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[Continued on next page]

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

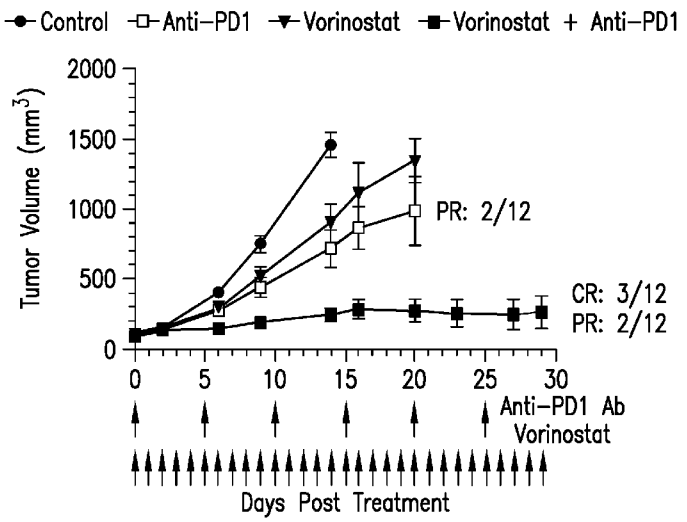

FIG.8A

(57) Abstract: The present disclosure describes combination therapies comprising an antagonist of Programmed Death 1 receptor (PD-1) and suberoylanilide hydroxamic acid (SAHA), and the use of the combination therapies for the treatment of cancer.

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COMBINATION OF A PD-1 ANTAGONIST AND VORINOSTAT FOR TREATING CANCER

FIELD OF THE INVENTION

[0001] 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 vorinostat, which is a histone deactylase (HDAC) inhibitor.

BACKGROUND OF THE INVENTION

[0002] 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).

[0003] 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.

[0004] 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. It has been proposed that the efficacy of such antibodies might be enhanced if administered in combination with other approved or experimental cancer therapies, e.g., radiation, surgery, chemotherapeutic agents, targeted therapies, agents that inhibit other signaling pathways that are disregulated in tumors, and other immune enhancing agents.

[0005] Vorinostat, also known as suberoylanilide hydroxamide acid (SAHA), belongs to a class of agents, histone deacetylase (HDAC) inhibitors, that have the ability to induce tumor cell growth arrest, differentiation and/or apoptosis (Richon, V.M., Webb, Y., Merger, R., et al.

(1996) *PNAS* 93:5705-8). These compounds are targeted towards mechanisms inherent to the ability of a neoplastic cell to become malignant, as they do not appear to have toxicity in doses effective for inhibition of tumor growth in animals (Cohen, L.A., Amin, S., Marks, P.A., Rifkind, R.A., Desai, D., and Richon, V.M. (1999) *Anticancer Research* 19:4999-5006). There are several lines of evidence that histone acetylation and deacetylation are mechanisms by which transcriptional regulation in a cell is achieved (Grunstein, M. (1997) *Nature* 389:349-52). These effects are thought to occur through changes in the structure of chromatin by altering the affinity of histone proteins for coiled DNA in the nucleosome. There are five types of histones that have been identified (designated H1, H2A, H2B, H3 and H4). Histones H2A, H2B, H3 and H4 are found in the nucleosomes and H1 is a linker located between nucleosomes. Each nucleosome contains two of each histone type within its core, except for H1, which is present singly in the outer portion of the nucleosome structure. It is believed that when the histone proteins are hypoacetylated, there is a greater affinity of the histone to the DNA phosphate backbone. This affinity causes DNA to be tightly bound to the histone and renders the DNA inaccessible to transcriptional regulatory elements and machinery. The regulation of acetylated states occurs through the balance of activity between two enzyme complexes, histone acetyl transferase (HAT) and histone deacetylase (HDAC). The hypoacetylated state is thought to inhibit transcription of associated DNA. This hypoacetylated state is catalyzed by large multiprotein complexes that include HDAC enzymes. In particular, HDACs have been shown to catalyze the removal of acetyl groups from the chromatin core histones.

[0006] It has been shown in several instances that the disruption of HAT or HDAC activity is implicated in the development of a malignant phenotype. For instance, in acute promyelocytic leukemia, the oncoprotein produced by the fusion of PML and RAR alpha appears to suppress specific gene transcription through the recruitment of HDACs (Lin, R.J., Nagy, L., Inoue, S., et al. (1998) *Nature* 391:811-14). In this manner, the neoplastic cell is unable to complete differentiation and leads to excess proliferation of the leukemic cell line. Zolinza® (Vorinostat, SAHA) was approved by the FDA in 2006 for the treatment of cutaneous T- cell lymphoma.

SUMMARY OF THE INVENTION

[0007] In one embodiment, the invention provides a method for treating cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and an HDAC inhibitor, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

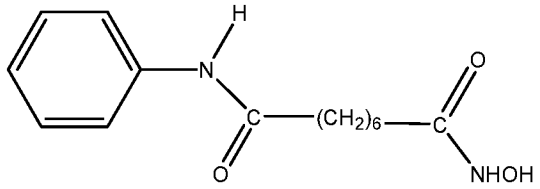
[0008] In another embodiment, the invention provides a medicament comprising a PD-1 antagonist for use in combination with an HDAC inhibitor for treating cancer, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof. In yet another embodiment, the invention provides a medicament comprising an HDAC inhibitor for use in combination with a PD-1 antagonist for treating cancer, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

[0009] Other embodiments provide use of a PD-1 antagonist in the manufacture of a medicament for treating cancer in an individual when administered in combination with an HDAC inhibitor and use of an HDAC inhibitor in the manufacture of a medicament for treating cancer in an individual when administered in combination with a PD-1 antagonist. In such embodiments, the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

[0010] In a still further embodiment, the invention provides use of a PD-1 antagonist and an HDAC inhibitor in the manufacture of medicaments for treating cancer in an individual, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof. 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 the HDAC inhibitor to treat cancer in an individual.

[0011] 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 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).

[0012] In some embodiments of the above treatment method, medicaments and uses, the HDAC inhibitor is suberoylanilide hydroxamic acid (SAHA), which is represented by the following structural formula:



Pharmaceutically acceptable salts of SAHA with inorganic bases, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like can also be used. SAHA or the pharmaceutically acceptable salt can be in crystalline or amorphous form, or a hydrate or solvate. Examples of the crystalline forms of SAHA are described in U.S. Patent 7,851,509. SAHA or the pharmaceutically acceptable salt particles may be micronized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid.

[0013] 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, squamous cell carcinoma of head and neck, lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer (RCC), small-cell lung cancer (SCLC) or triple negative breast cancer. In some embodiments, the cancer is NSCLC, endometrial cancer, urothelial cancer, squamous cell carcinoma of head and neck or melanoma.

[0014] In other embodiments of the above treatment method, medicaments and uses of 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), 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), cutaneous T- cell lymphoma, non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

[0015] Also, 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.

[0016] In one embodiment of the above treatment method, medicaments and uses, the individual is a human, the cancer tests positive for human PD-L1 and is selected from the group consisting of NSCLC, endometrial cancer, urothelial cancer, squamous cell carcinoma of head and neck or melanoma.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] 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).

[0018] 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).

[0019] 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).

[0020] 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).

[0021] FIGURE 5 shows 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).

[0022] FIGURE 6 shows amino acid sequences of the heavy and light chains for pembrolizumab (SEQ ID NOs. 21 and 22, respectively).

[0023] FIGURE 7 shows amino acid sequences of the heavy and light chains for nivolumab (SEQ ID NOs. 23 and 24, respectively).

[0024] FIGURE 8 (A) shows the mean tumor volume and demonstrates enhanced anti-tumor activity with concurrent administration of a PD-1 antagonist and Vorinostat compared to the monotherapy treatment arms in CT-26 tumor-bearing mice. Control: Isotype + Vehicle, anti-PD-1: a murine anti-mouse PD-1 mAb. CR = complete regressions; PR = partial regressions. (B) Animal survival curves are shown.

[0025] FIGURE 9 (A) shows the mean tumor volume and demonstrates enhanced anti-tumor activity with concurrent administration of a PD-1 antagonist and Vorinostat compared to the monotherapy treatment arms in RENCA tumor-bearing mice. Control: Isotype + Vehicle,

anti-PD-1: a murine anti-mouse PD-1 mAb. CR = complete regressions; PR = partial regressions. (B) Animal survival curves are shown.

DETAILED DESCRIPTION

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

[0026]	BOR	Best overall response
[0027]	BID	One dose twice daily
[0028]	CBR	Clinical Benefit Rate
[0029]	CDR	Complementarity determining region
[0030]	CHO	Chinese hamster ovary
[0031]	CR	Complete Response
[0032]	DCR	Disease Control Rate
[0033]	DFS	Disease free survival
[0034]	DLT	Dose limiting toxicity
[0035]	DOR	Duration of Response
[0036]	DSDR	Durable Stable Disease Rate
[0037]	FFPE	Formalin-fixed, paraffin-embedded
[0038]	FR	Framework region
[0039]	IgG	Immunoglobulin G
[0040]	IHC	Immunohistochemistry or immunohistochemical
[0041]	irRC	Immune related response criteria
[0042]	IV	Intravenous
[0043]	MTD	Maximum tolerated dose
[0044]	NCBI	National Center for Biotechnology Information
[0045]	NCI	National Cancer Institute
[0046]	ORR	Objective response rate
[0047]	OS	Overall survival
[0048]	PD	Progressive disease
[0049]	PD-1	Programmed Death 1
[0050]	PD-L1	Programmed Cell Death 1 Ligand 1
[0051]	PD-L2	Programmed Cell Death 1 Ligand 2
[0052]	PFS	Progression free survival
[0053]	PR	Partial response

[0054]	Q2W	One dose every two weeks
[0055]	Q3W	One dose every three weeks
[0056]	QD	One dose per day
[0057]	RECIST	Response Evaluation Criteria in Solid Tumors
[0058]	SD	Stable disease
[0059]	VH	Immunoglobulin heavy chain variable region
[0060]	VK	Immunoglobulin kappa light chain variable region

I. DEFINITIONS

[0061] 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.

[0062] 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.

[0063] "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. The term "subject" includes any organism, preferably an animal, more preferably a mammal (*e.g.*, rat, mouse, dog, cat, rabbit) and most preferably a human.

[0064] 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.

[0065] 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).

[0066] 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.

[0067] 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 chain 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] "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.

[0072] "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.

[0073] "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.

[0074] "Anti-tumor response" when referring to a cancer patient treated with a therapeutic regimen, such as a combination therapy described herein, means 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, reduced rate of tumor metastasis or tumor growth, or progression free survival. Positive therapeutic effects in cancer can be measured in a number of ways (See, W. A. Weber, J. Null. Med. 50:1S-10S (2009); Eisenhauer et al., *supra*). In some embodiments, an anti-tumor response to a combination therapy described herein is assessed using RECIST 1.1 criteria, bidimentional irRC or unidimensional irRC. In some embodiments, an anti-tumor response is any of SD, PR, CR, PFS, or DFS.

[0075] "Bidimensional irRC" refers to the set of criteria described in Wolchok JD, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412–7420. These criteria utilize bidimensional tumor measurements of target lesions, which are obtained by multiplying the longest diameter and the longest perpendicular diameter (cm^2) of each lesion.

[0076] "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. Classes of biotherapeutic agents include, but are 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.

[0077] 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: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma) colorectal; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia,

myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In another embodiment, the cancer is carcinoma, lymphoma, leukemia, blastoma, and sarcoma. More particular examples of such cancers include squamous cell carcinoma, myeloma, small-cell lung cancer, non-small cell lung cancer, 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 renal cell carcinoma. Yet another particular example of cancer is non-hodgkin's lymphoma or cutaneous T- cell lymphoma. Yet another particular example of cancer is acute myeloid leukemia (AML) or myelodysplastic syndrome. Cancers that may be treated in accordance with the present invention include those characterized by elevated expression of one or both of PD-L1 and PD-L2 in tested tissue samples.

[0078] "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.

[0079] "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, cytoxic/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.

[0080] "Chothia" as used herein means an antibody numbering system described in Al-Lazikani *et al.*, *JMB* **273:**927-948 (1997).

[0081] "Comprising" or variations such as "comprise", "comprises" or "comprised of" are used throughout the specification and claims in an inclusive sense, i.e., to specify the presence of the stated features but not to preclude the presence or addition of further features that may materially enhance the operation or utility of any of the embodiments of the invention, unless the context requires otherwise due to express language or necessary implication.

[0082] "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.

[0083] **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
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

[0084] "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.

[0085] "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.

[0086] 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).

[0087] 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).

[0088] "Framework region" or "FR" as used herein means the immunoglobulin variable regions excluding the CDR regions.

[0089] "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.

[0090] 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.

[0091] "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.

[0092] "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.).

[0093] "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.

[0094] "Non-responder patient", when referring to a specific anti-tumor response to treatment with a combination therapy described herein, means the patient did not exhibit the anti-tumor response.

[0095] "ORR" or "objective response rate" refers in some embodiments to CR + PR, and $ORR_{(week\ 24)}$ refers to CR and PR measured using irRECIST in each patient in a cohort after 24 weeks of treatment with SAHA in combination with pembrolizumab.

[0096] "Patient" or "subject" 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.

[0097] "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.

[0098] PD-1 antagonists useful in any of the treatment methods, 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.

[0099] 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: pembrolizumab (also known as 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.

[00100] 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, W02010/077634 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.

[00101] Other PD-1 antagonists useful in 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.

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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

[00107] "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.

[00108] 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).

[00109] 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 is at least 1%, and preferably 5% of total tumor cells.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] A "pembrolizumab biosimilar" means a biological product manufactured by an entity other than MSD and which is approved by a regulatory agency in any country for marketing as a pembrolizumab biosimilar. In an embodiment, a pembrolizumab biosimilar comprises a pembrolizumab variant as the drug substance. In an embodiment, a pembrolizumab biosimilar has the same amino acid sequence as pembrolizumab.

[00114] As used herein, a "pembrolizumab variant" means a monoclonal antibody which comprises heavy chain and light chain sequences that are identical to those in pembrolizumab, except for having three, two or one conservative amino acid substitutions at positions that are located outside of the light chain CDRs and six, five, four, three, two or one conservative amino acid substitutions that are located outside of the heavy chain CDRs, e.g, the variant positions are located in the FR regions or the constant region. In other words, pembrolizumab and a pembrolizumab variant comprise identical CDR sequences, but differ from each other due to having a conservative amino acid substitution at no more than three or six other positions in their full length light and heavy chain sequences, respectively. A pembrolizumab variant is substantially the same as pembrolizumab with respect to the following properties: binding affinity to PD-1 and ability to block the binding of each of PD-L1 and PD-L2 to PD-1.

[00115] "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.

[00116] "Responder patient" when referring to a specific anti-tumor response to treatment with a combination therapy described herein, means the patient exhibited the anti-tumor response.

[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" cancer as used herein means to administer a combination therapy of a PD-1 antagonist and SAHA or a pharmaceutically acceptable salt thereof to a subject having cancer, or diagnosed with 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 ≦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, response to a combination therapy described herein is assessed using RECIST 1.1 criteria or irRC (bidimensional or unidimensional) and 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 embodiments, response to a combination of the invention is any of PR, CR, PFS, DFS, OR and 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, 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 marrow. 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 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 cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and SAHA or a pharmaceutically acceptable salt thereof.

[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 SAHA, a biotherapeutic agent, 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). The specific dosage and dosage schedule of the additional therapeutic agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific therapeutic agent that is being used.

[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 gamma1I 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. In one embodiment the therapeutic agent is a pyrimidine analog, such as azacitidine.

[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 SAHA or a pharmaceutically acceptable salt thereof is administered before administration of the PD-1 antagonist, while in other embodiments, the SAHA or a pharmaceutically acceptable salt thereof is administered after administration of the PD-1 antagonist. In one embodiment, the SAHA or a pharmaceutically acceptable salt thereof is administered for 2 cycles of 28 days, followed by the administration of the PD-1 antagonist. In another embodiment, the SAHA or a pharmaceutically acceptable salt thereof is administered concurrently with the PD-1 antagonist.

[00131] In other embodiments, the SAHA or a pharmaceutically acceptable salt thereof and azacitidine is administered before administration of the PD-1 antagonist, while in other embodiments, the SAHA or a pharmaceutically acceptable salt thereof and azacitidine is administered after administration of the PD-1 antagonist. In one embodiment, the SAHA or a pharmaceutically acceptable salt thereof and azacitidine is first concurrently administered, followed by the administration of the PD-1 antagonist. In another embodiment, the SAHA or a pharmaceutically acceptable salt thereof is administered after azacitidine, followed by the administration of the PD-1 antagonist. In another embodiment, the SAHA or a pharmaceutically acceptable salt thereof and azacitidine is administered concurrently with the PD-1 antagonist.

[00132] 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.

[00133] 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.

[00134] 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.

[00135] 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.

[00136] 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.

[00137] A combination therapy of the invention is preferably administered to a human patient who has a cancer that tests positive for PD-L1 expression. In some preferred 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. Typically, the patient's physician would order a diagnostic test to determine PD-L1 expression in a tumor tissue sample removed from the patient prior to initiation of treatment with the PD-1 antagonist and the SAHA or a pharmaceutically acceptable salt thereof, 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.

[00138] 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.

[00139] 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 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.

[00140] 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 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.

[00141] 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.

[00142] In certain embodiments, a subject will be administered an intravenous (IV) infusion of a medicament comprising any of the PD-1 antagonists described herein.

[00143] In one preferred 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.

[00144] In another preferred embodiment of the invention, the PD-1 antagonist in the combination therapy is pembrolizumab, a pembrolizumab variant or a pembrolizumab biosimilar, which is administered in a liquid medicament 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, 10 mg Q3W and flat-dose equivalents of any of these doses, i.e., such as 200 mg Q3W. In some embodiments, pembrolizumab is provided as a liquid medicament which comprises 25 mg/ml pembrolizumab, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5.

[00145] In some embodiments, the selected dose of pembrolizumab is administered by IV infusion. In one embodiment, the selected dose of pembrolizumab is administered by IV infusion over a time period of between 25 and 40 minutes, or about 30 minutes.

[00146] The optimal dose for pembrolizumab in combination with SAHA or a pharmaceutically acceptable salt thereof may be identified by dose escalation or dose de-escalation of one or both of these agents. In an embodiment, the combination therapy comprises a 21 day treatment cycle in which pembrolizumab is administered at 200 mg Q3W and SAHA is orally administered at 400 mg once daily, 300 mg once daily, 200 mg once daily or 100 mg once daily. In an embodiment, a patient is treated with 200 mg of pembrolizumab Q3W and SAHA is orally administered at 300 mg twice daily, 200 mg twice daily or 100 mg twice daily.

[00147] In another aspect of the invention, SAHA or a pharmaceutically acceptable salt thereof and azacitidine is administered for 2 cycles of 28 days, followed by administration of 200 mg pembrolizumab every two weeks or three weeks. In a further embodiment, SAHA is administered orally 400 mg once daily and azacitidine is administered 40 mg/m^2 subcutaneous days 1-6, 8-10 for 2 cycles of 28 days, followed by administration of 200 mg pembrolizumab every three weeks. In one embodiment, azacitidine is administered subcutaneously once a day at 75 mg/m^2/day on days 1-7 and SAHA is orally administed 200 mg or 300 mg 2-3 times daily on days 3-5, 3-9, 3-11 or 3-16, for 2 cycles of 28 days, followed by administration of 200 mg pembrolizumab every three weeks. In another embodiment, azacitidine is subcutaneously administered 75 mg/m^2/day daily for 5 days (Days 1 - 5), SAHA is administered 200 mg orally three times a day for 5 days (Days 1 - 5), for 2 cycles of 28 days, followed by administration of 200 mg pembrolizumab every three weeks. In one example of the above embodiments, pembrolizumab is administered via IV infusion.

[00148] In some embodiments, the patient is treated with the combination therapy for at least 24 weeks, e.g., eight 3-week cycles. In some embodiments, treatment with the combination therapy continues until the patient exhibits evidence of PD or a CR.

[00149] SAHA can be administered in accordance with any dose and dosing schedule that, together with the effect of the PD-1 antagonist, achieves a dose effective to treat cancer. For example, SAHA can be administered in a total daily dose of up to 800 mg, preferably orally,

once, twice or three times daily, continuously (every day) or intermittently (e.g., 3-5 days a week).

[00150] In one embodiment, SAHA is administered once daily at a dose of about 200-600 mg. In another embodiment, SAHA is administered twice daily at a dose of about 200-300 mg. In another embodiment, SAHA is administered twice daily at a dose of about 200-300 mg intermittently, for example three, four or five days per week. In one embodiment, the daily dose of SAHA is 200 mg which can be administered once-daily, twice-daily or three-times daily. In one embodiment, the daily dose of SAHA is 300 mg which can be administered once-daily, or twice-daily. In one embodiment, the daily dose of SAHA is 400 mg which can be administered once-daily. In other embodiments, SAHA is administered once daily at a dose of 200, 300 or 400 mg for 3, 4 or 5 days a week.

[00151] In some embodiments, the patient selected for treatment with the combination therapy of the invention if the patient has been diagnosed with NSCLC, RCC, endometrial cancer, urothelial cancer, squamous cell carcinoma of head and neck or melanoma.

[00152] 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.

[00153] 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 pembrolizumab that are suitable for use in the present invention. In some embodiments, a medicament comprising pembrolizumab is provided in a glass vial which contains about 100 mg of pembrolizumab in 4 ml of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP. The solution requires dilution for IV infusion.

[00154] The present invention also provides a medicament which comprises an HDAC inhibitor and a pharmaceutically acceptable excipient, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

[00155] The 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 a PD-1 antagonist, the second container contains at least one dose of a medicament comprising SAHA, 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 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.

[00156] 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 cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and an HDAC inhibitor, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

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

3. A medicament comprising a PD-1 antagonist for use in combination with an HDAC inhibitor for treating cancer in an individual, wherein the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof and the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

4. A medicament comprising an HDAC inhibitor for use in combination with a PD-1 antagonist for treating cancer in an individual, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

5. The medicament of embodiment 3 or 4, which further comprises a pharmaceutically acceptable excipient.

6. Use of a PD-1 antagonist in the manufacture of medicament for treating cancer in an individual when administered in combination with an HDAC inhibitor, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

7. Use of an HDAC inhibitor in the manufacture of a medicament for treating cancer in an individual when administered in combination with a PD-1 antagonist, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

8. Use of a PD-1 antagonist and an HDAC inhibitor in the manufacture of medicaments for treating cancer in an individual, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

9. 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 anti-PD-1 antagonist, the second container comprises at least one dose of a medicament comprising an HDAC inhibitor, and the package insert comprises instructions for treating an individual for cancer using the medicaments, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof.

10. The kit of embodiment 9, 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.

11. The method, medicament, use or kit of any 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 10, 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 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 11, 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 13, 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.

16. The method, medicament, use or kit of embodiment 13, 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 13, 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 13, 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 1-18, wherein the cancer is a solid tumor.

20. The method, medicament, use or kit of any of embodiments 1-18, 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) or triple negative breast cancer.

21. The method, medicament, use or kit of any of embodiments 1-18, wherein the cancer is NSCLC, RCC, endometrial cancer, urothelial cancer, squamous cell carcinoma of head and neck or melanoma.

22. The method, medicament, use or kit of any of embodiments 1-18, wherein the individual has not been previously treated for NSCLC, RCC, endometrial cancer, urothelial cancer, squamous cell carcinoma of head and neck or melanoma.

23. The method, medicament, use or kit of any of embodiments 1-18, wherein the cancer is acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), 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), cutaneous T- cell lymphoma, or small lymphocytic lymphoma (SLL).

24. The method, medicament, use or kit of any of embodiments 1-23, wherein the cancer tests positive for human PD-L1.

25. The method, medicament, use or kit of embodiment 24, wherein the human PD-L1 expression is elevated.

26. The method, medicament, use or kit of embodiment 24, wherein the PD-1 antagonist is pembrolizumab, a pembrolizumab variant, a pembrolizumab biosimilar or nivolumab.

27. The method, medicament, use or kit of embodiment 26, wherein pembrolizumab is formulated as a liquid medicament which comprises 25 mg/ml pembrolizumab, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5.

28. A method for treating a human individual diagnosed with cancer, comprising administering to the individual a combination therapy which comprises pembrolizumab and an HDAC inhibitor, wherein the HDAC inhibitor is SAHA or a pharmaceutically acceptable salt thereof, and wherein the HDAC inhibitor is orally administered at a dose of 400 mg once daily, and pembrolizumab is administered at 200 mg Q3W.

29. A medicament comprising pembrolizumab for use in combination with SAHA or a pharmaceutically acceptable salt thereof for treating cancer in a human individual by a method comprising administering to the individual SAHA or a pharmaceutically acceptable salt thereof at an oral dose of 400 mg once daily, and pembrolizumab at 200 mg Q3W.

30. A medicament comprising SAHA or a pharmaceutically acceptable salt thereof for use in combination with pembrolizumab for treating cancer in a human individual by a method comprising administering to the individual SAHA or a pharmaceutically acceptable salt thereof, at an oral dose of 400 mg once daily, and pembrolizumab at 200 mg Q3W.

31. The method or medicament of any of embodiments 28 to 30, wherein the cancer is NSCLC, RCC, endometrial cancer, urothelial cancer, squamous cell carcinoma of head and neck or melanoma.

32. The method or medicament of embodiment 31, wherein the individual has not been previously treated for NSCLC, RCC, endometrial cancer, urothelial cancer, squamous cell carcinoma of head and neck or melanoma.

33. The method or medicament of any of embodiments 28 to 32, wherein a tissue section of the cancer removed from the individual prior to administration of the combination therapy tested positive for PD-L1 expression.

34. The method or medicament of embodiment 33, wherein at least 50% of the tumor cells in the tissue section tested positive for PD-L1 expression by an immunohistochemical (IHC) assay.

35. The method or medicament of embodiment 34, wherein the IHC assay employed the antibody 22C3 to detect PD-L1 expression.

36. The method or medicament of any of embodiments 28 to 35, wherein pembrolizumab is administered by IV infusion for 25 to 40 minutes or about 30 minutes.

37. The method, medicament, kit or use of any of embodiments 1-36, wherein the HDAC inhibitor is SAHA.

38. A combination of i) SAHA (suberoylanilide hydroxamic acid) or a pharmaceutically acceptable salt thereof and pembrolizumab or a pembrolizumab biosimilar, for use in treating cancer, wherein SAHA or the pharmaceutically acceptable salt is for oral administration once daily at a dose of 400 mg, and pembrolizumab is administered at a dose of 200 mg Q3W.

GENERAL METHODS

[00157] 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).

[00158] 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 Protcols 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).

[00159] 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).

[00160] 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).

[00161] 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 fuse 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).

[00162] 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).

[00163] 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).

[00164] 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).

[00165] 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).

Table 3 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
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

SEQ ID NO:	Description
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	Pembrolizumab Heavy chain
22	Pembrolizumab Light chain
23	Nivolumab Heavy chain
24	Nivolumab light chain
25	Human PD-L1

[00166] The manufacturing process for the drug product Zolinza® (Vorinostat) is described in WO2006/127321.

[00167] Example 1. Anti-tumor response of concurrent administration of a PD-1 antagonist and Vorinostat in tumor-bearing mice.

[00168] This experiment compared the anti-tumor response of tumor-bearing mice to treatment with one of three regimens: monotherapy with a murine anti-mouse PD-l monoclonal antibody (anti-PD-l), monotherapy with Vorinostat and combination therapy with these two agents administered concurrently.

[00169] Tumor-bearing mice for this study were initiated by implanting 3 x 10^5 log-phase and sub-confluent CT-26 cells on the right lower dorsal flank of 7-8 week old female BALB/cAnN mice with an average body weight of 18 grams. When the mean tumor volume in these mice reached ~ 100 cubic mm (60mm^3-150 mm^3) (Figure 1(A)), the tumor-bearing mice were randomized to 4 treatment groups of 12 mice per group: (1) Isotype control + Vehicle control group;(2) anti-PD-l + Vehicle control; (3) Vorinostat + Isotype control and; (4) anti-PD-l

+ Vorinostat. A monoclonal antibody of murine isotype IgG1 against murine PD-1 and isotype control were obtained from internal sources. The isotype control was a mouse monoclonal antibody specific for adenoviral hexon 25 and was of the isotype IgG1. Formulations for each reagent were as follows: Isotype control:75mM NaCl, 10mM sodium phosphate, 3% sucrose, pH7.3; anti-PD-1: 20mM sodium acetate, 7% sucrose, pH5.5; and Vorinostat: 0.5% HPC (hydroxypropylcellulose) with 0.002% SDS (sodium dodecyl sulfate) in sterile water. Anti-PD-1 was administered to treatment groups 2 and 4 at 10 mg/kg i.p. every 5 days for each of 5 cycles. Vorinostat was administered to treatment groups 3 and 4 at 150 mg/kg every day for 27 days.

[00170] Administration of Vorinostat did not demonstrate antagonistic effects on anti-PD-1 anti-tumor activity in the combination treatment arm. As demonstrated by the results, which are shown in Figure 8(A), the mean anti-tumor response of combination therapy with the PD-l antagonist and Vorinostat was significantly greater than the anti-tumor response observed with either Vorinostat single agent treatment ($p<0.001$) or anti-PD-1 ($p<0.01$) single agent treatment, One-way ANOVA/Bonferroni multiple comparison test at Day 20. The combination of these two agents demonstrated 25% complete regressions (CR) such that no measureable tumor remained in 3 out of 12 animals and 17% partial regressions (PRs) as measured through Day 29. The anti-PD-1 monotherapy arm resulted in 17% CRs as measured through Day 29. No CRs were observed in the Vorinostat monotherapy treatment group. As shown in Figure 8 (B), combination treatment demonstrated significantly enhanced survival (100%) at Day 30 as compared to anti-PD-1 (42%) and Vorinostat (10%) single agent treatment.

Example 2. Anti-tumor response of concurrent administration of a PD-1 antagonist and Vorinostat in tumor-bearing mice.

[00171] This experiment compared the anti-tumor response of tumor-bearing mice to treatment with one of three regimens: monotherapy with a murine anti-mouse PD-l monoclonal antibody (anti-PD-l), monotherapy with Vorinostat and combination therapy with these two agents administered concurrently.

[00172] Tumor-bearing mice for this study were initiated by implanting 1 x 10^6 log-phase andsub-confluent RENCA cells on the right lower dorsal flank of 7-8 week old female BALB/cmice with an average body weight of 19 grams. When the mean tumor volume in these mice reached ~ 100 cubic mm (65mm^3-140 mm^3) (Figure 9(A)), the tumor-bearing mice were randomized to 4 treatment groups of 12 mice per group: (1) Isotype control + Vehicle control group;(2) Anti-PD-l + Vehicle control; (3) Vorinostat + Isotype control and; (4) Anti-PD-l + Vorinostat. A monoclonal antibody of murine isotype IgG1 against murine PD-1 and isotype

control were obtained from internal sources. The isotype control was a mouse monoclonal antibody specific for adenoviral hexon 25 and was of the isotype IgG1. The formulations for each reagent was as follows: Isotype control:75mM NaCl, 10mM sodium phosphate, 3% sucrose, pH7.3; anti-PD-1: 20mM sodium acetate, 7% sucrose, pH5.5; and Vorinostat vehicle: 0.5% HPC (hydroxypropylcellulose) with 0.002% SDS (sodium dodecyl sulfate) in sterile water. Anti-PD-1 was administered to treatment groups 2 and 4 at 5 mg/kg i.p. every 5 days for each of 5 cycles. Vorinostat was administered to treatment groups 3 and 4 at 150 mg/kg every day for 29 days.

[00173] Administration of Vorinostat did not demonstrate antagonistic effects on anti-PD-1 anti-tumor activity in the combination treatment arm. As demonstrated by the results, which are shown in Figure 9 (A), the mean anti-tumor response of combination therapy with the PD-l antagonist and Vorinostat was significantly greater than the anti-tumor response observed with either Vorinostat single agent treatment ($p<0.0001$) or anti-PD-1 ($p<0.05$) single agent treatment, One-Way ANOVA/Bonferroni comparison test at Day 19. The combination of these two agents demonstrated 50% complete regressions (CR) such that no measureable tumor remained in 6 out of 12 animals as measured through Day 30. One partial regression (PR) was observed. The anti-PD-1 monotherapy arm resulted in 17% CRs as measured through Day 29. No CRs were observed in the Vorinostat monotherapy treatment group. As shown in Figure 9 (B), combination treatment demonstrated significantly enhanced survival (92%) at Day 30 as compared to anti-PD-1 (42%) and Vorinostat (23%) single agent treatment.

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[00174] 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. The contents of the priority U.S. provisional application 62/136,017 is also incorporated herein 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. To the extent that the references provide a definition for a claimed term that conflicts with the definitions provided in the instant specification, the definitions provided in the instant specification shall be used to interpret the claimed invention.

CLAIMS

1. A method for treating cancer in a human patient comprising administering to the patient a combination therapy which comprises an antagonist of a human Programmed Death 1 protein (PD-1) and a histone deactylase (HDAC) inhibitor, wherein the HDAC inhibitor is suberoylanilide hydroxamic acid (SAHA) or a pharmaceutically acceptable salt thereof.

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

3. A medicament comprising an antagonist of a Programmed Death 1 protein (PD-1) for use in combination with a histone deactylase (HDAC) inhibitor for treating cancer in an individual, wherein the HDAC inhibitor is suberoylanilide hydroxamic acid (SAHA) or a pharmaceutically acceptable salt thereof.

4. The medicament of claim 3, wherein the individual is a human.

5. The medicament of any of claims 3 to 4, wherein the cancer is NSCLC, RCC, endometrial cancer, urothelial cancer, squamous cell carcinoma of head and neck or melanoma.

6. The medicament of any of claims 3 to 5, wherein the cancer is a solid tumor that tests positive for PD-L1 expression by an immunohistochemical (IHC) assay.

7. The medicament of any of claims 3 to 6, wherein the PD-1 antagonist is a monoclonalantibody, 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.

8. The medicament of any of claims 3 to 7, 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.

9. The medicament of any of claims 3 to 8, wherein the PD-1 antagonist is pembrolizumab and the HDAC inhibitor is SAHA.

10. The medicament of claim 9, wherein pembrolizumab is formulated as a liquid medicament which comprises 25 mg/ml pembrolizumab, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5 and SAHA is formulated as a 100 mg capsule.

11. A medicament comprising:

(a) pembrolizumab for use in combination with SAHA or a pharmaceutically acceptable salt thereof for treating cancer in a human individual by a method comprising administering to the individual SAHA or a pharmaceutically acceptable salt thereof at a once daily dose of 400 mg, and pembrolizumab at a dose of 200 mg Q3W; or

(b) SAHA or a pharmaceutically acceptable salt thereof for use in combination with pembrolizumab for treating cancer in a human individual by a method comprising administering to the individual SAHA or a pharmaceutically acceptable salt thereof at a once daily dose of 400 mg, and pembrolizumab at a dose of 200 mg Q3W.

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

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

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

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

K09A-L-l1 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

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

Pembrolizumab

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

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

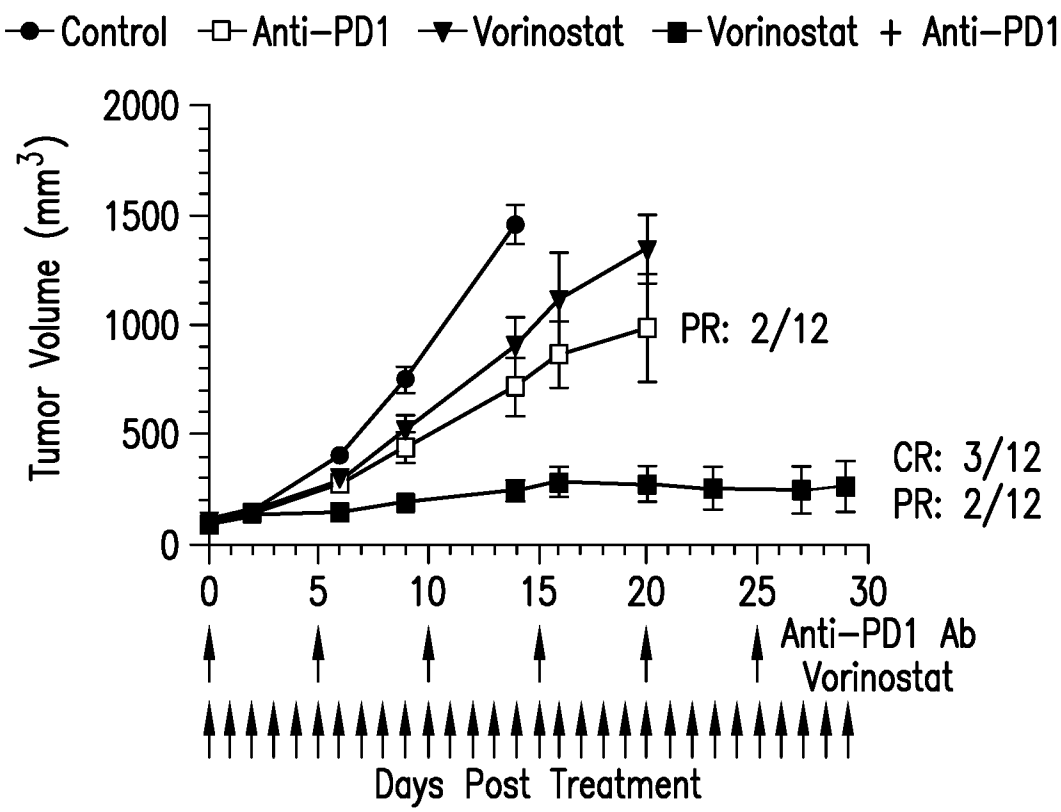
Control
Anti-PD1
Vorinostat
Vorinostat + Anti-PD1
Tumor Volume (mm3)
2000
1500
1000
500
0
PR: 2/12
CR: 3/12
PR: 2/12
0
5
10
15
20
25
30
Anti-PD1 Ab
Vorinostat
Days Post Treatment

FIG.8A

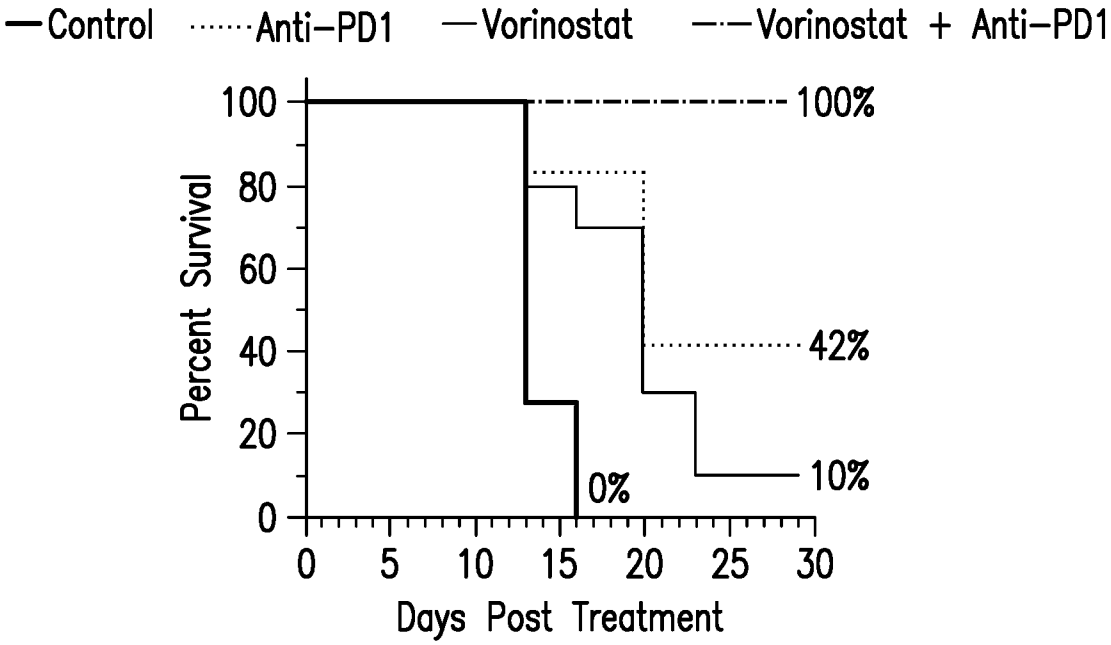
Control
Anti-PD1
Vorinostat
Vorinostat + Anti-PD1
Percent Survival
100
80
60
40
20
0
100%
42%
10%
0%
0
5
10
15
20
25
30
Days Post Treatment

FIG.8B

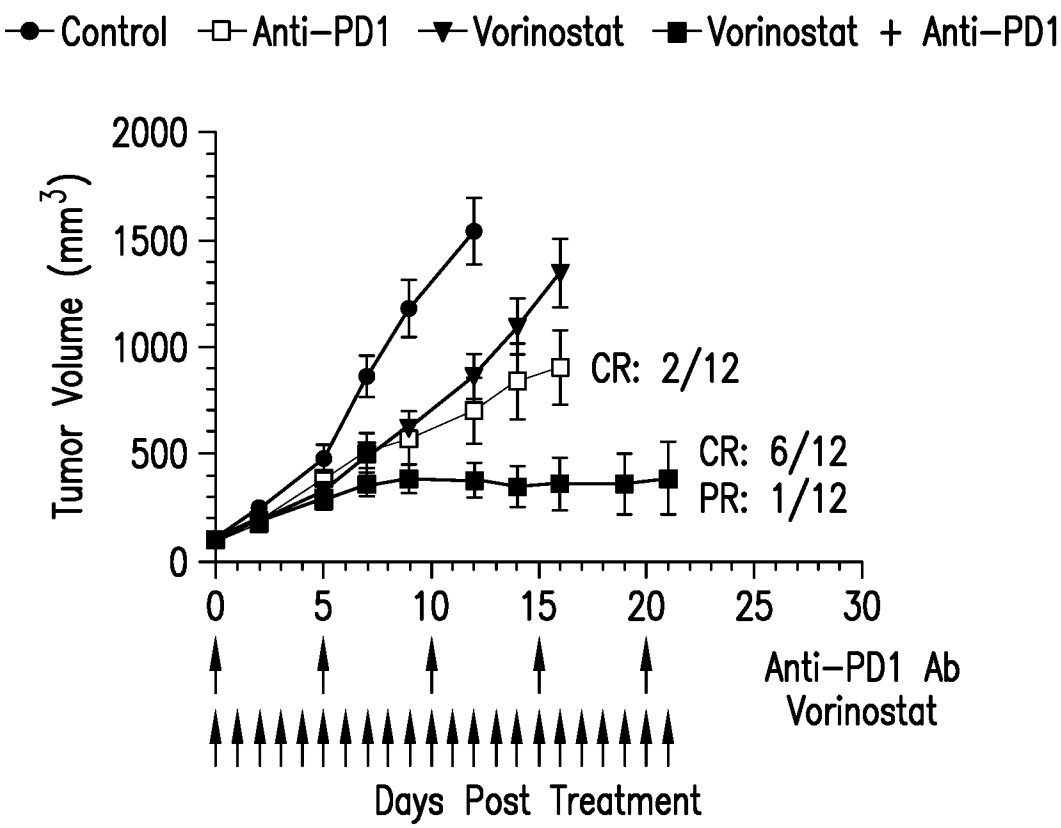
Control
Anti-PD1
Vorinostat
Vorinostat + Anti-PD1
Tumor Volume (mm3)
2000
1500
1000
500
0
CR: 2/12
CR: 6/12
PR: 1/12
0
5
10
15
20
25
30
Anti-PD1 Ab
Vorinostat
Days Post Treatment

FIG.9A

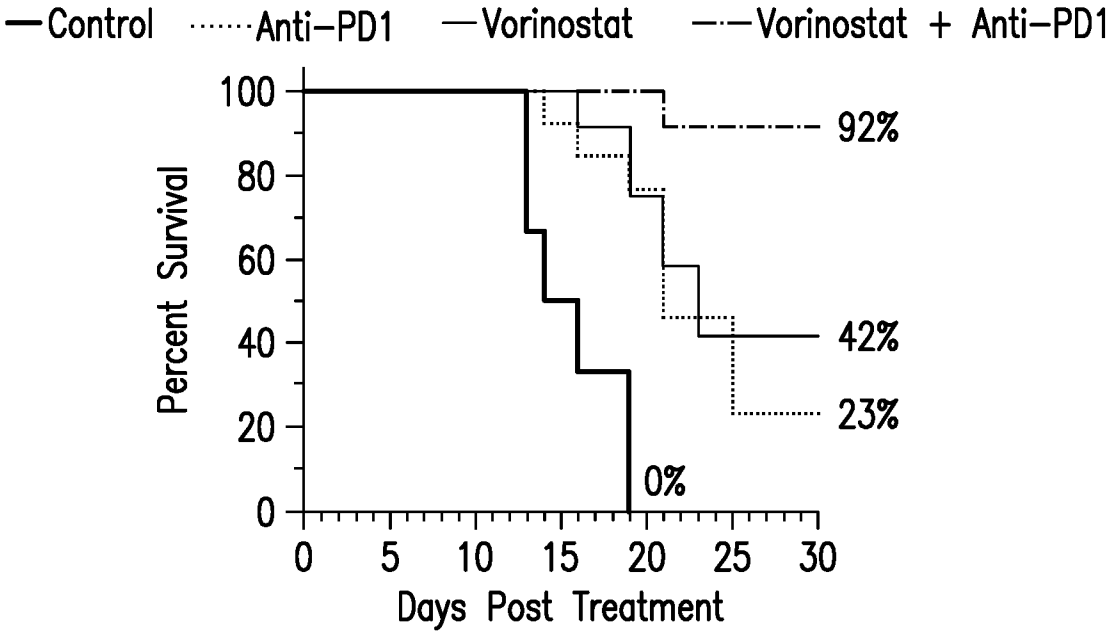
Control
Anti-PD1
Vorinostat
Vorinostat + Anti-PD1
Percent Survival
100
80
60
40
20
0
92%
42%
23%
0%
0
5
10
15
20
25
30
Days Post Treatment

FIG.9B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/22402

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/395, C07K16/28, A61P 37/02 (2016.01)
CPC - A61K 39/3955, 39/39558; C07K 16/28
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)
IPC(8): A61K 39/395; C07K 16/28; A61P 37/02 (2016.01)
CPC:A61K 39/3955, 39/39558; C07K 16/28

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; Pubmed; EBSCO
Keywords: cancer, combination, therap*, PD-1, inhibit*, anatgon*, HDAC, dose, SAHA, suberoylanilide hydroxamic acid, Pembrolizumab, MK-3475, Q3W

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2015/035112 A1 (THE JOHNS HOPKINS UNIVERSITY) 12 March 2015; abstract; page 2, lines 10-12; page 5, line 15; page 6, lines 26-32; page 30, line 26; claim 1	1-4, 5/3-4 ---------- 11
Y	(DUVIC, M et al.) Phase 2 Trial of Oral Vorinostat (Suberoylanilide Hydroxamic Acid, SAHA) for Refractory Cutaneous T-cell Lymphoma (CTCL). Blood. 7 September 2006; Vol. 109, No. 1; pages 31-39; abstract; page 31, column 2, paragraph 3; DOI: 10.1182/blood-2006-06-025999	11
Y	(ROBERT, C et al.) Anti-programmed-death-receptor-1 Treatment with Pembrolizumab in Ipilimumab-refractory Advanced Melanoma: a Randomised Dose-comparison Cohort of a Phase 1 Trial. Lancet. 15 July 2014; Vol. 384, No. 9948; pages 1-9; abstract; page 2, column 1, paragraph 1; page 2, column 2, paragraph 3; DOI: 10.1016/S0140-6736(14)60958-2.	11

☐ Further documents are listed in the continuation of Box C. ☐ 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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"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
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2016 (16.05.2016)	03 JUN 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/22402

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/22402

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-10
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.