or 3 times longer than the treatment duration.

[00118]   "Tissue Section" refers to a single part or piece of a tissue sample, e.g., a thin slice of tissue cut from a sample of a normal tissue or of a tumor.

[00119]   "Treat" or "treating" a cancer as used herein means to administer a combination therapy of a PD-1 antagonist and an ALK inhibitor to a subject having a cancer, or diagnosed with a cancer, to achieve at least one positive therapeutic effect, such as for example, reduced number of cancer cells, reduced tumor size, reduced rate of cancer cell infiltration into peripheral organs, or reduced rate of tumor metastasis or tumor growth. Positive therapeutic effects in cancer can be measured in a number of ways (See, W. A. Weber, *J. Nucl. Med.* 50:1S-10S (2009)). For example, with respect to tumor growth inhibition, according to NCI standards, a T/C $\leqq 42\%$ is the minimum level of anti-tumor activity. A T/C < 10% is considered a high anti-tumor

activity level, with T/C (%) = Median tumor volume of the treated/Median tumor volume of the control × 100. In some embodiments, the treatment achieved by a combination of the invention is any of PR, CR, OR, PFS, DFS and OS. PFS, also referred to as "Time to Tumor Progression" indicates the length of time during and after treatment that the cancer does not grow, and includes the amount of time patients have experienced a CR or PR, as well as the amount of time patients have experienced SD. DFS refers to the length of time during and after treatment that the patient remains free of disease. OS refers to a prolongation in life expectancy as compared to naive or untreated individuals or patients. In some preferred embodiments, response to a combination of the invention is any of PR, CR, PFS, DFS, OR or OS that is assessed using RECIST 1.1 response criteria. The treatment regimen for a combination of the invention that is effective to treat a cancer patient may vary according to factors such as the disease state, age, and weight of the patient, and the ability of the therapy to elicit an anti-cancer response in the subject. While an embodiment of any of the aspects of the invention may not be effective in achieving a positive therapeutic effect in every subject, it should do so in a statistically significant number of subjects as determined by any statistical test known in the art such as the Student's t-test, the chi^2-test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Jonckheere-Terpstra-test and the Wilcoxon-test.

[00120]   The terms "treatment regimen", "dosing protocol" and dosing regimen are used interchangeably to refer to the dose and timing of administration of each therapeutic agent in a combination of the invention.

[00121]   "Tumor" as it applies to a subject diagnosed with, or suspected of having, a cancer refers to a malignant or potentially malignant neoplasm or tissue mass of any size, and includes primary tumors and secondary neoplasms. A solid tumor is an abnormal growth or mass of tissue that usually does not contain cysts or liquid areas. Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas. Leukemias (cancers of the blood) generally do not form solid tumors (National Cancer Institute, Dictionary of Cancer Terms).

[00122]   "Tumor burden" also referred to as "tumor load", refers to the total amount of tumor material distributed throughout the body. Tumor burden refers to the total number of cancer cells or the total size of tumor(s), throughout the body, including lymph nodes and bone narrow. Tumor burden can be determined by a variety of methods known in the art, such as, e.g. by measuring the dimensions of tumor(s) upon removal from the subject, e.g., using calipers, or

- 23 -

while in the body using imaging techniques, e.g., ultrasound, bone scan, computed tomography (CT) or magnetic resonance imaging (MRI) scans.

[00123]   The term "tumor size" refers to the total size of the tumor which can be measured as the length and width of a tumor. Tumor size may be determined by a variety of methods known in the art, such as, e.g. by measuring the dimensions of tumor(s) upon removal from the subject, e.g., using calipers, or while in the body using imaging techniques, e.g., bone scan, ultrasound, CT or MRI scans.

[00124]   "Variable regions" or "V region" as used herein means the segment of IgG chains which is variable in sequence between different antibodies. It extends to Kabat residue 109 in the light chain and 113 in the heavy chain.

II. METHODS, USES AND MEDICAMENTS

[00125]   In one aspect of the invention, the invention provides a method for treating a cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and an ALK inhibitor.

[00126]   The combination therapy may also comprise one or more additional therapeutic agents. The additional therapeutic agent may be, e.g., a chemotherapeutic other than an ALK inhibitor, a biotherapeutic agent (including but not limited to antibodies to VEGF, EGFR, Her2/neu, other growth factor receptors, CD20, CD40, CD-40L, CTLA-4, OX-40, 4-1BB, and ICOS), an immunogenic agent (for example, attenuated cancerous cells, tumor antigens, antigen presenting cells such as dendritic cells pulsed with tumor derived antigen or nucleic acids, immune stimulating cytokines (for example, IL-2, IFNα2, GM-CSF), and cells transfected with genes encoding immune stimulating cytokines such as but not limited to GM-CSF).

[00127]   Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine,

cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as the enediyne antibiotics (e.g. calicheamicin, especially calicheamicin gammaII and calicheamicin phiI1, see, e.g., Agnew, Chem. Intl. Ed. Engl., 33:183-186 (1994); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2, 2′,2″-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g. paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic

acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestane, fadrozole, vorozole, letrozole, and anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[00128]   Each therapeutic agent in a combination therapy of the invention may be administered either alone or in a medicament (also referred to herein as a pharmaceutical composition) which comprises the therapeutic agent and one or more pharmaceutically acceptable carriers, excipients and diluents, according to standard pharmaceutical practice.

[00129]   Each therapeutic agent in a combination therapy of the invention may be administered simultaneously (i.e., in the same medicament), concurrently (i.e., in separate medicaments administered one right after the other in any order) or sequentially in any order. Sequential administration is particularly useful when the therapeutic agents in the combination therapy are in different dosage forms (one agent is a tablet or capsule and another agent is a sterile liquid) and/or are administered on different dosing schedules, e.g., a chemotherapeutic that is administered at least daily and a biotherapeutic that is administered less frequently, such as once weekly, once every two weeks, or once every three weeks.

[00130]   In some embodiments, the ALK inhibitor is administered before administration of the PD-1 antagonist, while in other embodiments, the ALK inhibitor is administered after administration of the PD-1 antagonist.

[00131]   In some embodiments, at least one of the therapeutic agents in the combination therapy is administered using the same dosage regimen (dose, frequency and duration of treatment) that is typically employed when the agent is used as monotherapy for treating the same cancer. In other embodiments, the patient receives a lower total amount of at least one of the therapeutic agents in the combination therapy than when the agent is used as monotherapy, e.g., smaller doses, less frequent doses, and/or shorter treatment duration.

[00132]   Each small molecule therapeutic agent in a combination therapy of the invention can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, topical, and transdermal routes of administration.

[00133]   A combination therapy of the invention may be used prior to or following surgery to remove a tumor and may be used prior to, during or after radiation therapy.

[00134]   In some embodiments, a combination therapy of the invention is administered to a patient who has not been previously treated with a biotherapeutic or chemotherapeutic agent, i.e., is treatment-naïve. In other embodiments, the combination therapy is administered to a patient who failed to achieve a sustained response after prior therapy with a biotherapeutic or chemotherapeutic agent, i.e., is treatment-experienced.

[00135]   A combination therapy of the invention is typically used to treat a tumor that is large enough to be found by palpation or by imaging techniques well known in the art, such as MRI, ultrasound, or CAT scan. In some preferred embodiments, a combination therapy of the invention is used to treat an advanced stage tumor having dimensions of at least about 200 mm^3, 300 mm^3, 400 mm^3, 500 mm^3, 750 mm^3, 1000 mm^3, 1500 mm^3, 2000 mm^3, 2500 mm^3, or up to 3000 mm^3.

[00136]   In an embodiment, the combination therapy of the invention is administered to a human patient who has a cancer that tests positive for evidence of rearrangement of the ALK gene (i.e., "ALK-positive"). A variety of methods for the detection of ALK rearrangements have been described. (Shackelford RE et al., *Genes Cancer*, 2014, 5(1-2): 1-14). In some embodiments, rearrangement of the ALK gene is detected using an FDA approved test. In some embodiments, rearrangement of the ALK gene is detected using an assay that analyzes ALK or ALK fusion polynucleotides, such as the Vysis ALK Break Apart FISH Probe Kit (available from Abbott Molecular), or such as assays employing RT-PCR or Next Generation sequencing (NGS) technology. In other embodiments, rearrangement of the ALK gene is inferred based on ALK expression, which is detected using a diagnostic anti-ALK antibody, or antigen binding fragment thereof, in an IHC assay on an FFPE or frozen tissue section of a tumor sample removed from the patient.

[00137]   In an embodiment, a combination therapy of the invention is administered to a human patient who has a cancer that tests positive for PD-L1 expression, and in some embodiments tests positive for expression of both PD-L1 and ALK. In some embodiments, PD-L1 expression is detected using a diagnostic anti-human PD-L1 antibody, or antigen binding

fragment thereof, in an IHC assay on an FFPE or frozen tissue section of a tumor sample removed from the patient.

[00138]   Typically, the patient's physician would order a diagnostic test to determine ALK and/or PD-L1 expression in a tumor tissue sample removed from the patient prior to initiation of treatment with the PD-1 antagonist and ALK inhibitor, but it is envisioned that the physician could order the first or subsequent diagnostic tests at any time after initiation of treatment, such as for example after completion of a treatment cycle.

[00139]   Selecting a dosage regimen (also referred to herein as an administration regimen) for a combination therapy of the invention depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the immunogenicity of the entity, and the accessibility of the target cells, tissue or organ in the individual being treated. Preferably, a dosage regimen maximizes the amount of each therapeutic agent delivered to the patient consistent with an acceptable level of side effects. Accordingly, the dose amount and dosing frequency of each biotherapeutic and chemotherapeutic agent in the combination depends in part on the particular therapeutic agent, the severity of the cancer being treated, and patient characteristics. Guidance in selecting appropriate doses of antibodies, cytokines, and small molecules are available. *See, e.g.*, Wawrzynczak (1996) *Antibody Therapy*, Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) *Monoclonal Antibodies, Cytokines and Arthritis*, Marcel Dekker, New York, NY; Bach (ed.) (1993) *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases*, Marcel Dekker, New York, NY; Baert *et al.* (2003) *New Engl. J. Med.* 348:601-608; Milgrom *et al.* (1999) *New Engl. J. Med.* 341:1966-1973; Slamon *et al.* (2001) *New Engl. J. Med.* 344:783-792; Beniaminovitz *et al.* (2000) *New Engl. J. Med.* 342:613-619; Ghosh *et al.* (2003) *New Engl. J. Med.* 348:24-32; Lipsky *et al.* (2000) *New Engl. J. Med.* 343:1594-1602; Physicians' Desk Reference 2003 (Physicians' Desk Reference, 57th Ed); Medical Economics Company; ISBN: 1563634457; 57th edition (November 2002). Determination of the appropriate dosage regimen may be made by the clinician, *e.g.*, using parameters or factors known or suspected in the art to affect treatment or predicted to affect treatment, and will depend, for example, the patient's clinical history (e.g., previous therapy), the type and stage of the cancer to be treated and biomarkers of response to one or more of the therapeutic agents in the combination therapy.

[00140]   Biotherapeutic agents in a combination therapy of the invention may be administered by continuous infusion, or by doses at intervals of, *e.g.*, daily, every other day, three times per week, or one time each week, two weeks, three weeks, monthly, bimonthly, etc. A

- 28 -

total weekly dose is generally at least 0.05 µg/kg, 0.2 µg/kg, 0.5 µg/kg, 1 µg/kg, 10 µg/kg, 100 µg/kg, 0.2 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg body weight or more. *See, e.g.*, Yang *et al.* (2003) *New Engl. J. Med.* 349:427-434; Herold *et al.* (2002) *New Engl. J. Med.* 346:1692-1698; Liu *et al.* (1999) *J. Neurol. Neurosurg. Psych.* 67:451-456; Portielji *et al.* (20003) *Cancer Immunol. Immunother.* 52:133-144.

[00141]   Dosage units for a PD-1 antagonist (e.g., MK-3475) may be expressed as a flat dose, i.e., 100 mg, 200 mg, 300 mg, or as a patient-specific dose, i.e., mg/kg (mg therapeutic agent/kg of body weight) or mg/m^2 (quantity in milligrams per square meter of body surface area).

[00142]   In some embodiments that employ an anti-human PD-1 mAb as the PD-1 antagonist in the combination therapy, the dosing regimen will comprise administering the anti-human PD-1 mAb at a flat dose of 100 to 500 mg or a weight-based dose of 1 to 10 mg/kg at intervals of about 14 days (± 2 days) or about 21 days (± 2 days) or about 30 days (± 2 days) throughout the course of treatment.

[00143]   In other embodiments that employ an anti-human PD-1 mAb as the PD-1 antagonist in the combination therapy, the dosing regimen will comprise administering the anti-human PD-1 mAb at a dose of 1, 2, 3, 5 or 10mg/kg at intervals of about 14 days (± 2 days) or about 21 days (± 2 days) or about 30 days (± 2 days) throughout the course of treatment.

[00144]   In other embodiments that employ an anti-human PD-1 mAb as the PD-1 antagonist in the combination therapy, the dosing regimen will comprise administering the anti-human PD-1 mAb at a dose of from about 0.005 mg/kg to about 10 mg/kg, with intra-patient dose escalation. In other escalating dose embodiments, the interval between doses will be progressively shortened, e.g., about 30 days (± 2 days) between the first and second dose, about 14 days (± 2 days) between the second and third doses. In certain embodiments, the dosing interval will be about 14 days (± 2 days), for doses subsequent to the second dose.

[00145]   In certain embodiments, a subject will be administered an intravenous (IV) infusion of a medicament comprising any of the PD-1 antagonists described herein.

[00146]   In one embodiment of the invention, the PD-1 antagonist in the combination therapy is nivolumab, which is administered intravenously at a dose selected from the group consisting of: 1 mg/kg Q2W, 2 mg/kg Q2W, 3 mg/kg Q2W, 5 mg/kg Q2W, 10 mg Q2W, 1 mg/kg Q3W, 2 mg/kg Q3W, 3 mg/kg Q3W, 5 mg/kg Q3W, and 10 mg Q3W.

[00147]   In another embodiment of the invention, the PD-1 antagonist in the combination therapy is MK-3475, which is administered in a liquid medicament at a dose selected from the group consisting of 200 mg Q3W, 1 mg/kg Q2W, 2 mg/kg Q2W, 3 mg/kg Q2W, 5 mg/kg Q2W, 10 mg Q2W, 1 mg/kg Q3W, 2 mg/kg Q3W, 3 mg/kg Q3W, 5 mg/kg Q3W, and 10 mg Q3W. The dose of MK-3475 may be an equivalent of any of the aforesaid doses (e.g., a PK model of MK-3475 estimates that the fixed dose of 200 mg Q3W provides exposures that are consistent with those obtained with 2 mg/kg Q3W). In some embodiments, MK-3475 is administered as a liquid medicament which comprises 25 mg/ml MK-3475, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5, and the selected dose of the medicament is administered by IV infusion over a time period of about 30 minutes.

[00148]   The optimal dose for MK-3475 in combination with crizotinib may be identified by dose escalation of one or both of these agents. Crizotinib will be administered orally (PO), either once daily (QD) or twice daily (BID), with or without food on a continuous schedule starting on Cycle 1 Day 1. MK-3475 will be administered as a 30-minute intravenous (IV) infusion every 3 weeks (Q3W) or in case of dose reduction, every 4 weeks (Q4W), starting on Cycle 1 Day 1, except in the case of a crizotinib lead-in. On the day of MK-3475 administration, crizotinib may be given prior to or after the MK-3475 administration.

[00149]   In one embodiment, crizotinib is administered at 250 mg BID and MK-3475 is administered at a starting dose of 2 mg/kg Q3W.   In another embodiment, crizotinib is administered at 250 mg BID for a 3-week lead-in period and then MK-3475 is administered at a starting dose of 2 mg/kg Q3W or 200 mg Q3W after the lead-in period. In another embodiment, crizotinib is administered at 250 mg BID and MK-3475 is administered at a starting dose of 2 mg/kg Q4W or 200 mg Q4W. In another embodiment, crizotinib is administered at 200 mg BID and MK-3475 is administered at a starting dose of 2 mg/kg Q3W or 200 mg Q3W. In another embodiment, crizotinib is administered at 200 mg BID and MK-3475 is administered at a starting dose of 2 mg/kg Q4W or 200 mg Q4W. In another embodiment, crizotinib is administered at 250 mg QD and MK-3475 is administered at a starting dose of 2 mg/kg Q3W or 200 mg Q3W. In another embodiment, crizotinib is administered at 250 mg QD and MK-3475 is administered at a starting dose of 2 mg/kg Q4W or 200 mg Q3W.

[00150]   In some embodiments, the patient is treated with a 3-week lead-in period of single-agent crizotinib directly preceding the administration of the MK-3475 and crizotinib combination.

[00151]   In some embodiments, a treatment cycle begins with the first day of combination treatment and last for 3 weeks. In such embodiments, the combination therapy is preferably administered for at least 18 weeks (6 cycles of treatment), more preferably at least 24 weeks (8 cycles of treatment), and even more preferably at least 2 weeks after the patient achieves a CR.

[00152]   In some embodiments, the dose of crizotinib is increased up to a maximum dose of 250 mg BID if the patient tolerates the combination treatment at a lower total dose of crizotinib.

[00153]   In some embodiments, the ALK inhibitor in the combination therapy is ceritinib or alectinib. In some such embodiments, the ALK inhibitor is ceritinib, which is administered orally at a dose of 750 mg QD. In other such embodiments, the ALK inhibitor is alectinib, which is administered orally at a dose of 300 mg BID.

[00154]   In some embodiments, the patient is selected for treatment with the combination therapy of the invention if the patient has been diagnosed with advanced non-squamous NSCLC that tests positive for human ALK. In some embodiments, the primary tumor has been resected. In an embodiment, the patient has not received prior systemic therapy for advanced NSCLC.

[00155]   The present invention also provides a medicament which comprises a PD-1 antagonist as described above and a pharmaceutically acceptable excipient. When the PD-1 antagonist is a biotherapeutic agent, e.g., a mAb, the antagonist may be produced in CHO cells using conventional cell culture and recovery/purification technologies.

[00156]   In some embodiments, a medicament comprising an anti-PD-1 antibody as the PD-1 antagonist may be provided as a liquid formulation or prepared by reconstituting a lyophilized powder with sterile water for injection prior to use. WO 2012/135408 describes the preparation of liquid and lyophilized medicaments comprising MK-3475 that are suitable for use in the present invention. In some embodiments, a medicament comprising MK-3475 is provided in a glass vial which contains about 50 mg of MK-3475.

[00157]   The present invention also provides a medicament which comprises crizotinib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. The compound may be formulated with precedented excipients filled in hard gelatin capsules composed of gelatin and precedented colorants, packaged in appropriate packaging material and stored in line with labeled storage conditions.

[00158]   The anti-PD-1 and ALK inhibitor medicaments described herein may be provided as a kit which comprises a first container and a second container and a package insert. The first

container contains at least one dose of a medicament comprising an anti-PD-1 antagonist, the second container contains at least one dose of a medicament comprising an ALK inhibitor, and the package insert, or label, which comprises instructions for treating a patient for cancer using the medicaments. The first and second containers may be comprised of the same or different shape (e.g., vials, syringes and bottles) and/or material (e.g., plastic or glass). The kit may further comprise other materials that may be useful in administering the medicaments, such as diluents, filters, IV bags and lines, needles and syringes. In some preferred embodiments of the kit, the anti-PD-1 antagonist is an anti-PD-1 antibody and the instructions state that the medicaments are intended for use in treating a patient having a cancer that tests positive for PD-L1 expression by an IHC assay.

[00159]   These and other aspects of the invention, including the exemplary specific embodiments listed below, will be apparent from the teachings contained herein.

Exemplary Specific Embodiments of the Invention

1.   A method for treating a cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and an ALK inhibitor.

2.   The method of embodiment 1, wherein the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof.

3.   The method of embodiment 1 or 2, wherein the ALK inhibitor is a small molecule ALK inhibitor.

4.   A medicament comprising a PD-1 antagonist for use in combination with an ALK inhibitor for treating a cancer in an individual, wherein the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof.

5.   A medicament comprising an ALK inhibitor for use in combination with a PD-1 antagonist for treating a cancer in an individual.

6.   The medicament of embodiment 4 or 5, which further comprises a pharmaceutically acceptable excipient.

7.   Use of a PD-1 antagonist in the manufacture of a medicament for treating a cancer in an individual when administered in combination with an ALK inhibitor.

6.   Use of an ALK inhibitor in the manufacture of a medicament for treating a cancer in an individual when administered in combination with a PD-1 antagonist.

7.   Use of a PD-1 antagonist and an ALK inhibitor in the manufacture of a medicament for treating a cancer in an individual.

8.   A kit which comprises a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising a PD-1 antagonist, the second container comprises at least one dose of a medicament comprising an ALK inhibitor, and the package insert comprises instructions for treating an individual for cancer using the medicaments.

9.   The kit of embodiment 8, wherein the instructions state that the medicaments are intended for use in treating an individual having a cancer that tests positive for PD-L1 expression by an immunohistochemical (IHC) assay.

10.   The kit of embodiment 8 or 9, wherein the instructions state that the medicaments are intended for use in treating an individual having a cancer that tests positive for ALK.

11.   The method, medicament, use or kit of any one of embodiments 1 to 10, wherein the individual is a human and the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to human PD-L1 and blocks the binding of human PD-L1 to human PD-1.

12.   The method, medicament, use or kit of embodiment 11, wherein the PD-1 antagonist is MPDL3280A, BMS-936559, MEDI4736, MSB0010718C or a monoclonal antibody which comprises the heavy chain and light chain variable regions of SEQ ID NO:24 and SEQ ID NO:21, respectively, of WO2013/019906.

13.   The method, medicament, use or kit of any one of embodiments 1 to 10, wherein the individual is a human, and the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to human PD-1 and blocks the binding of human PD-L1 to human PD-1.

14.   The method, medicament, use or kit of embodiment 13, wherein the PD-1 antagonist also blocks binding of human PD-L2 to human PD-1.

15.   The method, medicament, use or kit of embodiment 14, wherein the monoclonal antibody, or antigen binding fragment thereof, comprises: (a) light chain CDRs of SEQ ID NOs: 1, 2 and 3 and heavy chain CDRs of SEQ ID NOs: 4, 5 and 6; or (b) light chain CDRs of SEQ ID NOs: 7, 8 and 9 and heavy chain CDRs of SEQ ID NOs: 10, 11 and 12.

- 33 -

16.   The method, medicament, use or kit of embodiment 14, wherein the monoclonal antibody, or antigen binding fragment thereof, comprises light chain CDRs of SEQ ID NOs: 7, 8 and 9 and heavy chain CDRs of SEQ ID NOs: 10, 11 and 12.

17.   The method, medicament, use or kit of embodiment 14, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, and wherein the heavy chain comprises SEQ ID NO:21 and the light chain comprises SEQ ID NO:22.

18.   The method, medicament, use or kit of embodiment 14, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, and wherein the heavy chain comprises SEQ ID NO:23 and the light chain comprises SEQ ID NO:24.

19.   The method, medicament, use or kit of any of embodiments 11-18, wherein the cancer is a solid tumor.

20.   The method, medicament, use or kit of any one of embodiments 11-18, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), neuroblastoma, glioblastoma or rhabdomycosarcoma.

21.   The method, medicament, use or kit of any one of embodiments 11-18, wherein the cancer is NSCLC.

22.   The method, medicament, use or kit of embodiment 21, wherein the individual has not been previously treated for NSCLC.

23. The method, medicament, use or kit of claim 21 or 22, wherein the cancer is advanced non-squamous NSCLC.

24.   The method, medicament, use or kit of any one of embodiments 11-18, wherein the cancer is diffuse large B-cell lymphoma (DLBCL) or anaplastic large-cell lymphoma (ALCL).

25.   The method, medicament, use or kit of any one of embodiments 11-24, wherein the cancer tests positive for human PD-L1.

26.   The method, medicament, use or kit of embodiment 25, wherein the human PD-L1 expression is elevated.

27.   The method, medicament, use or kit of any one of embodiments 11-26, wherein the cancer tests positive for human ALK.

28.   The method, medicament, use or kit of embodiment 27, wherein the human ALK expression is elevated.

29.   The method, medicament, use or kit of embodiment 13, wherein the PD-1 antagonist is MK-3475 or nivolumab.

30.   The method, medicament, use or kit of embodiment 29, wherein the MK-3475 is formulated as a liquid medicament which comprises 25 mg/ml MK-3475, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5.

31.   The method, medicament, use or kit of any one of embodiments 1 to 30, wherein the ALK inhibitor is crizotinib, ceritinib or alectinib, or a pharmaceutically acceptable salt thereof.

32.   The method, medicament, use or kit of any one of embodiments 1 to 30, wherein the ALK inhibitor is PF-06463922, NVP-TAE684, AP26113, TSR-011, X-396, CEP-37440 or RXDX-101, or a pharmaceutically acceptable salt thereof.

33.   The method, medicament, use or kit of any one of embodiments 1 to 31, wherein the ALK inhibitor is crizotinib, or a pharmaceutically acceptable salt thereof.

34.   The method, medicament, use or kit of embodiment 33, wherein crizotinib is formulated as a 200 mg capsule or a 250 mg capsule.

GENERAL METHODS

[00160]   Standard methods in molecular biology are described Sambrook, Fritsch and Maniatis (1982 & 1989 2nd Edition, 2001 3rd Edition) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Sambrook and Russell (2001) *Molecular Cloning, 3rd ed.,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Wu (1993) *Recombinant DNA*, Vol. 217, Academic Press, San Diego, CA). Standard methods also appear in Ausbel, *et al.* (2001) *Current Protocols in Molecular Biology, Vols.1-4,* John Wiley and Sons, Inc. New York, NY, which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

[00161]   Methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization are described (Coligan, *et al.* (2000) *Current Protocols in Protein Science, Vol. 1*, John Wiley and Sons, Inc., New York). Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described (see, *e.g.*, Coligan, *et al.* (2000) *Current Protocols in*

Protein Science, Vol. 2, John Wiley and Sons, Inc., New York; Ausubel, *et al.* (2001) *Current Protocols in Molecular Biology, Vol. 3*, John Wiley and Sons, Inc., NY, NY, pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) *Products for Life Science Research*, St. Louis, MO; pp. 45-89; Amersham Pharmacia Biotech (2001) *BioDirectory*, Piscataway, N.J., pp. 384-391). Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (Coligan, *et al.* (2001) *Current Protocols in Immunology, Vol. 1*, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) *Using Antibodies*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Harlow and Lane, *supra*). Standard techniques for characterizing ligand/receptor interactions are available (see, *e.g.*, Coligan, *et al.* (2001) *Current Protocols in Immunology, Vol. 4*, John Wiley, Inc., New York).

[00162] Monoclonal, polyclonal, and humanized antibodies can be prepared (see, *e.g.*, Sheperd and Dean (eds.) (2000) *Monoclonal Antibodies*, Oxford Univ. Press, New York, NY; Kontermann and Dubel (eds.) (2001) *Antibody Engineering*, Springer-Verlag, New York; Harlow and Lane (1988) *Antibodies A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 139-243; Carpenter, *et al.* (2000) *J. Immunol.* 165:6205; He, *et al.* (1998) *J. Immunol.* 160:1029; Tang *et al.* (1999) J. Biol. Chem. 274:27371-27378; Baca *et al.* (1997) *J. Biol. Chem.* 272:10678-10684; Chothia *et al.* (1989) *Nature* 342:877-883; Foote and Winter (1992) *J. Mol. Biol.* 224:487-499; U.S. Pat. No. 6,329,511).

[00163] An alternative to humanization is to use human antibody libraries displayed on phage or human antibody libraries in transgenic mice (Vaughan *et al.* (1996) *Nature Biotechnol.* 14:309-314; Barbas (1995) *Nature Medicine* 1:837-839; Mendez *et al.* (1997) *Nature Genetics* 15:146-156; Hoogenboom and Chames (2000) *Immunol. Today* 21:371-377; Barbas *et al.* (2001) *Phage Display: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; Kay *et al.* (1996) *Phage Display of Peptides and Proteins: A Laboratory Manual*, Academic Press, San Diego, CA; de Bruin *et al.* (1999) *Nature Biotechnol.* 17:397-399).

[00164] Purification of antigen is not necessary for the generation of antibodies. Animals can be immunized with cells bearing the antigen of interest. Splenocytes can then be isolated from the immunized animals, and the splenocytes can fused with a myeloma cell line to produce a hybridoma (see, *e.g.*, Meyaard *et al.* (1997) *Immunity* 7:283-290; Wright *et al.* (2000) *Immunity* 13:233-242; Preston *et al.*, *supra*; Kaithamana *et al.* (1999) *J. Immunol.* 163:5157-5164).

[00165] Antibodies can be conjugated, *e.g.*, to small drug molecules, enzymes, liposomes, polyethylene glycol (PEG). Antibodies are useful for therapeutic, diagnostic, kit or other purposes, and include antibodies coupled, *e.g.*, to dyes, radioisotopes, enzymes, or metals, *e.g.*,

colloidal gold (see, *e.g.*, Le Doussal *et al.* (1991) *J. Immunol.* 146:169-175; Gibellini *et al.* (1998) *J. Immunol.* 160:3891-3898; Hsing and Bishop (1999) *J. Immunol.* 162:2804-2811; Everts *et al.* (2002) *J. Immunol.* 168:883-889).

[00166]   Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (see, *e.g.*, Owens, *et al.* (1994) *Flow Cytometry Principles for Clinical Laboratory Practice*, John Wiley and Sons, Hoboken, NJ; Givan (2001) *Flow Cytometry, 2nd ed.*; Wiley-Liss, Hoboken, NJ; Shapiro (2003) *Practical Flow Cytometry*, John Wiley and Sons, Hoboken, NJ). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, *e.g.*, as diagnostic reagents, are available (Molecular Probesy (2003) *Catalogue*, Molecular Probes, Inc., Eugene, OR; Sigma-Aldrich (2003) *Catalogue*, St. Louis, MO).

[00167]   Standard methods of histology of the immune system are described (see, *e.g.*, Muller-Harmelink (ed.) (1986) *Human Thymus: Histopathology and Pathology*, Springer Verlag, New York, NY; Hiatt, *et al.* (2000) *Color Atlas of Histology*, Lippincott, Williams, and Wilkins, Phila, PA; Louis, *et al.* (2002) *Basic Histology: Text and Atlas*, McGraw-Hill, New York, NY).

[00168]   Software packages and databases for determining, *e.g.*, antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available (see, *e.g.*, GenBank, Vector NTI® Suite (Informax, Inc, Bethesda, MD); GCG Wisconsin Package (Accelrys, Inc., San Diego, CA); DeCypher® (TimeLogic Corp., Crystal Bay, Nevada); Menne, *et al.* (2000) *Bioinformatics* 16: 741-742; Menne, *et al.* (2000) *Bioinformatics Applications Note* 16:741-742; Wren, *et al.* (2002) *Comput. Methods Programs Biomed.* 68:177-181; von Heijne (1983) *Eur. J. Biochem.* 133:17-21; von Heijne (1986) *Nucleic Acids Res.* 14:4683-4690).

Equivalents

[00169]   The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the disclosure. The foregoing description and Examples detail certain exemplary embodiments of the disclosure. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the disclosure may be practiced in many ways and the disclosure should be construed in accordance with the appended claims and any equivalents thereof.

Exemplary Embodiments

[00170]   The invention is further described in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

EXAMPLES

[00171]   *Example 1: Treatment of Patients with Cancer, (e.g., NSCLC) with a Combination of Crizotinib and MK-3475*

[00172]   This study will evaluate the efficacy of a combination of crizotinib and MK-3475 in human patients with cancer (e.g., NSCLC). Patients will be treated with varying doses of crizotinib (e.g., 200 mg or 250 mg BID) and MK-3475 (e.g., 1 mg/kg or 2 mg/kg) or a placebo every three weeks or every four weeks by intravenous infusion for a predetermined period of time (e.g., 24 weeks). Optionally additional patients may be treated with either crizotinib or MK-3475 as a further control.

[00173]   Table 3 provides exemplary dosing information for the combinationof crizotinib and MK-3475.

Dose Level	MK-3475	Crizotinib
-1a	2 mg /kg IV q3wk	200 mg BID
-1b	1 mg/kg IV q3wk	250 mg BID
-1c	2 mg/kg IV q4wk	200 mg BID
-1d	1 mg/kg IV q4wk	250 mg BID

BID: twice daily; q3wk: every 3 weeks.

[00174]   It is expected that the combination of crizotinib and MK-3475 will be more efficacious than either treatment alone according to at least one of the following outcome measures: reduced number of cancer cells, reduced tumor size, reduced rate of cancer cell infiltration into peripheral organs, reduced rate of tumor metastasis or tumor growth, or increased progression-free or overall survival.

Table 4 provides a brief description of the sequences in the sequence listing.

SEQ ID NO:	Description
1	hPD-1.08A light chain CDR1
2	hPD-1.08A light chain CDR2
3	hPD-1-08A light chain CDR3

SEQ ID NO:	Description
4	hPD-1.08A heavy chain CDR1
5	hPD-1.08A heavy chain CDR2
6	hPD-1.08A heavy chain CDR3
7	hPD-1.09A light chain CDR1
8	hPD-1.09A light chain CDR2
9	hPD-1.09A light chain CDR3
10	hPD-1.09A heavy chain CDR1
11	hPD-1.09A heavy chain CDR2
12	hPD-1.09A heavy chain CDR3
13	109A-H heavy chain variable region
14	409A-H heavy chain full length
15	K09A-L-11 light chain variable region
16	K09A-L-16 light chain variable region
17	K09A-L-17 light chain variable region
18	K09A-L-11 light chain full length
19	K09A-L-16 light chain full length
20	K09A-L-17 light chain full length
21	MK-3475 Heavy chain
22	MK-3475 Light chain
23	Nivolumab Heavy chain
24	Nivolumab light chain
25	Human PD-L1

REFERENCES

1. Sharpe, A.H, Wherry, E.J., Ahmed R., and Freeman G.J. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nature Immunology* (2007); 8:239-245.

2. Dong H *et al*. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002 Aug;8(8):793-800.

3. Yang *et al*. PD-1 interaction contributes to the functional suppression of T-cell responses to human uveal melanoma cells in vitro. *Invest Ophthalmol Vis Sci*. 2008 Jun;49(6 (2008): 49: 2518-2525.

4. Ghebeh *et al*. The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. *Neoplasia* (2006) 8: 190-198.

5. Hamanishi J *et al*. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proceeding of the National Academy of Sciences* (2007): 104: 3360-3365.

6. Thompson RH et al. Significance of B7-H1 overexpression in kidney cancer. *Clinical Genitourin Cancer* (2006): 5: 206-211.

7. Nomi, T. Sho, M., Akahori, T., *et al*. Clinical significance and therapeutic potential of the programmed death- 1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clinical Cancer Research* (2007);13:2151-2157.

8. Ohigashi Y et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand 2 expression in human esophageal cancer. *Clin. Cancer Research* (2005): 11: 2947-2953.

9. Inman *et al*. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer* (2007): 109: 1499-1505.

10. Shimauchi T *et al*. Augmented expression of programmed death-1 in both neoplasmatic and nonneoplastic CD4+ T-cells in adult T-cell Leukemia/ Lymphoma. *Int. J. Cancer* (2007): 121:2585-2590.

11. Gao *et al*. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clinical Cancer Research* (2009) 15: 971-979.

12. Nakanishi J. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer Immunol Immunother*. (2007) 56: 1173- 1182.

13. Hino *et al*. Tumor cell expression of programmed cell death-1 is a prognostic factor for malignant melanoma. *Cancer* (2010): 00: 1-9.

14. Ghebeh H. Foxp3+ tregs and B7-H1+/PD-1+ T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer patients: implication for immunotherapy. *BMC Cancer*. 2008 Feb 23;8:57.

15. Ahmadzadeh M et al. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood* (2009) 114: 1537-1544.

16. Thompson RH et al. PD-1 is expressed by tumor infiltrating cells and is associated with poor outcome for patients with renal carcinoma. *Clinical Cancer Research* (2007) 15: 1757-1761.

[00175] All references cited herein are incorporated by reference to the same extent as if each individual publication, database entry (e.g. Genbank sequences or GeneID entries), patent application, or patent, was specifically and individually indicated to be incorporated by reference. This statement of incorporation by reference is intended by Applicants, pursuant to 37 C.F.R. §1.57(b)(1), to relate to each and every individual publication, database entry (e.g. Genbank sequences or GeneID entries), patent application, or patent, each of which is clearly identified in compliance with 37 C.F.R. §1.57(b)(2), even if such citation is not immediately adjacent to a dedicated statement of incorporation by reference. The inclusion of dedicated statements of incorporation by reference, if any, within the specification does not in any way weaken this general statement of incorporation by reference. Citation of the references herein is not intended as an admission that the reference is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

CLAIMS

1.   A method for treating a cancer in a human comprising administering to the individual a combination therapy which comprises an antagonist of a Programmed Death 1 protein (PD-1) and an ALK inhibitor, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, and further wherein the ALK inhibitor is 3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine (crizotinib) or a pharmaceutically acceptable salt thereof.

2.   The method of claim 1, wherein the cancer is a solid tumor.

3.   The method of claim 1 or 2, wherein the cancer is non-small cell lung cancer (NSCLC).

4.   The method of any one of claims 1 to 3, wherein the cancer tests positive for PD-L1 expression by an immunohistochemical (IHC) assay.

5.   The method of any one of claims 1 to 4, wherein the cancer tests positive for ALK.

6.   The method of any one of claims 1 to 5, wherein the PD-1 antagonist is MK-3475 and the ALK inhibitor is crizotinib.

7.   A medicament comprising an antagonist of a Programmed Death 1 protein (PD-1) for use in combination with an ALK inhibitor for treating a cancer in a human, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, and further wherein the ALK inhibitor is crizotinib or a pharmaceutically acceptable salt thereof.

8.   A medicament comprising an ALK inhibitor for use in combination with an antagonist of a Programmed Death 1 protein (PD-1) for treating a cancer in a human, wherein the ALK inhibitor is crizotinib or a pharmaceutically acceptable salt thereof, and further wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22.

9.   The medicament of claim 7 or 8, wherein the cancer is a solid tumor.

10.   The medicament of claim 7 or 8, wherein the cancer is non-small cell lung cancer (NSCLC).

11.   The medicament of any one of claims 7 to 10, wherein the cancer tests positive for PD-L1 expression by an immunohistochemical (IHC) assay.

12.   The medicament of any one of claims 7 to 11, wherein the cancer tests positive for ALK.

13.   The medicament of any of claims 7 to 12, wherein the PD-1 antagonist is MK-3475 and the ALK inhibitor is crizotinib.

14.   The medicament of claim 13, wherein the MK-3475 is formulated as a liquid medicament which comprises 25 mg/ml MK-3475, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5 and crizotinib is formulated as a 200 mg capsule or a 250 mg capsule.

15.   A kit which comprises a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising an antagonist of a Programmed Death 1 protein (PD-1), the second container comprises at least one dose of a medicament comprising an ALK inhibitor, and the package insert comprises instructions for treating a human for cancer using the medicaments, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, and further wherein the ALK inhibitor is crizotinib or a pharmaceutically acceptable salt thereof.

16.   The kit of claim 15, wherein the instructions state that the medicaments are intended for use in treating a human having a cancer that tests positive for PD-L1 expression by an immunohistochemical (IHC) assay.

17.   The kit of claim 15 or 16, wherein the instructions state that the medicaments are intended for use in treating a human having a cancer that tests positive for ALK.

18.   The kit of any one of claims 15 to 17, wherein the PD-1 antagonist is MK-3475 and the ALK inhibitor is crizotinib.

19.   The kit of any one of claims 15 to 17, wherein the PD-1 antagonist is MK-3475 formulated as a liquid medicament and the ALK inhibitor is crizotinib formulated as a 200 mg capsule or a 250 mg capsule.

20.   The method, use or kit of any one of claims 1, 2, 4-9 or 11-19, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian

cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), neuroblastoma, glioblastoma, rhabdomycosarcoma, diffuse large B-cell lymphoma (DLBCL), anaplastic large-cell lymphoma (ALCL), EBV-positive DLBCL, primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, follicular lymphoma, Hodgkin's

5   lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

21.   The method, medicament or kit of any one of claims 1 to 19, wherein the cancer is advanced non-squamous NSCLC that tests positive for human ALK.

10   22.   The method, medicament or kit of any one of claims 1 to 21, wherein the cancer tests strongly positive for PD-L1 expression by an IHC assay.

1/8

hPD-1.08A light chain CDR1 (SEQ ID NO:1)

Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Phe Ser Tyr Leu His

hPD-1.08A light chain CDR2 (SEQ ID NO:2)

Leu Ala Ser Asn Leu Glu Ser

hPD-1-08A light chain CDR3 (SEQ ID NO:3)

Gln His Ser Trp Glu Leu Pro Leu Thr

hPD-1.08A heavy chain CDR1 (SEQ ID NO:4)

Ser Tyr Tyr Leu Tyr

hPD-1.08A heavy chain CDR2 (SEQ ID NO:5)

Gly Val Asn Pro Ser Asn Gly Gly Thr Asn Phe Ser Glu Lys Phe Lys Ser

hPD-1.08A heavy chain CDR3 (SEQ ID NO:6)

Arg Asp Ser Asn Tyr Asp Gly Gly Phe Asp Tyr

Fig. 1

SUBSTITUTE SHEET (RULE 26)

hPD-1.09A light chain CDR1 (SEQ ID NO:7)

Arg Ala Ser Lys Gly Val Ser Thr Ser Gly Tyr Ser Tyr Leu His

hPD-1.09A light chain CDR2 (SEQ ID NO:8)

Leu Ala Ser Tyr Leu Glu Ser

hPD-1.09A light chain CDR3 (SEQ ID NO:9)

Gln His Ser Arg Asp Leu Pro Leu Thr

hPD-1.09A heavy chain CDR1 (SEQ ID NO:10)

Asn Tyr Tyr Met Tyr

hPD-1.09A heavy chain CDR2 (SEQ ID NO:11)

Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe Lys Asn

hPD-1.09A heavy chain CDR3 (SEQ ID NO:12)

Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr

Fig. 2

3/8

109A-H heavy chain variable region (SEQ ID NO:13)

```
Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala Ser Val Lys
Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Met Tyr Trp Val Arg
Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Gly Ile Asn Pro Ser Asn Gly Gly
Thr Asn Phe Asn Glu Lys Phe Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr
Thr Thr Ala Tyr Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr
Cys Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr Trp Gly Gln Gly Thr
Thr Val Thr Val Ser Ser
```

409A-H heavy chain full length (SEQ ID NO:14)

```
Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala Ser Val Lys
Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Met Tyr Trp Val Arg
Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Gly Ile Asn Pro Ser Asn Gly Gly
Thr Asn Phe Asn Glu Lys Phe Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr
Thr Thr Ala Tyr Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr
Cys Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr Trp Gly Gln Gly Thr
Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
```

Fig. 3

4/8

K09A-L-11 light chain variable region (SEQ ID NO:15)

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser Gly Tyr Ser Tyr Leu His
Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Leu Ala Ser Tyr
Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser
Arg Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

K09A-L-16 light chain variable region (SEQ ID NO:16)

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala
Ser Ile Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser Gly Tyr Ser Tyr Leu His
Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Ala Ser Tyr
Leu Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln His Ser
Arg Asp Leu Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys

K09A-L-17 light chain variable region (SEQ ID NO:17)

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala
Ser Ile Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser Gly Tyr Ser Tyr Leu His
Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Ala Ser Tyr
Leu Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr
Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Leu Tyr Tyr Cys Gln His Ser
Arg Asp Leu Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys

Fig. 4

5/8

K09A-L-11 light chain full length (SEQ ID NO:18)

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser Gly Tyr Ser Tyr Leu His
Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Leu Ala Ser Tyr
Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser
Arg Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val
Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
Thr Lys Ser Phe Asn Arg Gly Glu Cys

K09A-L-16 light chain full length (SEQ ID NO:19)

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala
Ser Ile Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser Gly Tyr Ser Tyr Leu His
Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Ala Ser Tyr
Leu Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln His Ser
Arg Asp Leu Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val
Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
Thr Lys Ser Phe Asn Arg Gly Glu Cys

Fig 5A

6/8

K09A-L-17 light chain full length (SEQ ID NO:20)

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala
Ser Ile Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser Gly Tyr Ser Tyr Leu His
Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Ala Ser Tyr
Leu Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr
Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Leu Tyr Tyr Cys Gln His Ser
Arg Asp Leu Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val
Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
Thr Lys Ser Phe Asn Arg Gly Glu Cys

Fig. 5B

7/8

Heavy chain (SEQ ID NO:21)

```
QVQLVQSGVE  VKKPGASVKV  SCKASGYTFT  NYYMYWVRQA  PGQGLEWMGG  50

INPSNGGTNF  NEKFKNRVTL  TTDSSTTTAY  MELKSLQFDD  TAVYYCARRD  100

YRFDMGFDYW  GQGTTVTVSS  ASTKGPSVFP  LAPCSRSTSE  STAALGCLVK  150

DYFPEPVTVS  WNSGALTSGV  HTFPAVLQSS  GLYSLSSVVT  VPSSSLGTKT  200

YTCNVDHKPS  NTKVDKRVES  KYGPPCPPCP  APEFLGGPSV  FLFPPKPKDT  250

LMISRTPEVT  CVVVDVSQED  PEVQFNWYVD  GVEVHNAKTK  PREEQFNSTY  300

RVVSVLTVLH  QDWLNGKEYK  CKVSNKGLPS  SIEKTISKAK  GQPREPQVYT  350

LPPSQEEMTK  NQVSLTCLVK  GFYPSDIAVE  WESNGQPENN  YKTTPPVLDS  400

DGSFFLYSRL  TVDKSRWQEG  NVFSCSVMHE  ALHNHYTQKS  LSLSLGK     447
```

Light chain (SEQ ID NO:22)

```
EIVLTQSPAT  LSLSPGERAT  LSCRASKGVS  TSGYSYLHWY  QQKPGQAPRL  50

LIYLASYLES  GVPARFSGSG  SGTDFTLTIS  SLEPEDFAVY  YCQHSRDLPL  100

TFGGGTKVEI  KRTVAAPSVF  IFPPSDEQLK  SGTASVVCLL  NNFYPREAKV  150

QWKVDNALQS  GNSQESVTEQ  DSKDSTYSLS  STLTLSKADY  EKHKVYACEV  200

THQGLSSPVT  KSFNRGEC                                        219
```

Fig. 6

8/8

Nivolumab

Heavy chain (SEQ ID NO:23)

```
QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV  50
IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND  100
DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV  150
TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH  200
KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP  250
EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT  300
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE  350
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY  400
SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK              440
```

Light chain (SEQ ID NO:24)

```
EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD  50
ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ SSNWPRTFGQ  100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV  150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG  200
LSSPVTKSFN RGEC                                         214
```

Fig. 7

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4545   A61K39/395   A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DAVID F. MCDERMOTT ET AL: "PD-1 as a potential target in cancer therapy", CANCER MEDICINE, 21 July 2013 (2013-07-21), pages n/a-n/a, XP055157252, ISSN: 2045-7634, DOI: 10.1002/cam4.106 abstract page 663 pages 665-669 ----- -/--	1-22

[X] Further documents are listed in the continuation of Box C.   [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 2015	30/11/2015

| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer Weisser, Dagmar |

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

C(Continuation).   DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	OMID HAMID ET AL: "Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma", NEW ENGLAND JOURNAL OF MEDICINE, vol. 369, no. 2, 11 July 2013 (2013-07-11) , pages 134-144, XP055182016, ISSN: 0028-4793, DOI: 10.1056/NEJMoa1305133 the whole document	1-22
Y	Clinical Trials: "A Phase 1 Study Of The 4-1BB Agonist PF-05082566 In Combination With The PD-1 Inhibitor MK-3475 In Patients With Advanced Solid Tumors", , 1 July 2014 (2014-07-01), pages 1-6, XP055179633, Retrieved from the Internet: URL:https://clinicaltrials.gov/archive/NCT 02179918/2014_07_01 [retrieved on 2015-03-26] the whole document	1-22
Y	Anonymous: "NCT02014636 A Phase I/II Study to Assess the Safety and Efficacy of Pazopanib and MK 3475 in Subjects With Advanced Renal Cell Carcinoma", Clinical Trials.gov, 24 January 2014 (2014-01-24), pages 1-11, XP055180536, Retrieved from the Internet: URL:https://clinicaltrials.gov/archive/NCT 02014636/2014_01_24 [retrieved on 2015-03-31] the whole document	1-22
Y	EUNICE L. KWAK ET AL: "Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer", NEW ENGLAND JOURNAL OF MEDICINE, vol. 363, no. 18, 28 October 2010 (2010-10-28), pages 1693-1703, XP055081495, ISSN: 0028-4793, DOI: 10.1056/NEJMoa1006448 abstract page 1694, column 3 page 1695, column 3 page 1702, column 5	1-22
Y	WO 2013/017989 A1 (PFIZER [US]; CHRISTENSEN JAMES GAIL [US]; ZOU YAHONG [US]) 7 February 2013 (2013-02-07) abstract claims 1,11,12	1-22

1

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2013017989	A1	07-02-2013	AR	087731 A1	16-04-2014
			AU	2012291744 A1	20-02-2014
			CA	2842493 A1	07-02-2013
			CN	103841972 A	04-06-2014
			EP	2739284 A1	11-06-2014
			HK	1198133 A1	13-03-2015
			JP	2013032355 A	14-02-2013
			KR	20140041906 A	04-04-2014
			RU	2014102935 A	10-09-2015
			TW	201313698 A	01-04-2013
			WO	2013017989 A1	07-02-2013