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(54) Benævnelse: **BEHANDLING AF TYKTARMSKRÆFT MED EN KOMBINATION AF HDAC-INHIBITOREN HBI-8000 OG EN PD-L1-INHIBITOR**

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DESCRIPTION

Description

FIELD OF THE INVENTION

[0001] The present invention relates to combinations of HDACi and PD-1 inhibitors and the use of such combinations in the treatment of colon cancer.

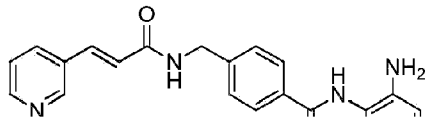
BACKGROUND OF THE INVENTION

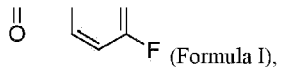
[0002] Cancer is a significant cause of morbidity and mortality worldwide. While the standards of care for many different cancer types have greatly improved over the years, current standards of care still fail to meet the need for effective therapies to improve treatment of cancer. The clinical use of immuno - oncology agents targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death receptor -1 (PD-1) and its ligand PD-L1, have resulted in improvements over the standard of care in the treatment of many cancer types. While these checkpoint inhibitors have produced improved clinical responses in such certain cancers, durable clinical responses only occur in approximately 10 - 45% of patients. Moreover, a significant number of tumors are either resistant or become refractory. Epigenetic modifiers such as histone deacetylase inhibitors (HDACi) have been successful in the treatment of some hematologic malignancies, but despite preclinical data demonstrating activity against solid tumors, this result has not translated to the clinic as a monotherapy. Accordingly, there is a need in the art for new therapies, including for example combination therapies, for the treatment of cancers. Provided herein are solutions to these and other problems in the art.

BRIEF SUMMARY

[0003] Provided herein, *inter alia,* are combinations that include a HDAC inhibitor (HDACi) and a PD-1 inhibitor as defined in the claims. The combinations are the compound of formula I or a pharmaceutically acceptable salt thereof and a PD-1 inhibitor. In certain instances the PD-1 inhibitor is a PD-1 antibody.

1. 1. In a first aspect, the invention refers to the compound represented by the structure:



 (Formula I),

or a pharmaceutically acceptable salt thereof,
for use in a method of treating colon cancer in a patient in need thereof and whose cancer has been previously treated with a PD-L1 inhibitor, wherein said method further comprises administering a PD-1 inhibitor.

[0004] The compound of formula I is N-(2-amino-4-fluorophenyl)-4-[[[(2E)-1-oxo-3-(3-pyridinyl)-2-propen-1-yl]amino]methyl]benzamide, also referred to herein as HBI-8000, or chidamide.

[0005] In another embodiment, the PD-1 inhibitor is a small molecule compound, a nucleic acid, a peptide, a protein, an antibody, a peptibody, a diabody, a minibody, a single-chain variable fragment (ScFv), or a fragment or variant thereof.

[0006] In still another embodiment, the PD-1 inhibitor is an antibody.

[0007] In yet another embodiment, the PD-1 antibody is selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR001, SHR-1210 or MEDI0680.

[0008] The invention also refers to the compound of formula I for use in the treatments as defined in the claims.

[0009] The PD-1 antibody can be nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR001, SHR-1210 or MEDI0680.

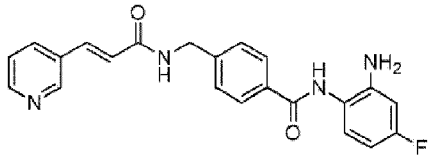
[0010] In one aspect the treatment is a method for reducing a level of myeloid-derived suppressor cells (MDSC) in a patient in need thereof by administering a therapeutically effective amount of a compound described herein.

[0011] In yet another aspect the treatment is a method for reducing a level of regulatory T cells (Treg cells) in a patient in need thereof by administering a therapeutically effective amount of a compound described herein.

[0012] In another aspect the treatment is a method for enhancing the activity of a natural killer (NK) or cytotoxic T-cell activity *in-vivo* in a cancer patient by administering a therapeutically effective amount of a compound described herein.

[0013] In another aspect the treatment is a method for enhancing antibody-dependent cell-mediated cytotoxicity in a cancer patient by administering a therapeutically effective amount of a compound described herein.

[0014] The methods described herein include administering a therapeutically effective amount of a combination of a histone deacetylase inhibitor of formula I and PD-1 inhibitor. The compound of formula I has the following structure:



[0015] The compound of formula I is also referred to as N-(2-amino-4-fluorophenyl)-4-[[[(2E)-1-oxo-3-(3-pyridinyl)-2-propen-1-yl]amino]methyl]benzamide. In some aspects the compound of formula I is administered in an amount greater than about 5 mg or in a range of about 5 to 50 mg.

[0016] In some aspects, the PD1 inhibitor is a small molecule compound, a nucleic acid, a peptide, a protein, an antibody, a peptibody, a diabody, a minibody, a single-chain variable fragment (ScFv), or a fragment or variant thereof. In some aspects the PD-1 inhibitor is AMP-24, or an antibody, such as a monoclonal antibody, including a human antibody or humanized antibody such as nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In some aspects the PD-1 antibody is administered at an amount of about 1 mg/kg, 2 mg/kg, 3 mg/kg, or 5 mg/kg.

[0017] In yet other aspects, in the methods for reducing or preventing metastasis using a compound as defined in the claims, the compound is administered prior, concurrently, subsequently, or combinations of prior, concurrently and subsequently to treatment of the primary tumor. Treatment of the primary tumor can include one or more of radiation, surgery, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplant, cryotherapy, laser therapy, and precision medicine.

[0018] In some aspects, the metastasis that is reduced is metastasis of one or more of the adrenal gland, brain and/or spinal cord, bone, lung, liver and/or pleura, gastrointestinal tract, peritoneum, muscle, lymph nodes and skin.

[0019] The methods can further comprise treatment of the subject with an E-selectin inhibitor, or plerixafor, or a combination of an E-selectin inhibitor and plerixafor. In some aspects of this method the E-selectin inhibitor and/or plerixafor is given prior, concurrently, or subsequently, or combinations of prior, concurrently or subsequently, to the HDACi and PD-1 combination.

[0020] The methods can further comprises treating the subject with an αv integrin inhibitor, or an antibody from the group comprising etaracizumab, intetumumab, or abituzumab or a combination of an αv integrin inhibitor and an antibody from the group comprising etaracizumab, etaracizumab, intetumumab, or abituzumab. In other aspects of this embodiment, the method further comprises treating the subject with a matrix metalloproteinase inhibitor, wherein said matrix metalloproteinase inhibitor is given prior, concurrently, or

subsequently, or combinations of prior, concurrently or subsequently, to the HDACi and PD-1 inhibitor.

DESCRIPTION OF THE FIGURES

[0021]

Fig. 1 illustrates group tumor growth as median tumor volume (mm^3, y-axis) over time (days, x-axis) for all groups in the study described in the study described in Example 1 herein.

Fig. 2 illustrates group tumor growth as median tumor volume (mm^3, y-axis) over time (days, x-axis) for mice treated with compound (HBI-8000) at 50 mg/kg in the study described in Example 1 herein.

Fig. 3 illustrates survival (Kaplan-Meier) for all groups tested in the study described in Example 1 herein.

Fig. 4 illustrates survival (Kaplan-Meier) for mice treated with compound (HBI-8000) at 50 mg/kg in the study described in Example 1 herein.

Fig. 5 illustrates group tumor growth as median tumor volume (mm^3, y-axis) over time (days, x-axis) for all groups in the study described in Example 2 herein.

Fig. 6 illustrates survival (Kaplan-Meier) for all groups tested in the study described in Example 2 herein.

Fig. 7 shows individual times to study endpoint for each animal in Example 2 herein.

Fig. 8- illustrates survival (Kaplan-Meier) in the study described in Example 3 herein.

Fig. 9- shows individual times to study endpoint for each animal in Example 3 herein.

Fig. 10- shows number of metastatic lung foci for study described in Example 4 herein.

Fig. 11- shows the median tumor growth curves for all study groups.

DETAILED DESCRIPTION

Definitions

[0022] Unless defined otherwise, all technical and scientific terms used herein have the same

meaning as commonly understood by those of ordinary skill in the art to which the invention belongs. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts. Should a discrepancy exist between a depicted structure and a name given for that structure, the depicted structure is to be accorded more weight. Where the stereochemistry of a structure or a portion of a structure is not indicated in a depicted structure or a portion of the depicted structure, the depicted structure is to be interpreted as encompassing all of its possible stereoisomers.

[0023] Any methods, devices and materials similar or equivalent to those described herein can be used in the practice of this invention. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise. Headings used herein are for organizational purposes only and in no way limit the invention described herein.

[0024] The term "PD-1 inhibitor" refers to a moiety (e.g., compound, nucleic acid, polypeptide, antibody) that decreases, inhibits, blocks, abrogates or interferes with the activity or expression of PD-1 (*e.g.,* Programmed Cell Death Protein 1; PD-1 (CD279); GI: 145559515), including variants, isoforms, species homologs of human PD-1 (*e.g.,* mouse) and analogs that have at least one common epitope with PD-1. A PD-1 inhibitor includes molecules and macromolecules such as, for example, compounds, nucleic acids, polypeptides, antibodies, peptibodies, diabodies, minibodies, single-chain variable fragments (ScFv), and fragments or variants thereof. Thus, a PD-1 inhibitor as used herein refers to any moiety that antagonizes PD-1 activity or expression. PD-1 inhibitor efficacy can be measured, for example, by its inhibitor concentration at 50% (half-maximal inhibitor concentration or IC_{50}). PD-1 inhibitors include exemplary compounds and compositions described herein. A PD-1 antibody refers to a PD-1 inhibitor which is a monoclonal or polyclonal antibody as described herein.

[0025] The terms "nivolumab," "pembrolizumab," "pidilizumab," "AMP-224," "REGN2810," "PDR 001,", "SHR-1210", "SAR-439684" and "MEDI0680" are used in accordance with their plain and ordinary meaning as understood in the art.

[0026] The terms "polypeptide" and "protein" are used interchangeably herein and refer to any molecule that includes at least 2 or more amino acids.

[0027] The term "effective amount" refers to the amount of a therapy (e.g., a combination provided herein or another active agent described herein such as an anti-cancer agent described herein) which is sufficient to accomplish a stated purpose or otherwise achieve the effect for which it is administered. An effective amount can be sufficient to reduce and/or ameliorate the progression, development, recurrence, severity and/or duration of a given disease, disorder or condition and/or a symptom related thereto, or can be sufficient to reduce the level of activity of a polypeptide (*e.g.,* PD-1). An effective amount can be a "therapeutically effective amount" which refers to an amount sufficient to provide a therapeutic benefit such as, for example, the reduction or amelioration of the advancement or progression of a given

disease, disorder or condition, reduction or amelioration of the recurrence, development or onset of a given disease, disorder or condition, and/or to improve or enhance the prophylactic or therapeutic effect(s) of another therapy. A therapeutically effective amount of a composition described herein can enhance the therapeutic efficacy of another therapeutic agent.

[0028] The term "regimen" refers to a protocol for dosing and timing the administration of one or more therapies (*e.g.,* combinations described herein or another active agent such as for example an anti-cancer agent described herein) for treating a disease, disorder, or condition described herein. A regimen can include periods of active administration and periods of rest as known in the art. Active administration periods include administration of combinations and compositions described herein and the duration of time of efficacy of such combinations and compositions. Rest periods of regimens described herein include a period of time in which no compound is actively administered, and in certain instances, includes time periods where the efficacy of such compounds can be minimal. Combination of active administration and rest in regimens described herein can increase the efficacy and/or duration of administration of the combinations and compositions described herein.

[0029] The terms "therapies" and "therapy" refer to any protocol(s), method(s), and/or agent(s) that can be used in the prevention, treatment, management, and/or amelioration of a disease, disorder, or condition or one or more symptoms thereof. In certain instances the term refers to other active agents such as anti-cancer agents described herein. The terms "therapy" and "therapy" can refer to anti-viral therapy, anti-bacterial therapy, anti-fungal therapy, anti-cancer therapy, biological therapy, supportive therapy, and/or other therapies useful in treatment, management, prevention, or amelioration of a disease, disorder, or condition or one or more symptoms thereof known to one skilled in the art, for example, a medical professional such as a physician.

[0030] The term "patient" or "subject" refers to a mammal, such as a human, bovine, rat, mouse, dog, monkey, ape, goat, sheep, cow, or deer. Generally a patient as described herein is human.

[0031] The terms "inhibition", "inhibit", "inhibiting" refer to a reduction in the activity or expression of a polypeptide or reduction or amelioration of a disease, disorder, or condition or a symptom thereof. Inhibiting as used here can include partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating protein or enzyme activity.

[0032] Antibodies described herein can be polyclonal or monoclonal and include xenogeneic, allogeneic, or syngeneic forms and modified versions thereof (*e.g.,* humanized or chimeric). An "antibody" is intended to mean a polypeptide product of B cells within the immunoglobulin class of polypeptides that is able to bind to a specific molecular antigen and is composed of two identical pairs of polypeptide chains, wherein each pair has one heavy chain (about 50-70 kDa) and one light chain (about 25 kDa) and each amino-terminal portion of each chain includes a variable region of about 100 to about 130 or more amino acids and each carboxy-terminal

portion of each chain includes a constant region (See Borrebaeck (ed.) (1995) Antibody Engineering, Second Edition, Oxford University Press.; Kuby (1997) Immunology, Third Edition, W.H. Freeman and Company, New York). Specific molecular antigens that can be bound by an antibody described herein include PD-1 and its epitopes.

[0033] The term "monoclonal antibody(ies)" refers to a population of antibody molecules that contain one species of an antigen binding site capable of immunoreacting with a particular epitope of an antigen, whereas the term "polyclonal antibody(ies)" refers to a population of antibody molecules that contain multiple species of antigen binding sites capable of interacting with a particular antigen. A monoclonal antibody, typically displays a single binding affinity for a particular antigen with which it immuno-reacts. For example, the monoclonal antibodies to be used in accordance with the present invention can be made by a variety of techniques, including, for example, the hybridoma method (*e.g.,* Kohler and Milstein., Nature, 256:495-97 (1975); Hongo et al., Hybridoma, 14 (3): 253-260 (1995), Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981)), recombinant DNA methods (see, *e.g.,* U.S. Patent No. 4,816,567), phage-display technologies (see, *e.g.,* Clackson et al., Nature, 352: 624-628 (1991); Marks et al., J Mol. Biol. 222: 581-597 (1992); Sidhu et al., J. Mol. Biol. 338(2): 299-310 (2004); Lee et al., J. Mol. Biol. 340(5): 1073-1093 (2004); Fellouse, Proc. Natl. Acad. Sci. USA 101(34): 12467-12472 (2004); and Lee et al., J. Immunol. Methods 284(1-2): 119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, *e.g.,* WO 1998/24893; WO 1996/34096; WO 1996/33735; WO 1991/10741; Jakobovits et al., Proc. Natl. Acad. Sci. USA 90: 2551 (1993); Jakobovits et al., Nature 362: 255-258 (1993); Bruggemann et al., Year in Immunol. 7:33 (1993); U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks et al., Bio/Technology 10: 779-783 (1992); Lonberg et al., Nature 368: 856-859 (1994); Morrison, Nature 368: 812-813 (1994); Fishwild et al., Nature Biotechnol. 14: 845-851 (1996); Neuberger, Nature Biotechnol. 14: 826 (1996); and Lonberg and Huszar, Intern. Rev. Immunol. 13: 65-93 (1995).

[0034] The monoclonal antibodies herein also include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is(are) identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison et al., Proc. Natl. Acad. Sci. USA, pp.6851-6855 (1984)). "Humanized antibody(ies)" can be considered as a subset of chimeric antibodies described herein.

[0035] The term "human" when used in reference to an antibody or a functional fragment thereof (*e.g.,* "humanized antibody(ies))" refers an antibody or functional fragment thereof that has a human variable region or a portion thereof corresponding to human germline

immunoglobulin sequences. Such human germline immunoglobulin sequences are described by Kabat et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242. A human antibody, in the context of the present invention, can include an antibody that binds to PD-1 or variants thereof as described herein.

[0036] In certain instances a human antibody is an antibody that possesses an amino acid sequence corresponding to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. Human antibodies can be produced using various techniques known in the art, including phage-display libraries. Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222 :581 (1991). Also available for the preparation of human monoclonal antibodies are methods described in Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985); Boemer et al., J. Immunol., 147(1):86-95 (1991). See also van Dijk and van de Winkel, Curr. Opin. Pharmacol., .2.: 368-74 (2001). Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, e.g., immunized xenomice (see, *e.g.,* U.S. Pat. Nos. 6,075.181 and 6, 150,584 regarding XENOMOUSE technology). See also, for example, Li et al., Proc. Natl. Acad. Sci. USA, 103:3557-3562 (2006) regarding human antibodies generated via a human B-cell hybridoma technology.

[0037] A "humanized antibody" refers to antibodies made by a non-human cell having variable or variable and constant regions which have been altered to more closely resemble antibodies that would be made by a human cell. For example, by altering the non-human antibody amino acid sequence to incorporate amino acids found in human germline immunoglobulin sequences. The humanized antibodies of the invention can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.,* mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs. Humanized antibodies can also include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0038] Humanized forms of non-human (*e.g.,* murine) antibodies are antibodies that contain minimal sequence derived from non-human immunoglobulin. In one embodiment, a humanized antibody is a human immunoglobulin (recipient antibody) in which residues from a hypervariable of the recipient are replaced by residues from an hypervariable region of a nonhuman species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired specificity, affinity, and/or capacity. In some instances, framework ("FR") residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications can be made to further refine antibody performance, such as binding affinity. In general, a 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 sequence, and all or substantially all of the FR regions are those of a human immunoglobulin sequence, although the FR regions can include one or more individual FR residue substitutions that improve antibody performance, such as binding affinity, isomerization, immunogenicity, etc. The number of these amino acid substitutions in the FR are typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally can also include at least a portion of an immunoglobulin constant region (Fc), which can be a human immunoglobulin. Exemplary methods and humanized antibodies include those described by Jones et al. Nature 321:522-525 (1986); Riechmann et al. Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992); Vaswani and Hamilton, Ann. Allergy. Asthma & Immunol. 1: 105-115 (1998); Harris, Biochem. Soc. Transactions 23:1035-1038 (1995); Burle and Gross, Curr. Op. Biotech. 5:428-433 (1994); and U.S. Pat. Nos. 6,982,321 and 7,087,409.

[0039] The term "functional fragment" when used in reference to an antibody refers to a portion of the antibody including heavy or light chain polypeptides that retains some or all of the binding activity as the antibody from which the fragment was derived. Such functional fragments can include, for example, an Fd, Fv, Fab, F(ab'), $F(ab)_2$, $F(ab')_2$, single chain Fv (ScFv), diabody, triabody, tetrabody and minibody. Other functional fragments can include, for example, heavy or light chain polypeptides, variable region polypeptides or CDR polypeptides or portions thereof so long as such functional fragments retain binding activity. Such antibody binding fragments can be found described in, for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York (1989); Myers (ed.), Molec. Biology and Biotechnology: A Comprehensive Desk Reference, New York: VCH Publisher, Inc.; Huston et al., Cell Biophysics, 22:189-224 (1993); Plückthun and Skerra, Meth. Enzymol., 178:497-515 (1989) and in Day, E.D., Advanced Immunochemistry, Second Ed., Wiley-Liss, Inc., New York, NY (1990). Antibody Engineering, Second Edition, Oxford University Press, 1995.

[0040] The term "heavy chain" when used in reference to an antibody refers to a polypeptide chain of about 50-70 kDa, wherein the amino-terminal portion includes a variable region of about 120 to 130 or more amino acids and a carboxy-terminal portion that includes a constant region. The constant region can be one of five distinct types, referred to as alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino acid sequence of the heavy chain constant region. The distinct heavy chains differ in size: α, δ and γ contain approximately 450 amino acids, while μ and ε contain approximately 550 amino acids. When combined with a light chain, these distinct types of heavy chains give rise to five well known classes of antibodies, IgA, IgD, IgE, IgG and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG2, IgG3 and IgG4. A heavy chain can be a human heavy chain.

[0041] The term "light chain" when used in reference to an antibody refers to a polypeptide chain of about 25 kDa, wherein the amino-terminal portion includes a variable region of about 100 to about 110 or more amino acids and a carboxy-terminal portion that includes a constant region. The approximate length of a light chain is 211 to 217 amino acids. There are two distinct types, referred to as kappa (κ) of lambda (λ) based on the amino acid sequence of the

constant domains. Light chain amino acid sequences are well known in the art. A light chain can be a human light chain.

[0042] The term "variable domain" or "variable region" refers to a portion of the light or heavy chains of an antibody that is generally located at the amino-terminal of the light or heavy chain and has a length of about 120 to 130 amino acids in the heavy chain and about 100 to 110 amino acids in the light chain, and are used in the binding and specificity of each particular antibody for its particular antigen. The variable domains can differ extensively in sequence between different antibodies. The variability in sequence is concentrated in the CDRs while the less variable portions in the variable domain are referred to as framework regions (FR). The CDRs of the light and heavy chains are primarily responsible for the interaction of the antibody with antigen. Numbering of amino acid positions used herein is according to the EU Index, as in Kabat et al. (1991) *Sequences of proteins of immunological interest.* (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed. A variable region can be a human variable region.

[0043] A CDR refers to one of three hypervariable regions (H1, H2 or H3) within the non-framework region of the immunoglobulin (Ig or antibody) VH β-sheet framework, or one of three hypervariable regions (L1, L2 or L3) within the non-framework region of the antibody VL β-sheet framework. Accordingly, CDRs are variable region sequences interspersed within the framework region sequences. CDR regions are well known to those skilled in the art and have been defined by, for example, Kabat as the regions of most hypervariability within the antibody variable (V) domains (Kabat et al., J. Biol. Chem. 252:6609-6616 (1977); Kabat, Adv. Prot. Chem. 32:1-75 (1978)). CDR region sequences also have been defined structurally by Chothia as those residues that are not part of the conserved β-sheet framework, and thus are able to adapt different conformations (Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)). Both terminologies are well recognized in the art. The positions of CDRs within a canonical antibody variable domain have been determined by comparison of numerous structures (Al-Lazikani et al., J. Mol. Biol. 273:927-948 (1997); Morea et al., Methods 20:267-279 (2000)). Because the number of residues within a hypervariable region varies in different antibodies, additional residues relative to the canonical positions are conventionally numbered with a, b, c and so forth next to the residue number in the canonical variable domain numbering scheme (Al-Lazikani et al., *supra* (1997)). Such nomenclature is similarly well known to those skilled in the art.

[0044] For example, CDRs defined according to either the Kabat (hypervariable), Chothia (structural), or MacCallum (J. Mol. Biol. 262:732-745 (1996)) designations, as set forth in the Table 1 below:

Table 1: CDR Definitions

	Kabat [1]	Chothia [2]	MacCallum [3]	Loop Location
V_H CDR1	**31-35**	**26-32**	**30-35**	linking B and C strands
V_H CDR2	**50-65**	**53-55**	**47-58**	linking C' and C'' strands

	Kabat [1]	Chothia [2]	MacCallum [3]	Loop Location
V_H CDR3	**95-102**	**96-101**	**93-101**	linking F and G strands
V_L CDR1	**24-34**	**26-32**	**30-36**	linking B and C strands
V_L CDR2	**50-56**	**50-52**	**46-55**	linking C' and C'' strands
V_L CDR3	**89-97**	**91-96**	**89-96**	linking F and G strands
[1] Residue numbering follows the nomenclature of Kabat et al., *supra* [2] Residue numbering follows the nomenclature of Chothia et al., *supra*				

[0045] The term "cancer" refers to any physiological condition in mammals characterized by unregulated cell growth. Cancers described herein include solid tumors and hematological (blood) cancers. A "hematological cancer" refers to any blood home cancer and includes, for example, myelomas, lymphomas and leukemias. A "solid tumor" or "tumor" refers to a lesion and neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues resulting in abnormal tissue growth. "Neoplastic," as used herein, refers to any form of dysregulated or unregulated cell growth, whether malignant or benign, resulting in abnormal tissue growth.

[0046] The terms "treating" or "treatment" refer to any indicia of success or amelioration of the progression, severity, and/or duration of a disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; or improving a patient's physical or mental well-being.

[0047] The term "enhance" refers to an increase or improvement in the function or activity of a protein or cell after administration or contacting with a combination described herein compared to the protein or cell prior to such administration or contact.

[0048] The term "administering" refers to the act of delivering a combination or composition described herein into a subject by such routes as oral, mucosal, topical, suppository, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration. Parenteral administration includes intravenous, intramuscular, intra-arterial, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial administration. Administration generally occurs after the onset of the disease, disorder, or condition, or its symptoms but, in certain instances, can occur before the onset of the disease, disorder, or condition, or its symptoms (*e.g.,* administration for patients prone to such a disease, disorder, or condition).

[0049] The term "coadministration" refers to administration of two or more agents (*e.g.,* a combination described herein and another active agent such as an anti-cancer agent

described herein). The timing of coadministration depends in part of the combination and compositions administered and can include administration at the same time, just prior to, or just after the administration of one or more additional therapies, for example cancer therapies such as chemotherapy, hormonal therapy, radiotherapy, or immunotherapy. The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (*e.g.,* to reduce metabolic degradation). The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating a disease associated with cells expressing a particular kinase as described herein, or with adjunctive agents that cannot be effective alone, but can contribute to the efficacy of the active agent.

[0050] The term "anti-cancer agent" is used in accordance with its plain ordinary meaning and refers to a composition having anti-neoplastic properties or the ability to inhibit the growth or proliferation of cells. In embodiments, an anti-cancer agent is a chemotherapeutic. In embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer.

[0051] The term "chemotherapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having anti-neoplastic properties or the ability to inhibit the growth or proliferation of cells. "Chemotherapy" refers to a therapy or regimen that includes administration of a chemotherapeutic or anti-cancer agent described herein.

[0052] The terms "halo," "halogen," and "halide" refer to -F, -Cl, -Br, and -I.

[0053] The term "alkyl" by itself or as part of another substituent refers to, unless otherwise stated, a straight (*i.e.,* unbranched) or branched carbon chain (or carbon), or combination thereof, having no unsaturation and can include mono-, di- and multivalent radicals. An alkyl as defined herein can be designated by its number of carbon atoms (*i.e.,* C_1-C_{10} means one to ten carbons). Alkyls herein can include C_1-C_{10}, C_1-C_8, C_1-C_6, and C_1-C_4 lengths. A "perfluoroalkyl" refers to an alkyl in which all of the hydrogens in the alkyl chain are replaced with fluoro.

[0054] The term "alkoxy" refers to an alkyl group (e.g., C_1-C_{10}, C_1-C_8, C_1-C_6, and C_1-C_4 alkyl) attached to the remainder of the molecule via an oxygen linker (-O-). Exemplary alkoxy groups include groups having the formula -OR, where R is branched or linear alkyl. A "perfluoroalkoxyl" moiety refers to an alkoxy in which all of the hydrogens in the alkyl chain are replaced with fluoro.

[0055] The term "aminoalkyl" refers to an alkyl group (e.g., C_1-C_{10}, C_1-C_8, C_1-C_6, and C_1-C_4

alkyl) in which one or more hydrogen atoms are replaced with an amino group.

[0056] The term "alkylamino" refers to an alkyl group (e.g., C_1-C_{10}, C_1-C_8, C_1-C_6, and C_1-C_4 alkyl) attached to the remainder of the molecule via a nitrogen linker (-NR-). Exemplary alkylamino groups include N-methylamino, N-ethylamino, N-isopropylamino, and the like.

[0057] The term "acyl" refers to a moiety having the formula, -C(O)R, where R is a substituted or unsubstituted alkyl, haloalkyl, or amino group. The term "acylamino" refers to an acyl moiety having an attached amino group and includes, for example, such moieties as acetylamino, propionylamino, butyrylamino, isobuytrylamino, and others.

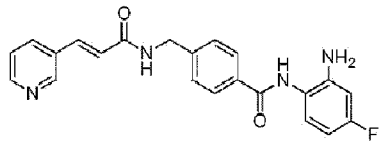
[0058] The term "alkythio" refers to an alkyl group (e.g., C_1-C_{10}, C_1-C_8, C_1-C_6, and C_1-C_4 alkyl) attached to the remainder of the molecule via a sulfur linker (-S-). Exemplary alkylthio groups include methylthio, ethylthio, propylthio, and others.

[0059] The term "heterocycle" or "heterocyclyl" refers to a stable 3- to 15-membered monocyclic group that is saturated or unsaturated and contains one or more heteroatoms (*e.g.,* N, O, or S). Exemplary heterocycles include, but are not limited to morpholinyl, piperidinyl, piperazinyl, pyranyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, oxetanyl, azetidinyl, and others.

Compositions

[0060] Provided herein is the compound for use in methods of treatment as defined in the claims.

[0061] The compound of formula I has the formula Ia as set forth below:



I

the compound of formula I as described herein include pharmaceutically acceptable salts, pharmaceutically acceptable stereoisomers, prodrugs, enantiomers, diastereomers, hydrates, co-crystals, and polymorphs thereof.

[0062] In certain instances, the compound of formula I is present at an amount of greater than about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 85 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg. The compound of formula I can be present at an amount greater than about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, or 10 mg. In certain instances the compound of formula I is present in an amount greater than about 5 mg or about 10 mg. The compound of

formula I can be present at an amount greater than about: 1 mg to about 10 mg, 1 mg to about 25 mg, 1 mg to about 50 mg, 5 mg to about 10 mg, 5 mg to about 25 mg, 5 mg to about 50 mg, 10 mg to about 25 mg, 10 mg to about 50 mg, 50 mg to about 100 mg, or 100 mg to about 200 mg.

[0063] The compound can be present in an amount of at least about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 85 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg. The compound of formula I can be present at an amount of at least about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, or 10 mg. In certain instances the compound of formula I is present in an amount of at least about 5 mg or about 10 mg. The compound of formula I can be present at an amount of at least about: 1 mg to about 10 mg, 1 mg to about 25 mg, 1 mg to about 50 mg, 5 mg to about 10 mg, 5 mg to about 25 mg, 5 mg to about 50 mg, 10 mg to about 25 mg, 10 mg to about 50 mg, 50 mg to about 100 mg, or 100 mg to about 200 mg.

[0064] The compound can be present in an amount of about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 85 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg. The compound of formula I can be present at an amount of about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, or 10 mg. In certain instances the compound of formula I is present in an amount of about 5 mg or about 10 mg. The compound of formula I can be present at an amount of about: 1 mg to about 10 mg, 1 mg to about 25 mg, 1 mg to about 50 mg, 5 mg to about 10 mg, 5 mg to about 25 mg, 5 mg to about 50 mg, 10 mg to about 25 mg, 10 mg to about 50 mg, 50 mg to about 100 mg, or 100 mg to about 200 mg.

[0065] The compound of formula I can be present relative to the weight of the patient (i.e., mg/kg). In some instances, the compound of formula I is present in an amount equivalent to about: 0.0001 mg/kg to about 200 mg/kg, 0.001 mg/kg to about 200 mg/kg, 0.01 mg/kg to about 200 mg/kg, 0.01 mg/kg to about 150 mg/kg, 0.01 mg/kg to about 100 mg/kg, 0.01 mg/kg to about 50 mg/kg, 0.01 mg/kg to about 25 mg/kg, 0.01 mg/kg to about 10 mg/kg, or 0.01 mg/kg to about 5 mg/kg, 0.05 mg/kg to about 200 mg/kg, 0.05 mg/kg to about 150 mg/kg, 0.05 mg/kg to about 100 mg/kg, 0.05 mg/kg to about 50 mg/kg, 0.05 mg/kg to about 25 mg/kg, 0.05 mg/kg to about 10 mg/kg, or 0.05 mg/kg to about 5 mg/kg, 0.5 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 150 mg/kg, 0.5 mg/kg to about 100 mg/kg, 0.5 mg/kg to about 50 mg/kg, 0.5 mg/kg to about 25 mg/kg, 0.5 mg/kg to about 10 mg/kg, or 0.5 mg/kg to about 5 mg/kg. In other instances the compound of formula I is present in an amount equivalent to about: 1 mg/kg to about 200 mg/kg, 1 mg/kg to about 150 mg/kg, 1 mg/kg to about 100 mg/kg, 1 mg/kg to about 50 mg/kg, 1 mg/kg to about 25 mg/kg, 1 mg/kg to about 10 mg/kg, or 1 mg/kg to about 5 mg/kg.

[0066] PD-1 inhibitors useful herein include any molecule capable of inhibiting, blocking, abrogating or interfering with the activity or expression of PD-1. In particular, a PD-1 inhibitor can be a small molecule compound, a nucleic acid, a polypeptide, an antibody, a peptibody, a diabody, a minibody, a single-chain variable fragment (ScFv), or a functional fragment or

variant thereof. In one instance the PD-1 inhibitor is a small molecule compound *(e.g.,* a compound having a molecule weight of less than about 1000 Da.) In other instances, useful PD-1 inhibitors include nucleic acids and polypeptides. The PD-1 inhibitor can be a polypeptide (e.g., macrocyclic polypeptide) such as those exemplified in U.S. Patent Application Publication No.: 2014/0294898. In one example, the PD-1 inhibitor is an antibody, peptibody, diabody, minibody, ScFv, or a functional fragment thereof. In one example, the PD-1 inhibitor is AMP-224 (GSK).

[0067] AMP-224 is a recombinant fusion protein comprising an extracellular domain of the PD-1 ligand programmed cell death ligand 2 (PD-L2) and an Fc region of human IgG. Certain cancers can evade and suppress the immune system, in part, and without being bound by any particular theory by interactions between PD-1 and B7-H1. AMP-224 appears to block this interaction and therefore appears to overcome immune suppression.

[0068] In another example, the PD-1 inhibitor is a PD-1 antibody. The PD-1 antibody can be a monoclonal or polyclonal antibody. In certain embodiments, the PD-1 antibody is a monoclonal antibody.

[0069] PD-1 antibodies include all known types of antibodies and functional fragments thereof, including but not limited to, those exemplified herein such as, for example, human antibodies, mouse antibodies, chimeric antibodies, humanized antibodies, or chimeric humanized antibodies.

[0070] In one embodiment, the PD-1 antibody is a human antibody. In another embodiment, the PD-1 antibody is a mouse antibody. In still another embodiment, the PD-1 antibody is a chimeric antibody. In yet another embodiment, the PD-1 antibody is a humanized antibody. In yet another embodiment, the PD-1 antibody is a chimeric humanized antibody. The PD-1 antibody can be a human antibody or humanized antibody. The PD-1 antibody can be nivolumab, pembrolizumab, pidilizumab, REGN2810, PDR 001, or MEDI0680. In some embodiments, two or more PD-1 antibodies are administered in combination with the compound of formula I as described herein.

[0071] The PD-1 antibody can be nivolumab. Nivolumab (marketed as OPDIVO) is a fully human monoclonal antibody directed against PD-1 with immunopotentiation activity. Without being bound by any particular theory, nivolumab binds to and blocks the activation of PD-1 by its cognate ligands, resulting in the activation of T-cells and cell-mediated immune responses against tumor cells or pathogens.

[0072] The PD-1 antibody can be pembrolizumab. Pembrolizumab (MK-3475, marketed as KEYTRUDA) is a humanized monoclonal IgG4 antibody directed against human cell surface receptor PD-1 with potential immuno-potentiating activity. Without being bound by any particular theory, pembrolizumab binds to PD-1, an inhibitory signaling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its cognate ligands. The blocking of binding and activity results in the activation of T-cell-mediated immune

responses against tumor cells.

[0073] The PD-1 antibody can be pidilizumab. Pidilizumab (CT-011) is a humanized monoclonal antibody directed against human PD-1 with immunomodulating and antitumor activities. Without being bound by any particular theory, pidilizumab blocks interaction between the receptor PD-1 with its ligands, resulting in the attenuation of apoptotic processes in lymphocytes, primarily effector/memory T cells, and the augmentation of the anti-tumor activities of NK cells.

[0074] The PD-1 antibody can be REGN2810. REGN2810 is a human monoclonal antibody directed against PD-1, with potential immune checkpoint inhibitory and anti-neoplastic activity. Without being bound by any particular theory REGN2810 binds to PD-1, inhibits binding to its cognate ligand, and prevents the activation of its downstream signaling pathways. This can restore immune function through the activation of cytotoxic T-cells.

[0075] The PD-1 antibody can be PDR 001. PDR 001 is a fully humanized monoclonal antibody directed against PD-1, with immune checkpoint inhibitory and anti-neoplastic activities. Without being bound by any particular theory, PDR 001 binds to PD-1 expressed on activated T-cells and blocks the interaction with its cognate ligands. The inhibition of ligand binding prevents PD-1-mediated signaling and results in both T-cell activation and the induction of T-cell-mediated immune responses against tumor cells.

[0076] The PD-1 antibody can be MEDI0680. MEDI0680 (AMP-514) is a monoclonal antibody directed against the PD-1, with potential immunomodulating and anti-neoplastic activity. Without being bound by any particular theory, MEDI0680 appears to inhibit the activation of PD-1 and its downstream signaling pathways. This inhibition can restore immune function through the activation both of T-cells and cell-mediated immune responses against PD-1 overexpressing tumor cells.

[0077] A PD-1 antibody can be of any antibody isotype. The term isotype refers to the antibody class that is encoded by heavy chain constant region genes. The heavy chains of a given antibody or functional fragment determine the class of that antibody or functional fragment: IgM, IgG, IgA, IgD or IgE. Each class can have either K or Z light chains. The term subclass refers to the minor differences in amino acid sequences of the heavy chains that differentiate the subclasses. In humans there are two subclasses of IgA (subclasses IgA1 and IgA2) and there are four subclasses of IgG (subclasses IgG1, IgG2, IgG3 and IgG4). Such classes and subclasses are well known to those skilled in art.

[0078] Useful PD-1 antibodies bind to PD-1 with sufficient strength to inhibit activity of PD-1. Bind as used herein refer to an interaction between molecules to form a complex. Interactions can be, for example, non-covalent interactions including hydrogen bonds, ionic bonds, hydrophobic interactions, and/or van der Waals interactions. A complex can also include the binding of two or more molecules held together by covalent or non-covalent bonds, interactions or forces. Binding of an antibody or functional fragment thereof can be detected using, for

example, an enzyme-linked immunosorbant assay or any one of a number of methods that are well known to those skilled in the art.

[0079] The strength of the total non-covalent interactions between a single antigen-binding site on a PD-1 antibody or functional fragment and a single epitope of a target molecule, such as PD-1, is the affinity of the antibody or functional fragment for that epitope. The ratio of association (k_1) to dissociation (k_{-1}) of an antibody or functional fragment thereof to a monovalent antigen (k_1/k_{-1}) is the association constant *K,* which is a measure of affinity. The value of *K* varies for different complexes of antibody or functional fragment and antigen and depends on both k_1 and k_{-1}. The association constant *K* for an antibody or functional fragment of the invention can be determined using any method provided herein or any other method well known to those skilled in the art.

[0080] The affinity at one binding site does not always reflect the true strength of the interaction between an antibody or functional fragment and an antigen. When complex antigens containing multiple, repeating antigenic determinants come in contact with antibodies containing multiple binding sites, the interaction of such an antibody or functional fragment with antigen at one site will increase the probability of a reaction at a second site. The strength of such multiple interactions between a multivalent antibody and antigen is called the avidity. The avidity of an antibody or functional fragment can be a better measure of its binding capacity than is the affinity of its individual binding sites. For example, high avidity can compensate for low affinity as is sometimes found for pentameric IgM antibodies, which can have a lower affinity than IgG, but the high avidity of IgM, resulting from its multivalence, enables it to bind antigen effectively.

[0081] The specificity of a PD-1 antibody or functional fragment thereof refers to the ability of an individual antibody or functional fragment thereof to react with only one antigen (e.g., a single epitope of PD-1). An antibody or functional fragment can be considered specific when it can distinguish differences in the primary, secondary or tertiary structure of an antigen or isomeric forms of an antigen.

[0082] The PD-1 antibody can be present in an amount as a measure with regards to the weight of the patient in need thereof. For example, the PD-1 antibody can be present in an amount of about: 0.1 mg/kg to about 30 mg/kg, 0.1 mg/kg to about 25 mg/kg, 0.1 mg/kg to about 20 mg/kg, 0.1 mg/kg to about 15 mg/kg, 0.1 mg/kg to about 10 mg/kg, 0.1 mg/kg to about 7.5 mg/kg, 0.1 mg/kg to about 5 mg/kg, 0.1 mg/kg to about 2.5 mg/kg, or about 0.1 mg/kg to about 1 mg/kg. The PD-1 antibody can be present in an amount of about: 0.5 mg/kg to about 30 mg/kg, 0.5 mg/kg to about 25 mg/kg, 0.5 mg/kg to about 20 mg/kg, 0.5 mg/kg to about 15 mg/kg, 0.5 mg/kg to about 10 mg/kg, 0.5 mg/kg to about 7.5 mg/kg, 0.5 mg/kg to about 5 mg/kg, 0.5 mg/kg to about 2.5 mg/kg, or about 0.5 mg/kg to about 1 mg/kg. The PD-1 antibody can be present in an amount of about 0.5 mg/kg to about 5 mg/kg or about 0.1 mg/kg to about 10 mg/kg. The PD-1 antibody can be present in an amount of about 0.5 mg/kg to about 15 mg/kg or about 0.1 mg/kg to about 20 mg/kg.

[0083] In still other embodiments, the PD-1 antibody can be present at an amount of about: 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg or 30 mg/kg. The PD-1 antibody can be present at an amount of about: 1 mg/kg, 2 mg/kg, 3 mg/kg, or 5 mg/kg.

[0084] The PD-1 antibody can be present at an amount of about: 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 75 mg, 80 mg, 90 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, or 2000 mg. The PD-1 antibody can be present in the combination at an amount of about: 1 mg to about 10 mg, 10 mg to about 20 mg, 25 mg to about 50 mg, 30 mg to about 60 mg, 40 mg to about 50 mg, 50 mg to about 100 mg, 75 mg to about 150 mg, 100 mg to about 200 mg, 200 mg to about 500 mg, 500 mg to about 1000 mg, 1000 mg to about 1200 mg, 1000 mg to about 1500 mg, 1200 mg to about 1500 mg, or 1500 mg to about 2000 mg.

[0085] The PD-1 antibody can be present in an amount of about: 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 150 mg/mL, 200 mg/mL, 250 mg/mL, 300 mg/mL, 400 mg/mL, or 500 mg/mL. In one embodiment, the PD-1 antibody is present in the combination in an amount of about: 1 mg/mL to about 10 mg/mL, 5 mg/mL to about 10 mg/mL, 5 mg/mL to about 15 mg/mL, 10 mg/mL to about 25 mg/mL; 20 mg/mL to about 30 mg/mL; 25 mg/mL to about 50 mg/mL, or 50 mg/mL to about 100 mg/mL.

[0086] In certain instances the therapeutically effective amount of a PD-1 antibody is determined as an amount provided in a package insert provided with the PD-1 antibody. The term package insert refers to instructions customarily included in commercial packages of medicaments approved by the FDA or a similar regulatory agency of a country other than the USA, which contains information about, for example, the usage, dosage, administration, contraindications, and/or warnings concerning the use of such medicaments.

[0087] The compound of formula I as described herein can be provided in amounts that are synergistic with the amount of the PD-1 inhibitor. The term synergistic refers to a combination described herein (*e.g.,* the compound of formula I and a PD-1 inhibitor - including coadministration with another active agent such as an anti-cancer agent described herein) or a combination of regimens such as those described herein that is more effective than the additive effects of each individual therapy or regimen.

[0088] A synergistic effect described herein can permit the use of lower dosages of one or more of the components (*i.e.,* the compound of formula I or a PD-1 inhibitor). A synergistic effect can permit less frequent administration of at least one of the administered therapies (*i. e.,* the compound of formula I or a PD-1 inhibitor) to a subject with a disease, disorder, or condition described herein. Such lower dosages and reduced frequency of administration can reduce the toxicity associated with the administration of at least one of the therapies (*e.g.,* the

compound of formula I or a PD-1 inhibitor) to a subject without reducing the efficacy of the treatment. A synergistic effect as described herein avoid or reduce adverse or unwanted side effects associated with the use of any therapy.

Pharmaceutical Compositions

[0089] The compound of formula I described herein can be provided as a pharmaceutical composition suitable for administration via any route to a patient described herein including but not limited to: oral, mucosal (*e.g.,* nasal, inhalation, pulmonary, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.,* subcutaneous, intravenous, bolus injection, intramuscular, or intra-arterial), topical (*e.g.,* eye drops or other ophthalmic preparations), transdermal or transcutaneous administration to a patient.

[0090] Exemplary of dosage forms include: tablets; caplets; capsules (*e.g.*, gelatin capsules); cachets; lozenges; suppositories; powders; gels; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (*e.g.,* crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

[0091] Pharmaceutical compositions and dosage forms described herein typically include one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors such as, for example, the intended route of administration to the patient. Pharmaceutical compositions described herein can include other agents such as stabilizers, lubricants, buffers, and disintegrants that can reduce the rate by which an active ingredient can decompose in a particular formulation.

[0092] Pharmaceutical compositions described herein can in certain instances include additional active agents other than those described herein (*e.g.,* an anti-cancer agent such as those described herein) in an amount provided herein.

[0093] In one embodiment, the compound of formula I is provided in an oral dosage form such as a tablet or capsule. In another embodiment, the compound of formula I is supplied as a powder (*e.g.,* lyophilized powder) that can be resuspended in a liquid suitable for parenteral administration.

[0094] PD-1 inhibitors described herein can be provided in forms convenient to or facilitate their administration to a patient. For example, where the PD-1 inhibitor is a PD-1 antibody as described herein, the PD-1 inhibitor can be formulated as a ready to use solution for parenteral administration. In other examples, the PD-1 inhibitor, including for example a PD-1 antibody, can be formulated as a powder (*e.g.,* lyophilized powder) that can be resuspended in a liquid suitable for parenteral administration. In one embodiment, the combination includes a PD-1 antibody formulated for intravenous administration. In still another embodiment the combination includes the compound of formula I formulated as an oral dosage form *(e.g.,* a

tablet or capsule) and a PD-1 inhibitor formulated for intravenous administration.

[0095] Combinations described herein can be provided as controlled release pharmaceutical products, which have a goal of improving drug therapy over that achieved by their non-controlled counterparts. Controlled release formulations can extend activity of the drug, reduce dosage frequency, and increase subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

Kits

[0096] The combinations and pharmaceutical compositions described herein can be provided as part of a kit. Such kits can, for example, improve patient compliance or improve the accuracy or ease of preparation for administering the combination. The kit includes the compound of formula I where the compound is supplied in a formulation as described herein. The kit also includes a PD-1 inhibitor as described herein. The kit can include AMP-224. In some embodiments, the kit includes a PD-1 antibody, as described herein, such as for example, nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. The kit can include a package insert or other information (*e.g.,* prescribing information) useful for administration of the combination to a patient in need thereof, such as a cancer patient described herein.

[0097] Kits can include the combinations described herein (*i.e.,* the compound of formula I and a PD-1 antibody) having the same or different formulation. Each component of a combination described herein in a kit can be supplied in a separate, individual container. Alternatively or additionally, components of the combinations described herein can be supplied in a single container. In such instances, the container can be a container that is ready for administration to a patient in need thereof, such as for example, an IV bag, ampoule, or a syringe. In one embodiment, the compound of formula I in the kit is formulated for oral administration (*e.g.,* a tablet, capsule, or sachet). The PD-1 inhibitor can be supplied as, for example, a powder (*e.g.,* lyophilized powder) or as a solution for parenteral administration. In certain instances the PD-1 inhibitor is a PD-1 antibody as described herein formulated for parenteral administration by, for example, intravenous administration.

[0098] The contents of kits described herein can be provided in sterile form. The kit and its contents can be provided in a form that is ready for administration to the subject in need. In such instances, the components of the combination of the kit are supplied as a formulation and optionally in an administration device such that administration requires little to no further action by the user. Where kits include administration devices, such devices include devices known and understood by those skilled in the art for routes of administration described herein, such as but not limited to, syringes, pumps, bags, cups, inhalers, droppers, patches, creams, or injectors.

Methods

[0099] The compound of formula I is useful for treating diseases, disorders, or alleviating or eliminating the symptoms of diseases and disorders as defined in the claims. It is to be understood that the methods described herein pertain to administration of combinations and pharmaceutical compositions described herein, and such combinations and pharmaceutical compositions can be provided in the form of a kit as described herein. Provided herein is the compound of formula I for use in methods of treating cancer by administering a therapeutically effective amount of a combination described herein to a patient in need thereof as defined in the claims.

[0100] The PD-1 inhibitors for use in the methods described herein are those PD-1 inhibitors described herein. For example, the PD-1 inhibitor can be a small molecule compound, a nucleic acid, a polypeptide, an antibody, a peptibody, a diabody, a minibody, a single-chain variable fragment (ScFv), or functional fragment or variant thereof. In one example, the PD-1 inhibitor is AMP-224. In other examples, the PD-1 inhibitor can be a PD-1 antibody as set forth above. In one instance, the PD-1 antibody for use in the methods described herein is nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 orMEDI0680.

[0101] It should be understood that the compound of formula I and the PD-1 inhibitor constituting the combination for use in such methods includes each therapy in amounts as described herein and are administered as described herein. For example, the compound of formula I can be present in a combination administered to patient in need thereof at an amount of about 5 mg to about 50 mg or about 5 mg to about 100 mg. As another example, the PD-1 inhibitor can be a PD-1 antibody present in an amount of about 0.1 mg/kg to about 10 mg/kg or about 0.1 mg/kg to about 20 mg/kg. These amounts are merely exemplary and do not limit in any way the amount of each therapy that can be present in the combination as described herein.

[0102] It is also understood that the combination for use in the methods described herein can be provided as a kit as set forth above. Such kits include each component of the combination as described herein and optionally additional kit components including, for example, containers and administration devices such as those described above.

[0103] The cancer can be a solid tumor.

[0104] The compound of formula I for use in methods of treating colorectal cancer can be administered at a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680 are also provided herein. In another aspect the method includes treating

colorectal cancer by administering AMP-224 in combination with the compound of formula I described herein. In some embodiments the colorectal cancer is a Stage I cancer. In another embodiment, the colorectal cancer is a Stage IIA, Stage IIB, or Stage IIC cancer. In still another embodiment, the colorectal cancer is a Stage IIIA, Stage IIIB, or Stage IIIC cancer. In yet another embodiment, the colorectal cancer is a Stage IVA or Stage IVB cancer. In certain instances the colorectal cancer is further characterized by the grade of the cancer. The colorectal cancer can be a Grade 1, Grade 2, Grade 3, or Grade 4 cancer in any of the stages provided herein. In one aspect the method is a method of treating Stage I colorectal cancer by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In another aspect the method includes treating Stage I colorectal cancer by administering AMP-224 in combination with the compound of formula I described herein. In another aspect the method is a method of treating Stage II (*e.g.,* Stage IIA, IIB, or IIC) colorectal cancer by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In another aspect the method includes treating Stage II (*e.g.,* Stage IIA, IIB, or IIC) colorectal cancer by administering AMP-224 in combination with the compound of formula I described herein. In still another aspect the method is a method of treating Stage III (*e.g.,* Stage IIIA, IIIB, or IIIC) colorectal cancer by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In another aspect the method includes treating Stage III (*e.g.,* Stage IIIA, IIIB, or IIIC) colorectal cancer by administering AMP-224 in combination with the compound of formula I described herein. In yet another aspect is a method of treating Stage IV (*e.g.,* Stage IVA or IVB) colorectal cancer by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In another aspect the method includes treating Stage IV (*e.g.,* Stage IVA or IVB) colorectal cancer by administering AMP-224 in combination with the compound of formula I described herein.

[0105] The cancer patient can have a cancer that is refractory.

[0106] However, cancer morbidity and mortality is often associated with ineffective therapy or a cancer gaining resistant to or becoming refractory to one or more cancer therapies. The combinations described herein can, therefore, be administered to patients in need thereof as a second, third, fourth, fifth, sixth, or more line of treatment. The combinations described herein can be administered to a cancer patient who has been treated with at least one anti-cancer therapy or anti-cancer agent. In certain instances the patient has received at least one anti-cancer therapy including, for example, chemotherapy, radiotherapy, surgery, targeted therapy, immunotherapy, or a combination thereof. The patient can have a cancer that is

resistant/refractory to treatment with at least one anti-cancer agent.

[0107] The methods of treating cancers herein refer to treating subjects who have been treated with a PD-L1 checkpoint inhibitor and have experienced no response to treatment, or a partial response, or stable disease, but then develop resistance to treatment with progression of disease or who have experienced a complete response to treatment, but then develop resistance to treatment with progression of disease (as defined by RECIST or other criteria). Resistance is defined as disease progression during treatment or a lack of response to treatment. Such PD-L1 inhibitor antibody treatment failures can be treated with PD-1 in combination with an HDAC inhibitor, such as, without limitation, HBI-8000 or an HDAC inhibitor that inhibits cancer-associated Class I HDAC selected from one or more of HDAC1, HDAC2, or HDAC3. In some instances the HDAC inhibitor also inhibits Class IIb HDAC10. HBI-8000 is reported to inhibit HDAC 1, 2, 3, and 10 at low nanomolar concentrations (see Zhi-Qiang Ning et al., Cancer Chemother Pharmacol (2012) 69:901-909). It also has activity at HDAC 8 and 11. Ning et al. also report that HBI-8000 is more active than Entinostat at HDAC 1, 2, 3, 8, 10 and 11. Further HBI-8000 has a favorable pharmacokinetic profile and safety profile that allows for continuous dosing-oral administration pK ($t_{1/2}$ about 17 hours).

Response Criteria

RECIST:

[0108] RECIST is a set of established criteria or standards, internationally recognized for evaluating patient response, stability and progression in clinical trials and in the clinical practice. Originally published in 2000, and revised in 2009 (Eisenhauer EA, et al.; New response criteria in solid tumors: revised RECIST guideline (version 1.1); Eur J Cancer 2009; 45:228-47), as a joint effort of the European Organization for Research and Treatment of Cancer, the National Cancer Institute of the United States and the National Cancer Institute of Canada Clinical Trials Group, RECIST has traditionally been utilized in the evaluation of response to chemotherapy.

Evaluation of target lesions:

[0109] Complete Response (CR): Disappearance of all target lesions; Partial Response (PR): At least a 30% decrease in the sum of the LD (longest diameter) of target lesions, taking as reference the baseline sum LD; Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started; Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Evaluation of non-target lesions

[0110] Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level; Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits; Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Other Response Criteria

[0111] Other response criteria include the Immune-Related Response Criteria or iRECIST, as defined by Wolchok et al., in 2009 (Wolchok JD, et al.; Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res 2009; 15(23):7412-20) and the revised International Working Group Response Criteria (Cheson BD et al,. Revised response criteria for malignant lymphoma. J. Clin. Oncol. 2007; 25:579-586).

[0112] The methods of treating cancer include methods for inhibiting cell growth by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 inhibitor described herein. In one example, the PD-1 inhibitor is AMP-224. In another example, is a method for inhibiting cell growth by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 orMEDI0680.

[0113] In one example the PD-1 inhibitor is AMP-224. In another example the method inhibits metastasis of a cancer as defined in the claims where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In some embodiments, metastasis is inhibited by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

[0114] In another aspect the method reduces pre-existing tumor metastasis in a cancer patient in need thereof by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 inhibitor described herein. In one example the PD-1 inhibitor is AMP-224. In another example the method of reduces pre-existing tumor metastasis in a cancer patient in need thereof by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In some embodiments, pre-existing tumor metastasis is reduced by at least

about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

[0115] In still another aspect the methods as defined in the claims also provide for methods for reducing tumor burden in an individual by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 inhibitor described herein. In one example the PD-1 inhibitor is AMP-224. In another example the method reduces tumor burden in an individual by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from n nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In some embodiments, tumor burden is reduced by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

[0116] In another aspect the methods as defined in the claims reduce tumor burden in a subject by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 inhibitor described herein. In one example the PD-1 inhibitor is AMP-224. In another example the method reduces tumor burden in an individual by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In some embodiments, tumor burden is reduced by at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

[0117] The methods of treating cancer described herein also provide for methods for increasing or otherwise prolonging time to disease progression of certain stages (including advanced stages of cancer such as Stage III and IV cancer described herein). Time to disease progression can be prolonged in a patient by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 inhibitor described herein. In one example the PD-1 inhibitor is AMP-224. In another example the method increases time to disease progression in a patient by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In some embodiments, the increase is a comparison between the time to disease progression without treatment and with treatment with a combination described herein. In some embodiments, the methods described herein prolong the time to disease progression by at least 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, or more, including values therein.

[0118] The methods of treating cancer described herein also provide for methods for increasing or otherwise prolonging survival (including overall survival) of patients diagnosed with cancer as described herein. Patient survival can be prolonged by administering a

therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 inhibitor described herein. In one example the PD-1 inhibitor is AMP-224. In another example the method of prolonging patient survival by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In some embodiments, the increase is a comparison between the survival without treatment and with treatment with a combination as described herein. In some embodiments, the methods described herein prolong survival by at least 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, or more, including values therein.

[0119] The methods of treating cancer described herein also provide for methods for increasing progression-free survival of patients diagnosed with cancer as described herein. Patient progression-free survival can be prolonged in a patient by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 inhibitor described herein. In one example the PD-1 inhibitor is AMP-224. In another example the method increases progression-free survival of patients diagnosed with cancer by administering a therapeutically effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In some embodiments, the increase is a comparison between the progression-free survival without treatment and with treatment with a combination as described herein. In some embodiments, the methods described herein increase progression-free survival by at least 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 1 year, 2 years, or more, including values therein.

[0120] The methods may reduce the percentage or level of Treg cells in a patient in need thereof. Such methods include administering an effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 inhibitor described herein. In one example the PD-1 inhibitor is AMP-224. In another example the method reduces the percentage or level of Treg cells in a patient in need thereof by administering an effective amount of a combination described herein where the combination includes the compound of formula I and a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680 to the patient, wherein the administration decreases the percentage or level of Treg cells in the patient compared to the level prior to the administration. The reduction of Treg cells can benefit the treatment of a cancer described herein. The level of Treg cells in a human patient can be measured before, during, and after administration of a combination described herein. In some embodiments, it can be useful to compare pre-and post-administration amounts of Treg cells in the patient. A reduction in the amount, level, or number of Treg cells following administration can indicate effectiveness of the combination in, for example, treating a cancer described herein. Treg cell levels can be monitored over the course of a treatment or

regimen described herein with a combination described herein. In such instances, the determination of Treg cells levels at various points during the course of administration can indicate the effectiveness of the regimen.

[0121] The methods may enhance activity of natural killer (NK) cells. The combinations described herein can also be useful for enhancing activity of cytotoxic T-cells. The methods of enhancing include contacting a NK cell or cytotoxic T-cell with a combination described herein where the combination enhances the activity of the NK cell or cytotoxic T-cell relative to its activity prior to the contact. Such combinations useful for enhancing activity of NK cells or cytotoxic T-cells can include AMP-224. In other examples, combinations described herein useful in methods for enhancing activity of NK cells or cytotoxic T-cells include a PD-1 selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680.

[0122] The combinations described herein can also enhance antibody-dependent cell-mediated cytotoxicity in a cancer patient upon administration of a combination as described herein.

[0123] The combinations described herein can include administration of each therapy *(i.e.,* the compound of formula I and a PD-1 inhibitor), where the administration is performed simultaneously or sequentially (in either order). In one embodiment, the compound of formula I and the PD-1 inhibitor are administered simultaneously *(e.g.,* within at least 1 to 5 min of each other). In another embodiment, the compound of formula I and the PD-1 inhibitor are administered sequentially *(e.g.,* within at least 10 min, 15 min, 30 min, 1 h, 2 h, 5 h, 10 h, 12 h, 1 day, 2 days, 5 days, 7 days, 14 days, or 21 days of each other).

[0124] In one example the compound of formula I is administered concurrently with a PD-1 antibody selected from nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR 001, SHR-1210 or MEDI0680. In another example, the compound of formula I can be administered prior to the administration of nivolumab. In another example, the compound of formula I can be administered prior to the administration of pembrolizumab. In another example, the compound of formula I can be administered prior to the administration of pidilizumab. In another example, the compound of formula I can be administered prior to the administration of REGN2810 (also known as SAR-439684). In still another example, the compound of formula I can be administered prior to the administration of PDR 001. In yet another example, the compound of formula I can be administered prior to the administration of MEDI0680. In another example, the compound of formula I can be administered after the administration of nivolumab. In another example, the compound of formula I can be administered after the administration of pembrolizumab, atezolizumab or SHR-1210. In another example, the compound of formula I can be administered after the administration of pidilizumab, atezolizumab or SHR-1210. In another example, the compound of formula I can be administered after the administration of REGN2810 (also known as SAR-439684). In still another example, the compound of formula I can be administered prior after administration of PDR 001. In yet another example, the compound of formula I can be administered after the

administration of MEDI0680.

[0125] In another example the compound of formula I is administered concurrently with AMP-224. In still another example the compound of formula I is administered prior to administration of AMP-224. In yet another example the compound of formula I is administered after administration of AMP-224.

[0126] The compound of formula I can be administered, for example, once a day (QD), twice daily (BID), once a week (QW), twice weekly (BIW), three times a week (TIW), or monthly (QM). For example, the compound of formula I can be administered BID. The compound of formula I can be administered TIW. In certain instances, the compound of formula I is administered 2 to 3 times a week. In another embodiment, the compound of formula I is administered QD. The compound can be administered QD for about: 1 day to about 7 days, 1 day to about 14 days, 1 day to about 21 days, 1 day to about 28 days, or daily until disease progression or unacceptable toxicity. The administration of the compound of formula I can, in part, depend upon the tolerance of the patient where greater tolerance can allow greater or more frequent administration. Alternatively, where a patient shows poor tolerance to the compound of formula I, a less amount of the compound or a less frequent dosing can be performed. The administration of compound can also cease when maximum treatment effect is achieve and then resume when further administration is warranted, albeit with an -alternative schedule and dose. Compounds of formula I can be administered in any regimen as described herein.

[0127] For example, the compound of formula I can be administered at an amount of about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 85 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg, QD. For example, the compound of formula I can be administered at an amount of about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 85 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg, BIW. For example, the compound of formula I can be administered at an amount of about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 85 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg, TIW. For example, the compound of formula I can be administered at an amount of about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 85 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg, QW. For example, the compound of formula I can be administered at an amount of about: 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 85 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg, Q2W. For example, the compound of formula I can be administered at an amount of about 5 mg or about 10 mg, QD. For example, the compound of formula I can be administered at an amount of about 5 mg or about 10 mg, BIW. For example, the compound of formula I can be administered at an amount of about 5 mg or about 10 mg, TIW. For example, the compound of formula I can be administered at an amount of about 5 mg or about 10 mg, QW. For example, the compound of formula I can be administered at an amount of about 5 mg or about 10 mg,

Q2W. Administration of the compound of formula I can be continuous. Administration of the compound of formula I can be intermittent.

[0128] For example, the compound of formula I can be administered at an amount of about: 1 mg to about 10 mg, 1 mg to about 25 mg, 1 mg to about 50 mg, 5 mg to about 10 mg, 5 mg to about 25 mg, 5 mg to about 50 mg, 10 mg to about 25 mg, 10 mg to about 50 mg, 50 mg to about 100 mg, or 100 mg to about 200 mg, QD. For example, the compound of formula I can be administered at an amount of about: 1 mg to about 10 mg, 1 mg to about 25 mg, 1 mg to about 50 mg, 5 mg to about 10 mg, 5 mg to about 25 mg, 5 mg to about 50 mg, 10 mg to about 25 mg, 10 mg to about 50 mg, 50 mg to about 100 mg, or 100 mg to about 200 mg, BIW. For example, the compound of formula I can be administered at an amount of about: 1 mg to about 10 mg, 1 mg to about 25 mg, 1 mg to about 50 mg, 5 mg to about 10 mg, 5 mg to about 25 mg, 5 mg to about 50 mg, 10 mg to about 25 mg, 10 mg to about 50 mg, 50 mg to about 100 mg, or 100 mg to about 200 mg, TIW. For example, the compound of formula I can be administered at an amount of about: 1 mg to about 10 mg, 1 mg to about 25 mg, 1 mg to about 50 mg, 5 mg to about 10 mg, 5 mg to about 25 mg, 5 mg to about 50 mg, 10 mg to about 25 mg, 10 mg to about 50 mg, 50 mg to about 100 mg, or 100 mg to about 200 mg, QW. For example, the compound of formula I can be administered at an amount of about: 1 mg to about 10 mg, 1 mg to about 25 mg, 1 mg to about 50 mg, 5 mg to about 10 mg, 5 mg to about 25 mg, 5 mg to about 50 mg, 10 mg to about 25 mg, 10 mg to about 50 mg, 50 mg to about 100 mg, or 100 mg to about 200 mg, Q2W. Administration of the compound of formula I can be continuous. Administration of the compound of formula I can be intermittent.

[0129] For example, the compound of formula I can be administered at an amount of about: 0.0001 mg/kg to about 200 mg/kg, 0.001 mg/kg to about 200 mg/kg, 0.01 mg/kg to about 200 mg/kg, 0.01 mg/kg to about 150 mg/kg, 0.01 mg/kg to about 100 mg/kg, 0.01 mg/kg to about 50 mg/kg, 0.01 mg/kg to about 25 mg/kg, 0.01 mg/kg to about 10 mg/kg, or 0.01 mg/kg to about 5 mg/kg, 0.05 mg/kg to about 200 mg/kg, 0.05 mg/kg to about 150 mg/kg, 0.05 mg/kg to about 100 mg/kg, 0.05 mg/kg to about 50 mg/kg, 0.05 mg/kg to about 25 mg/kg, 0.05 mg/kg to about 10 mg/kg, or 0.05 mg/kg to about 5 mg/kg, 0.5 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 150 mg/kg, 0.5 mg/kg to about 100 mg/kg, 0.5 mg/kg to about 50 mg/kg, 0.5 mg/kg to about 25 mg/kg, 0.5 mg/kg to about 10 mg/kg, or 0.5 mg/kg to about 5 mg/kg, QD. For example, the compound of formula I can be administered at an amount of about: 0.0001 mg/kg to about 200 mg/kg, 0.001 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 150 mg/kg, 0.5 mg/kg to about 100 mg/kg, 0.5 mg/kg to about 50 mg/kg, 0.5 mg/kg to about 25 mg/kg, 0.5 mg/kg to about 10 mg/kg, or 0.5 mg/kg to about 5 mg/kg, BIW. For example, the compound of formula I can be administered at an amount of about: 0.0001 mg/kg to about 200 mg/kg, 0.001 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 150 mg/kg, 0.5 mg/kg to about 100 mg/kg, 0.5 mg/kg to about 50 mg/kg, 0.5 mg/kg to about 25 mg/kg, 0.5 mg/kg to about 10 mg/kg, or 0.5 mg/kg to about 5 mg/kg, TIW. For example, the compound of formula I can be administered at an amount of about: 0.0001 mg/kg to about 200 mg/kg, 0.001 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 150 mg/kg, 0.5 mg/kg to about 100 mg/kg, 0.5 mg/kg to about 50 mg/kg, 0.5 mg/kg to about 25 mg/kg, 0.5 mg/kg to about 10 mg/kg, or 0.5 mg/kg to about 5

mg/kg, QW. For example, the compound of formula I can be administered at an amount of about: 0.0001 mg/kg to about 200 mg/kg, 0.001 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 200 mg/kg, 0.5 mg/kg to about 150 mg/kg, 0.5 mg/kg to about 100 mg/kg, 0.5 mg/kg to about 50 mg/kg, 0.5 mg/kg to about 25 mg/kg, 0.5 mg/kg to about 10 mg/kg, or 0.5 mg/kg to about 5 mg/kg, Q2W. Administration of the compound of formula I can be continuous. Administration of the compound of formula I can be intermittent.

[0130] For example, the compound of formula I can be administered at an amount of about: 1 mg/kg to about 200 mg/kg, 1 mg/kg to about 150 mg/kg, 1 mg/kg to about 100 mg/kg, 1 mg/kg to about 50 mg/kg, 1 mg/kg to about 25 mg/kg, 1 mg/kg to about 10 mg/kg, or 1 mg/kg to about 5 mg/kg, QD. For example, the compound of formula I can be administered at an amount of about: 1 mg/kg to about 200 mg/kg, 1 mg/kg to about 150 mg/kg, 1 mg/kg to about 100 mg/kg, 1 mg/kg to about 50 mg/kg, 1 mg/kg to about 25 mg/kg, 1 mg/kg to about 10 mg/kg, or 1 mg/kg to about 5 mg/kg, BIW. For example, the compound of formula I can be administered at an amount of about: 1 mg/kg to about 200 mg/kg, 1 mg/kg to about 150 mg/kg, 1 mg/kg to about 100 mg/kg, 1 mg/kg to about 50 mg/kg, 1 mg/kg to about 25 mg/kg, 1 mg/kg to about 10 mg/kg, or 1 mg/kg to about 5 mg/kg, TIW. For example, the compound of formula I can be administered at an amount of about: 1 mg/kg to about 200 mg/kg, 1 mg/kg to about 150 mg/kg, 1 mg/kg to about 100 mg/kg, 1 mg/kg to about 50 mg/kg, 1 mg/kg to about 25 mg/kg, 1 mg/kg to about 10 mg/kg, or 1 mg/kg to about 5 mg/kg, QW. For example, the compound of formula I can be administered at an amount of about: 1 mg/kg to about 200 mg/kg, 1 mg/kg to about 150 mg/kg, 1 mg/kg to about 100 mg/kg, 1 mg/kg to about 50 mg/kg, 1 mg/kg to about 25 mg/kg, 1 mg/kg to about 10 mg/kg, or 1 mg/kg to about 5 mg/kg, Q2W. In one example, the compound of formula I can be administered at an amount of about 15 mg/kg to about 75 mg/kg, QD. In another example, the compound of formula I can be administered at an amount of about 20 mg/kg to about 50 mg/kg. In still another example, the compound of formula I can be administered at an amount of about 0.001 mg/kg, 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 40 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, 175 mg/kg, or 200 mg/kg. Administration of the compound of formula I can be continuous. Administration of the compound of formula I can be intermittent.

[0131] As used herein, the term daily is intended to mean that a therapeutic compound of a combination described herein, such as the compound of formula I, is administered once or more than once each day for a period of time. The term continuous is intended to mean that a therapeutic compound of a combination described herein, such as the compound of formula I, is administered daily for an uninterrupted period of at least 10 days to 52 weeks. The term intermittent or intermittently as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of a therapeutic compound of a combination described herein, such as the compound of formula I, includes administration for one to six days per week *(e.g.,* 2 to 3 times per week or QD), administration in cycles *(e.g.,* daily administration for two to eight consecutive weeks, then a rest period with no administration at least one day), or, for example, administration on alternate days.

[0132] Where the PD-1 inhibitor is a PD-1 antibody, it can be administered according to established regimens such as those provided in a package insert. The PD-1 antibody can be administered in an amount described herein and can be administered QW, once every 2 weeks (Q2W), or once every 3 weeks (Q3W). In one embodiment, the PD-1 antibody is administered once every two or three weeks. In another embodiment, the PD-1 antibody is administered Q2W. In yet another embodiment, the PD-1 antibody is administered Q3W. In still another embodiment, the PD-1 antibody is administered BIW for at least 3 weeks.

[0133] For example, nivolumab can be administered at an amount of about 0.1 to about 10 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg), QW. For example, nivolumab can be administered at an amount of about 0.1 to about 10 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg), Q2W. For example, nivolumab can be administered at an amount of about 0.1 to about 10 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg), Q4W. For example, nivolumab can be administered at an amount of about 0.1 to about 10 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg), B4W (twice every 4 weeks). For example, nivolumab can be administered at an amount of about 0.1 to about 10 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg), Q3W. Administration of nivolumab can be continuous. Administration of nivolumab can be intermittent.

[0134] Nivolumab can be administered as an intravenous infusion over about 10, 20, 30, 40, 50, or 60 or more minutes. Nivolumab can be administered as an intravenous infusion over about 60 minutes once every 1, 2, 3, 4, 5 or more weeks. Nivolumab can be administered as an intravenous infusion over about 60 minutes once every two weeks. Nivolumab can be administered as an intravenous infusion over about 60 minutes once every three weeks. Nivolumab can be administered as an intravenous infusion over about 60 minutes once every four weeks. Nivolumab can be administered as an intravenous infusion according to a package insert. Administration of nivolumab can be continuous. Administration of nivolumab can be intermittent.

[0135] For example, pembrolizumab can be administered at an amount of about 0.5 to about 20 mg/kg (including for example, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg). For example, pembrolizumab can be administered at an amount of about 0.5 to about 20 mg/kg (including for example, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg) QW. For example, pembrolizumab can be administered at an amount of about 0.5 to about 20 mg/kg (including for example, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg) Q2W. For example, pembrolizumab can be administered at an amount of

about 0.5 to about 20 mg/kg (including for example, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg) Q3W. For example, pembrolizumab can be administered at an amount of about 0.5 to about 20 mg/kg (including for example, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg) Q4W. Administration of pembrolizumab can be continuous. Administration of pembrolizumab can be intermittent.

[0136] Pembrolizumab can be administered as an intravenous infusion over about 10, 20, 30, 40, 50, or 60 or more minutes. Pembrolizumab can be administered as an intravenous infusion over about 60 minutes once every 1, 2, 3, 4, 5 or more weeks. Pembrolizumab can be administered as an intravenous infusion over about 60 minutes once every two weeks. Pembrolizumab can be administered as an intravenous infusion over about 60 minutes once every three weeks. Pembrolizumab can be administered as an intravenous infusion over about 60 minutes once every four weeks. Pembrolizumab can be administered according to a provided package insert. Administration of pembrolizumab can be continuous. Administration of pembrolizumab can be intermittent.

[0137] For example, pidilizumab can be administered at an amount of about 0.1 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), QW. For example, pidilizumab can be administered at an amount of about 0.1 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q2W. For example, pidilizumab can be administered at an amount of about 0.1 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q3W. For example, pidilizumab can be administered at an amount of about 0.1 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q4W. Administration of pidilizumab can be continuous. Administration of pidilizumab can be intermittent.

[0138] Pidilizumab can be administered as an intravenous infusion over about 10, 20, 30, 40, 50, or 60 or more minutes. Pidilizumab can be administered as an intravenous infusion over about 60 minutes once every 1, 2, 3, 4, 5 or more weeks. Pidilizumab can be administered as an intravenous infusion over about 60 minutes once every two weeks. Pidilizumab can be administered as an intravenous infusion over about 60 minutes once every three weeks. Pidilizumab can be administered as an intravenous infusion over about 60 minutes once every four weeks. Administration of pidilizumab can be continuous. Administration of pidilizumab can be intermittent.

[0139] For example, AMP-224 can be administered at an amount of about 1 to about 50 mg/kg (including for example 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg,

40 mg/kg, 45 mg/kg, 50 mg/kg), QW. For example, AMP-224 can be administered at an amount of about 1 to about 50 mg/kg (including for example 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg), Q2W. For example, AMP-224 can be administered (for example by subcutaneous administration) at an amount of about 1 to about 50 mg/kg (including for example 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg), Q3W. For example, AMP-224 can be administered (for example by subcutaneous administration) at an amount of about 1 to about 50 mg/kg (including for example 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg), Q4W. Administration of AMP-224 can be continuous. Administration of AMP-224 can be intermittent.

[0140] AMP-224 can be administered as an intravenous infusion over about 10, 20, 30, 40, 50, or 60 or more minutes. AMP-224 can be administered as an intravenous infusion over about 60 minutes once every 1, 2, 3, 4, 5 or more weeks. AMP-224 can be administered as an intravenous infusion over about 60 minutes once every two weeks. AMP-224 can be administered as an intravenous infusion over about 60 minutes twice every three weeks. AMP-224 can be administered as an intravenous infusion over about 60 minutes three times every six weeks. Administration of AMP-224 can be continuous. Administration of AMP-224 can be intermittent.

[0141] For example, REGN2810 (also known as SAR-439684) can be administered at an amount of about 0.1 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q2W. For example, REGN2810 (also known as SAR-439684) can be administered at an amount of about 0.1 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q4W. For example, REGN2810 (also known as SAR-439684) can be administered at an amount of about 0.1 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), B4W. For example, REGN2810 (also known as SAR-439684) can be administered at an amount of about 0.1 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), QW. Administration of REGN2810 (also known as SAR-439684) can be continuous. Administration of REGN2810 can be intermittent.

[0142] REGN2810 (also known as SAR-439684) can be administered as an intravenous infusion over about 10, 20, 30, 40, 50, or 60 or more minutes. REGN2810 (also known as SAR-439684) can be administered as an intravenous infusion over about 60 minutes once every 1, 2, 3, 4, 5 or more weeks. REGN2810 (also known as SAR-439684) can be administered as an intravenous infusion over about 60 minutes once every two weeks. REGN2810 (also known as SAR-439684) can be administered as an intravenous infusion over about 60 minutes twice every three weeks. REGN2810 (also known as SAR-439684) can be

administered as an intravenous infusion over about 60 minutes three times every six weeks. Administration of REGN2810 (also known as SAR-439684) can be continuous. Administration of REGN2810 (also known as SAR-439684) can be intermittent.

[0143] For example, PDR 001 can be administered at an amount of about 0.5 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), QW. For example, PDR 001 can be administered at an amount of about 0.5 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q2W. For example, PDR 001 can be administered at an amount of about 0.5 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q3W. For example, PDR 001 can be administered at an amount of about 0.5 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q4W. Administration of PDR 001 can be continuous. Administration of PDR 001 can be intermittent.

[0144] PDR 001 can be administered as an intravenous infusion over about 10, 20, 30, 40, 50, or 60 or more minutes. PDR 001 can be administered as an intravenous infusion over about 60 minutes once every 1, 2, 3, 4, 5 or more weeks. PDR 001 can be administered as an intravenous infusion over about 60 minutes once every two weeks. PDR 001 can be administered as an intravenous infusion over about 60 minutes twice every three weeks. PDR 001 can be administered as an intravenous infusion over about 60 minutes once every three weeks. Administration of PDR 001 can be continuous. Administration of PDR 001 can be intermittent.

[0145] For example, MEDI0680 can be administered at an amount of about 0.5 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), QW. For example, MEDI0680 can be administered at an amount of about 0.5 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q2W. For example, MEDI0680 can be administered at an amount of about 0.5 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q3W. For example, MEDI0680 can be administered at an amount of about 0.5 to about 30 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg), Q4W. Administration of MEDI0680 can be continuous. Administration of MEDI0680 can be intermittent.

[0146] MEDI0680 can be administered as an intravenous infusion over about 10, 20, 30, 40, 50, or 60 or more minutes. MEDI0680 can be administered as an intravenous infusion over about 60 minutes once every 1, 2, 3, 4, 5 or more weeks. MEDI0680 can be administered as an intravenous infusion over about 60 minutes once every two weeks. MEDI0680 can be administered as an intravenous infusion over about 60 minutes twice every three weeks. MEDI0680 can be administered as an intravenous infusion over about 60 minutes once every three weeks. Administration of MEDI0680 can be continuous. Administration of MEDI0680 can be intermittent.

[0147] For example, SHR-1210 can be administered at an amount of about 0.5 to about 20 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg), QW. For example, SHR-1210 can be administered at an amount of about 0.5 to about 20 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg), Q2W. For example, SHR-1210 can be administered at an amount of about 0.5 to about 20 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg), Q3W. For example, SHR-1210 can be administered at an amount of about 0.5 to about 20 mg/kg (including for example 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg), Q4W. Administration of SHR-1210 can be continuous. Administration of SHR-1210 can be intermittent.

[0148] SHR-1210 can be administered as an intravenous infusion over about 10, 20, 30, 40, 50, or 60 or more minutes. SHR-1210 can be administered as an intravenous infusion over about 60 minutes once every 1, 2, 3, 4, 5 or more weeks. SHR-1210 can be administered as an intravenous infusion over about 60 minutes once every two weeks. SHR-1210 can be administered as an intravenous infusion over about 60 minutes twice every three weeks. SHR-1210 can be administered as an intravenous infusion over about 60 minutes once every three weeks. Administration of SHR-1210 can be continuous. Administration of SHR-1210 can be intermittent.

[0149] The combinations described herein can be administered in a regimen. The regimen can be structured to provide therapeutically effective amounts of the compound of formula I and a PD-1 inhibitor *(e.g.,* a PD-1 antibody) over a predetermined period of time *(e.g.,* an administration time). The regimen can be structured to limit or prevent side-effects or undesired complications of each of the components of the combination described herein. The regimen can be structured in a manner that results in increased effect for both therapies of the combination *(e.g.,* synergy). Regimens useful for treating cancer can include any number of days of administration which can be repeated as necessary. Administration periods can be broken by a rest period that includes no administration of at least one therapy. For example, a regimen can include administration periods that include 2, 3, 5, 7, 10, 15, 21, 28, or more days. These periods can be repeated. For example, a regimen can include a set number of days as

previously described where the regimen is repeated 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or more times.

[0150] Regimens can include a rest period of at least 1, 2, 3, 5, 7, 10, or more days, where at least one therapy is no longer administered to a patient. The rest period can be determined by, for example, monitoring the reaction of the patient to the drug or by measuring the efficacy of the treatment. A rest period can be applicable to a single therapy, such that only one therapy of a combination described herein is discontinued in the rest period but the other therapy(ies) are still administered. Rest periods can be applied to all of the therapies administered to the subject such that the subject receives no therapy for a set period of time during the rest period.

[0151] Regimens described herein for the treatment of cancer using the combinations described herein can be continued until disease progression or unacceptable toxicity.

[0152] Regimens for administration of combinations described herein include, for example administration of the compound of formula I BIW or TIW and administration of a PD-1 inhibitor. For example, the compound of formula I can be administered QD for about 21 days and a PD-1 antibody described herein can be administered Q2W or Q4W). For example, the compound of formula I can be administered BIW or TIW and a PD-1 antibody described herein can be administered Q2W. In another exemplary regimen, the compound of formula I can be administered BIW or TIW and a PD-1 antibody can be administered BIW for 2 or 3 weeks. In still another exemplary regimen, the compound of formula I can be administered BIW or TIW and a PD-1 antibody can be administered Q3W. In still another exemplary regimen, the compound of formula I can be administered BIW and a PD-1 inhibitor described herein can be administered QW, Q2W, or Q3W. In certain instances, such regimens include administration of PD-1 antibody administered QW, Q2W, or Q3W. In yet another exemplary regimen, the compound of formula I can be administered TIW and a PD-1 inhibitor described herein can be administered QW, Q2W, or Q3W. In certain instances, such regimens include administration of PD-1 antibody administered QW, Q2W, or Q3W. In certain instances, such regimens include administration of the compound of formula I administered QD. In certain instances, such regimens include administration of the compound of formula I administered QD for at least 21 days. In yet another exemplary regimen, the compound of formula I can be administered QD or QW and a PD-1 inhibitor *(e.g.,* a PD-1 antibody) is administered QW, Q2W, or Q3W.

[0153] The regimen can be a regimen for administration of pembrolizumab with the compound of formula I as described herein. In one exemplary regimen including pembrolizumab, the compound of formula I can be administered BIW or TIW and pembrolizumab is administered in accordance with the prescribing information provided in, for example, a package insert. In another exemplary regimen, pembrolizumab is administered at an amount of about 1 mg/kg to about 10 mg/kg on day 1 of the regimen, and BIW for at least three weeks thereafter until disease progression or unacceptable toxicity and the compound of formula I is administered BIW or TIW over the same period of time. In another exemplary regimen, pembrolizumab is administered at an amount of about 1 mg/kg to about 10 mg/kg on day 1 of a regimen, and once Q3W thereafter until disease progression or unacceptable toxicity and the compound of

formula I is administered BIW or TIW over the same period of time. Pembrolizumab can be administered BIW for 3 weeks with the compound of formula I, where the compound of formula I is administered, for example, BIW or TIW during the course of such a regimen. Pembrolizumab can be administered QW for 3 weeks with the compound of formula I, where the compound of formula I is administered, for example, BIW or TIW during the course of such a regimen. In still another exemplary regimen, pembrolizumab can be administered QW for 3 weeks with the compound of formula I, where the compound of formula I is administered, for example, QD or QW during the course of such a regimen. Such regimens can be repeated as described above *(e.g.,* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more times).

[0154] In another exemplary regimen including pembrolizumab, the compound of formula I can be administered QD and pembrolizumab is administered in accordance with the prescribing information provided in, for example, a package insert. In another exemplary regimen, pembrolizumab is administered at an amount of about 1 mg/kg to about 10 mg/kg on day 1 of the regimen, and BIW for at least three weeks thereafter until disease progression or unacceptable toxicity and the compound of formula I is administered QD over the same period of time. In another exemplary regimen, pembrolizumab is administered at an amount of about 1 mg/kg to about 10 mg/kg on day 1 of a regimen, and once Q3W thereafter until disease progression or unacceptable toxicity and the compound of formula I is administered QD over the same period of time. Pembrolizumab can be administered BIW for 3 weeks with the compound of formula I, where the compound of formula I is administered, for example, QD during the course of such a regimen. Pembrolizumab can be administered QW for 3 weeks with the compound of formula I, where the compound of formula I is administered, for example, QD during the course of such a regimen. Such regimens can be repeated as described above (*e.g., 1,2,3,* 4, 5, 6, 7, 8, 9, 10, 11, 12, or more times).

[0155] The regimen can be a regimen for administration of nivolumab with the compound of formula I as described herein. In one exemplary regimen including nivolumab, the compound of formula I can be administered BIW or TIW and nivolumab is administered in accordance with the prescribing information provided in, for example, a package insert. In another exemplary regimen, nivolumab is administered at an amount of about 1 mg/kg to about 5 mg/kg on day 1 and BIW for 3 weeks thereafter until disease progression or unacceptable toxicity and the compound of formula I is administered BIW or TIW over the same period of time. In still another exemplary regimen, nivolumab is administered at an amount of about 1 mg/kg to about 5 mg/kg on day 1 and Q2W thereafter until disease progression or unacceptable toxicity and the compound of formula I is administered BIW or TIW over the same period of time. In still another exemplary regimen, nivolumab can be administered Q2W, where the compound of formula I is administered, for example, BIW or TIW during the course of such a regimen. In yet another exemplary regimen, nivolumab can be administered Q2W, where the compound of formula I is administered, for example, QD or QW during the course of such a regimen. Such regimens can be repeated as described above *(e.g.,* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more times).

[0156] In another exemplary regimen including nivolumab, the compound of formula I can be

administered QD and nivolumab is administered in accordance with the prescribing information provided in, for example, a package insert. In another exemplary regimen, nivolumab is administered at an amount of about 1 mg/kg to about 5 mg/kg on day 1 and BIW for 3 weeks thereafter until disease progression or unacceptable toxicity and the compound of formula I is administered QD over the same period of time. In still another exemplary regimen, nivolumab is administered at an amount of about 1 mg/kg to about 5 mg/kg on day 1 and Q2W thereafter until disease progression or unacceptable toxicity and the compound of formula I is administered QD over the same period of time. In still another exemplary regimen, nivolumab can be administered Q2W, where the compound of formula I is administered, for example, QD during the course of such a regimen. Such regimens can be repeated as described above *(e.g.,* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more times).

[0157] It should also be appreciated that the combinations described herein for treating cancer can be coadministered with other active agents other than those present in the combinations described herein *(e.g.,* anti-cancer agents). Regimens for administration of a combination described herein, including the exemplary regimens set forth above, can be modified as necessary to include administration of such active agents. Administration of such active agents, *e.g.,* anti-cancer agents, can be performed QD, QW, QM, BID, BIW, TIW, Q2W, Q3W, or Q4W, or in accordance with prescribing information for such anti-cancer agents as set forth, for example, in a package insert. Exemplary anti-cancer agents include but are not limited to: ABRAXANE; abiraterone; ace-11; aclarubicin; acivicin; acodazole hydrochloride; acronine; actinomycin; acylfulvene; adecypenol; adozelesin; adriamycin; aldesleukin; all trans-retinoic acid (ATRA); altretamine; ambamustine; ambomycin; ametantrone acetate; amidox; amifostine; aminoglutethimide; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; antarelix; anthramycin; aphidicolin glycinate; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; ARRY-162; ARRY-300; ARRY-142266; AS703026; asparaginase; asperlin; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; azacitidine; AZD8330; azetepa; azotomycin; balanol; batimastat; BAY 11-7082; BAY 43-9006; BAY 869766; bendamustine; benzochlorins; benzodepa; benzoylstaurosporine; beta-alethine; betaclamycin B; betulinic acid; b-FGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bisnafide dimesylate; bistratene A; bisantrene hydrochloride; bleomycin; bleomycin sulfate; busulfan; bizelesin; breflate; bortezomib; brequinar sodium; bropirimine; budotitane; buthionine sulfoximine; bryostatin; cactinomycin; calusterone; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; castanospermine; cecropin B; cedefingol; celecoxib; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; chlorambucil; Chlorofusin; cirolemycin; cisplatin; CI-1040; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; crisnatol mesylate; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cyclophosphamide; cytarabine; cytarabine ocfosfate; cytolytic factor; cytostatin; dacarbazine; dactinomycin; daunorubicin; daunorubicin hydrochloride; decarbazine; dacliximab; dasatinib; decitabine; dehydrodidemnin B; deslorelin; dexamethasone;

dexifosfamide; dexrazoxane; dexverapamil; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; didemnin B; didox; diethylnorspermine; dihydro 5 azacytidine; dihydrotaxol; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; docetaxel; doxorubicin; doxorubicin hydrochloride; doxifluridine; droloxifene; droloxifene citrate; dromostanolone propionate; dronabinol; duazomycin; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; edatrexate; eflornithine hydrochloride; eflomithine; elemene; emitefur; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin; epirubicin hydrochloride; epristeride; erbulozole; eribulin; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; exemestane; fadrozole; fadrozole hydrochloride; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; floxuridine; fludarabine phosphate; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fluorouracil; floxouridine; flurocitabine; fosquidone; fostriecin sodium; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; geldanamycin; gossyphol; GDC-0973; GSK1120212/trametinib; herceptin; hydroxyurea; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; ibrutinib; idarubicin; idarubicin hydrochloride; ifosfamide; canfosfamide; ilmofosine; iproplatin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imatinib (e.g., GLEEVEC); imiquimod; iobenguane; iododoxorubicin; ipomeanol; irinotecan; irinotecan hydrochloride; irsogladine; isobengazole; isohomohalicondrin B; itasetron; iimofosine; interleukin IL-2 (including recombinant interleukin II; or rIL.sub.2); interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-la; interferon gamma-1b; jasplakinolide; kahalalide F; lamellarin N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leuprorelin; levamisole; lenalidomide; lenvatinib; liarozole; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lanreotide acetate; lapatinib; letrozole; leucovorin; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; pomalidomide; LY294002; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitonafide; mitoxantrone; mofarotene; molgramostim; mopidamol; mycaperoxide B; myriaporone; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nafarelin; nagrestip; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; nocodazole; nogalamycin; oblimersen (GENASENSE); octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; oxisuran; oxaloplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; porfiromycin; prednisone; prostaglandin J2; pyrazoloacridine; paclitaxel; PD035901; PD184352; PD318026; PD98059; peliomycin;

pentamustine; peplomycin sulfate; PKC412; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; podophyllotoxin; polyphenol E; porfimer sodium; porfiromycin; prednimustine; procarbazine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; raltitrexed; ramosetron; retelliptine demethylated; rhizoxin; rituximab; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; riboprine; romidepsin; safingol; safingol hydrochloride; saintopin; sarcophytol A; sargramostim; semustine; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; sonermin; sorafenib; sunitinib; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; Spongistatin 2; Spongistatin 3; Spongistatin 4; Spongistatin 5; Spongistatin 6; Spongistatin 7; Spongistatin 8; and Spongistatin 9; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; suradista; suramin; swainsonine; SB239063; selumetinib/AZD6244; simtrazene; SP600125; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiroplatin; streptonigrin; streptozocin; sulofenur; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thymalfasin; thymopoietin receptor agonist; thymotrinan; tirapazamine; titanocene bichloride; topsentin; toremifene; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrphostins; talisomycin; TAK-733; taxotere; tegafur; teloxantrone hydrochloride; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trastuzumab; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; tumor necrosis factor-related apoptosis-inducing ligand (TRAIL); UBC inhibitors; ubenimex; U0126; uracil mustard; uredepa; vapreotide; variolin B; velaresol; veramine; verteporfin; vinorelbine; vinxaltine; vitaxin; vinblastine; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; wortmannin; XL518; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer; zinostatin; and zorubicin hydrochloride.

[0158] Other exemplary anti-cancer agents include Erbulozole *(e.g.,* R-55104); Dolastatin 10 *(e.g.,* DLS-10 and NSC-376128); Mivobulin isethionate *(e.g.,* CI-980); NSC-639829; Discodermolide *(e.g.,* NVP-XX-A-296); ABT-751 (Abbott; e.g., E-7010); Altorhyrtin A; Altorhyrtin C; Cemadotin hydrochloride (e.g., LU-103793 and NSC-D-669356); Epothilone A; Epothilone B; Epothilone C; Epothilone D; Epothilone E; Epothilone F; Epothilone B N-oxide; Epothilone A N-oxide; 16-aza-epothilone B; 21-aminoepothilone B; 21-hydroxyepothilone D; 26-fluoroepothilone; Auristatin PE *(e.g.,* NSC-654663); Soblidotin *(e.g.,* TZT-1027); LS-4559-P (Pharmacia; *e.g.,* LS-4577); LS-4578 (Pharmacia; *e.g.,* LS-477-P); LS-4477 (Pharmacia); LS-4559 (Pharmacia); RPR-112378 (Aventis); DZ-3358 (Daiichi); FR-182877 (Fujisawa; e.g., WS-9265B); GS-164 (Takeda); GS-198 (Takeda); KAR-2 (Hungarian Academy of Sciences); BSF-223651 (BASF; e.g., ILX-651 and LU-223651); SAH-49960 (Lilly/Novartis); SDZ-268970 (Lilly/Novartis); AM-97 (Armad/Kyowa Hakko); AM-132 (Armad); AM-138 (Armad/Kyowa Hakko); IDN-5005 (Indena); Cryptophycin 52 *(e.g.,* LY-355703); AC-7739 (Ajinomoto; e.g., AVE-8063A and CS-39.HCl); AC-7700 (Ajinomoto; e.g., AVE-8062; AVE-8062A; CS-39-L-Ser.HCl; and RPR-258062A); Virilevuamide; Tubulysin A; Canadensol; CA-170 (Curis, Inc.); Centaureidin *(e.g.,* NSC-106969); T-138067 (Tularik; e.g., T-67; TL-138067 and TI-138067);

COBRA-1 (Parker Hughes Institute; e.g., DDE-261 and WHI-261); H10 (Kansas State University); H16 (Kansas State University); Oncocidin A1 (*e.g.,* BTO-956 and DIME); DDE-313 (Parker Hughes Institute); Fijianolide B; Laulimalide; SPA-2 (Parker Hughes Institute); SPA-1 (Parker Hughes Institute; e.g., SPIKET-P); 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine; *e.g.,* MF-569); Narcosine *(e.g.,* NSC-5366); Nascapine; D-24851 (Asta Medica); A-105972 (Abbott); Hemiasterlin; 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine; *e.g.,* MF-191); TMPN (Arizona State University); Vanadocene acetylacetonate; T-138026 (Tularik); Monsatrol; Inanocine *(e.g.,* NSC-698666); 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine); A-204197 (Abbott); T-607 (Tuiarik; *e.g.,* T-900607); RPR-115781 (Aventis); Eleutherobins *(e.g.,* Desmethyleleutherobin; Desaetyleleutherobin; Isoeleutherobin A; and Z-Eleutherobin); Caribaeoside; Caribaeolin; Halichondrin B; D-64131 (Asta Medica); D-68144 (Asta Medica); Diazonamide A; A-293620 (Abbott); NPI-2350 (Nereus); Taccalonolide A; TUB-245 (Aventis); A-259754 (Abbott); Diozostatin; (-)-Phenylahistin *(e.g.,* NSCL-96F037); D-62638 (Asta Medica); D-62636 (Asta Medica); Myoseverin B; D-43411 (Zentaris; *e.g.,* D-81862); A-289099 (Abbott); A-318315 (Abbott); HTI-286 *(e.g.,* SPA-110; trifluoroacetate salt) (Wyeth); D-82317 (Zentaris); D-82318 (Zentaris); SC-12983 (NCI); Resverastatin phosphate sodium; BPR-OY-007 (National Health Research Institutes); and SSR-250411 (Sanofi)); goserelin; leuprolide; triptolide; homoharringtonine; topotecan; itraconazole; deoxyadenosine; sertraline; pitavastatin; clofazimine; 5-nonyloxytryptamine; vemurafenib; dabrafenib; gefitinib (IRESSA); erlotinib (TARCEVA); cetuximab (ERBITUX); lapatinib (TYKERB); panitumumab (VECTIBIX); vandetanib (CAPRELSA); afatinib/BIBW2992; CI-1033/canertinib; neratinib/HKI-272; CP-724714; TAK-285; AST-1306; ARRY334543; ARRY-380; AG-1478; dacomitinib/PF299804; OSI-420/desmethyl erlotinib; AZD8931; AEE726; pelitinib/EKB-569; CUDC-101; WZ8040; WZ4002; WZ3146; AG-490; XL647; PD153035; 5-azathioprine; 5-aza-2'-deoxycytidine; 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG); 20-epi-1,25 dihydroxyvitamin D3; 5 ethynyluracil; and BMS-599626.

[0159] In certain embodiments, the combinations described herein are coadministered with an anti-cancer agent described above, where the anti-cancer agent has known activity against a particular cancer *(e.g.,* gemcitibine coadministered with a combination described herein for treating pancreatic cancer). The anti-cancer agents above can be approved for use in treating certain indications *(e.g.,* certain cancers) at concentrations, amounts, and using treatment regimens known in the art.

[0160] It is understood that modifications which do not substantially affect the activity of the various embodiments of this invention are also included within the definition of the invention provided herein. Accordingly, the following examples are intended to illustrate but not limit the present invention.

Examples:

Example 1:

[0161] In the present example, HBI-8000 was tested as monotherapy and in combination with anti-PD-1 at 5 mg/kg. The experiment included a vehicle-treated group, and a PD-1 inhibitor antibody monotherapy group, which served as the control groups for analysis of efficacy. Tumors were measured twice per week until the study was ended on Day 47. Each animal was euthanized when its tumor attained the endpoint tumor volume of 1000 mm^3 or on the final day of the study, whichever came first, and the time to endpoint (TTE) for each mouse was calculated. Treatment response was determined from an analysis of percent tumor growth delay (%TGD), defined as the percent increase in the median time to endpoint (TTE) for treated versus control mice; and by log rank significance of differences in survival among groups and regression responses.

[0162] Mice: Female C57BL/6 mice (Charles River Laboratories) were eight weeks old, with a body weight (BW) range of 15.4 to 22.0 grams on Day 1 of the study. The animals were fed ad libitum water (reverse osmosis, 1 ppm Cl), and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice were housed on irradiated Enrich-o'cobs™ Laboratory Animal Bedding in static microisolators on a 12-hour light cycle at 20-22 °C (68-72 °F) and 40-60% humidity.

[0163] Tumor Cells: MC38 murine colon carcinoma cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum and 2 mM glutamine, 100 units/mL penicillin G sodium, 100 µg/mL streptomycin sulfate, and 25 µg/mL gentamicin. Cell cultures were maintained in tissue culture flasks in a humidified incubator at 37 °C, in an atmosphere of 5% CO2 and 95% air.

[0164] Tumor Implantation: Cells were harvested during exponential growth, and resuspended in cold DMEM. Each mouse was inoculated subcutaneously in the right flank with 1×10^6 cells (0.1 mL of cell suspension). Tumors were calipered in two dimensions to monitor growth as their mean volume approached the desired 100-150 mm^3 range. Tumor burden was calculated using the formula:

$$\text{Tumor volume } (mm^3) = \frac{w^2 x\, l}{2}$$

where w = width and 1 = length, in mm, of the tumor. Tumor weight may be estimated with the assumption that 1 mg is equivalent to 1 mm^3 of tumor volume. Fourteen days after tumor implantation, which was designated as Day 1 of the study, animals with individual tumor volumes from 75 to 221 mm^3 were sorted into eleven groups (n=10/group) with group mean tumor volume of 130 - 133 mm^3.

[0165] Test Articles: HUYA Bioscience International provided HBI-8000 (Lot No. 1384:0033). The antibody anti-PD-1 RMP1-14 (Lot No. 5611-10/0615) was purchased from BioXcell.

[0166] Dosing Solutions: Antibody dosing solutions were prepared fresh daily and stored at 4

°C. HBI-8000 was dissolved in 0.2% CMC (carboxy methyl cellulose) in 0.1% Tween 80. Anti-PD-1 antibody dosing solution was prepared by diluting an aliquot of the stock (6.48 mg/mL) to 0.5 mg/mL in sterile PBS resulting in a 5 mg/kg dosage in a 10 mL/kg dosing volume.

[0167] Six groups of C57BL/6 mice were dosed according to the protocol shown in Table 2. All doses were prepared as described above. HBI-8000 was administered orally (p.o.), once daily for twenty-one days (qd × 21). Dosing was adjusted per animal body weight. Antibody regimen was administered at 5 mg/kg, intraperitoneally (i.p.), twice weekly for three weeks (biwk × 3), and dosing was adjusted per animal body weight.

Table 2:

Group	Treatment	Frequency
Group 1*	Vehicle (2% CMC : 0.1% Tween 80)	p.o., qd × 21
Group 2*	HBI-8000 at 20 mg/kg	p.o., qd × 21
Group 3*	HBI-8000 at 50 mg/kg	p.o., qd × 21
Group 4*	PD-1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
Group 5*	HBI-8000 at 20 mg/kg plus	p.o., qd × 21
	PD-1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
Group 6*	HBI-8000 at 50 mg/kg plus	p.o., qd × 21
	PD-1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
* not claimed		

[0168] Tumor Growth Delay: Tumors were measured using calipers twice per week, and each animal was euthanized when its tumor reached a volume of 1000 mm^3 or at the end of the study (D47), whichever came first. Animals that exited the study for tumor volume endpoint were documented as euthanized for tumor progression (TP), with the date of euthanasia. The time to endpoint (TTE) for analysis was calculated for each mouse by the following equation:

$$TTE = \frac{\log c_{10}(\text{endpoint volume}) - b}{m}$$

where TTE is expressed in days, endpoint volume is expressed in mm^3, b is the intercept, and m is the slope of the line obtained by linear regression of a log-transformed tumor growth data set. The data set consisted of the first observation that exceeded the endpoint volume used in analysis and the three consecutive observations that immediately preceded the attainment of this endpoint volume. The calculated TTE is usually less than the TP date, the day on which the animal was euthanized for tumor burden. Animals with tumors that did not reach the endpoint volume were assigned a TTE value equal to the last day of the study. In instances in which the log-transformed calculated TTE preceded the day prior to reaching endpoint or exceeded the day of reaching tumor volume endpoint, a linear interpolation was performed to approximate the TTE. Any animal classified as having died from NTR (non-treatment-related) causes due to accident (NTRa) or due to unknown etiology (NTRu) were excluded from TTE calculations (and all further analyses). Animals classified as TR (treatment-related) deaths or NTRm (non-treatment-related death due to metastasis) were assigned a TTE value equal to

the day of death.

[0169] Treatment Outcome : Treatment outcome was evaluated from tumor growth delay (TGD), which is defined as the increase in the median time to endpoint (TTE) in a treatment group compared to the control group:

$$TGD = T - C$$

expressed in days, or as a percentage of the median TTE of the control group:

$$\%TGD = \frac{T - C}{C} \times 100$$

where T = median TTE for a treatment group, and C = median TTE for the designated control group.

[0170] Treatment Efficacy: Treatment efficacy may be determined from the tumor volumes of animals remaining in the study on the last day. The MTV (n) was defined as the median tumor volume on the last day of the study in the number of animals remaining (n) whose tumors had not attained the endpoint volume. Treatment efficacy may also be determined from the incidence and magnitude of regression responses observed during the study. Treatment may cause partial regression (PR) or complete regression (CR) of the tumor in an animal. In a PR response, the tumor volume was 50% or less of its Day 1 volume for three consecutive measurements during the course of the study, and equal to or greater than 13.5 mm^3 for one or more of these three measurements. In a CR response, the tumor volume was less than 13.5 mm^3 for three consecutive measurements during the course of the study. An animal with a CR response at the termination of a study is additionally classified as a tumor-free survivor (TFS). Animals were monitored for regression responses.

[0171] Statistics: Prism (GraphPad) for Windows 6.07 was used for graphical presentations and statistical analyses. The log rank test, which evaluates overall survival experience, was used to analyze the significance of the differences between the TTE values of two groups. Log rank analysis includes the data for all animals in a group except those assessed as NTR deaths. Two-tailed statistical analyses were conducted at significance level P = 0.05. Group median tumor volumes were plotted as a function of time. When an animal exited the study due to tumor burden, the final tumor volume recorded for the animal was included with the data used to calculate the median volume at subsequent time points. Kaplan-Meier plots show the percentage of animals in each group remaining in the study versus time.

[0172] Animals in Example 1 were treated in accordance with the protocol described in Table 1. Figure 1 shows the median tumor growth curves for all study groups and Figure 2 shows the median tumor volumes for the combination of HBI-8000 at 50 mg/kg plus PD-1 inhibitor antibody vs. the single agent and vehicle controls. The combination of HBI-8000 at 50 mg/kg plus PD-1 inhibitor antibody produced statistically significant tumor growth inhibition. Figure 3 depicts the Kaplan Meier plots for all groups, and Figure 4 depicts the Kaplan Meier plots for the combination of HBI-8000 at 50 mg/kg plus PD-1 inhibitor antibody vs. the single agent controls. The combination of HBI-8000 at 50 mg/kg plus PD-1 inhibitor antibody produced statistically significant survival benefit. Table 3 describes the values calculated for TTE and

%TGD.

Table 3: Median TTE and %TGD (Example 1)

Group	n	Treatment Regimen		Median TTE	%TGD
		Agent 1	Agent 2		
1*	10	vehicle	-	20.5	-
2*	10	HBI-8000 (20 mpk)	-	18.9	-8
3*	10	HBI-8000 (50 mpk)	-	22.8	11
4*	10	anti-PD-1	-	22.0	7
5*	10	HBI-8000 (20 mpk)	anti-PD-1	26.1	27
6*	10	HBI-8000 (50 mpk)	anti-PD-1	28.7	40
* not claimed					

Example 2:

[0173] In the present example, HBI-8000 was tested as monotherapy and in combination with PD-1 inhibitor antibody at 5 mg/kg. The experiment included a vehicle-treated group and an PD-1 inhibitor antibody monotherapy group, which served as the control groups for analysis of efficacy. Tumors were measured twice per week until the study was ended on Day 50. Each animal was euthanized when its tumor attained the endpoint tumor volume of 1000 mm^3 or on the final day of the study, whichever came first, and the time to endpoint (TTE) for each mouse was calculated. Treatment response was determined from an analysis of percent tumor growth delay (%TGD), defined as the percent increase in the median time to endpoint (TTE) for treated versus control mice; and by log rank significance of differences in survival among groups and regression responses.

[0174] Mice: Details of the animals used in this example can be found in paragraph [00216].

[0175] Tumor Cell Culture: Details of the tumor cells used in this example can be found in paragraph [00217].

[0176] Tumor Implantation and Measurement: Details of tumor implantation and measurement of tumor growth used in this example can be found in paragraph [00218]. In this example, each mouse was inoculated subcutaneously in the right flank with 5×10^5 cells (0.1 mL of cell suspension).

Test Articles: Details of the test articles used in this example can be found in paragraph [00219].

[0177] Dosing Solutions: Details of the dosing solutions used in this example can be found in paragraph [00220].

[0178] Treatment: Four groups of C57BL/6 mice (n = 10) were dosed according to the protocol in Table 4. Dosing began on day 1 unless otherwise noted. HBI-8000 was administered p.o. at 50 mg/kg. PD-1 inhibitor antibody was administered i.p. at 5 mg/kg. Vehicle (0.2% carboxymethyl cellulose: 0.1% Tween 80 in deionized water) was administered p.o. All agents were delivered in a dosing volume of 10 mL/kg adjusted per body weight of the individual animals.

Table 4:

Group	Treatment	Frequency
Group 1*	Vehicle (2% CMC : 0.1% Tween 80)	p.o., qd × 21
Group 2*	HBI-8000 at 50 mg/kg	p.o., qd × 21
Group 3*	PD-1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
Group 4*	HBI-8000 at 50 mg/kg plus	p.o., qd × 21
	PD-1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
* not claimed		

[0179] Tumor Growth Delay: Details of the tumor growth delay measurements and calculations can be found in paragraph [00223].

[0180] Treatment Outcome: Details of treatment outcome measurements and calculations can be found in paragraph [00224].

[0181] Treatment Efficacy: Details of treatment efficacy measurements and calculations can be found in paragraph [00225].

[0182] Statistics: Details of the statistics and software used in this study can be found in paragraph [00226]. Figure 5 shows the median tumor volume measurements for all groups, and Figure 6 shows the Kaplan-Meier plot, depicting the percentage of animals in each group remaining in the study versus time. Table 6 describes the values calculated for TTE and %TGD for each treatment group.

[0183] Animals in Example 2 were treated in accordance with the protocol described in Table 4. Figure 5 shows the median tumor growth curves for all study groups; the combination of HBI-8000 at 50 mg/kg plus PD-1 inhibitor antibody approached statistical significance in terms of tumor growth inhibition. Figure 6 depicts the Kaplan Meier plots for all groups; the combination of HBI-8000 at 50 mg/kg plus PD-1 inhibitor antibody produced statistically significant survival benefit vs. vehicle as well as the single agents. Figure 7 depicts the Individual Times to Endpoint for all groups in Example 7. Table 5 describes the values calculated for TTE and %TGD.

Table 5: Median TTE and %TGD (Example 2)

Group	n	Treatment Regimen		Median TTE	%TGD
		Agent 1	Agent 2		
1*	10	vehicle	-	16.3	-
2*	10	HBI-8000 (50 mpk)	-	19.4	19
3*	10	anti-PD-1	-	18.0	11
4*	10	HBI-8000 (50 mpk)	anti-PD-1	28.5	75
* not claimed					

Example 3

[0184] In this model, a proportion of the animals treated 1st line with the PD-L1 checkpoint inhibitor antibody experience complete tumor regression. However, a similar proportion of animals treated 1st line with the PD-L1 inhibitor antibody experience rapid tumor progression. The balance of the animals treated in this way experience slow tumor progression or stable disease, which is a result which approximates the situation in a number of human cancer patients receiving PD-L1 inhibitor antibody therapy, i.e., they experience a transient partial response, including stable disease, but then develop resistance and rapidly progress, failing PD-1 inhibitor antibody therapy. In this example, the efficacy of HBI-8000 as a second-line therapy, alone and in combination with PD-1 inhibitor antibody RMPI-14, was evaluated for the ability to cause tumor growth delay (TGD) in animals which tumors which are progressing following PD-L1 inhibitor antibody first line therapy in the MC38 murine colon carcinoma syngeneic model in immunocompetent C57BL/6 mice. Hence, addressing a need in the clinic for human patients failing PD-L1 inhibitor antibody therapy.

[0185] Female C57BL/6 mice bearing subcutaneous MC38 tumors (mean tumor volume: 114 mm^3 when treatment began) were treated with a first line of therapy of PD-L1 inhibitor antibody treatment, administered intraperitoneally (i.p.) at 5 mg/kg, twice weekly for two weeks (biwk × 2). When tumors met the failure criteria and showed two consecutive increases in tumor volume and tumor volume was < 500 mm^3, these were subsequently reenrolled in a second line of therapy efficacy study, which consisted of six groups (n = 10 per group) of mice. Dosing began on D1, which represents the day of recruitment and varied among mice (this was normalized for each group). The second-line therapies were as follows. Vehicle was administered orally (p.o.). HBI-8000 was administered p.o. at 50 mg/kg. PD-1 inhibitor antibody and anti-PDL-1 were administered intraperitoneally (i.p) at 5 mg/kg. Group 1 mice served as controls and received 0.2% carboxymethyl cellulose: 0.1% Tween 80 in deionized water (vehicle) once daily for twenty-one days (qd × 21). Group 2 received HBI-8000 qd × 21. Group 3 received a second course of PD-L1 inhibitor antibody biwk × 2. Group 4 received HBI-8000 qd × 21 and PD-L1 inhibitor antibody biwk × 2. Group 5 received anti-PD-1 biwk × 2. Group 6

received HBI-8000 qd × 21 and anti-PD-1 biwk × 2. The study endpoint was tumor volume of 1500 mm^3 or 45 days, whichever came first. Tumor measurements were taken twice weekly until D44 with individual animals exiting the study upon reaching the tumor volume endpoint.

[0186] Mice: At the onset of the initial PD-1 inhibitor antibody treatment, female C57BL/6 mice (Charles River) were eight weeks old and had a BW range of 18.1 - 24.1 g. The animals were fed ad libitum water (reverse osmosis, 1 ppm Cl) and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice were housed on irradiated Enrich-o'cobs™ bedding in static microisolators on a 12-hour light cycle at 20 - 22 °C (68 - 72 °F) and 40 - 60% humidity.

[0187] Tumor Implantation and Measurement: Details of tumor implantation and measurement of tumor growth used in this example can be found in paragraph [00218]. In this example, each mouse was inoculated subcutaneously in the right flank with 5 × 10^5 cells (0.1 mL of cell suspension).

[0188] Test Articles: HUYA Bioscience International provided HBI-8000 (Lot No. 1384:0033). PD-1 inhibitor antibody RMPI-14 (Lot No. 5611-10/0615) and PDL-1 antibody 10F.9G2 (anti-PDL-1, Lot No. 5786-7-8/0815) were purchased from Bio X cell (West Lebanon, NH). All agents were prepared according to protocol instructions.

[0189] Dosing Solutions: HBI-8000 was prepared by diluting in 0.2% CMC: 0.1% Tween 80 to yield a 5 mg/mL dosing solution. Dosing solutions were prepared fresh weekly and stored at 4 °C. PD-1 inhibitor antibody dosing solution was prepared by diluting an aliquot of the stock (8.62 mg/mL) to 0.5 mg/mL in sterile PBS. The dosing solution was prepared twice weekly and stored at 4 °C. Anti-PDL-1 antibody dosing solution was prepared by diluting an aliquot of the stock (5.37 mg/mL) to 0.5 mg/mL in sterile PBS. The anti-PDL-1 antibody dosing solution was prepared twice weekly and stored at 4 °C.

[0190] Treatment: For the initial PD-L1 inhibitor antibody failure part of this study, 150 C57BL/6 mice were dosed i.p. with first line PD-L1 inhibitor antibody at 5 mg/kg, biwk × 2. Animals that met the criteria for reenrollment comprised the efficacy study; this included animals with two consecutive increases in tumor volume and tumor volumes below 500 mm^3. The first sixty animals which became available were placed sequentially into six efficacy groups until all groups were filled; this occurred either sixteen or twenty-two days following initiation of first line dosing. For the efficacy study, six groups of C57BL/6 mice (n = 10) were dosed according to protocol in Table 6. Second-line therapy began on day 1, which was the day of enrollment of each individual animal.

Table 6:

Group	Treatment	Frequency
Group 1*	Vehicle (2% CMC : 0.1% Tween 80)	p.o., qd × 21
Group 2*	HBI-8000 at 50 mg/kg	p.o., qd × 21

Group	Treatment	Frequency
Group 3*	PD-L1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
Group 4*	HBI-8000 at 50 mg/kg plus	p.o., qd × 21
	PD-L1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
Group 5*	PD-1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
Group 6	HBI-8000 at 50 mg/kg plus	p.o., qd × 21
	PD-1 inhibitor antibody at 5 mg/kg	i.p., biwk × 3
* not claimed		

[0191] Tumor Growth Delay: Details of the tumor growth delay measurements and calculations that were used for the study are found in paragraph [00223].

[0192] Treatment Outcome: Details of treatment outcome measurements and calculations that were used in the study are found in paragraph [00224].

[0193] Treatment Efficacy: Details of treatment efficacy measurements and calculations that were used for the study are found in paragraph [00225].

[0194] Statistics: Details of the statistics and software that were used in this study can be found in paragraph [00226]. Responses of each group, categorized as no response (NR), partial response (PR) and complete response (CR), to the therapy received were tabulated. Mean tumor volume measurements for all groups were obtained and data for a Kaplan-Meier plot, showing the percentage of animals in each group remaining in the study versus time was obtained.

[0195] Animals in Example 3 were treated in accordance with the protocol described in Table 6. Figure 8 shows the median tumor growth curves for all study groups. Figure 8 depicts the Kaplan Meier plots for all groups; the combination of HBI-8000 at 50 mg/kg plus PD-1 inhibitor antibody produced statistically significant survival benefit vs. vehicle as well as the single agents. Figure 9 depicts the Individual Times to Endpoint for all groups in Example 3. Table 7 describes the values calculated for TTE and %TGD.

Table 7:

Treatment Group	Median TTE	Mean T-C	%TGD	NR	PR	CR
Vehicle*	9.8	0.0	0.0	8	2	0
HBI-8000*	11.4	3.0	31.8	8	1	1
PD-1 Ab*	13.8	10.4	106.3	6	2	2
PD-1 Ab + HBI-8000	24.2	10.1	103.3	3	1	6
PD-L1 Ab*	17.7	8.5	86.7	5	3	2
PD-L1 Ab + HBI-8000*	14.7	3.8	39.2	6	4	0

* not claimed

Example 4

[0196] In this Example 4, antitumor responses induced by HBI-8000, administered alone and in combination with anti-PD-1 RMP1-14 (anti-PD-1) were characterized in the 4T1 murine mammary carcinoma xenograft model in BALB/c mice. The impact of these therapies on lung metastasis was evaluated.

[0197] Treatments began on Day (D) 1 in BALB/c mice bearing established 4T1 tumors. HBI-8000 was administered orally (p.o.) and anti-PD-1 was administered intraperitoneally (i.p.), at a single dose level. Test agents were administered alone and in combination with HBI-8000. Control animals received vehicle. The study ended on D14 as the endpoint for metastatic foci was reached. Treatment response was determined based on metastases counts taken from animals remaining on D14.

[0198] Mice: Female BALB/c mice (BALB/c AnNcr1, Charles River) were seven weeks old on D1 of the study and had a body weight (BW) range of 14.7 to 20.7 g. The animals were fed ad libitum water (reverse osmosis, 1 ppm Cl) and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice were housed on irradiated Enrich-o'Cobs™ bedding in static microisolators on a 12-hour light cycle at 20-22 °C (68-72 °F) and 40-60% humidity.

[0199] Tumor Cell Culture: The 4T1 mammary carcinoma cell line was grown to mid-log phase in RPMI medium containing 10% fetal bovine serum, 2 mM glutamine, 100 units/mL sodium penicillin G, 25 µg/mL gentamicin, and 100 µg/mL streptomycin sulfate. The cells were cultured in tissue culture flasks in a humidified incubator at 37 °C, in an atmosphere of 5% CO2 and 95% air.

[0200] *In Vivo* Implantation and Tumor Growth: 4T1 tumor cells were harvested during exponential growth and resuspended in PBS. Each test mouse was injected orthotopically in the mammary fat pad with 1 × 106 cells (0.1 mL cell suspension). Tumor growth was monitored as the average size of tumors approached the target range of 80 - 120 mm^3.

[0201] Test Agents: HUYA Bioscience International, LLC provided HBI-8000 (Lot No. 1384:0033). Anti-PD-1 RMP-14 (anti-PD-1, Lot No. 5792-599016J1) was purchased from Bio X cell (West Lebanon, NH). All agents were prepared according to protocol instructions. The vehicle used in this study was 0.2% carboxymethyl cellulose: 0.1% Tween 80 in DI water. HBI-8000 was prepared by diluting in 0.2% CMC: 0.1% TW80 to yield a 5 mg/mL dosing solution. Dosing solutions were prepared fresh weekly and stored at 4 °C. Anti-PD-1 antibody dosing solution was prepared by diluting an aliquot of the stock (6.37 mg/mL) to 0.5 mg/mL in sterile

PBS. The dosing solution was prepared on each day of dosing and stored at 4 °C.

[0202] Treatment: On DI of the study, mice bearing established 4T1 tumors began dosing according to the treatment plan summarized below. All agents were administered in dosing volumes of 10 mL/kg; volumes were adjusted according to BW of the individual.

[0203] Group 1 served as efficacy controls and received vehicle, p.o., daily for thirteen days (qd × 13).

[0204] Group 2 received HBI-8000 at 50 mg/kg, p.o., qd × 13.

[0205] Group 3 received anti-PD-1 at 5 mg/kg, i.p., twice weekly for two weeks (biwk × 2).

[0206] Group 4 received HBI-8000 at 50 mg/kg, p.o., qd × 13, and anti-PD-1 at 5 mg/kg, i.p., biwk × 2.

Endpoint: Metastases Count

[0207] Results were analyzed by counting the lung metastatic foci on D14, the last day of the study. Animals were sacrificed at endpoint using isoflurane anesthesia and necropsies were performed to identify metastases. Total counts were obtained by adding the number of foci counted in the superior, middle, inferior, and post-caval lobes of the right lung to the number of foci counted in the left lung. Percent inhibition was defined as the difference between the number of metastatic foci of the designated control group and the number of metastatic foci of the drug-treated group, expressed as a percentage of the number of metastatic foci of the designated control group:

$$\% \text{ Inhibition} = \frac{(\#\text{Foci drug} - \text{treated}}{\#\text{Foci control})] \text{ x } 100}$$

[0208] Results: The day 14 lung metastatic foci count for Group 1 control animals was 35.0 ± 2.17 (Figure 10). HBI-8000 monotherapy produced non-significant inhibitions of -26%. Monotherapy treatment with anti-PD-1 resulted in inhibition of 30%. Combination therapy with HBI-8000 and anti-PD-1 produced foci inhibition of 72%, which was statistically significant. Results are shown in Figure 10.

Example 5

[0209] In the present example, HBI-8000 was tested as monotherapy and in combination with either anti-PD-1 antibody at 10 mg/kg or PD-L1 antibody at 10 mg/kg. The model used was the RENCA syngeneic model of renal cell carcinoma (RCC). The experiment included a vehicle-treated group, and both PD-1 inhibitor antibody and PD-1 inhibitor antibody monotherapy

groups, which served as the control groups for analysis of efficacy. Tumors were measured twice per week until the study was ended on Day 25. Treatment response was determined from an analysis of percent tumor growth delay (%TGD).

[0210] Mice: Details of the animals used in this example are similar to those which can be found in paragraph [00216]

[0211] Tumor Cell Culture: Details of the tumor cells used in this example are similar to those which can be found in paragraph [00217].

[0212] Tumor Implantation and Measurement: Details of tumor implantation and measurement of tumor growth used in this example are similar to those which can be found in paragraph [00218]. In this example, each mouse was inoculated subcutaneously in the right flank with 1×10^6 RENCA cells (0.1 mL of cell suspension).

[0213] Test Articles: Details of the test articles used in this example can be found in paragraph [00219].

[0214] Dosing Solutions: Details of the dosing solutions used in this example can be found in paragraph [00220].

[0215] Treatment: Six groups of female BALB/c mice bearing subcutaneous RENCA tumors (mean tumor volume: 62 mm^3 when treatment began) were treated according to the protocol in Table 8. Dosing began on day 1 unless otherwise noted. HBI-8000 was administered p.o. at 50 mg/kg. PD-1 and PD-L1 inhibitor antibodies were administered i.p. at 10 mg/kg. Vehicle (0.2% carboxymethyl cellulose: 0.1% Tween 80 in deionized water) was administered p.o. All agents were delivered in a dosing volume of 10 mL/kg adjusted per body weight of the individual animals.

Table 8:

Group	**Treatment**	**Frequency**
Group 1*	Vehicle (2% CMC : 0.1% Tween 80)	p.o., qd × 21
Group 2*	HBI-8000 at 50 mg/kg	p.o., qd × 21
Group 3*	PD-L1 inhibitor antibody at 10 mg/kg	i.p., biwk × 3
Group 4*	HBI-8000 at 50 mg/kg plus	p.o., qd × 21
	PD-L1 inhibitor antibody at 10 mg/kg	i.p., biwk × 3
Group 5*	PD-1 inhibitor antibody at 10 mg/kg	i.p., biwk × 3
Group 6*	HBI-8000 at 50 mg/kg plus	p.o., qd × 21
	PD-1 inhibitor antibody at 10 mg/kg	i.p., biwk × 3
* not claimed		

[0216] Tumor Growth Delay: Details of the tumor growth delay measurements and calculations that were used for the study are found in paragraph [00223].

[0217] Treatment Outcome: Details of treatment outcome measurements and calculations that were used in the study are found in paragraph [00224].

[0218] Treatment Efficacy: Details of treatment efficacy measurements and calculations that were used for the study are found in paragraph [00225].

[0219] Statistics: Details of the statistics and software that were used in this study can be found in paragraph [00226]. Responses of each group, categorized as no response (NR), partial response (PR) and complete response (CR), to the therapy received were tabulated. Mean tumor volume measurements for all groups were obtained and data for a Kaplan-Meier plot, showing the percentage of animals in each group remaining in the study versus time was obtained.

[0220] Animals in Example 5 were treated in accordance with the protocol described in Table 8. Figure 11 shows the median tumor growth curves for all study groups; the combination of HBI-8000 at 50 mg/kg plus PD-1 inhibitor antibody was statistically significant and different from either vehicle (P = 0.026) or PD-1 antibody monotherapy (P = 0.036) in terms of tumor growth inhibition.

Example 6- HDAC Enzyme Inhibition Assay

[0221] Selectivity and potency assays of chidamide inhibition of HDAC isotypes are performed using human recombinant HDAC proteins and as described in Ning et al. All of the enzymatic reactions are incubated for 17 h at room temperature in 50 pl of reaction mixture containing HDAC assay buffer (BPS catalog number 50031), 5 µg BSA, an HDAC substrate, a purified recombinant HDAC enzyme and a test compound at a pre-defined concentration. After enzymatic reactions, 50 µl of 29 HDAC Developer (BPS catalog number 50030) is added to each well and the plate is incubated at room temperature for an additional 20 min. Fluorescence intensity is measured at an excitation of 360 nm and an emission of 460 nm using a Synergy ™ 2 microplate reader from BioTek (Winooski, VT, USA). Each compound concentration is performed in duplicate. The IC_{50} values are determined by analyzing concentration-response inhibition curves.

REFERENCES CITED IN THE DESCRIPTION

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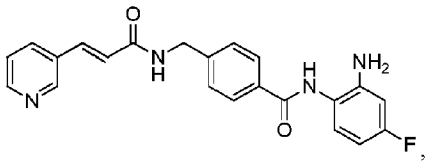
Patentkrav

1. Forbindelse repræsenteret ved strukturen:



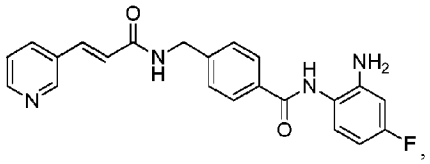
eller et farmaceutisk acceptabelt salt deraf,
til anvendelse i en fremgangsmåde til behandling af tyktarmskræft hos en patient med behov derfor, og hvis kræft tidligere er blevet behandlet med en PD-L1-inhibitor, hvor fremgangsmåden yderligere omfatter indgivelse af en PD-1-inhibitor.

2. Forbindelsen til anvendelse ifølge krav 1, hvor forbindelsen indgives 2 til 3 gange om ugen.

3. Forbindelsen til anvendelse ifølge krav 1, hvor PD-1-antistoffet er nivolumab, pembrolizumab, pidilizumab, REGN2810, PDR001, SHR-1210 eller MEDI0680; i særdeles nivolumab.

4. Forbindelsen til anvendelse ifølge krav 1, hvor fremgangsmåden omfatter indgivelse af forbindelsen og PD-1-inhitoren til patienten som et regime.

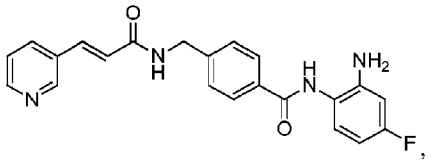
5. Forbindelse repræsenteret ved strukturen:



eller et farmaceutisk acceptabelt salt deraf,
til anvendelse i en fremgangsmåde til
(i) reduktion af et niveau af myeloid-afledte suppressorceller (MDSC) hos en patient med tyktarmskræft med behov derfor, og hvis kræft tidligere er blevet behandlet med en PD-L1-inhibitor, hvor fremgangsmåden yderligere omfatter indgivelse af en PD-1-inhibitor

til patienten med behov derfor og bestemmelse af niveauet af MDSC'er efter indgivelsen;
(ii) reduktion af et niveau af regulatoriske T-celler (Treg-celler) hos en patient med tyktarmskræft med behov derfor, og hvis tyktarmskræft tidligere er blevet behandlet med en PD-L1-inhibitor, hvor fremgangsmåden yderligere omfatter indgivelse af en PD-1-inhibitor til patienten med behov derfor og bestemmelse af niveauet af Treg-celler efter indgivelsen;
(iii) forøgelse af aktiviteten af en naturlig dræber (NK) eller cytotoksisk T-celleaktivitet *in vivo* hos en patient med tyktarmskræft med behov derfor, og hvis kræft tidligere er blevet behandlet med en PD-L1-inhibitor, hvor fremgangsmåden yderligere omfatter indgivelse af en terapeutisk effektiv mængde af forbindelsen i kombination med PD-1-inhibitoren til patienten; eller
(iv) forøgelse af antistofafhængig cellemedieret cytotoksicitet hos en patient med tyktarmskræft med behov derfor, og hvis kræft tidligere er blevet behandlet med en PD-L1-inhibitor, hvor fremgangsmåden yderligere omfatter indgivelse af en PD-1-inhibitor til patienten med behov derfor.

6. Forbindelse repræsenteret ved strukturen:



eller et farmaceutisk acceptabelt salt deraf,
til anvendelse i en fremgangsmåde til behandling af en primær eller sekundær tyktarmskræft hos et individ, hvis tyktarmskræft tidligere er blevet behandlet med en PD-L1-inhibitor, hvor fremgangsmåden yderligere omfatter indgivelse af en PD-1-inhibitor; og hvor behandlingen resulterer i en eller flere af følgende (i) reduktion af antallet af tyktarmskræftceller; (ii) reduktion af tumorvolumen; (iii) forøgelse af tumorregressionshastigheden; (iv) reduktion af eller opbremsning af tyktarmskræftcelleinfiltration i

perifere organer; (v) reduktion af eller opbremsning af tumormetastase; (vi) reduktion af eller inhibering af tumorvækst; (vii) forebyggelse eller forsinkelse af forekomst og/eller gentagelse af kræften og/eller forlængelse af sygdoms- eller tumorfri overlevelsestid; (viii) forøgelse af den samlede overlevelsestid; (ix) reduktion af behandlingshyppigheden; (x) reduktion af tyktarmskræftbyrden og (xi) lindring af et eller flere af symptomer forbundet med tyktarmskræften.

7. Forbindelsen til anvendelse ifølge krav 6, hvor forbindelsen indgives med PD-1-inhibitoren før, samtidig med, efterfølgende eller kombinationer deraf, til en behandling af den primære tumor;

i særdeles hvor behandlingen af den primære tumor er én eller flere af stråling, kirurgi, kemoterapi, immunterapi, målrettet terapi, hormonterapi, stamcelletransplantation, kryoterapi, laserterapi og præcisionsmedicin; eller hvor forbindelsen før indgivelse af kombinationen indgives som et enkelt middel i en periode.

8. HDAC-inhibitoren til anvendelse ifølge krav 1, hvor kræften efter behandling med PD-L1-inhibitoren resulterede i delvis respons, men senere udvikler resistens over for PD-L1-inhibitoren med progression af sygdom;

hvor kræften efter behandling med PD-L1-inhibitoren resulterede i stabil sygdom, men senere udvikler resistens over for PD-L1-inhibitoren med progression af sygdom;

hvor kræften efter behandling med PD-L1-inhibitoren resulterede i et fuldstændigt respons, men senere udvikler resistens over for PD-L1-inhibitoren med progression af sygdom; eller

hvor kræften efter behandling med PD-L1-inhibitoren ikke resulterede i noget respons på behandlingen.

9. Forbindelsen til anvendelse ifølge krav 1, hvor forbindelsen indgives i en mængde på ca. 20 mg, ca. 30 mg eller ca. 40 mg BIW; eller

hvor forbindelsen indgives dagligt; eller

hvor PD-1-inhibitoren og forbindelsen indgives samtidigt på dag 1 af et indgivelsesregime.

10. Forbindelsen til anvendelse ifølge krav 1,

hvor regimet omfatter en hvileperiode på mindst 1 dag mellem konsekutive indgivelsesperioder; eller

hvor forbindelsen indgives 2 til 3 gange om ugen i regimet, og PD-1-inhibitoren indgives hver 2. til 3. uge; eller

hvor forbindelsen indgives QD i 21 dage i regimet, og PD-1-inhibitoren indgives hver 2. til 3. uge.

DRAWINGS

Drawing

Fig. 1 Median Tumor Volume (Example 1, for all Groups)

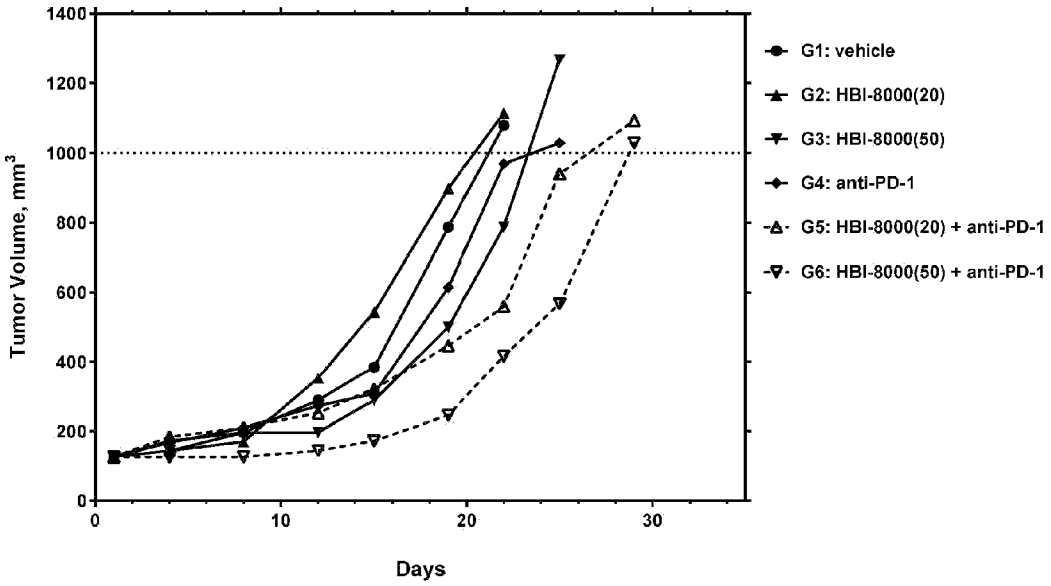


Fig. 2 Median Tumor Volume (Example 1, HBI-8000, 50 mpk groups)

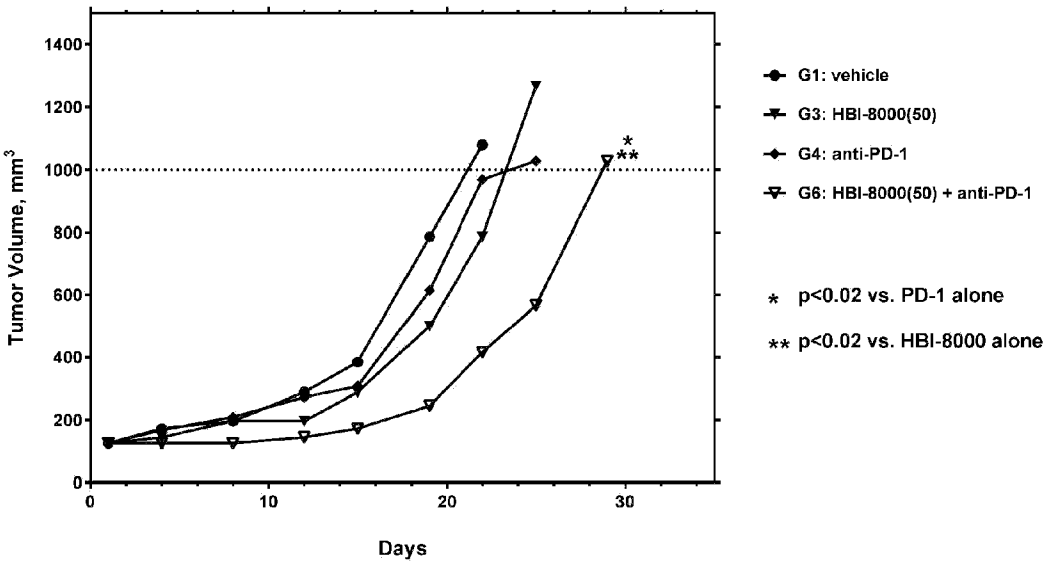
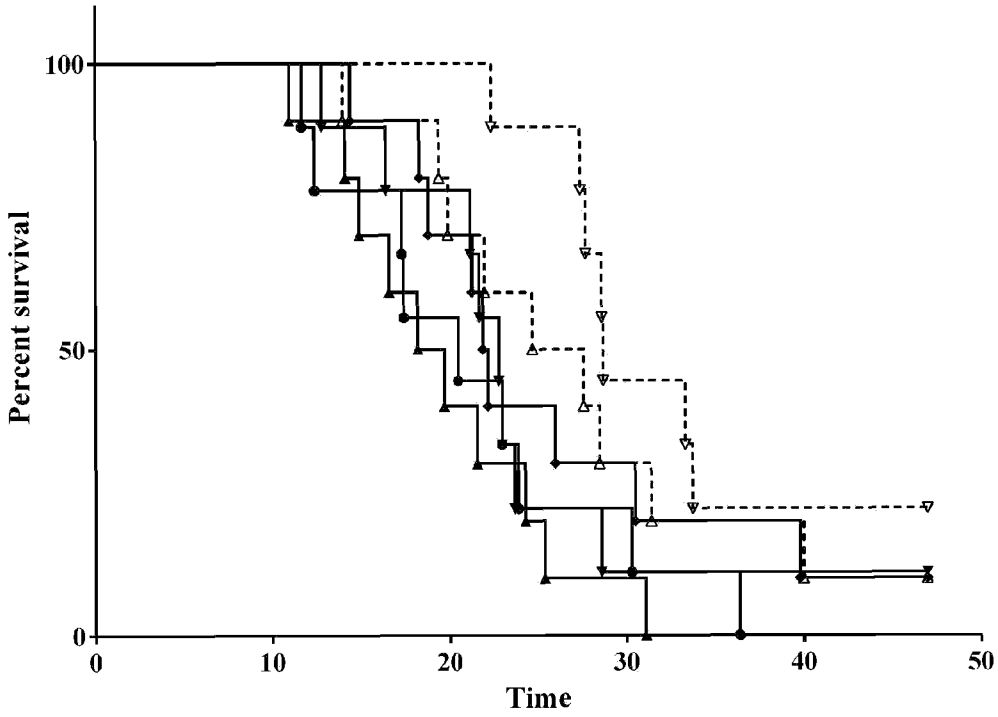
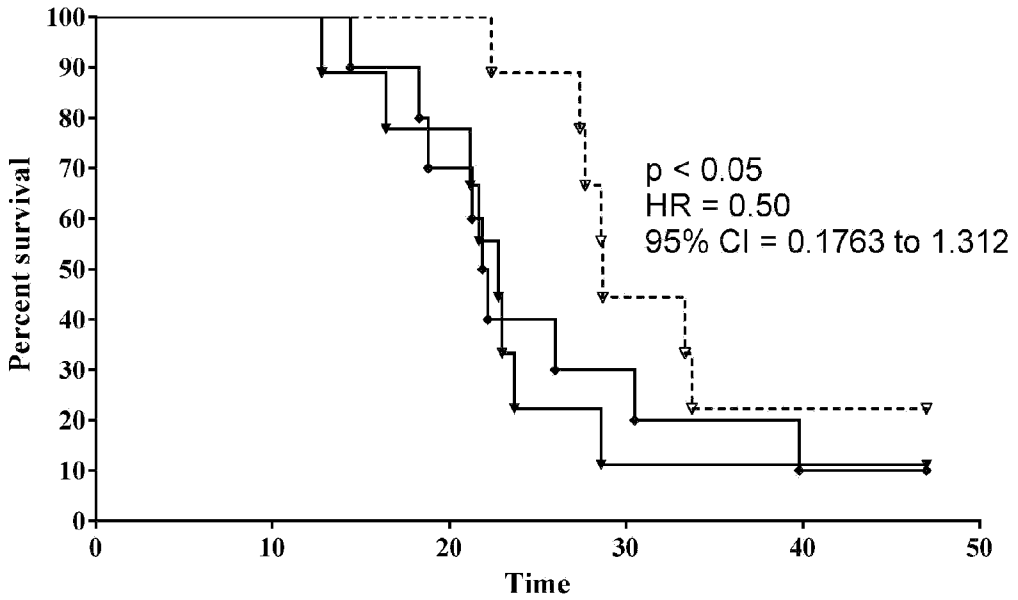


Fig. 3 Kaplan-Meier Survival Plot (Example 1, All groups)



- Group 1: vehicle (po, qd x 21)
- Group 2: HBI8000 (20 mpk po, qd x 21)
- Group 3: HBI8000 (50 mpk po, qd x 21
- Group 4: anti-PD-1 (5 mpk ip, biw x 3)
- Group 5: HBI8000 (20 mpk po, qd x 21), anti-PD-1 (5 mpk ip, biw x 3)
- Group 6: HBI8000 (50 mpk po, qd x 21), anti-PD-1 (5 mpk ip, biw x 3)

Fig. 4: Kaplan-Meier Survival Plot (Example 1, HBI-8000, 50 mpk groups)



Median Survival (d)	
22.8	Group 3: HBI8000 (50 mpk)
22.1	Group 4: anti-PD-1 (5 mpk)
28.7	Group 6: HBI8000 (50 mpk), anti-PD-1 (5 mpk)

Figure 5: Median Tumor Volume (Example 2, all groups)

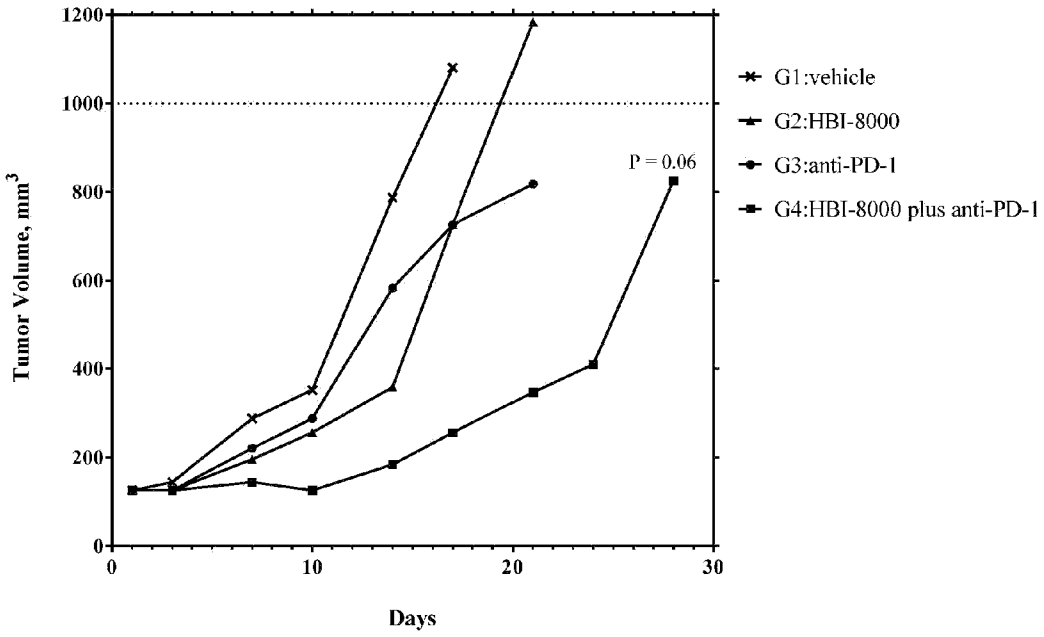


Figure 6: Kaplan-Meier Survival Plot (Example 2, All groups)

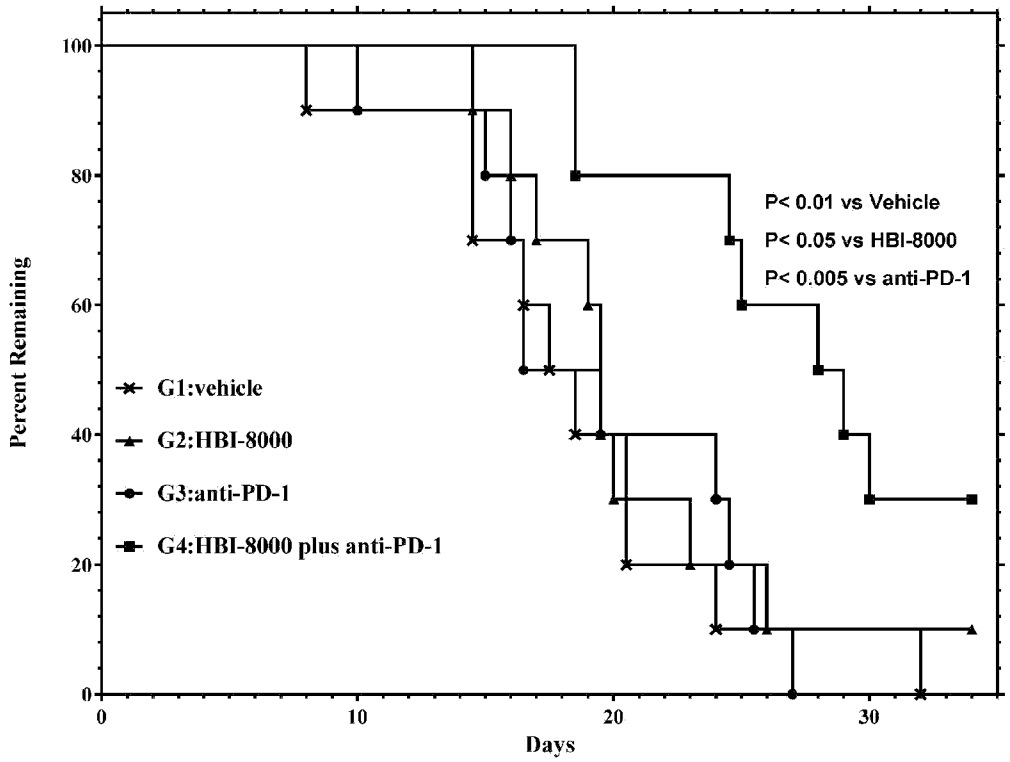


Figure 7: Individual Times to Study Endpoint for Each Animal (Example 2, all groups)

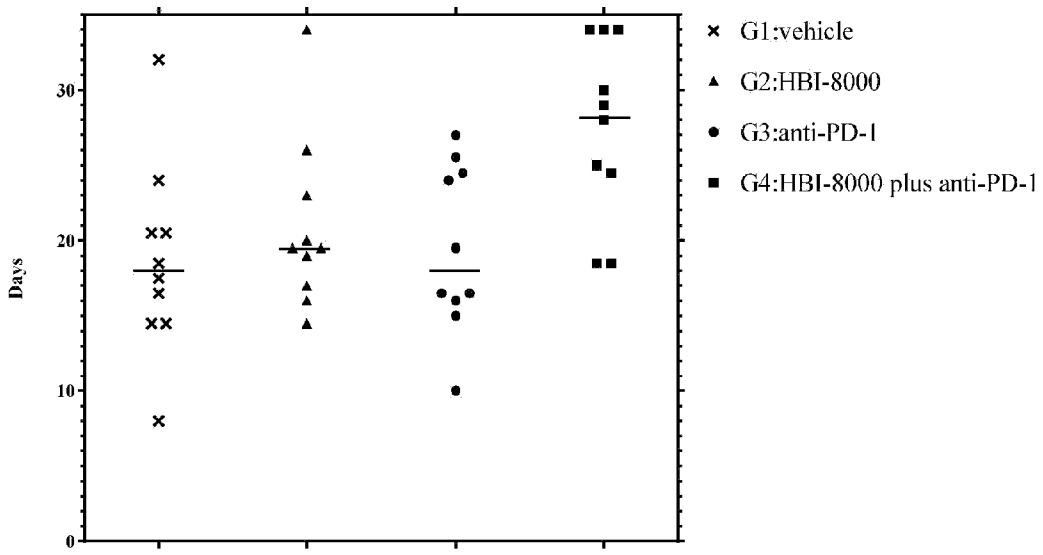


Figure 8: Kaplan-Meier Survival Plot (Example 3, All groups)

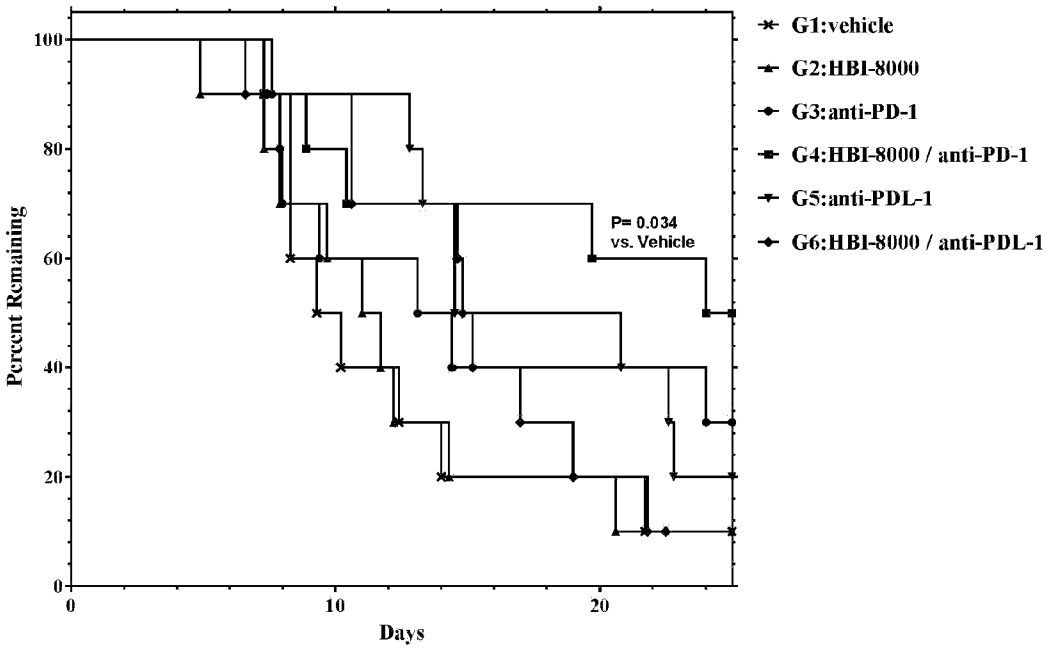


Figure 9: Individual Times to Study Endpoint for Each Animal (Example 3, all groups)

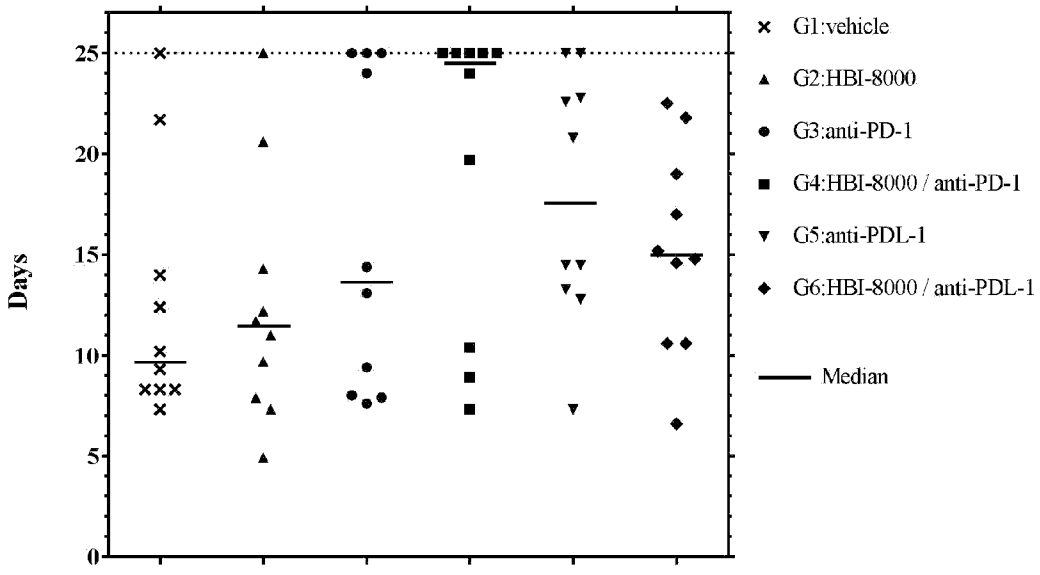


Figure 10: Number of Metastatic Lung Foci (Example 4, all groups)

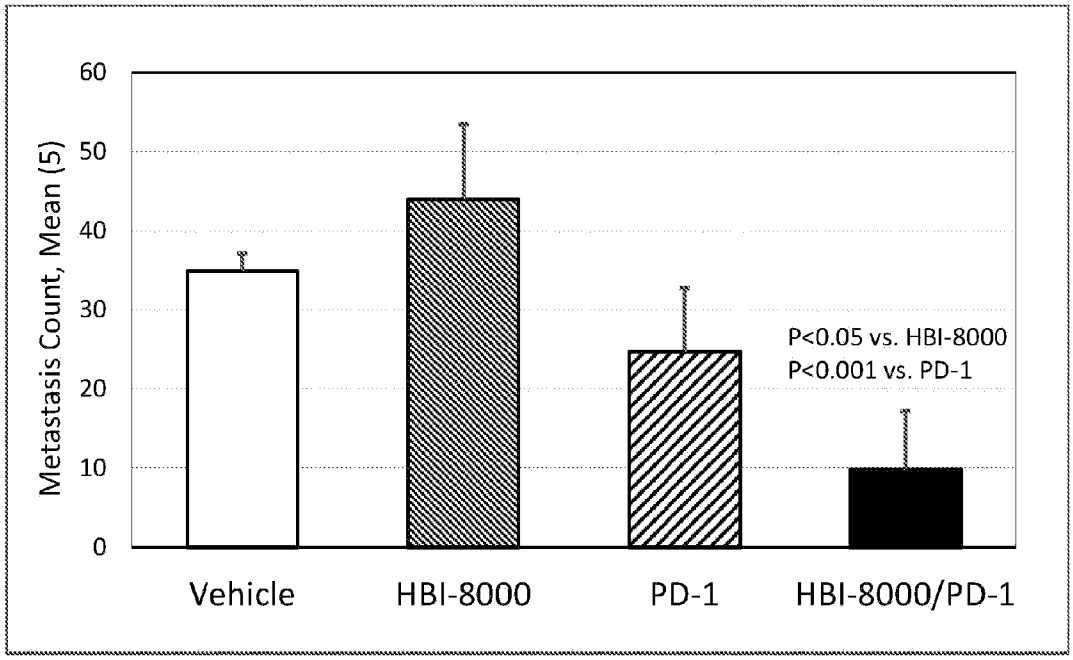


Figure 11: Median Tumor Volume (Example 5, all groups)