The present disclosure describes combination therapies comprising an antagonist of Programmed Death-1 receptor (PD-1) and the CDK inhibitor dinaciclib, and use of the combination therapies for the treatment of cancer, and in particular for treating cancers that express PD-L1.

FIG.8A
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— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(H))
— as to the applicant’s entitlement to claim the priority of the earlier application (Rule 4.17(Hi))
TREATING CANCER WITH A COMBINATION OF
A PD-1 ANTAGONIST AND DINACICLIB

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 dinaciclib, which is a pan cyclin-dependent kinase (CDK) 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] Disregulation of cell cycle control is a hallmark of all human cancers and is frequently associated with aberrant activation/regulation of cyclin-dependent kinases (CDKs). However, the CDK cascade is important for maintaining proper function of T cells in a context-
dependent manner. Thus, the development of CDK inhibitors (CKDIs) as anti-cancer agents has been complicated by immune cell toxicities and the consequent potential for immunosuppressive effects (17). Dinaciclib, a pan-CDK inhibitor which selectively inhibits CDK1, CDK2, CDK5, and CDK9, has been investigated as a potential therapy in a variety of cancers, with neutropenia being the most common dose-limiting toxicity observed in clinical trials (17, 18).

SUMMARY OF THE INVENTION

[0006] The present invention is based, in part, on the surprising finding that concurrent administration of dinaciclib and a murinized anti-mouse PD-1 antibody to tumor-bearing mice resulted in significantly higher anti-tumor efficacy compared to either agent alone. This finding was unexpected because the known activity of dinaciclib in potently inhibiting transcription and cell proliferation was predicted to counteract the effectiveness of anti-PD-1 therapy, which is believed to largely involve the activation and proliferation of T cells present in and recruited to a tumor.

[0007] Thus, in one embodiment, the invention provides a method for treating a cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and a dinaciclib compound.

[0008] In another embodiment, the invention provides a medicament comprising a PD-1 antagonist for use in combination with a dinaciclib compound for treating a cancer.

[0009] In yet another embodiment, the invention provides a medicament comprising a dinaciclib compound for use in combination with a PD-1 antagonist for treating a cancer.

[0010] Other embodiments provide use of a PD-1 antagonist in the manufacture of medicament for treating a cancer in an individual when administered in combination with a dinaciclib compound and use of a dinaciclib compound in the manufacture of a medicament for treating a cancer in an individual when administered in combination with a PD-1 antagonist.

[0011] In a still further embodiment, the invention provides use of a PD-1 antagonist and a dinaciclib compound in the manufacture of medicaments for treating a cancer in an individual. In some preferred 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 a dinaciclib compound to treat a cancer in an individual.
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 preferred 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 particularly preferred 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).

In all of the above embodiments of the treatment method, medicaments and uses, the dinaciclib compound is the compound of Formula I

![Formula I](image)

or a pharmaceutically acceptable salt of the compound of Formula I.

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 preferred embodiments, the solid tumor 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. In some preferred embodiments, the cancer is ipilimumab-naïve advanced melanoma and while in other preferred embodiments, the human has ipilimumab-refractory advanced melanoma.

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 preferred 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), myelodysplasia; syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

5 [0016] Also, in preferred embodiments of any of the above treatment method, medicaments and uses, the cancer expresses one or both of PD-L1 and PD-L2. In particularly preferred embodiments, PD-L1 expression is elevated in the cancer.

[0017] In one particularly preferred embodiment of the above treatment method, medicaments and uses, the individual is a human and the cancer is chronic lymphocytic leukemia (CLL) that expresses human PD-L1.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] 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).

15 [0019] 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).

[0020] 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).

[0021] 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).

[0022] FIGURE 5 shows amino acid sequences of alternative light chains for an exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NOs: 18-20).

[0023] FIGURE 6 shows amino acid sequences of the heavy and light chains for MK-3475 (SEQ ID NOs. 21 and 22, respectively).

[0024] FIGURE 7 shows amino acid sequences of the heavy and light chains for nivolumab (SEQ ID NOs. 23 and 24, respectively).
FIGURE 8 illustrates the anti-tumor effect of concurrent administration of a PD-1 antagonist and dinaciclib is superior to monotherapy with either agent alone in tumor-bearing mice, with FIG. 8A showing the mean tumor volume at various days during treatment with a control, a murine anti-mouse PD-1 mAb (Anti-PD1), dinaciclib, or both Anti-PD1 and dinaciclib, and FIG. 8B showing the tumor volume values for individual mice in each treatment group on the first day of treatment (left graph, Day 0) or after 25 days of treatment (right graph, Day 25). Experimental details are described in Example 1 below.

DETAILED DESCRIPTION

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

- **CDR**: Complementarity determining region
- **CHO**: Chinese hamster ovary
- **FFPE**: formalin-fixed, paraffin-embedded
- **FR**: Framework region
- **IgG**: Immunoglobulin G
- **IHC**: Immunohistochemistry or immunohistochemical
- **Q2W**: One dose every two weeks
- **Q3W**: One dose every three weeks
- **VH**: Immunoglobulin heavy chain variable region
- **VK**: Immunoglobulin kappa light chain variable region

I. DEFINITIONS

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.

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.

"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.

[0039] 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.

[0040] 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)).

[0041] 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.

[0042] Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), which are located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2 , CDR2, FR3,

[0043] 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.

[0044] 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.

[0045] 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.

"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.

"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.

"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.

The terms "cancer", "cancerous", or "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, leukemia, blastoma, and sarcoma. More particular examples of such cancers include squamous cell carcinoma, myeloma, small-cell lung cancer, 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. Particularly preferred 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.

[0050] "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.

[0051] "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

[0052] "Chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, kinase inhibitors, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase 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, anti-sense oligonucleotides that 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.

[0053] "Clothia" as used herein means an antibody numbering system described in Al-Lazikani et al., JMB 273:927-948 (1997).

[0054] "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 3.

**TABLE 1. Exemplary Conservative Amino Acid Substitutions**

<table>
<thead>
<tr>
<th>Original residue</th>
<th>Conservative substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ala (A)</td>
<td>Gly; Ser</td>
</tr>
<tr>
<td>Arg (R)</td>
<td>Lys; His</td>
</tr>
<tr>
<td>Asn (N)</td>
<td>Gln; His</td>
</tr>
<tr>
<td>Asp (D)</td>
<td>Glu; Asn</td>
</tr>
<tr>
<td>Cys (C)</td>
<td>Ser; Ala</td>
</tr>
<tr>
<td>Gln (Q)</td>
<td>Asn</td>
</tr>
<tr>
<td>Glu (E)</td>
<td>Asp; Gln</td>
</tr>
<tr>
<td>Gly (G)</td>
<td>Ala</td>
</tr>
<tr>
<td>His (H)</td>
<td>Asn; Gln</td>
</tr>
<tr>
<td>Ile (I)</td>
<td>Leu; Val</td>
</tr>
<tr>
<td>Leu (L)</td>
<td>Ile; Val</td>
</tr>
<tr>
<td>Lys (K)</td>
<td>Arg; His</td>
</tr>
<tr>
<td>Met (M)</td>
<td>Leu; Ile; Tyr</td>
</tr>
<tr>
<td>Phe (F)</td>
<td>Tyr; Met; Leu</td>
</tr>
<tr>
<td>Pro (P)</td>
<td>Ala</td>
</tr>
<tr>
<td>Ser (S)</td>
<td>Thr</td>
</tr>
<tr>
<td>Thr (T)</td>
<td>Ser</td>
</tr>
<tr>
<td>Trp (W)</td>
<td>Tyr; Phe</td>
</tr>
<tr>
<td>Tyr (Y)</td>
<td>Trp; Phe</td>
</tr>
<tr>
<td>Val (V)</td>
<td>Ile; Leu</td>
</tr>
</tbody>
</table>

"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.

"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.
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:

MRIFAVFIMTYWHLNAFTVTPKDLYVVEYGSNMTECKFPVEKQLDLALIVYKWEDE
IQFVHGEEDLKQHSSYQRARLKDQLSGNALQITDVKLDAGVYRCMISYGADYKRIV
KVNAPYNKINQRILVDPRTSEHELTCQAEGPKAEVIWTSDLVQLSGKTTTNSKREEKLF
VTSTRINTTTNEIFCTFRRLDPEENHAELVIPFLAPAHPNERTHLVILGAILLCGLV
ALT FIFRLKGRMMDVKKCGIQDTNSKKQSDTHLEET (SEQ ID NO:25).

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 the copending U.S. provisional patent application 61/745386, filed December 2012. These antibodies comprise the light chain and heavy chain variable region amino acid sequences shown in Table 2 below:

<table>
<thead>
<tr>
<th>Table 2. Monoclonal Antibodies 20C3 and 22C3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>20C3 Light Chain Mature Variable Region</strong></td>
</tr>
<tr>
<td>DIVMSQSPSSLAVSAEGKVTMCSKSSQLNSRTKHYLANYQQPKPGQSPKLLYIYASTRESGVFDRTGSGGTDFTLTISVQAEDLAVYQQYDVVTFGAGTKLELK</td>
</tr>
<tr>
<td><strong>20C3 Heavy Chain Mature Variable Region</strong></td>
</tr>
<tr>
<td>QVQVQQGSAELAEPGAVMSCKSAGYFTSYMVMLKWLRQRPQQGQLEIGYINPSDDYSESEKFKDKATLTADKASTTAYMLISLTSEDAYTYSCEFSGWLVHDQYYDFWQQGTTLTVSS</td>
</tr>
<tr>
<td><strong>22C3 Light Chain Mature Variable Region</strong></td>
</tr>
<tr>
<td>DIVMSQSPSSLAVSAEGKVTMCSKSSQHLMSTKHYLANYQQPKPGQSPKLLYIYASTRESGVFDRTGSGGTDFTLTISVQAEDLAVYQQYDVVTFGAGTKLELK</td>
</tr>
<tr>
<td><strong>22C3 Heavy Chain Mature Variable Region</strong></td>
</tr>
<tr>
<td>QVHQLQGSAELAEPGAVMSCKSAGYFTSYMVMLKWLRQRPQQGQLEIGYINPSDDYSESEEQFDKATLTADKASTTAYMLISLTSEDAYTYSCEFSGWLVHDQYYDFWQQGTTLTVSS</td>
</tr>
</tbody>
</table>

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).

"Dinaciclib compound" means the compound of Formula I, and pharmaceutically acceptable salts of the compound of Formula I. The chemical name of dinaciclib is 1-[3-ethyl-7-[[1-oxido-3-pyridinyl]methyl]amino]pyrazolo[1,5-a]pyrimidin-5-y]-2(5)-piperidineethanol. This compound may be synthesized as described in U.S. Patent No. US 7,119,200, or any other synthetic route that will be readily apparent to the skilled artisan.
Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable salts of the compound of Formula I may be formed, for example, by reacting the compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

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

Exemplary basic salts of the compound of Formula I include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of a dinaciclib compound used in the present invention and all acid and...
base salts are considered equivalent to the free forms of the corresponding compound for purposes of the invention.

[0065] Prodrugs of the compound of Formula I are also contemplated for use in the methods, medicaments and uses of the present invention. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula I or a salt thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

[0066] "Framework region" or "FR" as used herein means the immunoglobulin variable regions excluding the CDR regions.

[0067] "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 x 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.


[0069] "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.


[0071] "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

[0072] "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.

[0073] "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 NK 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, Btde 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.

[0074] PD-1 antagonists useful in the any of the treatment method, medicaments and uses of the present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and may include a human constant region. In some embodiments the human constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4 constant regions, and in preferred embodiments, the human constant region is an IgG1 or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')2, scFv and Fv fragments.

[0075] 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 US7521051, US8008449, and US8354509. Specific anti-human PD-1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include: MK-3475, a humanized IgG4 mAb with the structure described in WHO Drug Information, Vol. 27, No. 2, pages 161-162 (2013) and which comprises the heavy and light chain amino acid sequences shown in Figure 6, nivolumab (BMS-936558), a human IgG4 mAb with the structure
described in *WHO Drug Information*, Vol. 27, No. 1, pages 68-69 (2013) and which comprises
the heavy and light chain amino acid sequences shown in Figure 7; pidilizumab (CT-011, also
known as hBAT or hBAT-1); and the humanized antibodies h409All, h409A16 and h409A17,
which are described in WO2008/156712.

[0076] Examples of mAbs that bind to human PD-L1, and useful in the treatment
method, medicaments and uses of the present invention, are described in WO2013/019906,
WO2010/077634 A1 and US8383796. Specific anti-human PD-L1 mAbs useful as the PD-1
antagonist in the treatment method, medicaments and uses of the present invention include
MPDL3280A, BMS-936559, MEDI4736, MSB0010718C and an antibody which comprises the
heavy chain and light chain variable regions of SEQ ID NO:24 and SEQ ID NO:21, respectively,
of WO2013/019906.

[0077] Other PD-1 antagonists useful in the any of the treatment method, medicaments
and uses of the present invention include an immunoadhesin that specifically binds to PD-1 or
PD-L1, and preferably specifically binds to human PD-1 or human PD-L1, e.g., a fusion protein
containing the extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant
region such as an Fc region of an immunoglobulin molecule. Examples of immunoadhesions
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-
DC1g), which is a PD-L2-FC fusion protein and binds to human PD-1.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] Table 3 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>
<thead>
<tr>
<th>Table 3. Exemplary anti-human PD-1 antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Comprises light and heavy chain CDRs of hPD-1.08A in WO2008/156712</td>
</tr>
<tr>
<td>CDR1</td>
</tr>
<tr>
<td>CDR2</td>
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<td>CDR3</td>
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<td>CDRH1</td>
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<tr>
<td>CDRH2</td>
</tr>
<tr>
<td>CDRH3</td>
</tr>
<tr>
<td>B. Comprises light and heavy chain CDRs of hPD-1.09A in WO2008/156712</td>
</tr>
<tr>
<td>CDR1</td>
</tr>
<tr>
<td>CDR2</td>
</tr>
<tr>
<td>CDR3</td>
</tr>
<tr>
<td>CDRH1</td>
</tr>
<tr>
<td>CDRH2</td>
</tr>
<tr>
<td>CDRH3</td>
</tr>
<tr>
<td>C. Comprises the mature h109A heavy chain variable region and one of the mature K09A light chain variable regions in WO2008/156712</td>
</tr>
<tr>
<td>Heavy chain VR</td>
</tr>
<tr>
<td>Light chain VR</td>
</tr>
<tr>
<td>D. Comprises the mature 409 heavy chain and one of the mature K09A light chains in WO2008/156712</td>
</tr>
</tbody>
</table>

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"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.


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.

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.

A tissue section from a tumor that has been stained by IHC with a diagnostic PD-L1 antibody may also be scored for PD-L1 protein expression by assessing PD-L1 expression in
both the tumor cells and infiltrating immune cells in the tissue section, using a novel scoring process described in co-pending application 61/807581, filed 2 April 2013. This PD-L1 scoring process comprises examining each tumor nest in the tissue section for staining, and assigning to the tissue section one or both of a modified H score (MHS) and a modified proportion score (MPS). To assign the MHS, four separate percentages are estimated across all of the viable tumor cells and stained mononuclear inflammatory cells in all of the examined tumor nests: (a) cells that have no staining (intensity = 0), (b) weak staining (intensity =1+), (c) moderate staining (intensity =2+) and (d) strong staining (intensity =3+). A cell must have at least partial membrane staining to be included in the weak, moderate or strong staining percentages. The estimated percentages, the sum of which is 100%, are then input into the formula of 1 x (percent of weak staining cells) + 2 x (percent of moderate staining cells) + 3 x (percent of strong staining cells), and the result is assigned to the tissue section as the MHS. The MPS is assigned by estimating, across all of the viable tumor cells and stained mononuclear inflammatory cells in all of the examined tumor nests, the percentage of cells that have at least partial membrane staining of any intensity, and the resulting percentage is assigned to the tissue section as the MPS. In some embodiments, the tumor is designated as positive for PD-L1 expression if the MHS or the MPS is positive.

[0088] 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.

[0089] 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.

[0090] "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.
"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.

"Treat" or "treating" a cancer as used herein means to administer a combination therapy of a PD-1 antagonist and a dinaciclib compound to a subject having a cancer, or diagnosed with a cancer, to achieve at least one positive therapeutic effect, such as for example, reduced number of cancer cells, reduced tumor size, reduced rate of cancer cell infiltration into peripheral organs, or reduced rate of tumor metastasis or tumor growth. Positive therapeutic effects in cancer can be measured in a number of ways (See, W. A. Weber, J. Nucl. Med. 50: 1S-10S (2009)). For example, with respect to tumor growth inhibition, according to NCI standards, a T/C ≤ 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 x 100. In some embodiments, the treatment achieved by a therapeutically effective amount is any of progression free survival (PFS), disease free survival (DFS) or overall survival (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 complete response or a partial response, as well as the amount of time patients have experienced stable disease. 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. The dosage regimen of a combination therapy described herein 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 the treatment method, medicaments and uses of the present 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 chi²-test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Jonckheere-Terpstra-test and the Wilcoxon-test.

"Tumor" as it applies to a subject diagnosed with, or suspected of having, a cancer refers to a malignant or potentially malignant neoplasm or tissue mass of any size, and includes primary tumors and secondary neoplasms. A solid tumor is an abnormal growth or mass of tissue that usually does not contain cysts or liquid areas. Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas. Leukemias (cancers of the blood) generally do not form solid tumors (National Cancer Institute, Dictionary of Cancer Terms).
"Tumor burden" also referred to as "tumor load", refers to the total amount of tumor material distributed throughout the body. Tumor burden refers to the total number of cancer cells or the total size of tumor(s), throughout the body, including lymph nodes and bone narrow. Tumor burden can be determined by a variety of methods known in the art, such as, e.g. by measuring the dimensions of tumor(s) upon removal from the subject, e.g., using calipers, or while in the body using imaging techniques, e.g., ultrasound, bone scan, computed tomography (CT) or magnetic resonance imaging (MRI) scans.

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.

"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

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

The combination therapy may also comprise one or more additional therapeutic agents. The additional therapeutic agent may be, e.g., a chemotherapeutic other than a dinaciclib compound, a biotherapeutic agent (including but not limited to antibodies to VEGF, EGFR, Her2/neu, VEGF receptors, other growth factor receptors, CD20, CD40, CD-40L, CTLA-4, OX-40, 4-1BB, and ICOS), an immunogenic agent (for example, attenuated cancerous cells, tumor antigens, antigen presenting cells such as dendritic cells pulsed with tumor derived antigen or nucleic acids, immune stimulating cytokines (for example, IL-2, IFNa2, GM-CSF), and cells transfected with genes encoding immune stimulating cytokines such as but not limited to GM-CSF).

Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsusulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelines including altretamine, triethylenemelamine, trietylene phosphoramid, triethylenethiophosphoramid and trimethylolomelamine; acetogenins (especially bullatacin and...
bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; calyssatin; 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, chlorophosphamide, 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 gammall and calicheamicin phill, 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, carabinc, 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-azaauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, meptitiostane, testolactone; anti-adrenals such as aminogluthethimide, 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; lentinal; 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, verrucarin 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, LY17018, 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, aminogluthethimide, 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.

[00100] 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.

[00101] 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.

[00102] In some embodiments, the dinaciclib compound is administered before administration of the PD-1 antagonist, while in other embodiments, the dinaciclib compound is administered after administration of the PD-1 antagonist.

[00103] 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.

[00104] Each 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.

[00105] 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.

[00106] 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.

[00107] A combination therapy of the invention is typically used to treat a tumor that is large enough to be found by palpation or by imaging techniques well known in the art, such as MRI, ultrasound, or CAT scan. In some preferred embodiments, a combination therapy of the invention is used to treat an advanced stage tumor having dimensions of at least about 200 mm³, 300 mm³, 400 mm³, 500 mm³, 750 mm³, or up to 1000 mm³.

[00108] 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-L1 antagonist and dinaciclib compound, 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.

[00109] 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

**[00110]** 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. (2003) *Cancer Immunol. Immunother.* 52:133-144.

**[00111]** 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.

**[00112]** 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 0.005mg/kg to about 10mg/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.

[00113] In certain embodiments, a subject will be administered an intravenous (IV) infusion of a medicament comprising any of the PD-1 antagonists described herein.

[00114] 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.

[00115] In another preferred embodiment of the invention, the PD-1 antagonist in the combination therapy is MK-3475, which is administered in a liquid medicament at a dose selected from the group consisting of 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. In some particularly preferred embodiments, MK-3475 is administered as a liquid medicament which comprises 25 mg/ml MK-3475, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5, and the selected dose of the medicament is administered by IV infusion over a time period of 30 minutes. The optimal dose for MK-3475 in combination with dinaciclib may be identified by dose escalation starting with 2 mg/kg and going up to 10 mg/kg with the frequency of administration matched to that selected for dinaciclib.

[00116] In some embodiments, a liquid medicament comprising the dinaciclib compound is infused into the individual being treated at a dose of between 1 and 100 mg/m² over a time period of 1 hour to 24 hours on each of days 1, 8 and 15 of a 28 day cycle. In some embodiments, the time period for the IV infusion is 2 hours, 8 hours or 25 hours. In other embodiments, a dinaciclib medicament is administered by a 2 hour infusion at a dose of 50 mg/m² once every 21 days. In some embodiments in which the cancer is CLL, the dosage regimen for the dinaciclib medicament comprises at least two 28 day cycles: in the first cycle, the dinaciclib is administered over a 2 hour infusion at doses of 7 mg/m², 10 mg/m² and 14 mg/m² on Days 1, 8, and 15, respectively, and in the second and any subsequent cycles, the dinaciclib is administered on Days 1, 8 and 15 at a dose of 14 mg/m² over a 2 hour infusion. In some embodiments in which the cancer is a heme malignancy or a solid tumor, the dinaciclib is delivered once every two or three weeks, and the dose achieved may include up to 50 mg/m². In some embodiments, the highest steady state dose of up to 50 mg/m² of dinaciclib is achieved by dose escalation in 2 hour infusions separated by about 14 or 21 days.
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.

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

The present invention also provides a medicament which comprises a dinaciclib compound and a pharmaceutically acceptable excipient. The dinaciclib compound may be prepared as described in U.S. Patent No. 7,119,200, and may be formulated as an aqueous medicament for IV infusion as described in WO 2009/038701. In some preferred embodiments, the dinaciclib is formulated at 5 mg/mL in a sterile, aqueous citrate buffered solution at pH 3.0 to 4.2. This medicament is stable when stored in refrigerated conditions (2°C to 8°C) and protected from light. The sterile buffered dinaciclib solution is then diluted with 0.9% Sodium Chloride Injection (250 mL) United States Pharmacopeia (USP, weight/weight) to prepare various doses for IV administration, which should be administered within 24 hours when stored at controlled room temperature (20°C to 25°C, or 68°F to 77°F).

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

Exemplary Specific Embodiments of the Invention

1. A method for treating a cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and a dinaciclib compound, wherein the dinaciclib compound is the compound of Formula I

![Formula I](image)

or a pharmaceutically acceptable salt of the compound of Formula I.

2. A medicament comprising a PD-1 antagonist for use in combination with a dinaciclib compound for treating a cancer in an individual.

3. A medicament comprising a dinaciclib compound for use in combination with a PD-1 antagonist for treating a cancer in an individual.

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

5. Use of a PD-1 antagonist in the manufacture of medicament for treating a cancer in an individual when administered in combination with a dinaciclib compound.

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

7. Use of a PD-1 antagonist and a dinaciclib compound in the manufacture of medicaments for treating a cancer in an individual.

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

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

10. The method, medicament, use or kit of any of embodiments 1 to 9, 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.

11. The method, medicament, use or kit of embodiment 9, 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.

12. The method, medicament, use or kit of any of embodiments 1 to 9, 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.

13. The method, medicament, use or kit of embodiment 12, wherein the PD-1 antagonist also blocks binding of human PD-L2 to human PD-1.

14. 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.

15. 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.

16. 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.

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:23 and the light chain comprises SEQ ID NO:24.
18. The method, medicament, use or kit of any of embodiments 10-17, wherein the cancer is a solid tumor.

19. The method, medicament, use or kit of any of embodiments 10-17, 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.

20. The method, medicament, use or kit of any of embodiments 10-17, wherein the cancer is ipilimumab-naïve advanced melanoma and while in other preferred embodiments, the human has ipilimumab-refractory advanced melanoma.

21. The method, medicament, use or kit of any of embodiments 10-17, wherein the cancer is a Heme malignancy.

22. The method, medicament, use or kit of any of embodiments 10-17, 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), myelodysplasia; syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

23. The method, medicament, use or kit of any of embodiments 10-17, wherein the cancer is chronic lymphocytic leukemia (CLL).

24. The method, medicament, use or kit of any of embodiments 10-23, the cancer expresses human PD-L1.

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

26. The method, medicament, use or kit of embodiment 24 or 25, wherein the human PD-L1 expression is detected using a diagnostic anti-hPD-L1 mAb which comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises SEQ ID NO:28 and the HCVR comprises SEQ ID NO:29.

27. The method, medicament, use or kit of embodiment 16, wherein the PD-1 antagonist is MK-3475 or nivolumab and the dinaciclib compound is the compound of Formula I.
28. The method, medicament, use or kit of embodiment 27, wherein the MK-3475 is formulated as a liquid medicament which comprises 25 mg/ml MK-3475, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5 and the dinaciclib compound is formulated as a liquid medicament comprising 5 mg/mL of the compound of Formula I in a sterile, aqueous citrate buffered solution at pH 3.0 to 4.2.

29. The method, medicament, use or kit of embodiment 27 or 28, wherein the cancer is CLL.

30. The method, medicament, use or kit of any of embodiments 27-29, wherein the human PD-L1 expression is detected using a diagnostic anti-hPD-L1 mAb which comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises SEQ ID NO:28 and the HCVR comprises SEQ ID NO:29.

**GENERAL METHODS**


[00126] Purification of antigen is not necessary for the generation of antibodies. Animals can be immunized with cells bearing the antigen of interest. Splenocytes can then be isolated from the immunized animals, and the splenocytes can fused with a myeloma cell line to produce a hybridoma (see, e.g., Meyaard et al. (1997) Immunity 7:283-290; Wright et al. (2000) Immunity 13:233-242; Preston et al., supra; Kaithamana et al. (1999) J. Immunol. 163:5157-5164).


EXAMPLES

Example 1. Anti-tumor response of concurrent administration of a PD-1 antagonist and dinaciclib to tumor-bearing mice.

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-1 monoclonal antibody (Anti-PD1), monotherapy with dinaciclib and combination therapy with these two agents administered concurrently.

While human tumor cells or tumor explants can be grown in immunodeficient animals as xenografts, they cannot be used for testing immunotherapeutics because of the lack of a functional immune system. For a meaningful evaluation of immunotherapeutics or combination of immunotherapeutics with other agents, it is necessary to use a syngeneic model in which syngeneic tumors are grown in animals with an intact immune system. MC38 is a mouse colorectal adenocarcinoma syngeneic to C57BL/6 strain. This is a relevant model system for evaluating anti-PD-1’s mechanism of action because of the translatable molecular profile of this tumor post-anti-PD-1 therapy.

Tumor-bearing mice for this study were initiated by implanting 1 x 10^6 log-phase and sub-confluent MC38 cells on the right lower dorsal flank of 8 weeks old female C57BL/6 mice with an average body weight of 20 grams. When the mean tumor volume in these mice reached ~ 150 cubic mm (Figure 8B left panel marked day 0), the tumor-bearing mice were randomized to 4 treatment groups of 12 mice per group: (1) Isotype + Vehicle control group; (2) Anti-PD1 + Vehicle control; (3) dinaciclib + Isotype control and (4) Anti-PD1 + dinaciclib. The Vehicle control was 20% hydroxypropyl β-d-cyclodextrin made by dissolving Trappsol (Cyclodextrin Technologies Development Inc., Alachua, FL) in injection-grade water. The Isotype control was a mouse monoclonal antibody specific for adenoviral hexon and was of the isotype IgGl. Anti-PD1 was administered to treatment groups 2 and 4 at 5 mg/kg i.p. every 5 days for each of 5 cycles. Dinaciclib was administered to treatment groups 3 and 4 at 40 mg/kg every 5 days for each of 5 cycles.

As demonstrated by the results, which are shown in Figures 8A and 8B, the mean anti-tumor response of combination therapy with the PD-1 antagonist and dinaciclib was greater (p<0.05) than the anti-tumor response observed with either agent as monotherapy. As shown in Fig. 8A, the combination of these two agents provided significantly higher complete regressions (CR) such that no measureable tumor remained, compared to the best single agent response, which was 42% CR with anti-PD-1. Comparing mean tumor volumes at the end of the study
(Figure 8B, right panel) using one way ANOVA, the tumor volumes of mice treated with the combination of dinaciclib + anti-PD1 were significantly smaller than those treated with dinaciclib alone.

The statistical significance of the responses to the different treatments was determined using a Fishers Exact Pair-Wise Test, and the results are shown in Table 4 below.

Table 4: Fisher's exact test: pairwise comparison of tumor volumes at the end of study

<table>
<thead>
<tr>
<th>Treatment Pairs</th>
<th>Tumor Volume (day 25)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Zero</td>
<td>Zero</td>
</tr>
<tr>
<td>Isotype + Vehicle</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Pairs</th>
<th>Tumor Volume (day 25)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Zero</td>
<td>Zero</td>
</tr>
<tr>
<td>Dinaciclib</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Pairs</th>
<th>Tumor Volume (day 25)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Zero</td>
<td>Zero</td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Dinaciclib</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Pairs</th>
<th>Tumor Volume (day 25)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Zero</td>
<td>Zero</td>
</tr>
<tr>
<td>Dinaciclib</td>
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<td>0</td>
</tr>
<tr>
<td>Dinaciclib + Anti-PD1</td>
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<td>12</td>
</tr>
<tr>
<td>Total</td>
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<td>12</td>
</tr>
</tbody>
</table>
Table 5 provides a brief description of the sequences in the sequence listing.

<table>
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<tr>
<th>SEQ ID NO</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>2</td>
<td>hPD-1.08A light chain CDR2</td>
</tr>
<tr>
<td>3</td>
<td>hPD-1.08A light chain CDR3</td>
</tr>
<tr>
<td>4</td>
<td>hPD-1.08A heavy chain CDR1</td>
</tr>
<tr>
<td>5</td>
<td>hPD-1.08A heavy chain CDR2</td>
</tr>
<tr>
<td>6</td>
<td>hPD-1.08A heavy chain CDR3</td>
</tr>
<tr>
<td>7</td>
<td>hPD-1.09A light chain CDR1</td>
</tr>
<tr>
<td>8</td>
<td>hPD-1.09A light chain CDR2</td>
</tr>
<tr>
<td>9</td>
<td>hPD-1.09A light chain CDR3</td>
</tr>
<tr>
<td>10</td>
<td>hPD-1.09A heavy chain CDR1</td>
</tr>
<tr>
<td>11</td>
<td>hPD-1.09A heavy chain CDR2</td>
</tr>
<tr>
<td>12</td>
<td>hPD-1.09A heavy chain CDR3</td>
</tr>
<tr>
<td>13</td>
<td>109A-H heavy chain variable region</td>
</tr>
<tr>
<td>14</td>
<td>409A-H heavy chain full length</td>
</tr>
<tr>
<td>15</td>
<td>K09A-L-11 light chain variable region</td>
</tr>
<tr>
<td>16</td>
<td>K09A-L-16 light chain variable region</td>
</tr>
<tr>
<td>17</td>
<td>K09A-L-17 light chain variable region</td>
</tr>
<tr>
<td>18</td>
<td>K09A-L-11 light chain full length</td>
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<td>19</td>
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</tr>
<tr>
<td>20</td>
<td>K09A-L-17 light chain full length</td>
</tr>
<tr>
<td>21</td>
<td>MK-3475 Heavy chain</td>
</tr>
<tr>
<td>22</td>
<td>MK-3475 Light chain</td>
</tr>
<tr>
<td>23</td>
<td>Nivolumab Heavy chain</td>
</tr>
<tr>
<td>24</td>
<td>Nivolumab light chain</td>
</tr>
<tr>
<td>25</td>
<td>Precursor human PD-L1</td>
</tr>
</tbody>
</table>

REFERENCES


[00131] All references cited herein are incorporated by reference to the same extent as if each individual publication, database entry (e.g. Genbank sequences or GenelD entries), patent application, or patent, was specifically and individually indicated to be incorporated by reference. This statement of incorporation by reference is intended by Applicants, pursuant to 37 C.F.R. §1.57(b)(1), to relate to each and every individual publication, database entry (e.g. Genbank sequences or GenelD entries), patent application, or patent, each of which is clearly identified in compliance with 37 C.F.R. §1.57(b)(2), even if such citation is not immediately adjacent to a dedicated statement of incorporation by reference. The inclusion of dedicated statements of incorporation by reference, if any, within the specification does not in any way weaken this general statement of incorporation by reference. Citation of the references herein is not intended as an admission that the reference is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.
CLAIMS

1. A method for treating a cancer in an individual comprising administering to the individual a combination therapy which comprises an antagonist of a Programmed Death 1 protein (PD-1) and a dinaciclib compound, wherein the dinaciclib compound is the compound of Formula I

\[ \text{Formula I} \]

or a pharmaceutically acceptable salt of the compound of Formula I.

2. The method of claim 1, wherein the individual is a human and the PD-1 antagonist is (a) 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; or (b) 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.

3. The method of claim 2, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, or SEQ ID NO:23 and SEQ ID NO:24, respectively.

4. The method of any of claims 1 to 3, wherein the cancer is a solid tumor.

5. The method of any of claims 1 to 3, wherein the cancer is a Heme malignancy.

6. The method of any of claims 3 to 5, wherein the PD-1 antagonist is MK-3475 and the dinaciclib compound is the compound of Formula I.

7. A medicament comprising an antagonist of a Programmed Death 1 protein (PD-1) for use in combination with a dinaciclib compound for treating a cancer in an individual, wherein the dinaciclib compound is the compound of Formula I
or a pharmaceutically acceptable salt of the compound of Formula I.

8. A medicament comprising a dinaciclib compound for use in combination with an antagonist of a Programmed Death 1 protein (PD-1) for treating a cancer in an individual, wherein the dinaciclib compound is the compound of Formula I.

9. The medicament of claim 7 or 8, wherein the individual is a human and the PD-1 antagonist is
(a) 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; or
(b) 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.

10. The medicament of any of claims 7 to 9, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, or SEQ ID NO:23 and SEQ ID NO:24, respectively.

11. The medicament of any of claims 7 to 10, wherein the cancer is a solid tumor.
12. The medicament of any of claims 7 to 11, wherein the cancer is a Heme malignancy.

13. The medicament of any of claims 10 to 12, wherein the PD-1 antagonist is MK-3475 or nivolumab.

14. The medicament of claim 13, wherein the MK-3475 is formulated as a liquid medicament which comprises 25 mg/ml MK-3475, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5 and the dinaciclib compound is formulated as a liquid medicament comprising 5 mg/mL of the compound of Formula I in a sterile, aqueous citrate buffered solution at pH 3.0 to 4.2.

15. The medicament of claim 8, wherein the dinaciclib compound is formulated as a liquid medicament comprising 5 mg/mL of the compound of Formula I in a sterile, aqueous citrate buffered solution at pH 3.0 to 4.2.

16. A kit which comprises a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising an antagonist of a Programmed Death 1 protein (PD-1), the second container comprises at least one dose of a medicament comprising a dinaciclib compound, and the package insert comprises instructions for treating an individual for cancer using the medicaments, wherein the dinaciclib compound is the compound of Formula I

![Formula I](image)

17. The kit of claim 16, 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.

18. The kit of claim 16 or 17, wherein the individual is a human and the PD-1 antagonist is
(a) 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; or
(b) 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.

19. The kit of any of claims 16-18, wherein the PD-1 antagonist is MK-3475.

20. The method, use or kit of any of claims 1 to 19, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), triple negative breast cancer, 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), or small lymphocytic lymphoma (SLL).
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 Val Ser Ala Ser Thr Lys Gly Pro Ser Val 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 Tyr 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 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Ser Val Leu Thr Val 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 Glu Val Tyr Thr Leu Pro Pro Ser Gln Glu Met Thr Lys Asn Gln Val Ser Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asp Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Ser Gly Ser Asp Val Asp Gly 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

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 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 Tyr 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 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Ser Val Leu Thr Val 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 Glu Val Tyr Thr Leu Pro Pro Ser Gln Glu Met Thr Lys Asn Gln Val Ser Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asp Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Ser Gly Ser Asp Val Asp Gly 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 Glu Gln Lys Pro Gly Glu 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 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 Glu 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 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 Glu 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 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-11 light chain full length (SEQ ID NO:18)

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

FIG.5B
MK-3475 Heavy chain (SEQ ID NO:21)
QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYMYWVRQA PQQGLEWMGG 50
INPSNGGTNF NEKFKNRVTI TTDSSTTAY MELKSLQFDD TAVYYCARRD 100
YRFDMGFDYW GQGTTVTVS ASTKGPSVFV LAPCSRSTSE STAALGCLV 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLLSVVT VPSSSLGTKT 200
YTCNVDHKPS NTKVDKRVES KYGPPCPCCP APEFLGGPSV FLFPPKPDKT 250
LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY 300
RVVSVLTVLH QDWNLCGKEYK CKVSNKGLPS SIEKTISAK GQPREPVYVT 350
LPPSQEEMTK NQVSLSTCLVK GFYPSDAVNE WESNQQPENN YKTTPVLDI 400
DGSFFLYSLR TVDKSRSWQEG NVFSCSMHE ALHNYTQKS LSLSLGK 447

MK-3745 Light chain (SEQ ID NO:22)
EIVLTQSPAT LSLSPGERAT LSCRASKGVS TSGYSLHWY QQKPQAPRL 50
LIYLASYLES GVPRFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSDLPL 100
TFAQGKKEVI KRTEAAPSVP IFPPSDEQLK SGTASVCLL NNFYPREAV 150
QWQKVNDALQS GNSQESVTTEQ DSKDSTYSLSTLTLKADY EHKYVCEV 200
THQGLSSPVTV KSFNRGEC 219

FIG. 6
Nivolumab Heavy chain (SEQ ID NO:23)
QVQLVESGGG VVQPGSRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWAV 50
IWyDgSKRRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND 100
DYWQGQLTTLVT VASSASTKGPS VVFPLAPCSRS TSESTAALGC LVKYFPEPV 150
TVSwNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSLG TKTYTCNVDH 200
KPSNTKVDRK VESKYGPPCP PCPAEFLGG PSVFLFPPKP KTDLMISRTP 250
EVTcvVVDVVS QEDPevQFwV YVdGVEvhNA KTKPREEQFN STYRvSVLT 300
VLODwLNGK EYKcKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQE 350
MTrNQVSLTc LVKGFYpsDi AVEnEwNGQP EEnYKTTPPV LdSDGSFFLY 400
SRLTvDksrW QEGNvFSCsv MHEALHNHyT QKSLSLSLgK 440

Nivolumab Light chain (SEQ ID NO:24)
EVLTQSPAT LSLSPGERAT LSCblahVS SYLaWyQQKP QGAPRLLdYD 50
ASnRATGIPA RFSGSGSGTD FTTliSSlEP EDFAVYYQcQ SSNwPrTFGQ 100
GTWcIKRTv AALPSVIFpP SDEQLKGTA SvvCllNNFY PReAKvQKv 150
DNAlQSGNSQ EsvTeQDSKd STYsLsSSLt LSKADYKHK VyACEvTHQG 200
LSSPvTKSFN RGEc 214

FIG. 7
### A. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>IPC(8)</th>
<th>CPC</th>
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<tr>
<td>A61K 39/395, C07K 16/00, C07K 14/475, A01N 43/90</td>
<td>A61K 38/00, C07D 487/04</td>
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</tbody>
</table>

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)

IPCs: A61K 39/395, C07K 16/00, C07K 14/475, A01N 43/90 (2014.01)

CPC: A61K 38/00, C07D 487/04

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

USPC: 424/154.1, 530/389.1, 514/17.6, 514/259.3 (keyword limited, terms below)

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

PubWEST (USPT, PGDB, EPAB, JPAB), Google Patents/Scholar

Search Terms Used: PD-1, PD-L1, PD-L2, B7-H1, B7-DC, CD279, dinaciclib, flavopiridol, SCH727965, CDK, tumor-infiltrating lymphocyte

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 2010/005511 A1 (Sharma et al.) 04 March 2010 (04.03.2010) para [0009], [0076], [0077], [0085], [0090], [0099], [0110]</td>
<td>1-5, 7-9, 15-18</td>
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<td>Y</td>
<td>US 2010/0286038 A1 (Antochochuk et al.) 11 November 2010 (11.11.2010) para [0010], [0059], Table I</td>
<td>1-5, 7-9, 15-18</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* 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
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  - **X** - document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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  - **&** - document member of the same patent family

Date of the actual completion of the international search: 20 November 2014 (20.11.2014)

Date of mailing of the international search report: 04 DEC 2014

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Form PCT/ISA/210 (second sheet) (July 2009)
INTERNATIONAL SEARCH REPORT

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. [x] Claims Nos.: 6, 10-14, 19, 20 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.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (July 2009)