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(54) **Title:** THERAPEUTIC COMPOSITIONS AND METHODS FOR TREATING TUMORS

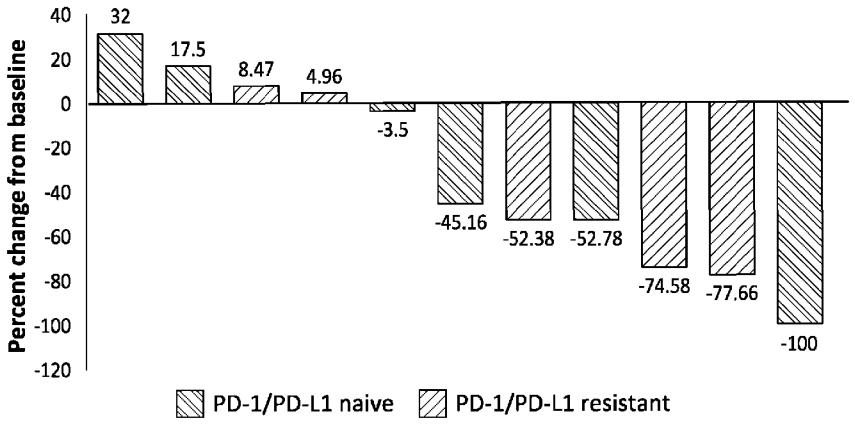


FIG. 1

(57) **Abstract:** Disclosed herein are methods of treating, preventing or ameliorating a disease or condition associated with cancer or a tumor. In some embodiments, the method includes administering a compound of Formula (I) to a subject in need thereof wherein the cancer or the tumor is or becomes resistant to one or more immune checkpoint inhibitors.

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THERAPEUTIC COMPOSITIONS AND METHODS FOR TREATING TUMORS

CROSS REFERENCE TO RELATED APPLIATIONS

[0001] This patent application claims the benefit of priority to U.S. Provisional Application No. 63/214010, filed June 23, 2021, and U.S. Provisional Application No. 63/173015, filed April 9, 2021. All of the foregoing applications are fully incorporated herein by reference in their entireties for all purposes.

Field of the Disclosure

[0002] The present disclosure relates to the field of chemistry and medicine. More particularly, the present disclosure relates to compositions containing Plinabulin, and its use in treatment.

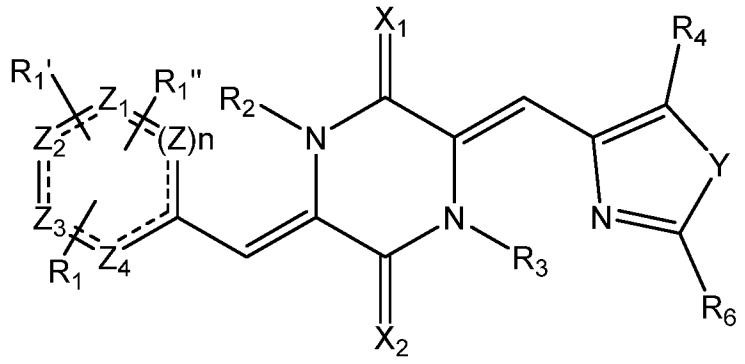
BACKGROUND

[0003] Human cancers harbor numerous genetic and epigenetic alterations, generating neoantigens potentially recognizable by the immune system (Sjoblom et al, 2006). The adaptive immune system, comprised of T and B lymphocytes, has powerful anti-cancer potential, with a broad capacity and exquisite specificity to respond to diverse tumor antigens.

[0004] Recent cancer immunotherapy research has focused substantial effort on approaches that enhance anti-tumor immunity by mediating an adaptive immune response to relevant antigens, providing specific immune-stimulatory agents such as immune checkpoint inhibitors. While cancer remains as an incurable disease for the great majority of patients, there exists a particular need for developing effective therapeutic agents and treatment regimens that can be used in cancer therapy. Patients receiving immune checkpoint inhibitors may initially respond to these checkpoint inhibitors, but at a later time become unresponsive (resistant) to these checkpoint inhibitors, or may not respond to these checkpoint inhibitors from the start of their administration ('non-responders').

SUMMARY OF THE DISCLOSURE

[0005] Some aspects described herein relate to a method of treating cancer in a subject. In some embodiments comprises administering to the subject a compound of Formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein: R_1, R_4, and R_6, are each separately selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1,-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups, hydroxy, carboxy, —CO—O—R_7,cyano, alkylthio, halogenated alkyl including polyhalogenated alkyl, halogenated carbonyl, and carbonyl —CH_2CO—R_7, wherein R_7 is selected from a hydrogen atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups; R_1' and R_1'' are each independently selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups, hydroxy, carboxy, —CO—O—R_7, cyano, alkylthio, halogenated alkyl including polyhalogenated alkyl, halogenated carbonyl, and carbonyl —CH_2CO—R_7, wherein R_7 is selected from a hydrogen atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups; R, R_1' and R_1''

are either covalently bound to one another or are not covalently bound to one another; R_2, R_3, and R_5 are each separately selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1-C_{12} alkyl, unsaturated C_1-C_{12} alkenyl, acyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, and substituted nitro groups, sulfonyl and substituted sulfonyl groups; m is an integer equal to zero, one or two; X_1 and X_2 are separately selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, and Y is selected from the group consisting of a NR_5, an oxygen atom, a sulfur atom, a oxidized sulfur atom, a methylene group and a substituted methylene group; Z, for each separate n, if non-zero, and Z_1, Z_2, Z_3 and Z_4 are each separately selected from a carbon atom, a sulfur atom, a nitrogen atom or an oxygen atom; the dashed bonds may be either single or double bonds, wherein the cancer was resistant to prior treatment with one or more immune checkpoint inhibitor.

[0006] In some embodiments, the subject has a tumor that is resistant to immune checkpoint inhibitors. In some embodiments, the tumor that progressed after using immune checkpoint inhibitors. In some embodiments, the tumor that did not respond to checkpoint inhibitors. In some embodiments, the method further comprises administering an additional chemotherapy agent. In some embodiments, the additional chemotherapy agent is administered before administering the compound of formula (I) to the subject. In some embodiments, the additional chemotherapy agent is a taxane. In some embodiments, the taxane is docetaxel. In some embodiments, the one or more immune checkpoint inhibitor to which the subject was resistant is a PD-1 inhibitor, PD-L1 inhibitor, a CTLA-4 inhibitor, or a combination thereof. In some embodiments, the one or more immune checkpoint inhibitor to which the subject was resistant is a PD-1 inhibitor. In some embodiments, the one or more immune checkpoint inhibitor to which the subject was resistant is a PD-L1 inhibitor. In some embodiments, the one or more immune checkpoint inhibitor to which the subject was resistant is a CTLA-4 inhibitor. In some embodiments, the one or more immune checkpoint inhibitor to which the subject was resistant is pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, pembrolizumab, pidilizumab, ipilimumab, BMS 936559, durvalumab, spartalizumab, or any combinations thereof. In some embodiments, the one or more immune checkpoint inhibitor to which the subject was resistant is nivolumab and

ipilimumab. In some embodiments, the cancer is selected from a breast cancer, a bladder cancer, a glioma, a glioblastoma, a head and neck cancer, a non-small cell lung cancer, a small cell lung cancer, recurrent small cell lung cancer (SCLC), a colorectal cancer, a gastrointestinal stromal tumor, a gastroesophageal carcinoma, a renal cell cancer, a prostate cancer, a liver cancer, a colon cancer, a pancreatic cancer, an ovarian cancer, a lymphoma, or a cutaneous T-cell lymphoma, or a melanoma. In some embodiments, the cancer is recurrent small cell lung cancer (SCLC).

[0007] In some embodiments, the method further comprises co-administering to the subject an immune checkpoint inhibitor. In some embodiments, the co-administered one or more immune checkpoint inhibitor is a PD-1 inhibitor, PD-L1 inhibitor, a CTLA-4 inhibitor, or a combination thereof. In some embodiments, the co-administered one or more immune checkpoint inhibitor is pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, pembrolizumab, pidilizumab, ipilimumab, BMS 936559, durvalumab, spartalizumab, or any combinations thereof. In some embodiments, the comprises administering a PD-1 antibody and a CTLA-4 antibody. In some embodiments, the PD-1 antibody is nivolumab and the CTLA-4 antibody is ipilimumab. In some embodiments, the nivolumab is administered first followed by administering ipilimumab. In some embodiments, the nivolumab is administered on the same day as ipilimumab. In some embodiments, the nivolumab and the ipilmumab are administered on the same day every two weeks. In some embodiments, of claim 21, wherein the nivolumab and the ipilmumab are administered on the same day every three weeks. In some embodiments, the nivolumab and the ipilmumab are administered on the same day every three weeks for four doses. In some embodiments, the nivolumab is administered at a range from about 100 mg to 600 mg. In some embodiments, the nivolumab is administered at a range from about 240 mg to 480 mg. In some embodiments, the co-administered one or more immune checkpoint inhibitor and the compound of Formula (I) is administered during four dosing cycles. In some embodiments, the subject receives the co-administered one or more immune checkpoint inhibitor and a compound of Formula (I) every 21-days. In some embodiments, the method further comprises administering radiation to the subject. In some embodiments, the radiation is administered before administering the compound of Formula (I) to the subject.

[0008] In some embodiments, the method further comprises administering a PD-1 or PD-L1 inhibitor and an additional chemotherapy agent to the subject. In some embodiments, further comprises administering a PD-1 or PD-L1 inhibitor and radiation to the subject. In some embodiments, the method further comprises administering a PD-1 or PD-L1 inhibitor and a CTLA-4 inhibitor to the subject. In some embodiments, the method further comprises administering a CTLA-4 inhibitor and radiation to the subject. In some embodiments, the compound of Formula (I) is administered at a dose from about 5 mg/m^2 to 150 mg/m^2. In some embodiments, the compound of Formula (I) is administered at a dose of about 20 mg/m^2 to about 30 mg/m^2. In some embodiments, the compound of formula (I) is administered orally, sublingually, buccally, subcutaneously, intravenously, intranasally, intratumorally, topically, transdermally, intradermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, or intraocularly. In some embodiments, the compound of Formula (I) is administered on day 1 of a 14 day dosing cycle. In some embodiments, the compound of Formula (I) is administered on day 1 of a 21 day dosing cycle. In some embodiments, the compound of Formula (I) is selected from plinabulin, (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-d-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(phenylmethylene-d)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenylmethylene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-d-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(4-Fluoro-(phenyl-2,3,5,6-d_4))-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(4-Fluoro-(phenyl-2,3,5,6-d_4))-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-fluorobenzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-benzoylbenzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(4-fluorobenzoyl)benzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(4-methoxybenzoyl)benzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-methoxybenzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-

yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(trifluoromethyenzydene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; and a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I) is plinabulin or a pharmaceutically acceptable salt thereof. In some embodiments, wherein a mass of the tumor is reduced from about 50% to about 100%. In some embodiments, the tumor mass is reduced from about 50% to about 70%.

[0009] Some aspects relate to a method of halting or reversing progressive cancer in a subject. In some embodiments, the method comprises administering a compound of Formula (I), wherein the subject was resistant to prior treatment with one or more immune checkpoint inhibitors. In some embodiments, the compound of Formula I is plinabulin or a pharmaceutically acceptable salt thereof. In some embodiments, the method comprises administering an additional chemotherapeutic agent to the subject. In some embodiments, the method comprises administering a PD-1 or PD-L1 inhibitor to the subject. In some embodiments, the method comprises administering a CTLA-4 inhibitor to the subject. In some embodiments, the method comprises administering radiation to the subject. In some embodiments, the method comprises administering a PD-1 or PD-L1 inhibitor to the subject. In some embodiments, the method comprises administering a CTLA-4 inhibitor to the subject. In some embodiments, the method comprises administering a PD-1 or PD-L1 inhibitor and CTLA-4 inhibitor to the subject. In some embodiments, the progressive disease is a tumor. In some embodiments, a mass of the tumor is reduced from about 50% to about 100%. In some embodiments, the tumor mass is reduced from about 50% to about 70%. In some embodiments, the radiation is administered after administering a compound of Formula (I). In some embodiments, the radiation is administered prior to administration of a compound of Formula (I). In some embodiments, the compound of Formula (I) is administered as a single dose after administering radiation. In some embodiments, wherein the compound of Formula (I) is administered in two doses after administering radiation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 illustrates a waterfall plot of best overall response in target lesions compared to baseline.

[0011] FIG. 2A illustrates the plots of log-transformed values for the mean erythrocyte sedimentation rate (ESR) at each cycle. FIG. 2B illustrates the plots of log-transformed values for the mean high sensitivity C-reactive protein (CRP) at each cycle.

DETAILED DESCRIPTION

[0012] The present disclosure provides method and therapeutic compositions for reversing non-response or enhancing response to immune checkpoint inhibitor therapy for treating, ameliorating, or preventing a cancer or a tumor in a subject. In some embodiments, methods and compositions provided herein are useful in treating, delaying the progression of, preventing relapse of or alleviating a symptom of a cancer or other neoplastic condition using a compound of Formula (I). In some embodiments, the compound of Formula (I) is plinabulin. Plinabulin, (3*Z*,6*Z*)-3-Benzylidene-6-{[5-(2-methyl-2-propanyl)-1*H*-imidazol-4-yl]methylene}-2,5-piperazinedione, is a synthetic analog of the natural compound phenylahistin. Plinabulin can efficiently promote antigen processing and presentation by dendritic cells to effector cells, such as T-cells, and migration of dendritic cells to lymph nodes where tumor-specific antigens are presented by dendritic cells to prime immune effector cells. Exposure of dendritic cells to Plinabulin can induce maturation of dendritic cells and significantly increase their ability to prime T cells.

[0013] Some embodiments disclosed herein include administration of a compound of Formula (I) (e.g., plinabulin) to a cancer subject who initially responded to, but became refractory to prior immuno oncology therapy, for example, therapy with one or more immune checkpoint inhibitors. As described herein, it was surprisingly discovered that plinabulin can be effective against such refractory cancers.

[0014] Some embodiments disclosed herein include administration of a compound of Formula (I) (e.g., plinabulin) to a cancer subject who initially did not respond ('non-responders') to prior immuno oncology therapy, for example, therapy with one or more immune checkpoint inhibitors. As described herein, it was surprisingly discovered that adding plinabulin to checkpoint inhibitors can be effective in non-responders.

[0015] Before the present disclosure is further described, it is to be understood that this disclosure is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of

describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims. Methods recited herein may be carried out in any order of the recited events which is logically possible, as well as the recited order of events.

[0016] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0017] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

[0018] It must be noted that as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

Definitions

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications, and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0020] The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

[0021] The term "antagonist" as used herein refers to a compound that can combine with a receptor (e.g., an immune checkpoint receptor) to block a cellular activity. An antagonist may be a ligand that directly binds to the receptor. Alternatively, an antagonist may combine with a receptor indirectly by, for example, (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise results in the modification of another compound so that the other compound directly binds to the receptor.

[0022] The term "ameliorate" as used herein refers to any reduction in the extent, severity, frequency, and/or likelihood of a symptom or clinical sign characteristic of a particular condition.

[0023] The term "antibody" or "antibody moiety" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. Antibodies utilized in the present disclosure may be polyclonal antibodies or monoclonal antibodies. Antibodies also include free antibodies and antigen binding fragments derived therefrom, and conjugates, e.g. pegylated antibodies, drug, radioisotope, or toxin conjugates, and the like. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the targeting and/or depletion of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Pat. No. 5,985,660; and Morrison et al. Cell, 96:737-49 (1999)). These techniques allow for the screening of particular populations of cells; in immunohistochemistry of biopsy samples; in detecting the presence of markers shed by cancer cells into the blood and other biologic fluids, and the like. Humanized versions of such antibodies are also within the scope of this disclosure. Humanized antibodies are especially useful for *in vivo* applications in humans due to their low antigenicity.

[0024] The terms "cancer", "neoplasm", and "carcinoma", are used interchangeably herein to refer to cells which exhibit relatively autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In general, cells of interest for detection or treatment in the present application include precancerous (e.g., benign), malignant, pre-metastatic, metastatic, and non-metastatic cells. Detection of cancerous cells is of particular interest.

[0025] The term "immune checkpoint inhibitor" as used herein refers to a molecule (e.g., small molecule, peptide, polypeptide, protein, antibody, antibody fragment and the like) that acts as an inhibitor (antagonist) of an immune checkpoint pathway. Inhibition of a pathway can include blockade of the pathway through binding to a receptor or signaling molecule that is part of the immune checkpoint pathway.

[0026] The term "polypeptide" is used herein as a generic term to refer to native protein, fragments, or analogs of a polypeptide sequence. Hence, native protein fragments, and analogs are species of the polypeptide genus.

[0027] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, which is incorporated herein by reference in its entirety. The pharmaceutically acceptable excipient can be a monosaccharide or monosaccharide derivative.

[0028] The term "subject" as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate.

[0029] The term "mammal" is used in its usual biological sense. Thus, it specifically includes, but is not limited to, primates, including simians (chimpanzees, apes,

monkeys) and humans, cattle, horses, sheep, goats, swine, rabbits, dogs, cats, rodents, rats, mice, guinea pigs, or the like.

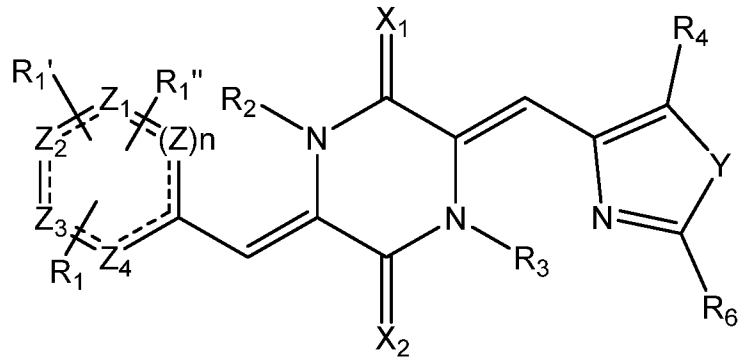
[0030] The terms "effective amount" or a "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent that is effective to relieve, to some extent, or to reduce the likelihood of onset of, one or more of the symptoms of a disease or condition, and can include curing a disease or condition.

[0031] The terms "treat," "treatment," or "treating," as used herein refers to administering a compound or pharmaceutical composition to a subject for prophylactic and/or therapeutic purposes. The term "prophylactic treatment" refers to treating a subject who does not yet exhibit symptoms of a disease or condition, but who is susceptible to, or otherwise at risk of, a particular disease or condition, whereby the treatment reduces the likelihood that the patient will develop the disease or condition. The term "therapeutic treatment" refers to administering treatment to a subject already suffering from a disease or condition.

[0032] As used herein, the term "chemotherapeutic agent" refers to an agent that reduces, prevents, mitigates, limits, and/or delays the growth of metastases or neoplasms, or kills neoplastic cells directly by necrosis or apoptosis of neoplasms or any other mechanism, or that can be otherwise used, in a pharmaceutically-effective amount, to reduce, prevent, mitigate, limit, and/or delay the growth of metastases or neoplasms in a subject with neoplastic disease. Chemotherapeutic agents include but are not limited to, for example, fluoropyrimidines; pyrimidine nucleosides; purine nucleosides; anti-folates, platinum-based agents; anthracyclines/anthracenediones; epipodophyllotoxins; camptothecins; hormones; hormonal complexes; antihormonals; enzymes, proteins, peptides and polyclonal and/or monoclonal antibodies; vinca alkaloids; taxanes; epothilones; antimicrotubule agents; alkylating agents; antimetabolites; topoisomerase inhibitors; antivirals; and various other cytotoxic and cytostatic agents.

Compounds

[0033] In some embodiments, the compounds and therapeutic compositions for treating a cancer or tumor described herein include a compound represented by Formula (I):



(I).

[0034] In some embodiments of Formula (I), R_1, R_4, and R_6, are each separately selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1,-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups, hydroxy, carboxy, —CO—O—R_7,cyano, alkylthio, halogenated alkyl including polyhalogenated alkyl, halogenated carbonyl, and carbonyl —CH_2CO—R_7, wherein R_7 is selected from a hydrogen atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups.

[0035] In some embodiments of Formula (I), R_1' and R_1'' are each independently selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups, hydroxy, carboxy, —CO—O—R_7, cyano, alkylthio, halogenated alkyl including polyhalogenated alkyl, halogenated carbonyl, and carbonyl —CH_2CO—R_7, wherein R_7 is selected from a hydrogen atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups.

[0036] In some embodiments of Formula (I), R, R_1' and R_1'' are either covalently bound to one another or are not covalently bound to one another.

[0037] In some embodiments of Formula (I), R_2, R_3, and R_5 are each separately selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1-C_{12} alkyl, unsaturated C_1-C_{12} alkenyl, acyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, and substituted nitro groups, sulfonyl and substituted sulfonyl groups.

[0038] In some embodiments of Formula (I), m is an integer equal to zero, one or two.

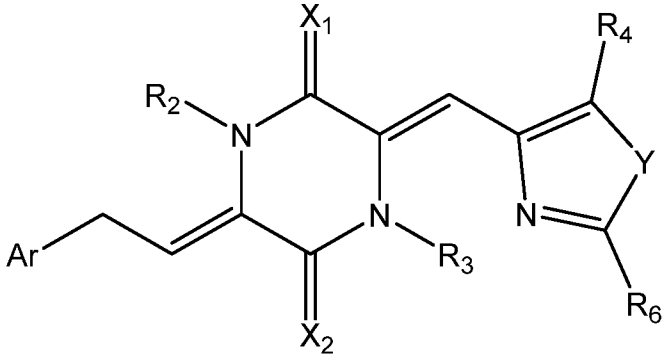
[0039] In some embodiments of Formula (I), X_1 and X_2 are separately selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom.

[0040] In some embodiments of Formula (I), Y is selected from the group consisting of NR_5, an oxygen atom, a sulfur atom, a oxidized sulfur atom, a methylene group and a substituted methylene group.

[0041] In some embodiments of Formula (I), Z, for each separate n, if non-zero, and Z_1, Z_2, Z_3 and Z_4 are each separately selected from a carbon atom, a sulfur atom, a nitrogen atom or an oxygen atom; and the dashed bonds may be either single or double bonds.

[0042] A compound of Formula (I) can be readily prepared according to methods and procedures detailed in U.S. Patent Nos. 7,064,201 and 7,919,497, which are incorporated herein by reference in their entireties.

[0043] In some embodiments, the compounds described herein are a dehydrophenylahistin represented by Formula (II):



(II).

[0044] In some embodiments of Formula (II), R_2 and R_3 are each separately selected from the group consisting of a hydrogen atom; a halogen atom; mono-substituted; poly-substituted or unsubstituted, straight or branched chain variants of the following residues: C_1-C_{12} alkyl, C_1-C_{12} alkenyl, acyl, and alkoxy; and mono-substituted, poly-substituted or unsubstituted variants of the following residues: cycloalkyl, cycloalkoxy, aryl, heteroaryl, amino, nitro, and sulfonyl; or R_2 is a bond to Ar.

[0045] In some embodiments of Formula (II), R_4 and R_6 are each separately selected from the group consisting of hydrogen; halogen; hydroxyl; mono-substituted, poly-substituted or unsubstituted, straight or branched chain variants of the following residues: C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, alkoxy, acyl, arylalkyl, heteroarylalkyl, alkyloxycarbonyloxy, ester, arylalkoxy, alkoxy, and alkylthio; mono-substituted, poly-substituted or unsubstituted variants of the following residues: acyloxy, aryloxycarbonyloxy, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, heteroaryl, aryloxy, arylcarbonyl, heterocycloalkyl, carbonyl, amino, aminocarbonyl, amide, aminocarbonyloxy, nitro, azido, phenyl, hydroxyl, thio, alkylthio, arylthio, thiooxysulfonyl, thiophene, carboxy, and cyano.

[0046] In some embodiments of Formula (II), X_1 and X_2 are separately selected from the group consisting of an oxygen atom, a sulfur atom, and a nitrogen atom substituted with a R_5 group.

[0047] In some embodiments of Formula (II), R_5 is selected from the group consisting of a hydrogen atom, a halogen atom, and saturated C_1-C_{12} alkyl, unsaturated C_1-C_{12} alkenyl, acyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, and substituted nitro groups, sulfonyl and substituted sulfonyl groups.

[0048] In some embodiments of Formula (II), Y is selected from the group consisting of NR_5, an oxygen atom, a sulfur atom, an oxidized sulfur atom, a methylene group, and a substituted methylene group.

[0049] In some embodiments of Formula (II), n is 0, 1, 2, 3, or 4.

[0050] In some embodiments of Formula (II), Ar is a cyclic or polycyclic aryl or heteroaryl ring system comprising between one and three rings. In some embodiments, each ring in said system is separately a 5, 6, 7, or 8 membered ring. In some embodiments, each ring in said system separately comprises 0, 1, 2, 3, or 4 heteroatoms selected from the group

consisting of oxygen, sulfur, and nitrogen. In some embodiments, each ring in said system is optionally substituted with one or more substituents selected from the group consisting of hydrogen; halogen; hydroxyl; mono-substituted, poly-substituted or unsubstituted, straight or branched chain variants of the following residues: C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, alkoxy, acyl, arylalkyl, heteroarylalkyl, alkyloxycarbonyloxy, ester, arylalkoxy, alkoxy, and alkylthio; mono-substituted, poly-substituted or unsubstituted variants of the following residues: acyloxy, aryloxycarbonyloxy, cycloalkyl, cycloalkenyl, cycloalkoxy, aryl, heteroaryl, aryloxy, arylcarbonyl, heterocycloalkyl, carbonyl, amino, aminocarbonyl, amide, aminocarbonyloxy, nitro, azido, phenyl, hydroxyl, thio, alkylthio, arylthio, thiophene, oxysulfonyl, sulfonyl, carboxy, and cyano; and an optionally substituted fused ring selected from the group consisting of dioxole, dithiole, oxathiole, dioxine, dithiine, and oxathiine.

[0051] A compound of Formula (II) can be readily prepared according to methods and procedures detailed in U.S. Patent Nos. 7,064,201 and 7,919,497, which are incorporated herein by reference in their entireties.

[0052] In some embodiments, a compound of Formula (I) is selected from plinabulin, (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-d-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(phenylmethylene-d)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenylmethylene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-d-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(4-Fluoro-(phenyl-2,3,5,6-d_4))-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(4-Fluoro-(phenyl-2,3,5,6-d_4))-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-fluorobenzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-benzoylbenzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(4-fluorobenzoyl)benzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(4-methoxybenzoyl)benzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-methoxybenzylidene)-6-((5-(tert-butyl)-

1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(trifluoromethyenzydene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; and pharmaceutically acceptable salts thereof.

[0053] In some embodiments, the compound of Formula (I) is plinabulin. In some embodiments, the compound of Formula (I) is plinabulin monohydrate. In some embodiments, the compound of Formula (I) is a salt form of plinabulin.

Immune Checkpoint Inhibitors

[0054] In some embodiments, one or more immune checkpoint inhibitor may be co-administered with a compound of Formula (I). A review describing immune checkpoint pathways and the blockade of such pathways with immune checkpoint inhibitor compounds is provided by Pardoll in *Nature Reviews Cancer* (April, 2012), pages 252-264, which is incorporated herein by reference in its entirety. Immune check point inhibitor compounds display anti-tumor activity by blocking one or more of the endogenous immune checkpoint pathways that downregulate an anti-tumor immune response. The inhibition or blockade of an immune checkpoint pathway typically involves inhibiting a checkpoint receptor and ligand interaction with an immune checkpoint inhibitor compound to reduce or eliminate the down regulation signal and resulting diminishment of the anti-tumor response.

[0055] In some embodiments of the present disclosure, the immune checkpoint inhibitor compound inhibits the signaling interaction between an immune checkpoint receptor and the corresponding ligand of the immune checkpoint receptor. The immune checkpoint inhibitor compound can act by blocking activation of the immune checkpoint pathway by inhibition (antagonism) of an immune checkpoint receptor (some examples of receptors include CTLA-4, PD-1, LAG-3, TIM-3, BTLA, and KIR) or by inhibition of a ligand of an immune checkpoint receptor (some examples of ligands include PD-L1 and PD-L2). In such embodiments, the effect of the immune checkpoint inhibitor compound is to reduce or eliminate down regulation of certain aspects of the immune system anti-tumor response in the tumor microenvironment.

[0056] The Programmed Death 1 (PD-1) protein is an inhibitory member of the extended CD28/CTLA-4 family of T cell regulators (Okazaki et al. (2002) Curr Opin

Immunol 14: 391779-82; Bennett et al. (2003) J. Immunol. 170:711-8; which are incorporated herein by reference in their entirety). Other members of the CD28 family include CD28, CTLA-4, ICOS and BTLA. PD-1 is suggested to exist as a monomer, lacking the unpaired cysteine residue characteristic of other CD28 family members. PD-1 is expressed on activated B cells, T cells, and monocytes.

[0057] The PD-1 gene encodes a 55 kDa type I transmembrane protein (Agata et al. (1996) Int Immunol. 8:765-72, which is incorporated herein by reference in its entirety). Although structurally similar to CTLA-4, PD-1 lacks the MYPPY motif that is important for B7-1 and B7-2 binding. Two ligands for PD-1 have been identified, PD-L1 (B7-H1) and PD-L2 (B7-DC), that have been shown to downregulate T cell activation upon binding to PD-1 (Freeman et al. (2000) J. Exp. Med. 192:1027-34; Carter et al. (2002) Eur. J. Immunol. 32:634-43; which are incorporated herein by reference in their entirety). Both PD-L1 and PD-L2 are B7 homologs that bind to PD-1, but do not bind to other CD28 family members. PD-L1 is abundant in a variety of human cancers (Dong et al. (2002) Nat. Med. 8:787-9, which is incorporated herein by reference in its entirety).

[0058] PD-1 is known as an immunoinhibitory protein that negatively regulates TCR signals (Ishida, Y. et al. (1992) EMBO J. 11:3887-3895; Blank, C. et al. (Epub 2006 Dec. 29) Immunol. Immunother. 56(5):739-745; which are incorporated herein by reference in their entirety). The interaction between PD-1 and PD-L1 can act as an immune checkpoint, which can lead to, e.g., a decrease in tumor infiltrating lymphocytes, a decrease in T-cell receptor mediated proliferation, and/or immune evasion by cancerous cells (Dong et al. (2003) J. Mol. Med. 81:281-7; Blank et al. (2005) Cancer Immunol. Immunother. 54:307-314; Konishi et al. (2004) Clin. Cancer Res. 10:5094-100; which are incorporated herein by reference in their entirety). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1 or PD-L2; the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai et al. (2002) Proc. Nat'l. Acad. Sci. USA 99:12293-7; Brown et al. (2003) J. Immunol. 170:1257-66; which are incorporated herein by reference in their entirety).

[0059] The immune checkpoint receptor cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) is expressed on T-cells and is involved in signaling pathways that reduce the level of T-cell activation. It is believed that CTLA-4 can downregulate T-cell activation

through competitive binding and sequestration of CD80 and CD86. In addition, CTLA-4 has been shown to be involved in enhancing the immunosuppressive activity of T_{Reg} cells.

[0060] The immune checkpoint receptor programmed death 1 (PD-1) is expressed by activated T-cells upon extended exposure to antigen. Engagement of PD-1 with its known binding ligands, PD-L1 and PD-L2, occurs primarily within the tumor microenvironment and results in downregulation of anti-tumor specific T-cell responses. Both PD-L1 and PD-L2 are known to be expressed on tumor cells. The expression of PD-L1 and PD-L2 on tumors has been correlated with decreased survival outcomes.

[0061] The immune checkpoint receptor T cell membrane protein 3 (TIM-3) is expressed on Th1 and Tc1 cells, but not other T-cells. Interaction of TIM-3 with its ligand, galectin-9, produces a Th1 cell death signal. TIM-3 has been reported to play a role in maintaining T-cell exhaustion and blockade of TIM-3 has been shown to restore activity to exhausted T-cells.

[0062] The immune checkpoint receptor B- and T-lymphocyte attenuator (BTLA) receptor is expressed on both resting and activated B-cells and T-cells. Activation of BTLA when combined with its ligand HVEM (herpes virus entry mediator) results in downregulation of both T-cell activation and proliferation. HVEM is expressed by certain tumors (e.g., melanoma) and tumor-associated endothelial cells.

[0063] The immune checkpoint receptors known as killer cell immunoglobulin-like receptors (KIR) are a polymorphic family of receptors expressed on NK cells and some T-cells and function as regulators of immune tolerance associated with natural killer (NK) cells. Blocking certain KIR receptors with inhibitor compounds can facilitate the destruction of tumors through the increased activity of NK cells.

[0064] In some embodiments of the present disclosure, the immune checkpoint inhibitor compound is a small organic molecule (molecular weight less than 1000 daltons), a peptide, a polypeptide, a protein, an antibody, an antibody fragment, or an antibody derivative. In some embodiments, the immune checkpoint inhibitor compound is an antibody. In some embodiments, the antibody is a monoclonal antibody, specifically a human or a humanized monoclonal antibody.

[0065] Monoclonal antibodies, antibody fragments, and antibody derivatives for blocking immune checkpoint pathways can be prepared by any of several methods known to those of ordinary skill in the art, including but not limited to, somatic cell hybridization techniques and hybridoma, methods. Hybridoma generation is described in *Antibodies, A Laboratory Manual, Harlow and Lane,* 1988, Cold Spring Harbor Publications, New York, which is incorporated herein by reference in its entirety. Human monoclonal antibodies can be identified and isolated by screening phage display libraries of human immunoglobulin genes by methods described for example in U.S. Pat. Nos. 5,223,409, 5,403,484, 5,571,698, 6,582,915, and 6,593,081, which are incorporated herein by reference in their entirety. Monoclonal antibodies can be prepared using the general methods described in U.S. Pat. No. 6,331,415 (Cabilly), which is incorporated herein by reference in its entirety.

[0066] As an example, human monoclonal antibodies can be prepared using a XenoMouse™ (Abgenix, Freemont, Calif.) or hybridomas of B cells from a XenoMouse. A XenoMouse is a murine host having functional human immunoglobulin genes as described in U.S. Pat. No. 6,162,963 (Kucherlapati), which is incorporated herein by reference in its entirety.

[0067] Methods for the preparation and use of immune checkpoint antibodies are described in the following illustrative publications. The preparation and therapeutic uses of anti-CTLA-4 antibodies are described in U.S. Pat. No. 7,229,628 (Allison), U.S. Pat. No. 7,311,910 (Linsley), and U.S. Pat. No. 8,017,144 (Korman), which are incorporated herein by reference in their entirety. The preparation and therapeutic uses of anti-PD-1 antibodies are described in U.S. Pat. No. 8,008,449 (Korman) and U.S. Patent Application No. 2011/0271358 (Freeman), which are incorporated herein by reference in their entirety. The preparation and therapeutic uses of anti-PD-L1 antibodies are described in U.S. Pat. No. 7,943,743 (Korman), which is incorporated herein by reference in its entirety. The preparation and therapeutic uses of anti-TIM-3 antibodies are described in U.S. Pat. No. 8,101,176 (Kuchroo) and U.S. Pat. No. 8,552,156 (Tagayanagi), which are incorporated herein by reference in their entirety. The preparation and therapeutic uses of anti-LAG-3 antibodies are described in U.S. Patent Application No. 2011/0150892 (Thudium) and International Publication Number WO2014/008218 (Lonberg), which are incorporated herein by reference in their entirety. The preparation and therapeutic uses of anti-KIR antibodies are

described in U.S. Pat. No. 8,119,775 (Moretta), which is incorporated herein by reference in its entirety. The preparation of antibodies that block BTLA regulated inhibitory pathways (anti-BTLA antibodies) are described in U.S. Pat. No. 8,563,694 (Mataraza), which is incorporated herein by reference in its entirety.

[0068] In some embodiments, the one or more immune checkpoint inhibitor is an inhibitor of PD-1, PD-L1, or CTLA-4. In some embodiments, the immune checkpoint inhibitor is a PD-1 inhibitor. In some embodiments, the immune checkpoint inhibitor is a binding ligand of PD-L1. In some embodiments, the immune checkpoint inhibitor is a PD-L1 inhibitor. In some embodiments, the immune checkpoint inhibitor is a CTLA-4 inhibitor.

[0069] In some embodiments, the one or more immune checkpoint inhibitor as described herein includes a first immune checkpoint inhibitor and a second immune checkpoint inhibitor, wherein the first immune checkpoint inhibitor is different from the second immune checkpoint inhibitor. In some embodiments, the first and the second immune checkpoint inhibitor are independently an inhibitor of PD-1, PD-L1 or CTLA-4. In some embodiments, the first immune checkpoint inhibitor is a PD-1 inhibitor, and the second immune checkpoint inhibitor is a CTLA-4 inhibitor.

[0070] In some embodiments, the immune checkpoint inhibitor is pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, pembrolizumab, pidilizumab, ipilimumab, BMS 936559, durvalumab, spartalizumab, or any combinations thereof. In some embodiments, the one or more immune checkpoint inhibitor may include an anti-PD-1 HuMAbs can be selected from 17D8, 2D3, 4H1, 5C4 (also referred to herein as nivolumab), 4A1 1, 7D3 and 5F4, all of which are described in U.S. Pat. No. 8,008,449, which is incorporated herein by reference in its entirety. In some embodiments, the anti-PD-1 HuMAbs can be selected from 3G10, 12A4 (also referred to herein as BMS-936559), 10A5, 5F8, 10H10, 1B12, 7H1, 1 1E6, 12B7, and 13G4, all of which are described in U.S. Pat. No. 7,943,743, which is incorporated herein by reference in its entirety.

[0071] In some embodiments, the one or more immune checkpoint inhibitor may be incorporated in a pharmaceutically acceptable formulation. In some embodiments, the one or more immune checkpoint inhibitor is incorporated in a pharmaceutically acceptable aqueous formulation. Examples of acceptable aqueous formulations include isotonic buffered and pH 4.5-8 adjusted saline solutions such as Lactated Ringer's Solution and the like.

[0072] In some embodiments, the immune checkpoint inhibitor compound is incorporated in a pharmaceutically acceptable liposome formulation, wherein the formulation is a passive or targeted liposome formulation. Examples of methods for the preparation of suitable liposome formulations of antibodies are described U.S. Pat. No. 5,399,331 (Loughrey), U.S. Pat. No. 8,304,565 (Wu) and U.S. Pat. No. 7,780,882 (Chang), which are incorporated herein by reference in their entirety.

[0073] In some embodiments, the one or more immune checkpoint inhibitor may be an antibody. In some embodiments, the antibody is a dry, lyophilized solid that is reconstituted with an aqueous reconstitution solvent prior to use. In some embodiments, the antibody is incorporated in a pharmaceutically acceptable formulation and the pharmaceutically acceptable formulation is injected directly into a tumor. In some embodiments, the immune checkpoint inhibitor antibody is incorporated in a pharmaceutically acceptable formulation and the pharmaceutically acceptable formulation is injected into the peritumoral region surrounding a tumor. The peritumoral region may contain antitumor immune cells. In some embodiments, the antibody is incorporated in a pharmaceutically acceptable formulation and the pharmaceutically acceptable formulation is administered by intravenous injection or infusion. In some embodiments, the immune checkpoint inhibitor antibody is incorporated in a pharmaceutically acceptable formulation and the pharmaceutically acceptable formulation is administered by subcutaneous injection or intradermal injection. In some embodiments, the antibody is incorporated in a pharmaceutically acceptable formulation and the pharmaceutically acceptable formulation is administered by intraperitoneal injection or lavage.

[0074] The precise amount of immune checkpoint inhibitor compound incorporated in a particular method or therapeutic combination of the disclosure may vary according to factors known in art such as for example, the physical and clinical status of the subject, the method of administration, the content of the formulation, the physical and chemical nature of the immune checkpoint inhibitor compound, the intended dosing regimen or sequence. Those of ordinary skill in the art, however, can readily determine the appropriate amount with due consideration of such factors.

Chemotherapeutic Agents

[0075] In some embodiments, the compound of Formula (I) is co-administered with an additional chemotherapeutic agent. In some embodiments, an additional chemotherapeutic agent can be selected from the group consisting of Abiraterone, Acetate, Abitrexate (Methotrexate), Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation), ABVD, ABVE, ABVE-PC, AC, AC-T, ADE, Ado-Trastuzumab Emtansine ,Adriamycin (Doxorubicin Hydrochloride), Afatinib Dimaleate, Afinitor (Everolimus), Akynzeo (Netupitant and Palonosetron Hydrochloride), Aldara (Imiquimod), Aldesleukin, Alecensa (Alectinib), Alectinib, Alemtuzumab, Alimta (Pemetrexed Disodium), Aloxi (Palonosetron Hydrochloride), Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Aminolevulinic Acid, \ Anastrozole, Aprepitant, Aredia (Pamidronate Disodium), Arimidex (Anastrozole), Aromasin (Exemestane), Arranon (Nelarabine), Arsenic Trioxide, Arzerra (Ofatumumab), Asparaginase Erwinia chrysanthemi, Avastin (Bevacizumab), Axitinib, Azacitidine, BEACOPP, Becenum (Carmustine), Beleodaq (Belinostat), Belinostat, Bendamustine Hydrochloride, BEP, Bevacizumab, Bexarotene, Bexxar (Tositumomab and Iodine I 131 Tositumomab), Bicalutamide, BiCNU (Carmustine), Bleomycin, Blinatumomab, Blincyto (Blinatumomab), Bortezomib, Bosulif (Bosutinib), Bosutinib, Brentuximab Vedotin, Busulfan, Cabazitaxel, Cabozantinib-S-Malate, CAF, Campath (Alemtuzumab), Camptosar (Irinotecan Hydrochloride), Capecitabine, CAPOX, Carac (Fluorouracil--Topical), Carboplatin, CARBOPLATIN-TAXOL, Carfilzomib, Carmubris (Carmustine), Carmustine, Carmustine Implant, Casodex (Bicalutamide), CeeNU (Lomustine), Ceritinib, Cerubidine (Daunorubicin Hydrochloride), Cervarix (Recombinant HPV Bivalent Vaccine), Cetuximab, Chlorambucil, CHLORAMBUCIL-PREDNISONE, CHOP, Cisplatin, Clafen (Cyclophosphamide), Clofarabine, Clofarex (Clofarabine), Clolar (Clofarabine), CMF, Cobimetinib, Cometriq (Cabozantinib-S-Malate), COPDAC, COPP, COPP-ABV, Cosmegen (Dactinomycin), Cotellic (Cobimetinib), Crizotinib, CVP, Cyclophosphamide, Cyfos (Ifosfamide), Cyramza (Ramucirumab), Cytarabine, Cytarabine Liposome, Cytosar-U (Cytarabine), Cytoxan (Cyclophosphamide), Dabrafenib, Dacarbazine, Dacogen (Decitabine), Dactinomycin, Daratumumab, Darzalex (Daratumumab), Dasatinib, Daunorubicin Hydrochloride, Decitabine, Degarelix, Denileukin Diftitox, Denosumab, DepoCyt (Cytarabine Liposome), Dexamethasone, Dexrazoxane Hydrochloride,

Dinutuximab, Docetaxel, Doxil (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride, Doxorubicin Hydrochloride Liposome, Dox-SL (Doxorubicin Hydrochloride Liposome), Efudex (Fluorouracil--Topical), Elitek (Rasburicase), Ellence (Epirubicin Hydrochloride), Elotuzumab, Eloxatin (Oxaliplatin), Eltrombopag Olamine, Emend (Aprepitant), Empliciti (Elotuzumab), Enzalutamide, Epirubicin Hydrochloride, EPOCH, Erbitux (Cetuximab), Eribulin Mesylate, Erivedge (Vismodegib), Erlotinib Hydrochloride, Erwinaze (Asparaginase Erwinia chrysanthemi), Etopophos (Etoposide Phosphate), Etoposide, Etoposide Phosphate, Evacet (Doxorubicin Hydrochloride Liposome), Everolimus, Evista (Raloxifene Hydrochloride), Exemestane, 5-FU (Fluorouracil Injection), 5-FU (Fluorouracil--Topical), Fareston (Toremifene), Farydak (Panobinostat), Faslodex (Fulvestrant), FEC, Femara (Letrozole), Filgrastim, Fludara (Fludarabine Phosphate), Fludarabine Phosphate, Fluoroplex (Fluorouracil--Topical), Fluorouracil Injection, Fluorouracil—Topical, Flutamide, Folex (Methotrexate), Folex PFS (Methotrexate), FOLFIRI, FOLFIRI-BEVACIZUMAB, FOLFIRI-CETUXIMAB, FOLFIRINOX, FOLFOX, Folotyn (Pralatrexate), FU-LV, Fulvestrant, Gardasil (Recombinant HPV Quadrivalent Vaccine), Gardasil 9 (Recombinant HPV Nonavalent Vaccine), Gazyva (Obinutuzumab), Gefitinib, Gemcitabine Hydrochloride, GEMCITABINE-CISPLATIN, GEMCITABINE-OXALIPLATIN, Gemtuzumab Ozogamicin, Gemzar (Gemcitabine Hydrochloride), Gilotrif (Afatinib Dimaleate), Gleevec (Imatinib Mesylate), Gliadel (Carmustine Implant), Gliadel wafer (Carmustine Implant), Glucarpidase, Goserelin Acetate, Halaven (Eribulin Mesylate), Herceptin (Trastuzumab), HPV Bivalent Vaccine, Recombinant, HPV Nonavalent Vaccine, Recombinant, HPV Quadrivalent Vaccine, Recombinant, Hycamtin (Topotecan Hydrochloride), Hyper-CVAD, Ibrance (Palbociclib), Ibritumomab Tiuxetan, Ibrutinib, ICE, Iclusig (Ponatinib Hydrochloride), Idamycin (Idarubicin Hydrochloride), Idelalisib, Ifex (Ifosfamide), Ifosfamide, IL-2 (Aldesleukin), Imatinib Mesylate, Imbruvica (Ibrutinib), Imiquimod, Imlygic (Talimogene Laherparepvec), Inlyta (Axitinib), Interferon Alfa-2b, Recombinant, Interleukin-2 (Aldesleukin), Intron A (Recombinant Interferon Alfa-2b), Iodine I 131 Tositumomab and Tositumomab, Iressa (Gefitinib), Irinotecan Hydrochloride, Irinotecan Hydrochloride Liposome, Istodax (Romidepsin), Ixabepilone, Ixazomib Citrate, Ixempra (Ixabepilone), Jakafi (Ruxolitinib Phosphate), Jevtana (Cabazitaxel), Kadcyla (Ado-Trastuzumab Emtansine), Keoxifene (Raloxifene Hydrochloride), Kepivance (Palifermin),

Kyprolis (Carfilzomib), Lanreotide Acetate, Lapatinib Ditosylate, Lenalidomide, Lenvatinib Mesylate, Lenvima (Lenvatinib Mesylate), Letrozole, Leucovorin Calcium, Leukeran (Chlorambucil), Leuprolide Acetate, Levulan (Aminolevulinic Acid), Linfolizin (Chlorambucil), LipoDox (Doxorubicin Hydrochloride Liposome), Lomustine, Lonsurf (Trifluridine and Tipiracil Hydrochloride), Lupron (Leuprolide Acetate) ,Lupron Depot (Leuprolide Acetate), Lupron Depot-Ped (Leuprolide Acetate), Lupron Depot-3 Month (Leuprolide Acetate), Lupron Depot-4 Month (Leuprolide Acetate), Lynparza (Olaparib), Marqibo (Vincristine Sulfate Liposome), Matulane (Procarbazine Hydrochloride), Mechlorethamine Hydrochloride, Megace (Megestrol Acetate), Megestrol Acetate, Mekinist (Trametinib), Mercaptopurine, Mesna, Mesnex (Mesna), Methazolastone (Temozolomide), Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Mitomycin C, Mitoxantrone Hydrochloride, Mitozytrex (Mitomycin C), MOPP,Mozobil (Plerixafor), Mustargen (Mechlorethamine Hydrochloride), Mutamycin (Mitomycin C), Myleran (Busulfan), Mylosar (Azacitidine), Mylotarg (Gemtuzumab Ozogamicin), Nanoparticle Paclitaxel (Paclitaxel Albumin-stabilized Nanoparticle Formulation), Navelbine (Vinorelbine Tartrate), Necitumumab, Nelarabine, Neosar (Cyclophosphamide), Netupitant and Palonosetron Hydrochloride, Neupogen (Filgrastim), Nexavar (Sorafenib Tosylate), Nilotinib, Ninlaro (Ixazomib Citrate), Nolvadex (Tamoxifen Citrate), Nplate (Romiplostim), Obinutuzumab, Odomzo (Sonidegib), OEPA, Ofatumumab, OFF, Olaparib, Omacetaxine Mepesuccinate, Oncaspar (Pegaspargase), Ondansetron Hydrochloride, Onivyde (Irinotecan Hydrochloride Liposome), Ontak (Denileukin Diftitox), OPPA, Osimertinib, Oxaliplatin, Paclitaxel, Paclitaxel Albumin-stabilized Nanoparticle Formulation, PAD, Palbociclib, Palifermin, Palonosetron Hydrochloride, Palonosetron Hydrochloride and Netupitant, Pamidronate Disodium, Panitumumab, Panobinostat, Paraplat (Carboplatin), Paraplatin (Carboplatin), Pazopanib Hydrochloride, PCV, Pegaspargase, Peginterferon Alfa-2b, PEG-Intron (Peginterferon Alfa-2b), Pemetrexed Disodium Perjeta (Pertuzumab), Pertuzumab, Platinol (Cisplatin), Platinol-AQ (Cisplatin), Plerixafor, Pomalidomide, Pomalyst (Pomalidomide), Ponatinib Hydrochloride, Portrazza (Necitumumab), Pralatrexate, Prednisone, Procarbazine Hydrochloride, Proleukin (Aldesleukin), Prolia (Denosumab), Promacta (Eltrombopag Olamine), Provenge (Sipuleucel-T), Purinethol (Mercaptopurine), Purixan (Mercaptopurine), Radium 223

Dichloride, Raloxifene Hydrochloride, Ramucirumab, Rasburicase, R-CHOP, R-CVP, Recombinant Human Papillomavirus (HPV) Bivalent Vaccine, Recombinant Human Papillomavirus (HPV) Nonavalent Vaccine, Recombinant Human Papillomavirus (HPV) Quadrivalent Vaccine, Recombinant Interferon Alfa-2b, Regorafenib, R-EPOCH, Revlimid (Lenalidomide), Rheumatrex (Methotrexate), Rituximab, Rolapitant Hydrochloride, Romidepsin, Romiplostim, Rubidomycin (Daunorubicin Hydrochloride), Ruxolitinib Phosphate, Sclerosol Intrapleural Aerosol (Talc),Siltuximab, Sipuleucel-T, Somatuline Depot (Lanreotide Acetate), Sonidegib, Sorafenib Tosylate, Sprycel (Dasatinib), STANFORD V, Sterile Talc Powder (Talc), Steritalc (Talc), Stivarga (Regorafenib), Sunitinib Malate, Sutent (Sunitinib Malate), Sylatron (Peginterferon Alfa-2b), Sylvant (Siltuximab), Synovir (Thalidomide), Synribo (Omacetaxine Mepesuccinate), Tabloid (Thioguanine), TAC, Tafinlar (Dabrafenib), Tagrisso (Osimertinib), Talc, Talimogene Laherparepvec, Tamoxifen Citrate, Tarabine PFS (Cytarabine), Tarceva (Erlotinib Hydrochloride), Targretin (Bexarotene), Tasigna (Nilotinib), Taxol (Paclitaxel), Taxotere (Docetaxel), Temodar (Temozolomide), Temozolomide, Temsirolimus, Thalidomide, Thioguanine, Thiotepa, Tolak (Fluorouracil--Topical), Toposar (Etoposide), Topotecan Hydrochloride, Toremifene, Torisel (Temsirolimus), Tositumomab and Iodine I 131, Tositumomab, Totect (Dexrazoxane Hydrochloride), TPF, Trabectedin, Trametinib, Trastuzumab, Treanda (Bendamustine Hydrochloride), Trifluridine and Tipiracil Hydrochloride, Trisenox (Arsenic Trioxide), Tykerb (Lapatinib Ditosylate), Unituxin (Dinutuximab), Uridine Triacetate, VAC, Vandetanib, VAMP, Varubi (Rolapitant Hydrochloride), Vectibix (Panitumumab), VeIP, Velban (Vinblastine Sulfate), Velcade (Bortezomib), Velsar (Vinblastine Sulfate), Vemurafenib, VePesid (Etoposide), Viadur (Leuprolide Acetate), Vidaza (Azacitidine), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, Vincristine Sulfate Liposome, Vinorelbine Tartrate, VIP, Vismodegib, Vistogard (Uridine Triacetate), Voraxaze (Glucarpidase), Vorinostat, Votrient (Pazopanib Hydrochloride), Wellcovorin (Leucovorin Calcium), Xalkori (Crizotinib), Xeloda (Capecitabine), XELIRI,XELOX, Xgeva (Denosumab), Xofigo (Radium 223 Dichloride), Xtandi (Enzalutamide), Yervoy (Ipilimumab),Yondelis (Trabectedin), Zaltrap (Ziv-Aflibercept), Zarxio (Filgrastim), Zelboraf (Vemurafenib), Zevalin (Ibritumomab Tiuxetan), Zinecard (Dexrazoxane Hydrochloride), Ziv-Aflibercept, Zofran (Ondansetron Hydrochloride), Zoladex (Goserelin

Acetate), Zoledronic Acid, Zolinza (Vorinostat), Zometa (Zoledronic Acid), Zydelig (Idelalisib), Zykadia (Ceritinib), and Zytiga (Abiraterone Acetate).

[0076] In some embodiments, the additional chemotherapeutic agent is docetaxel.

Radiation Therapy

[0077] In some embodiments, the compound of Formula (I) is co-administered with radiation. In some embodiments, the radiation may be selected from external beam radiation therapy or internal radiation therapy. In some embodiments, the external beam radiation therapy may be selected from three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), proton beam therapy, image-guided radiation therapy (IGRT), Stereotactic radiation therapy (SRT), or a combination thereof. In some embodiments, the radiation may be selected from intraoperative radiation therapy (IORT), systemic radiation therapy, radioimmunotherapy, radiosensitizers, radioprotectors, or a combination thereof.

Use and Method of Treatment

[0078] In aspects, the present disclosure provides methods and therapeutic compositions for treating, preventing, or ameliorating a cancer or tumor in a subject by administering a compound of Formula (I) (e.g., plinabulin), or a pharmaceutically acceptable salt thereof, wherein the subject was resistant to prior treatment with an immune checkpoint inhibitor. Some embodiments include identifying the subject as having been resistant to prior immune checkpoint inhibitor therapy and then administering the compound of Formula (I) (e.g., plinabulin).

[0079] In some embodiments, a method comprises treating a subject having exhibited resistance to a PD-1 inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, a method comprises treating a subject having exhibited resistance to a PD-L1 inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, a method comprises treating a subject having exhibited resistance to a PD-L2 inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, a method comprises treating a subject having exhibited resistance to a CTLA-4 inhibitor by

administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, the method includes administering the compound of Formula (I) when the subject has exhibited resistance to two different immune checkpoint inhibitors. The two different immune inhibitors can be selected from a CTLA-4 receptor inhibitor, a PD-1 receptor inhibitor, a LAG-3 receptor inhibitor, a TIM-3 receptor inhibitor, a BTLA receptor inhibitor, a KIR receptor inhibitor a PD-L1 inhibitor or a PD-L2 inhibitor. In some embodiments, a method comprises treating a subject having exhibited resistance to a PD-1 inhibitor and CTLA-4 inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, a method comprises treating a subject having exhibited resistance to a PD-L1 inhibitor and a CTLA-4 inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, a method comprises treating a subject having exhibited resistance to a PD-1 inhibitor, a PD-L1 inhibitor, and a CTLA-4 inhibitor by administering a therapeutically effective amount of a compound of Formula (I).

[0080] In some embodiments, a method comprises treating a subject having exhibited resistance to a LAG-3 inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, a method comprises treating a subject having exhibited resistance to a TIM-3 inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, a method comprises treating a subject having exhibited resistance to a BLTA inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, a method comprises treating a subject having exhibited resistance to a KIR inhibitor by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, the anti-KIR receptor antibody is lirilumab. In some embodiments, a method comprises treating a subject having exhibited resistance to a blocking antibody by administering a therapeutically effective amount of a compound of Formula (I). In some embodiments, the method comprises treating a subject having a tumor by administering therapeutically effective amounts of the compound of Formula (I) after a subject has failed treatment with an anti-CTLA-4 receptor antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab or tremelimumab. In some embodiments, the method comprises treating a subject having a tumor by administering therapeutically effective amounts of the compound

of Formula (I) after a subject has failed treatment with an anti-PD-1 receptor antibody. In some embodiments the anti-PD-1 antibody is cemiplimab, pembrolizumab, pidilizumab, or nivolumab.

[0081] In some embodiments, the compound of Formula (I) is co-administered with a chemotherapeutic agent. In some such embodiments, the compound of Formula (I) is administered after the chemotherapeutic agent, for example, at least 30 minutes, 1 hour, 2 hours, 4 hours, 1 day, 2 days, or 3 days after administration of the chemotherapeutic agent. In some embodiments, the chemotherapeutic agent is docetaxel. In some embodiments, the compound of Formula (I) is co-administered one or more immune checkpoint inhibitors, with or without the additional chemotherapeutic agent. In some embodiments, the compound of Formula (I) is co-administered radiation, with or without the additional chemotherapeutic agent, and with or without the one or more immune checkpoint inhibitors. In some such embodiments, the compound of Formula (I) is administered after the radiation therapy, for example, at least 30 minutes, 1 hour, 2 hours, 4 hours, 1 day, 2 days, or 3 days after administration of the radiation therapy. In some embodiments, the compound of Formula (I) may be administered with radiation on the same day that the radiation is being administered. In some embodiments, one or more immune checkpoint inhibitor may be administered prior to administration of a compound of Formula (I) and radiation. In some embodiments, one or more immune checkpoint inhibitor may be administered prior to administration of a compound of Formula (I), an additional chemotherapeutic agent, and radiation. In other embodiments, the one or more immune checkpoint inhibitor is administered after the administration of the compound of Formula (I) and the additional chemotherapeutic agent and/or radiation.

[0082] As used herein, the terms "co-administer," "co-administering," or "co-administration," refers to two or more agents or therapies that have a biological effect on a subject at the same time, regardless of when or how they are actually administered. In one embodiment, the agents or therapies are administered simultaneously. In one such embodiment, administration in combination is accomplished by combining the agents in a single dosage form. In another embodiment, the agents or therapies are administered sequentially. In some embodiments, the administration may be separated by a period of time, for example, 30 minutes, 1 hour, 2 hours, 1 day, 2 days, 3 days, or 1 week. In one

embodiment the agents are administered through the same route, such as orally. In another embodiment, the agents are administered through different routes, such as one being administered orally and another being administered i.v.

[0083] In some embodiments where an immune checkpoint inhibitor is co-administered, a method for treating a subject having a cancer or tumor may include administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, after the subject is administered the one or more immune checkpoint inhibitor. In some embodiments, a method of inhibiting the growth of cancer or tumor cells in a subject may include administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, after the subject is administered one or more immune checkpoint inhibitor. In some embodiments, a method for increasing a cell-mediated immune response of a cell population may include administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, after administering one or more immune checkpoint inhibitor.

[0084] In some embodiments, a compound of Formula (I) is co-administered with a CTLA-4 receptor inhibitor compound. In some embodiments, a compound of Formula (I) is co-administered a PD-1 or PD-L1 receptor inhibitor compound.

[0085] In some embodiments, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and a LAG-3 receptor inhibitor compound. In some embodiments, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and a TIM-3 receptor inhibitor compound. In some embodiments, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and a BTLA receptor inhibitor compound. In some embodiments, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and a KIR receptor inhibitor compound. In some embodiments, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and a PD-L1 inhibitor compound. In some embodiments, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and a PD-L2 inhibitor compound.

[0086] In some embodiments of the present disclosure, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and a blocking antibody of an immune checkpoint pathway. In some embodiments, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and an anti-CTLA-4 receptor antibody. In some embodiments, the method comprises treating a subject by co-administering a therapeutically effective amount of a compound of Formula (I) and an anti-PD-1 receptor antibody.

[0087] In some embodiments, the method comprises co-administering to a subject having a tumor a therapeutically effective amount of the compound of Formula (I) and an anti-LAG-3 receptor antibody. In some embodiments, the method comprises co-administering to a subject having a tumor a therapeutically effective amount of the compound of Formula (I) and an anti-TIM-3 receptor antibody. In some embodiments, the method comprises co-administering to a subject having a tumor a therapeutically effective amount of the compound of Formula (I) and an anti-BTLA receptor antibody. In some embodiments, the method comprises co-administering to a subject having a tumor a therapeutically effective amount of the compound of Formula (I) and an anti-KIR receptor antibody. In some embodiments, the anti-KIR receptor antibody is lirilumab. In some embodiments, the method comprises co-administering to a subject having a tumor a therapeutically effective amount of the compound of Formula (I) and an anti-PD-1 antibody. In some embodiments the anti-PD-1 antibody is cemiplimab, pembrolizumab, pidilizumab, or nivolumab. In some embodiments, the method comprises co-administering to a subject having a tumor a therapeutically effective amount of the compound of Formula (I) and an anti-PD-L1 antibody. In some embodiments, the method comprises co-administering to a subject having a tumor a therapeutically effective amount of the compound of Formula (I) and an anti-PD-L2 antibody. In some embodiments, the method comprises co-administering to a subject having a tumor a therapeutically effective amount of the compound of Formula (I) and an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab or tremelimumab.

[0088] In some embodiments, a method comprises treating a subject having exhibited resistance to one or more immune checkpoint inhibitors by co-administering a

therapeutically effective amount of a compound of Formula (I) and an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is a taxane. In some embodiments, the taxane is docetaxel.

[0089] In some embodiments, a method comprises treating a subject having exhibited resistance to one or more immune checkpoint inhibitors by co-administering a therapeutically effective amount of a compound of Formula (I) and radiation therapy.

[0090] In some embodiments, a method of treating a subject with a cancer that has failed prior immune checkpoint inhibitor therapy includes administering a therapeutic combination that includes a compound of Formula (I). In some embodiments, the compound of Formula (I) is plinabulin. In some embodiments, the therapeutic combination includes an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is docetaxel. In some embodiments the therapeutic combination includes radiation. In some embodiments, the therapeutic combination includes plinabulin, a chemotherapy agent, and radiation. In some embodiments, the therapeutic combination includes plinabulin, a PD-1 or PD-L1 inhibitor, and an additional chemotherapeutic agent. In some embodiments, the therapeutic combination includes plinabulin, a PD-1 or PD-L1 inhibitor, and radiation therapy. In some embodiments, the therapeutic combination includes plinabulin, a PD-1 or PD-1 inhibitor and a CTLA-4 inhibitor. In some embodiments, the therapeutic combination includes plinabulin, a PD-1 or PD-1 inhibitor, a CTLA-4 inhibitor, and an additional chemotherapeutic agent. In some embodiments, the therapeutic combination includes plinabulin, a PD-1 or PD-1 inhibitor, a CTLA-4 inhibitor, and radiation therapy.

[0091] In some embodiments, a method for halting or reversing a progressive cancer in a subject comprising administering a compound of Formula (I). In some embodiments, the method comprises co-administering a compound of Formula (I) with one or more additional chemotherapeutic agents, one or more immune checkpoint inhibitors, and/or radiation, as described above.

[0092] In some embodiments, the present disclosure provides a method for treating breast cancer, bladder cancer, glioblastoma, metastatic brain tumor, head and neck cancer, non-small cell lung cancer, small cell lung cancer, colorectal cancer, gastrointestinal cancer, gastroesophageal cancer, renal cell cancer, prostate cancer, liver cancer, colon cancer, pancreatic cancer tumor, ovarian cancer tumor, lymphoma, cutaneous T-cell lymphoma,

sarcoma, multiple myeloma, metastatic melanoma, hepatocellular carcinoma, malignant pleural mesothelioma, urothelial carcinoma, esophageal cancer, Merkel cell cancer, endometrial cancer, basal cell carcinoma or melanoma.

[0093] In some embodiments, the present disclosure provides a method for treating a solid tumor. In some embodiments, the present disclosure provides a method for treating a breast cancer tumor, a bladder cancer tumor, a glioblastoma tumor, metastatic brain tumor, a head and neck cancer tumor, a non-small cell lung cancer tumor, a small cell lung cancer tumor, a colorectal cancer tumor, a gastrointestinal stromal tumor, a gastroesophageal carcinoma, a renal cell cancer tumor, a prostate cancer tumor, a liver cancer tumor, a colon cancer tumor, a pancreatic cancer tumor, an ovarian cancer tumor, a lymphoma tumor, a cutaneous T-cell lymphoma tumor, a sarcoma tumor, a multiple myeloma tumor, metastatic melanoma tumor, hepatocellular carcinoma tumor, malignant pleural mesothelioma tumor, urothelial carcinoma tumor, esophageal cancer tumor, Merkel cell carcinoma tumor, endometrial carcinoma tumor, basal cell carcinoma tumor, or a melanoma tumor. In some embodiments, the present disclosure provides a method for treating an immune suppressed tumor. An immune suppressed tumor is a tumor that contains immune suppressive associated cells such as for example T_{Reg} cells, myeloid derived suppressor cells (MDSC), M2 macrophages, and the like or immune suppressive factors such as inducible nitric oxide synthase (iNOS), PD-L1, and the like.

[0094] In some embodiments, the cancer comprises cancer cells expressing a binding ligand of PD-1. In some embodiments, the binding ligand of PD-1 is PD-L1. In some embodiments, the binding ligand of PD-1 is PD-L2.

[0095] In some embodiments, the method of treating cancer described herein further includes identifying cancer cells expressing a binding ligand of PD-1. In some embodiments, the method of treating cancer described herein further includes identifying cancer cells expressing PD-L1. In some embodiments, the method of treating cancer described herein further includes identifying cancer cells expressing PD-L2.

[0096] In some embodiments, identifying cancer cells expressing a binding ligand of PD-1 includes using an assay to detect the presence of the binding ligand. Examples of applicable assay include but are not limited to PD-L1 IHC 22C3 pharmDx kit and PD-L1 IHC 28-8 pharmDx available from Dako.

[0097] In some embodiments, the cancer comprises cancer cells expressing a binding ligand of CTLA-4. In some embodiments, the binding ligand of CTLA-4 is B7.1 or B7.2.

[0098] In some embodiments, the method of treating cancer described herein further includes identifying cancer cells expressing a binding ligand of CTLA-4. In some embodiments, the method of treating cancer described herein further includes identifying cancer cells expressing B7.1 or B7.2.

[0099] In some embodiments, the cancer is head and neck cancer, lung cancer, stomach cancer, colon cancer, pancreatic cancer, prostate cancer, breast cancer, kidney cancer, bladder cancer, ovary cancer, cervical cancer, melanoma, gliomas including glioblastoma, myeloma, lymphoma, sarcoma, multiple myeloma, or leukemia. In some embodiments, the cancer is renal cell carcinoma, malignant melanoma, non-small cell lung cancer (NSCLC), ovarian cancer, Hodgkin's lymphoma or squamous cell carcinoma. In some embodiments, the cancer is selected from breast cancer, colon cancer, rectal cancer, lung cancer, prostate cancer, melanoma, leukemia, ovarian cancer, gastric cancer, renal cell carcinoma, liver cancer, pancreatic cancer, lymphomas and myeloma. In some embodiments, the cancer is a solid tumor or hematological cancer.

[0100] In some embodiments, the cancer does not have any cells expressing PD-1, PD-L1, or PD-L2 at detectable levels.

[0101] In some embodiments, the cancer is selected from breast cancer, colon cancer, glioma, metastatic brain tumor, rectal cancer, lung cancer, prostate cancer, melanoma, leukemia, ovarian cancer, gastric cancer, renal cell carcinoma, liver cancer, pancreatic cancer, lymphomas, sarcoma, multiple myeloma, and myeloma. In some embodiments, the cancer is a solid tumor or hematological cancer.

[0102] In some embodiments, the subject can be an animal, e.g., a mammal, a human. In some embodiments, the subject is a human.

[0103] In some embodiments, the compound of Formula (I) is incorporated in a pharmaceutically acceptable solution. In some embodiments, the compound of Formula (I) is incorporated in an injectable formulation. In some embodiments, the compound of Formula (I) is incorporated in an injectable formulation that substantially maintains the compound of Formula (I) at or near the injection site.

[0104] The precise amount of compound of Formula (I) incorporated in a particular method or therapeutic combination of the disclosure may vary according to factors known in art such as for example, the physical and clinical status of the subject, the method of administration, the content of the formulation, the intended dosing regimen or sequence. Accordingly, it is not practical to specifically set forth an amount that constitutes an amount of compound of Formula (I) therapeutically effective for all possible applications. Those of ordinary skill in the art, however, can readily determine an appropriate amount with due consideration of such factors.

[0105] Some embodiments relate to a method of treating cancer in a subject who exhibited resistance to checkpoint inhibitor therapy. In some embodiments, the method includes identifying a subject with a cancer that is resistant to one or more immune checkpoint inhibitor therapy, and co-administering to the subject plinabulin and one or more immune checkpoint inhibitors, wherein the one or more immune checkpoint inhibitors is an inhibitor of PD-1, PD-L1 or CTLA-4. In some embodiments, the inhibitor of PD-1 is nivolumab and is administered at 1 mg/kg. In some embodiments, the inhibitor CTLA-4 is ipilimumab and is administered at 3 mg/kg. In some embodiments, the plinabulin is administered at a dose from about 13.5 mg/m^2 to about 30 mg/m^2 on day 1 of a 21 day cycle. In some embodiments, the cancer is recurrent extensive-stage small cell lung cancer (SCLC). In some embodiments, the cancer was previously identified as unresponsive to platinum-based chemotherapy. In some embodiments, the PD-1 inhibitor and the CTLA-4 inhibitor may be administered on day 1 of a 21 day cycle. In some embodiments, the subject is administered 1, 2, 3, or 4 treatment cycles. In some embodiments, the subject may be administered 5 or more dose treatment cycles of a PD-1 inhibitor and plinabulin every two weeks.

Administration

[0106] Administration of the pharmaceutical compositions described herein can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, sublingually, buccally, subcutaneously, intravenously, intranasally, intratumorally, topically, transdermally, intradermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, or intraocularly. Oral and parenteral

administrations are customary in treating the indications that are the subject of the preferred embodiments.

[0107] The compositions described herein may be provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound or composition that is suitable for administration to an animal, preferably mammal subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, although a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.

[0108] The compositions useful as described above may be in any of a variety of suitable forms for a variety of routes for administration, for example, for oral, sublingual, buccal, nasal, rectal, topical (including transdermal and intradermal), ocular, intracerebral, intracranial, intrathecal, intra-arterial, intravenous, intramuscular, or other parental routes of administration. The skilled artisan will appreciate that oral and nasal compositions include compositions that are administered by inhalation, and made using available methodologies. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. Pharmaceutically-acceptable carriers include, for example, solid or liquid fillers, diluents, hydrotropies, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the compound or composition. The amount of carrier employed in conjunction with the compound or composition is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods described herein are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, 4th Ed., Chapters 9 and 10 (Banker & Rhodes,

editors, 2002); Lieberman *et al.*, Pharmaceutical Dosage Forms: Tablets (1989); and Ansel, Introduction to Pharmaceutical Dosage Forms 8th Edition (2004).

[0109] Various oral dosage forms can be used, including such solid forms as tablets, capsules (*e.g.* solid gel capsules and liquid gel capsules), granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

[0110] The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for peroral administration is well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical, and can be readily made by a person skilled in the art.

[0111] Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical

preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0112] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject composition is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0113] Compositions described herein may optionally include additional drug actives.

[0114] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0115] A liquid composition, which is formulated for topical ophthalmic use, is formulated such that it can be administered topically to the eye. The comfort may be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid may be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid may either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0116] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions may preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0117] Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0118] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0119] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. For many compositions, the pH will be between 4 and 9. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0120] Ophthalmically acceptable antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0121] Other excipient components, which may be included in the ophthalmic preparations, are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[0122] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the composition disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, co-solvent, emulsifier, penetration enhancer, preservative system, and emollient.

[0123] For intravenous administration, the compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium

formaldehyde, sulfoxylate, thiourea, and EDTA. In some embodiments, excipients utilized for intravenous delivery may include Kolliphor HS 15 (polyoxyl 15 hydroxystearate or Solutol HS-15), propylene glycol and 5% dextrose in water (D5W). Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., Compendium of Excipients for Parenteral Formulations, *PDA J Pharm Sci and Tech* **1998**, *52* 238-311 and Nema et al., Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions, *PDA J Pharm Sci and Tech* **2011**, *65* 287-332, both of which are incorporated herein by reference in their entirety. Antimicrobial agents may also be included to achieve a bacteriostatic or fungistatic solution, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol.

[0124] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer parenterally. In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound described herein and another agent, the combination may be provided to caregivers as a mixture, or the caregivers may mix the two agents prior to administration, or the two agents may be administered separately.

[0125] The actual dose of the active compounds described herein depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan. In some embodiments, a compound of Formula (I) may be administered at a dose in the range of about 1 mg/m^2 to about 50 mg/m^2. In some embodiments, a compound of Formula (I) is administered at a dose in the range of about 1-50 mg/m^2 of the body surface area. In some embodiments, a compound of Formula (I) is administered at a dose in the range of about 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 1-13, 1-13.75, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, 1-20, 1-22.5, 1-25, 1-27.5, 1-30, 1.5-2, 1.5-3, 1.5-4, 1.5-5, 1.5-6, 1.5-7, 1.5-8, 1.5-9, 1.5-10, 1.5-11, 1.5-12, 1.5-13, 1.5-13.75,

1.5-14, 1.5-15, 1.5-16, 1.5-17, 1.5-18, 1.5-19, 1.5-20, 1.5-22.5, 1.5-25, 1.5-27.5, 1.5-30, 2.5-2, 2.5-3, 2.5-4, 2.5-5, 2.5-6, 2.5-7, 2.5-8, 2.5-9, 2.5-10, 2.5-11, 2.5-12, 2.5-13, 2.5-13.75, 2.5-14, 2.5-15, 2.5-16, 2.5-17, 2.5-18, 2.5-19, 2.5-20, 2.5-22.5, 2.5-25, 2.5-27.5, 2.5-30, 2.5-7.5, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 3-11, 3-12, 3-13, 3-13.75, 3-14, 3-15, 3-16, 3-17, 3-18, 3-19, 3-20, 3-22.5, 3-25, 3-27.5, 3-30, 3.5- 6.5, 3.5-13.75, 3.5-15, 2.5-17.5, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, 4-12, 4-13, 4-13.75, 4-14, 4-15, 4-16, 4-17, 4-18, 4-19, 4-20, 4-22.5, 4-25, 4-27.5, 4-30, 5-6, 5-7, 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-13.75, 5-14, 5-15, 5-16, 5-17, 5-18, 5-19, 5-20, 5-22.5, 5-25, 5-27.5, 5-30, 6-7, 6-8, 6-9, 6-10, 6-11, 6-12, 6-13, 6-13.75, 6-14, 6-15, 6-16, 6-17, 6-18, 6-19, 6-20, 6-22.5, 6-25, 6-27.5, 6-30, 7-8, 7-9, 7-10, 7-11, 7-12, 7-13, 7-13.75, 7-14, 7-15, 7-16, 7-17, 7-18, 7-19, 7-20, 7-22.5, 7-25, 7-27.5, 7-30, 7.5-12.5, 7.5-13.5, 7.5-15, 8-9, 8-10, 8-11, 8-12, 8-13, 8-13.75, 8-14, 8-15, 8-16, 8-17, 8-18, 8-19, 8-20, 8-22.5, 8-25, 8-27.5, 8-30, 9-10, 9-11, 9-12, 9-13, 9-13.75, 9-14, 9-15, 9-16, 9-17, 9-18, 9-19, 9-20, 9-22.5, 9-25, 9-27.5, 9-30, 10-11, 10-12, 10-13, 10-13.75, 10-14, 10-15, 10-16, 10-17, 10-18, 10-19, 10-20, 10-22.5, 10-25, 10-27.5, 10-30, 11.5-15.5, 12.5-14.5, 7.5-22.5, 8.5-32.5, 9.5-15.5, 15.5-24.5, 5-35, 17.5-22.5, 22.5-32.5, 25-35, 25.5-34.5, 27.5-32.5, 2-20, 2.5-22.5, or 9.5-21.5 mg/m^2, of the body surface area. In some embodiments, a compound of Formula (I) is administered at a dose of about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 mg/m^2 of the body surface area. In some embodiments, a compound of Formula (I) is administered at a dose less than about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 mg/m^2 of the body surface area. In some embodiments, a compound of Formula (I) is administered at a dose greater than about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 mg/m^2 of the body surface area.

[0126] In some embodiments, a compound of Formula (I) dose is about 5 mg - 300 mg, 5 mg -200 mg, 7.5 mg - 200 mg, 10 mg - 100 mg, 15 mg - 100 mg, 20 mg - 100 mg, 30 mg - 100 mg, 40 mg - 100 mg, 10 mg - 80 mg, 15 mg - 80 mg, 20 mg - 80 mg, 30 mg - 80 mg, 40 mg - 80 mg, 10 mg - 60 mg, 15 mg - 60 mg, 20 mg - 60 mg, 30 mg - 60 mg, or about 40 mg - 60 mg. In some embodiments, a compound of Formula (I) administered is about 20 mg - 60 mg, 27 mg - 60 mg, 20 mg - 45 mg, or 27 mg - 45 mg. In some embodiments, a compound of Formula (I) administered is about 5 mg-7.5 mg, 5 mg-9 mg, 5 mg-10 mg, 5 mg-12mg, 5mg-14mg, 5mg-15 mg, 5 mg-16 mg, 5 mg-18 mg, 5 mg-20 mg, 5 mg-22 mg, 5 mg-24 mg, 5 mg-26 mg, 5 mg-28mg, 5mg-30mg, 5mg-32mg, 5mg-34mg, 5mg-36mg, 5mg-38mg, 5mg-40mg, 5mg-42mg, 5mg-44mg, 5mg-46mg, 5mg-48mg, 5mg-50mg, 5mg-52mg, 5mg-54mg, 5mg-56mg, 5mg-58mg, 5mg-60mg, 7 mg-7.7 mg, 7 mg-9 mg, 7 mg-10 mg, 7 mg-12mg, 7mg-14mg, 7mg-15 mg, 7 mg-16 mg, 7 mg-18 mg, 7 mg-20 mg, 7 mg-22 mg, 7 mg-24 mg, 7 mg-26 mg, 7 mg-28mg, 7mg-30mg, 7mg-32mg, 7mg-34mg, 7mg-36mg, 7mg-38mg, 7mg-40mg, 7mg-42mg, 7mg-44mg, 7mg-46mg, 7mg-48mg, 7mg-50mg, 7mg-52mg, 7mg-54mg, 7mg-56mg, 7mg-58mg, 7mg-60mg, 9 mg-10 mg, 9 mg-12mg, 9mg-14mg, 9mg-15 mg, 9 mg-16 mg, 9 mg-18 mg, 9 mg-20 mg, 9 mg-22 mg, 9 mg-24 mg, 9 mg-26 mg, 9 mg-28mg, 9mg-30mg, 9mg-32mg, 9mg-34mg, 9mg-36mg, 9mg-38mg, 9mg-40mg, 9mg-42mg, 9mg-44mg, 9mg-46mg, 9mg-48mg, 9mg-50mg, 9mg-52mg, 9mg-54mg, 9mg-56mg, 9mg-58mg, 9mg-60mg, 10 mg-12mg, 10mg-14mg, 10mg-15 mg, 10 mg-16 mg, 10 mg-18 mg, 10 mg-20 mg, 10 mg-22 mg, 10 mg-24 mg, 10 mg-26 mg, 10 mg-28mg, 10mg-30mg, 10mg-32mg, 10mg-34mg, 10mg-36mg, 10mg-38mg, 10mg-40mg, 10mg-42mg, 10mg-44mg, 10mg-46mg, 10mg-48mg, 10mg-50mg, 10mg-52mg, 10mg-54mg, 10mg-56mg, 10mg-58mg, 10mg-60mg, 12mg-14mg, 12mg-15 mg, 12 mg-16 mg, 12 mg-18 mg, 12 mg-20 mg, 12 mg-22 mg, 12 mg-24 mg, 12 mg-26 mg, 12 mg-28mg, 12mg-30mg, 12mg-32mg, 12mg-34mg, 12mg-36mg, 12mg-38mg, 12mg-40mg, 12mg-42mg, 12mg-44mg, 12mg-46mg, 12mg-48mg, 12mg-50mg, 12mg-52mg, 12mg-54mg, 12mg-56mg, 12mg-58mg, 12mg-60mg, 15 mg-16 mg, 15 mg-18 mg, 15 mg-20 mg, 15 mg-22 mg, 15 mg-24 mg, 15 mg-26 mg, 15 mg-28mg, 15mg-30mg, 15mg-32mg, 15mg-34mg, 15mg-36mg, 15mg-38mg, 15mg-40mg, 15mg-42mg, 15mg-44mg, 15mg-46mg, 15mg-48mg, 15mg-50mg, 15mg-52mg, 15mg-54mg, 15mg-56mg, 15mg-58mg, 15mg-60mg, 17 mg-18 mg, 17 mg-20 mg, 17 mg-22 mg, 17 mg-24 mg, 17 mg-26 mg, 17 mg-28mg, 17mg-30mg, 17mg-32mg, 17mg-34mg, 17mg-36mg, 17mg-38mg,

17mg-40mg, 17mg-42mg, 17mg-44mg, 17mg-46mg, 17mg-48mg, 17mg-50mg, 17mg-52mg, 17mg-54mg, 17mg-56mg, 17mg-58mg, 17mg-60mg, 20 mg-22 mg, 20 mg-24 mg, 20 mg-26 mg, 20 mg-28mg, 20mg-30mg, 20mg-32mg, 20mg-34mg, 20mg-36mg, 20mg-38mg, 20mg-40mg, 20mg-42mg, 20mg-44mg, 20mg-46mg, 20mg-48mg, 20mg-50mg, 20mg-52mg, 20mg-54mg, 20mg-56mg, 20mg-58mg, 20mg-60mg, 22 mg-24 mg, 22 mg-26 mg, 22 mg-28mg, 22mg-30mg, 22mg-32mg, 22mg-34mg, 22mg-36mg, 22mg-38mg, 22mg-40mg, 22mg-42mg, 22mg-44mg, 22mg-46mg, 22mg-48mg, 22mg-50mg, 22mg-52mg, 22mg-54mg, 22mg-56mg, 22mg-58mg, 22mg-60mg, 25 mg-26 mg, 25 mg-28mg, 25mg-30mg, 25mg-32mg, 25mg-34mg, 25mg-36mg, 25mg-38mg, 25mg-40mg, 25mg-42mg, 25mg-44mg, 25mg-46mg, 25mg-48mg, 25mg-50mg, 25mg-52mg, 25mg-54mg, 25mg-56mg, 25mg-58mg, 25mg-60mg, 27 mg-28mg, 27mg-30mg, 27mg-32mg, 27mg-34mg, 27mg-36mg, 27mg-38mg, 27mg-40mg, 27mg-42mg, 27mg-44mg, 27mg-46mg, 27mg-48mg, 27mg-50mg, 27mg-52mg, 27mg-54mg, 27mg-56mg, 27mg-58mg, 27mg-60mg, 30mg-32mg, 30mg-34mg, 30mg-36mg, 30mg-38mg, 30mg-40mg, 30mg-42mg, 30mg-44mg, 30mg-46mg, 30mg-48mg, 30mg-50mg, 30mg-52mg, 30mg-54mg, 30mg-56mg, 30mg-58mg, 30mg-60mg, 33mg-34mg, 33mg-36mg, 33mg-38mg, 33mg-40mg, 33mg-42mg, 33mg-44mg, 33mg-46mg, 33mg-48mg, 33mg-50mg, 33mg-52mg, 33mg-54mg, 33mg-56mg, 33mg-58mg, 33mg-60mg, 36mg-38mg, 36mg-40mg, 36mg-42mg, 36mg-44mg, 36mg-46mg, 36mg-48mg, 36mg-50mg, 36mg-52mg, 36mg-54mg, 36mg-56mg, 36mg-58mg, 36mg-60mg, 40mg-42mg, 40mg-44mg, 40mg-46mg, 40mg-48mg, 40mg-50mg, 40mg-52mg, 40mg-54mg, 40mg-56mg, 40mg-58mg, 40mg-60mg, 43mg-46mg, 43mg-48mg, 43mg-50mg, 43mg-52mg, 43mg-54mg, 43mg-56mg, 43mg-58mg, 42mg-60mg, 45mg-48mg, 45mg-50mg, 45mg-52mg, 45mg-54mg, 45mg-56mg, 45mg-58mg, 45mg-60mg, 48mg-50mg, 48mg-52mg, 48mg-54mg, 48mg-56mg, 48mg-58mg, 48mg-60mg, 50mg-52mg, 50mg-54mg, 50mg-56mg, 50mg-58mg, 50mg-60mg, 52mg-54mg, 52mg-56mg, 52mg-58mg, or 52mg-60mg. In some embodiments, a compound of Formula (I) dose is greater than about 5 mg, about 10 mg, about 12.5 mg, about 13.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, about 25 mg, about 27 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150mg, or about 200 mg. In some embodiments, a compound of Formula (I) dose is about less than about 5 mg, about 10 mg, about 12.5 mg, about 13.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, about 25 mg, about 27 mg, about 30 mg, about

40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150mg, or about 200 mg.

[0127] In some embodiments, a dose of one or more immune checkpoint inhibitors may be from about 100 μg to about 1000 mg, from about 500 μg or less to about 800 mg, from about 1.0 mg to about 600 mg, from about 100 mg to about 600 mg, or from about 200 mg to 500 mg. In some embodiments, a dose of one or more immune checkpoint inhibitors may be from about 240 mg to about 480 mg per dose. In some embodiments, the dose of the one or more immune checkpoint inhibitors is about 240 mg. In some embodiments, the dose of the one or more immune checkpoint inhibitors is about 480 mg.

[0128] In some embodiments, one or more immune checkpoint inhibitors may be administered at a dose in the range of about 100 mg/kg to about 5000 mg/kg. In some embodiments, one or more immune checkpoint inhibitors is administered at a dose in the range of about 100-1000 mg/kg. In some embodiments, one or more immune checkpoint inhibitors is administered at a dose in the range of about 100-200, 100-300, 100-400, 100-500, 100-600, 100-700, 100-800, 100-900, 100-1000, 100-1100, 100-1200, 100-1300, 100-1375, 100-1400, 100-1500, 100-1600, 100-1700, 100-1800, 100-1900, 100-2000, 100-2250, 100-2500, 100-2750, 100-3000, 150-200, 150-300, 150-400, 150-500, 150-600, 150-700, 150-800, 150-900, 150-1000, 150-1100, 150-1200, 150-1300, 150-1375, 150-1400, 150-1500, 150-1600, 150-1700, 150-1800, 150-1900, 150-2000, 150-2250, 150-2500, 150-2750, 150-3000, 250-2000, 250-3000, 250-4000, 250-5000, 250-600, 250-700, 250-800, 250-900, 250-1000, 250-1100, 250-1200, 250-1300, 250-1375, 250-1400, 250-1500, 250-1600, 250-1700, 250-1800, 250-1900, 250-2000, 250-2250, 250-2500, 250-2750, 250-3000, 250-750, 300-400, 300-500, 300-600, 300-700, 300-800, 300-900, 300-1000, 300-1100, 300-1200, 300-1300, 300-1375, 300-1400, 300-1500, 300-1600, 300-1700, 300-1800, 300-1900, 300-2000, 300-2250, 300-2500, 300-2750, or 300-3000, mg/kg. In some embodiments, one or more immune checkpoint inhibitors is administered at a dose of about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 mg.

[0129] In some embodiments, one or more immune checkpoint inhibitor dose is about 0.5 mg - 3000 mg, 0.5 mg - 2500 mg, 0.5 mg - 2000 mg, 0.5 mg - 1500 mg, 0.5 mg - 1000 mg, 0.5 mg - 500 mg,0.5 mg -200 mg, 0.75 mg - 200 mg, 1.0 mg - 100 mg, 1.5 mg - 100 mg, 2.0 mg - 100 mg, 3.0 mg - 100 mg, 4.0 mg - 100 mg, 1.0 mg - 80 mg, 1.5 mg - 80 mg, 2.0 mg - 80 mg, 3.0 mg - 80 mg, 4.0 mg - 80 mg, 1.0 mg - 60 mg, 1.5 mg - 60 mg, 2.0 mg - 60 mg, 3.0 mg - 60 mg, or about 4.0 mg - 60 mg. In some embodiments, one or more immune checkpoint inhibitors administered is about 20 mg - 60 mg, 27 mg - 60 mg, 20 mg - 45 mg, or 27 mg - 45 mg. In some embodiments, one or more immune checkpoint inhibitors administered is about 5 mg-7.5 mg, 5 mg-9 mg, 5 mg-10 mg, 5 mg-12mg, 5mg-14mg, 5mg-15 mg, 5 mg-16 mg, 5 mg-18 mg, 5 mg-20 mg, 5 mg-22 mg, 5 mg-24 mg, 5 mg-26 mg, 5 mg-28mg, 5mg-30mg, 5mg-32mg, 5mg-34mg, 5mg-36mg, 5mg-38mg, 5mg-40mg, 5mg-42mg, 5mg-44mg, 5mg-46mg, 5mg-48mg, 5mg-50mg, 5mg-52mg, 5mg-54mg, 5mg-56mg, 5mg-58mg, 5mg-60mg, 7 mg-7.7 mg, 7 mg-9 mg, 7 mg-10 mg, 7 mg-12mg, 7mg-14mg, 7mg-15 mg, 7 mg-16 mg, 7 mg-18 mg, 7 mg-20 mg, 7 mg-22 mg, 7 mg-24 mg, 7 mg-26 mg, 7 mg-28mg, 7mg-30mg, 7mg-32mg, 7mg-34mg, 7mg-36mg, 7mg-38mg, 7mg-40mg, 7mg-42mg, 7mg-44mg, 7mg-46mg, 7mg-48mg, 7mg-50mg, 7mg-52mg, 7mg-54mg, 7mg-56mg, 7mg-58mg, 7mg-60mg, 9 mg-10 mg, 9 mg-12mg, 9mg-14mg, 9mg-15 mg, 9 mg-16 mg, 9 mg-18 mg, 9 mg-20 mg, 9 mg-22 mg, 9 mg-24 mg, 9 mg-26 mg, 9 mg-28mg, 9mg-30mg, 9mg-32mg, 9mg-34mg, 9mg-36mg, 9mg-38mg, 9mg-40mg, 9mg-42mg, 9mg-44mg, 9mg-46mg, 9mg-48mg, 9mg-50mg, 9mg-52mg, 9mg-54mg, 9mg-56mg, 9mg-58mg, 9mg-60mg, 10 mg-12mg, 10mg-14mg, 10mg-15 mg, 10 mg-16 mg, 10 mg-18 mg, 10 mg-20 mg, 10 mg-22 mg, 10 mg-24 mg, 10 mg-26 mg, 10 mg-28mg, 10mg-30mg, 10mg-32mg, 10mg-34mg, 10mg-36mg, 10mg-38mg, 10mg-40mg, 10mg-42mg, 10mg-44mg, 10mg-46mg, 10mg-48mg, 10mg-50mg, 10mg-52mg, 10mg-54mg, 10mg-56mg, 10mg-58mg, 10mg-60mg, 12mg-14mg, 12mg-15 mg, 12 mg-16 mg, 12 mg-18 mg, 12 mg-20 mg, 12 mg-22 mg, 12 mg-24 mg, 12 mg-26 mg, 12 mg-28mg, 12mg-30mg, 12mg-32mg, 12mg-34mg, 12mg-36mg, 12mg-38mg, 12mg-40mg, 12mg-42mg, 12mg-44mg, 12mg-46mg, 12mg-48mg, 12mg-50mg, 12mg-52mg, 12mg-54mg, 12mg-56mg, 12mg-58mg, 12mg-60mg, 15 mg-16 mg, 15 mg-18 mg, 15 mg-20 mg, 15 mg-22 mg, 15 mg-24 mg, 15 mg-26 mg, 15 mg-28mg, 15mg-30mg, 15mg-32mg, 15mg-34mg, 15mg-36mg, 15mg-38mg, 15mg-40mg, 15mg-42mg, 15mg-44mg, 15mg-46mg, 15mg-48mg, 15mg-50mg, 15mg-52mg, 15mg-54mg, 15mg-56mg, 15mg-58mg, 15mg-60mg,

17 mg-18 mg, 17 mg-20 mg, 17 mg-22 mg, 17 mg-24 mg, 17 mg-26 mg, 17 mg-28mg, 17mg-30mg, 17mg-32mg, 17mg-34mg, 17mg-36mg, 17mg-38mg, 17mg-40mg, 17mg-42mg, 17mg-44mg, 17mg-46mg, 17mg-48mg, 17mg-50mg, 17mg-52mg, 17mg-54mg, 17mg-56mg, 17mg-58mg, 17mg-60mg, 20 mg-22 mg, 20 mg-24 mg, 20 mg-26 mg, 20 mg-28mg, 20mg-30mg, 20mg-32mg, 20mg-34mg, 20mg-36mg, 20mg-38mg, 20mg-40mg, 20mg-42mg, 20mg-44mg, 20mg-46mg, 20mg-48mg, 20mg-50mg, 20mg-52mg, 20mg-54mg, 20mg-56mg, 20mg-58mg, 20mg-60mg, 22 mg-24 mg, 22 mg-26 mg, 22 mg-28mg, 22mg-30mg, 22mg-32mg, 22mg-34mg, 22mg-36mg, 22mg-38mg, 22mg-40mg, 22mg-42mg, 22mg-44mg, 22mg-46mg, 22mg-48mg, 22mg-50mg, 22mg-52mg, 22mg-54mg, 22mg-56mg, 22mg-58mg, 22mg-60mg, 25 mg-26 mg, 25 mg-28mg, 25mg-30mg, 25mg-32mg, 25mg-34mg, 25mg-36mg, 25mg-38mg, 25mg-40mg, 25mg-42mg, 25mg-44mg, 25mg-46mg, 25mg-48mg, 25mg-50mg, 25mg-52mg, 25mg-54mg, 25mg-56mg, 25mg-58mg, 25mg-60mg, 27 mg-28mg, 27mg-30mg, 27mg-32mg, 27mg-34mg, 27mg-36mg, 27mg-38mg, 27mg-40mg, 27mg-42mg, 27mg-44mg, 27mg-46mg, 27mg-48mg, 27mg-50mg, 27mg-52mg, 27mg-54mg, 27mg-56mg, 27mg-58mg, 27mg-60mg, 30mg-32mg, 30mg-34mg, 30mg-36mg, 30mg-38mg, 30mg-40mg, 30mg-42mg, 30mg-44mg, 30mg-46mg, 30mg-48mg, 30mg-50mg, 30mg-52mg, 30mg-54mg, 30mg-56mg, 30mg-58mg, 30mg-60mg, 33mg-34mg, 33mg-36mg, 33mg-38mg, 33mg-40mg, 33mg-42mg, 33mg-44mg, 33mg-46mg, 33mg-48mg, 33mg-50mg, 33mg-52mg, 33mg-54mg, 33mg-56mg, 33mg-58mg, 33mg-60mg, 36mg-38mg, 36mg-40mg, 36mg-42mg, 36mg-44mg, 36mg-46mg, 36mg-48mg, 36mg-50mg, 36mg-52mg, 36mg-54mg, 36mg-56mg, 36mg-58mg, 36mg-60mg, 40mg-42mg, 40mg-44mg, 40mg-46mg, 40mg-48mg, 40mg-50mg, 40mg-52mg, 40mg-54mg, 40mg-56mg, 40mg-58mg, 40mg-60mg, 43mg-46mg, 43mg-48mg, 43mg-50mg, 43mg-52mg, 43mg-54mg, 43mg-56mg, 43mg-58mg, 42mg-60mg, 45mg-48mg, 45mg-50mg, 45mg-52mg, 45mg-54mg, 45mg-56mg, 45mg-58mg, 45mg-60mg, 48mg-50mg, 48mg-52mg, 48mg-54mg, 48mg-56mg, 48mg-58mg, 48mg-60mg, 50mg-52mg, 50mg-54mg, 50mg-56mg, 50mg-58mg, 50mg-60mg, 52mg-54mg, 52mg-56mg, 52mg-58mg, 52mg-60mg, 100mg-200mg, 200mg-300mg, 300mg-400mg, 400mg-500mg, 500mg-1000mg, 1000mg-2000mg, or 1000mg-3000mg . In some embodiments, one or more immune checkpoint inhibitor dose is greater than about 1 mg, 5 mg, about 10 mg, about 12.5 mg, about 13.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, about 25 mg, about 27 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg,

about 100 mg, about 125 mg, about 150mg, or about 200 mg. In some embodiments, one or more immune checkpoint inhibitor dose is about less than about 5 mg, about 10 mg, about 12.5 mg, about 13.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, about 25 mg, about 27 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150mg, or about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 1000 mg, about 2000 mg, or about 3000 mg.

[0130] In some embodiments, the initial dose of one or more immune checkpoint inhibitor is 1 mg on day 1 followed a dose of a second immune checkpoint inhibitor is 3 mg.

[0131] In some embodiments, a compound of Formula (I) is administered prior to the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered concurrently with one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered after one or more immune checkpoint inhibitor.

[0132] In some embodiments, a compound of Formula (I) is administered about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 19h, 20h, 24h, 30h, 36h, 40h, or 48h after the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 19h, 20h, 24h, 30h, 36h, 40h, or 48h before the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered in less than about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 19h, 20h, 21h, 22h, 23h, 24h, 30h, 36h, 40h, or 48h after the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered in more than about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 19h, 20h, 21h, 22h, 23h, 24h30h, 36h, 40h, or 48h after the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered in less than about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 19h, 20h, 21h, 22h, 23h,

24h, 30h, 36h, 40h, or 48h after the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered in more than about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 19h, 20h, 21h, 22h, 23h, 24h30h, 36h, 40h, or 48h before the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered in about 1min-5min, 1min-10min, 1min-15min, 1min-20min, 1 min-25min, 1 min-30min, 0.25h-0.5h, 0.25-0.75h, 0.25-1h,0.5h-1h, 0.5h-2h, 0.5h-2.5h, 1h-2h, 1h-3h, 1h-5h, 1h-24h, 1min-24h, or 1 min-2h, 1 day-2days, 1day - 3days, 1 day-4 days, 1 day-5 days, or 1 day-6 days after the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered in about 1min-5min, 1min-10min, 1min-15min, 1min-20min, 1 min-25min, 1 min-30min, 0.25h-0.5h, 0.25-0.75h, 0.25-1h,0.5h-1h, 0.5h-2h, 0.5h-2.5h, 1h-2h, 1h-3h, 1h-5h, 1h-24h, 1min-24h, or 1 min-2h, 1 day- 2days, 1day - 3days, 1 day-4 days, 1 day-5 days, or 1 day-6 before the administration of one or more immune checkpoint inhibitor.

[0133] In some embodiments, when a compound of Formula (I) is administered prior to one or more immune checkpoint inhibitor administration, the compound of Formula (I) is administered about 1min-5min, 1min-10min, 1min-15min, 1min-20min, 1 min-25min, 1 min-30min, 0.25h-0.5h, 0.25-0.75h, 0.25-1h,0.5h-1h, 0.5h-2h, 0.5h-2.5h, 1h-2h, 1h-3h, 1h-5h, 1h-24h, 1min-1h, 1min-2h, 1min-5h, 1min-24h, 1 day- 2days, 1day - 3days, 1 day-4 days, 1 day-5 days, or 1 day-6 days before the administration of the one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 30h, 36h, 40h, 48h, 4 days, 5 days, 6 days, or 7 days before the administration of the one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered in less than about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 19h, 20h, 21h, 22h, 23h, 24h, 30h, 36h, 40h, 48h, 4 days, 5 days, 6 days, or 7 days before the administration of one or more immune checkpoint inhibitor. In some embodiments, a compound of Formula (I) is administered in more than about 1 min, 5min, 10 min, 15 min, 20 min, 25 min, 30 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12h, 13h, 14h, 15h, 16h, 17h, 18h, 19h, 20h, 21h, 22h, 23h, 24h, 30h, 36h, 40h, 48h, 3 days,

4 days, 5 days, 6 days, or 7 days before the administration of the one or more immune checkpoint inhibitor.

[0134] In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I). In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) once every 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) two times every 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) once every 1 week in a treatment cycle of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) twice every 1 week in a treatment cycle of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) on day 1, day 8, and day 15 of a 21-day treatment cycle. In some embodiments, co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) includes administering one or more immune checkpoint inhibitor prior to administering plinabulin. In some embodiments, co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) includes administering one or more immune checkpoint inhibitor after administering plinabulin. In some embodiments, co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) includes administering the one or more immune checkpoint inhibitor concurrently with a compound of Formula (I). In some embodiments, one or more immune checkpoint inhibitor described in this paragraph can independently be a first, second, third, fourth, fifth, sixth, seventh, or eighth immune checkpoint inhibitor. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) every day of the week for a week. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) every day of the week for

2 weeks, 3 weeks, or 4 weeks. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) on day 1 in weekly treatment. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) on day 1 and day 2 in weekly treatment. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) on day 1, day 2, and day 3 in weekly treatment. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) on day 1, day 2, day 3 in weekly treatment. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) on day 1, day 2, day 3, and day 4 in weekly treatment. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) on day 1, day 2, day 3, day 4, and day 5 in weekly treatment. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor and a compound of Formula (I) on day 1, day 2, day 3, day 4, day 5, and day 6 in weekly treatment. In some embodiments, the treatment schedule includes co-administration of one or more immune checkpoint inhibitor composition and a compound of Formula (I) on day 1, day 3, and day 5 in weekly treatment. In some embodiments, the treatment cycle for the compound of Formula (I) and the one or more immune checkpoint inhibitors may be the same. In other embodiments, the treatment cycle for the compound of Formula (I) and the one or more immune checkpoint inhibitors may be different. For example, in some embodiments, the treatment cycle for the compound of Formula (I) is 21 days, whereas the treatment cycle for the one or more immune checkpoint inhibitors is 14 days. In some embodiments, one or more immune checkpoint inhibitor is used on each administration day can be the same or different. In some embodiments, one or more immune checkpoint inhibitor used on the first administration day is different from one or more immune checkpoint inhibitor used on the rest of the administration days. In some embodiments, one or more immune checkpoint inhibitor used on the first administration day is the same as or different from one or more immune checkpoint inhibitor used on the second administration day. In some embodiments, one or more immune checkpoint inhibitor used on the first administration day is the same as

or different from one or more immune checkpoint inhibitor used on the third administration day. In some embodiments, one or more immune checkpoint inhibitor composition used on the first administration day is the same as or different from one or more immune checkpoint inhibitor used on the fourth administration day. In some embodiments, one or more immune checkpoint inhibitor used on the first administration day is the same as or different from one or more immune checkpoint inhibitor used on the fifth administration day. In some embodiments, one or more immune checkpoint inhibitor used on the first administration day is the same as or different from one or more immune checkpoint inhibitor used on the sixth administration day. In some embodiments, one or more immune checkpoint inhibitor used on the first administration day is the same as or different from one or more immune checkpoint inhibitor used on the seventh administration day.

[0135] In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor (e.g., the first, the second, the third, the fourth, the fifth, the sixth, the seventh, or the eighth) once every 3 weeks. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor once every 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor two times every 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor once every 1 week in a treatment cycle of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor twice every 1 week in a treatment cycle of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor three times (e.g., day 1, 2, 3, or day 1, 3, 5) every week in a treatment cycle of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor day 1, day 8, and day 15 of a 21-day treatment cycle. The one or more immune checkpoint inhibitor described in this paragraph can independently be the first, second, third, fourth, fifth, sixth, seventh, or eighth one or more immune checkpoint inhibitor. In some embodiments, the treatment schedule

includes administration of one or more immune checkpoint inhibitor every day of the week for a week. In some embodiments, the treatment schedule includes administration of the one or more immune checkpoint inhibitor every day of the week for 2 weeks, 3 weeks, or 4 weeks. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor composition on day 1 in weekly treatment. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor on day 1 and day 2 in weekly treatment. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor on day 1, day 2, and day 3 in weekly treatment. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor on day 1, day 3, day 5 in weekly treatment. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor on day 1, day 2, day 3, and day 4 in weekly treatment. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor on day 1, day 2, day 3, day 4, and day 5 in weekly treatment. In some embodiments, the treatment schedule includes administration of one or more immune checkpoint inhibitor on day 1, day 2, day 3, day 4, day 5, and day 6 in weekly treatment.

[0136] In some embodiments, the treatment schedule includes administration of a compound of Formula (I) once every 3 weeks. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) once every 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) two times every 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) once every 1 week in a treatment cycle of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) twice every 1 week in a treatment cycle of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) three times (e.g., day 1, 2, 3, or day 1, 3, 5) every 1 week in a treatment cycle of 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks. In some embodiments, the treatment schedule includes

administration of a compound of Formula (I) on day 1 of a 21-day treatment cycle. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) on day 1 and day 8 of a 21-day treatment cycle. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) day 1, day 8, and day 15 of a 21-day treatment cycle. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) every day of the week for a week. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) every day of the week for 2 weeks, 3 weeks, or 4 weeks. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) on day 1 in weekly treatment. In some embodiments, the treatment schedule includes administration of plinabulin on day 1 and day 2 in weekly treatment. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) on day 1, day 2, and day 3 in weekly treatment. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) on day 1, day 3, day 5 in weekly treatment. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) on day 1, day 2, day 3, and day 4 in weekly treatment. In some embodiments, the treatment schedule includes administration of a compound of Formula (I) on day 1, day 2, day 3, day 4, and day 5 in weekly treatment. The treatment schedule includes administration of a compound of Formula (I) on day 1, day 2, day 3, day 4, day 5, and day 6 in weekly treatment.

[0137] The treatment cycle can be repeated as long as the regimen is clinically tolerated. In some embodiments, the treatment cycle for one or more immune checkpoint inhibitor and a compound of Formula (I) is repeated for n times, wherein n is an integer in the range of 2 to 30. In some embodiments, n is 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, a new treatment cycle can occur immediately after the completion of the previous treatment cycle. In some embodiments, a new treatment cycle can occur a period of time after the completion of the previous treatment cycle. In some embodiments, a new treatment cycle can occur after 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, or 7 weeks after the completion of the previous treatment cycle.

[0138] Administration of the compositions disclosed herein can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, subcutaneously, buccally, subcutaneously, intravenously, intranasally,

intratumorally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, intragastrically, or intraocularly. Oral and parenteral administrations are customary in treating the indications that are the subject of some embodiments.

[0139] In some embodiments, the compositions described herein can be used in combination with other therapeutic agents. In some embodiments, the compositions described herein can be administered or used in combination with treatments such as chemotherapy, radiation, and biologic therapies.

EXAMPLES

[0140] To further illustrate this disclosure, the following examples are included. The examples should not, of course, be construed as specifically limiting the disclosure. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the disclosure as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the disclosure without exhaustive examples.

Example 1

[0141] A Phase 3, randomized, single blinded, active-controlled trial in patients with advanced or metastatic NSCLC that has progressed after treatment with one or two, non-docetaxel containing systemic therapy regimen(s) and/or a PD-1/PD-L1 checkpoint inhibitor therapy for advanced or metastatic disease and with at least one measurable lung lesion was conducted. The study included two treatment arms: the experimental arm (docetaxel + plinabulin [DP]) and the control arm (docetaxel + placebo [D]).

[0142] On Day 1 in a 21-day cycle, all patients (in the DP and D Arms) received treatment with 75 mg/m$_2$ docetaxel administered via intravenous (IV) infusion over 1 hour (± 10 minutes). On Days 1 and 8, patients randomized to DP Arm received plinabulin (diluted in D5W) therapy. On Days 1 and 8, patients randomized to D Arm received D5W. Plinabulin and D5W was administered via IV infusion over 60 minutes (± 10 minutes) on Day 1 beginning 2 hours (± 10 minutes) from the time the docetaxel infusion begins and again on Day 8. Dexamethasone (16 mg, 8 mg twice daily, or as per institution standard; IV or oral

administration) was given the day prior to, the day of (Day 1), and the day following docetaxel infusion (Day 2). Premedication with dexamethasone was only required to be taken when docetaxel was given.

[0143] One patient in the DP arm who failed treatment with a platinum doublet and 13 cycles of anti-PD-1 therapy achieved stable disease for 29 cycles of therapy (21 day per cycle). Thus, surprisingly, docetaxel + plinabulin therapy was shown to be effective even in patients who exhibited resistance to immune checkpoint inhibitor therapy.

Example 2

[0144] In a dose-escalation Phase I study, patients with recurrent extensive-stage small cell lung cancer (SCLC) who had progressed on prior platinum-based chemotherapy were enrolled using a 3+3 design. The primary objective was to determine dose-limiting toxicities (DLT's) and recommended Phase 2 dose (RP2D). Patients were evaluable for DLT if they received at least two cycles of therapy; DLT period was defined as the first six weeks. Secondary endpoints were ORR, PFS and frequency of irAEs. Correlative analysis included inflammatory biomarkers: hsCRP, ESR, SAA and haptoglobin. The treatment schema is provided in Table 1.

Table 1. Treatment Schema

Day 1, Cycles 1-4 (cycle = 21 days)	
Nivolumab	1 mg/kg
Ipilimumab	3 mg/kg
Plinabulin	(-1) 13.5 mg/m^2
	(start) 20/m^2
	(+1) 30 mg/m^2
Day 1, Cycles 5+ (cycle = 14 days)	
Nivolumab	240 mg
Plinabulin	As above

[0145] Patients received nivolumab (1 mg/kg), ipilimumab (3 mg/kg) and plinabulin (as per dose escalation schema) IV on day 1 of each 21 day cycle. After completion of 4 cycles, patients continued therapy with nivolumab (240 mg) and plinabulin

every 2 weeks till progression or intolerable toxicity. Patients were evaluable for DLT if they received at least 2 cycles of therapy; DLT period was defined as the first 6 weeks from C1D1.

[0146] Seventeen patients were enrolled (1 patient withdrew consent before treatment, 16 evaluable for safety). Median age was 59 years (range 43 to 78); 9 patients were male and 10 had received prior checkpoint inhibitor (CPI) therapy. Eight patients (50%) were treated at dose level 1 of plinabulin (20 mg/m^2) and 8 patients at 30 mg/m^2 of plinabulin (level 2); dose-level 2 was determined to be RP2D. There were 2 DLTs; 1 at level 1 (grade 3 altered mental status lasting< 24 hours) and 1 at level 2 (grade 3 infusion reaction). Eight patients (50%) had at least one grade 3 or higher treatment-related AE; there were not any treatment-related deaths. The most common treatment-related AEs (all grades) were nausea (10; 63%), infusion reaction (8; 50%), vomiting (7; 44%), diarrhea (7; 44%) and fatigue (6, 32%). Seven patients (44%) had at least one ≥grade 3 treatment-related AE; there were no treatment-related deaths. Two patients (13%) had ≥ grade 3 irAE requiring steroids (1 diarrhea, 1 transaminitis); both at level 1, none at level 2. At data cutoff, three patients exhibited a partial response in patients who did not receive previous checkpoint inhibitors (CPI) (3/6; 50%) and three patients in 7 evaluable patients exhibited a partial response who had exhibited progressive disease after failing prior checkpoint inhibitor (CPI) treatment (3/7; 43%). These three patients continued on treatment for 3 months, 5 months (still on treatment) and 18 months. In the three CPI-resistant patients, the tumor reduction was 52%, 75%, and 78%. The treatment-related events are further described in Table 2.

Table 2. Treatment-related adverse events

	All grade	**≥ Grade 3**
Nausea	10 (63%)	0
Infusion reaction	8 (50%)	1 (6%)
Vomiting	7 (44%)	0
Diarrhea	7 (44%)	1 (6%)
Fatigue	6 (32%)	1 (6%)
Pyrexia	4 (25%)	0
Rash	3 (19%)	0

Hypertension	3 (19%)	1 (6%)

[0147] FIG. 1 illustrates a waterfall plot of best overall response in target lesions compared to baseline.

[0148] Thirteen patients were evaluable for efficacy (1 withdrew consent, 1 death from unrelated cause, 1 replaced for DLT); 6 patients had PR (ORR 46%). There were 3 PRs in PD-1/PD-L1 therapy naïve patients (3/6; 50%). There were 3 PRs in PD-1/PD-L1 resistant patients (3/7; 43%). These three patients continued on treatment for 3 months, 5 months (still on treatment) and 18 months.

[0149] Levels of high sensitivity C-reactive protein [hsCRP], erythrocyte sedimentation rate [ESR] and serum amyloid A [SAA] were measured in who blood on day 1 of each cycle. FIGs 2A and 2B illustrate the plots of log-transformed values for the mean at each cycle. Levels of hsCRP, ESR and SAA transiently increased around cycle 4 before returning to baseline values.

[0150] Plinabulin in combination with nivolumab and ipilimumab was safe and well tolerated. Surprisingly, plinabulin in combination with CPI therapy was shown to be effective, even in patients who exhibit resistance to CPI therapy.

Example 3

[0151] This is an open label, single-center study to assess the safety and tolerability of plinabulin when administered in combination with radiation/immunotherapy regimens in subjects with one of seven metastatic or locally advanced cancers who had disease progression on anti-PD-1/PD-L1 mAb treatment as standard of care, and to assess objective response rate of the study regimen. The seven targeted cancer types for this study are as follows: bladder cancer, melanoma, Merkel cell cancer, MSI-H Cancers (of any histology), non-small cell lung cancer, renal cell cancer, and small cell lung cancer.

[0152] The study cohort was tumor type specific. There were seven study cohorts from seven tumor types mentioned above for this study. Anti-PD-1/PD-L1 mAb treatment cycle was defined for the subject's treatment cycle for the study.

[0153] All subjects in Phase 1b will receive a triple combo treatment of Radiation Therapy (RT) + Plinabulin + anti-PD-1/PD-L1 mAb in Cycle 1, followed by anti-PD-1/PD-

L1 mAb and plinabulin combo regimen in Cycle 2 and beyond until disease progression or development of unacceptable toxicity, withdrawal from study treatment, or discontinuation of this study (see table below). A short course of local consolidative radiation therapy (RT) will be administered in Cycle 1 starting from Day 1. Optional sequential RT may be administered to target other untreated lesions at discretion of the treating doctor in Cycle 2 of any regimens. Plinabulin will be dosed on Day 1 and Day 4 of Cycle 1 of any anti-PD-1/PD-L1 regimen, and if optional RT is given in Cycle 2, Plinabulin will also be given on Day 4 of Cycle 2. Plinabulin will be given on day 1 of Cycle 3 and thereafter. Anti-PD-1/PD-L1 mAb will be dosed on Day 1 of every treatment cycle (also on Day 15 [Q4W] in case of regimen containing Avelumab or Durvalumab or Nivolumab as Anti-PD-1/PD-L1 mAb). Subjects must continue receiving the same anti-PD-1/PD-L1 mAb they failed in the prior treatment.

Table 3. Phase 1b/Phase 2: Study Drugs/Regimen

Phase 1b/Phase 2: Study Drugs/Regimen	**Cycle Length**	**Radiation Therapy (RT)**	**Plinabulin** **30 mg/m2 (Starting dose) or 20 mg/m2**	**Anti-PD-1/PD-L1 mAb**
RTX + Plinabulin + Avelumab	1 Cycle = 4 weeks	C1D1-3 (8 Gy x 3 fractions) or C1D1-4 (12.5 Gy x 4 fractions) or C1D1-5 (4 Gy x 5 fractions) C2D1 (optional)	C1D1, 4 C2D1 C2D4 (optional if RT on C2D1) C3 onward D1	Avelumab (800 mg): D1, 15 of every cycle
RTX + Plinabulin + Durvalumab	1 Cycle = 4 weeks			Durvalumab (10 mg/kg): D1, 15 of every cycle
RTX + Plinabulin + Nivolumab	1 Cycle = 4 weeks			Nivolumab (240 mg): D1, 15 of every cycle
RTX + Plinabulin + Atezolizumab	1 Cycle = 3 weeks			Atezolizumab (1200 mg): D1 of every cycle
RTX + Plinabulin + Pembrolizumab	1 Cycle = 3 weeks			Pembrolizumab (200 mg): D1 of every cycle

C = cycle, D = day, mAb = monoclonal antibody, PD = progression disease, RT = radiation therapy.

[0154] The study will begin with 30 mg/m^2 plinabulin in combination with a full dose of anti-PD-1/PD-L1 mAb and RT. A lower dose level at 20 mg/m^2 of plinabulin will be

explored as necessary depending on observed toxicity. Anti-PD-1 or PD-L1 antibody dose according to FDA drug inserts will not change in phase 1b.

[0155] Once a minimum toxicity dose (MTD) is determined, an additional 10 patients will be enrolled for additional experience with safety and efficacy in each of the seven cancer type cohort and to determine the recommended phase 2 dose (RP2D). The RP2D will be selected based on both safety and totality of clinical evidence (e.g., PK/PD data), and is not necessarily the MTD. Patients treated at the MTD/RP2D in the dose finding will roll over into the cohort expansion. Anti-PD-1/PD-L1 mAb dose will follow FDA recommendations to each indication and will not change in the expansion.

[0156] Phase 2:

[0157] Subjects with the selected tumor type will be accrued to receive the plinabulin MTD/RP2D in combination with RT and anti-PD-1/PD-L1 mAb. Anti-PD-1/PD-L1 mAb dose will follow FDA recommendations to each indication and will not change in the study. They will be randomized to one of two treatment arms in a 1:1 ratio. The randomization will be stratified by the number of mets (oligo (<=3 vs > 3) and ECOG 0-1 vs 2.

[0158] Arm A: Radiation Therapy + Plinabulin + anti-PD-1/PD-L1 mAb (experimental)

[0159] Arm B: Radiation Therapy + anti-PD-1/PD-L1 mAb (control)

[0160] Subjects in arm A will receive triple combo in Cycle 1, followed by plinabulin and anti-PD-1/PD-L1 mAb double combo for Cycle 2 and beyond (see table below).

[0161] Subjects in arm B will receive combo regimen of RT and anti-PD-1/PD-L1 mAb in Cycle 1, followed by anti-PD-1/PD-L1 mAb alone for Cycle 2 and beyond (see table below).

[0162] Treatment will continue until disease progression, development of unacceptable toxicity, withdrawal from study treatment, or discontinuation of this study. Because the experimental combination arm is not expected to be worse than the control arm, no futility monitoring is planned.

[0163] A short course of local consolidative RT will be administered in Cycle 1 starting from Day 1. An optional sequential RT to other untreated lesions at discretion of the

treating doctor is allowed (Cycle 2 Q4W; Cycle 2 Q3W). Plinabulin will be dosed on Day 1 of every treatment cycle and/ or anti-PD-1/PD-L1 mAb will be dosed on Day 1 of every treatment cycle ((also on Day 15 [Q4W] in case of regimen containing Avelumab or Durvalumab or Nivolumab as Anti-PD-1/PD-L1 mAb) to subjects based on their treatment assignment.

[0164] For subjects in Phase 1b and Phase 2, toxicity will be managed by treatment interruption, dose reduction and/or treatment discontinuation in accordance with prespecified dose modification instructions.

Table 4: Phase 2 Only: Study Drugs/Regimen

Phase 2 only: Study Drugs/Regimen	**Cycle Length**	**Radiation Therapy (RT)**	**Plinabulin 30 mg/m2 (Starting dose) or 20 mg/m2**	**Anti-PD-1/PD-L1 mAb**
RTX + Avelumab	1 Cycle = 4 weeks	C1D1-3 (8 Gy x 3 fractions) or C1D1-4 (12.5 Gy x 4 fractions) or C1D1-5 (4 Gy x 5fractions) C2D1 (optional)	N/A[a]	Avelumab (800 mg): D1, 15 of every cycle
RTX + Durvalumab	1 Cycle = 4 weeks			Durvalumab (10 mg/kg): D1, 15 of every cycle
RTX + Nivolumab	1 Cycle = 4 weeks			Nivolumab (240 mg): D1, 15 of every cycle
RTX + Atezolizumab	1 Cycle = 3 weeks			Atezolizumab (1200 mg): D1 of every cycle
RTX + Pembrolizumab	1 Cycle = 3 weeks			Pembrolizumab (200 mg): D1 of every cycle

C = cycle, D = day, mAb = monoclonal antibody, N/A = not applicable, PD = progression disease, RT = radiation therapy.

a. Plinabulin marked N/A only applies to Arm B for phase 2, not arm A. Plinabulin will be administered to subjects in Arm A on days listed in Phase 1b/Phase 2: Study Drugs/Regimen table above.

[0165] **Radiation Therapy (RT) Administration.** Radiation therapy will be delivered using external beam radiation, with either 2D/conventional techniques, three-dimensional conformal therapy, intensity modulated radiation therapy (IMRT), stereotactic

radiosurgery (SRS) or proton beam therapy (PBT), at the discretion of the treating radiation oncologist.

[0166] Radiation Therapy (RT) will be administered with one of three regimens: 8 Gy x 3 fractions, 12.5 Gy x 4 fractions, and/or 4 Gy x 5 fractions from Days 1 to 3 (3 fractions), Days 1 to 4 (4 fractions), or Days 1 to 5 (5 fractions) in Cycle 1. The choice of RT regimens for tumors and lesions is at the discretion of the treating radiation oncologist. RT will target up to a maximum of 5 tumor lesions, and any of the radiation regimens could be use simultaneously or sequentially. Optional sequential RT is at the discretion of the treating radiation oncologist is warranted to target other untreated lesions with same regimens described above (Cycle 2 Q4W; Cycle 2 Q3W). Treatment can be for any lesions in nodes and organs including brain and bone. At least one measurable lesion will be left untreated for disease assessment during the study. Assessment of responses however are not reliant on RT treated tumor lesions and bony lesions. Brain metastasis are treated and not be used for irRECIST response assessment.

[0167] If patients develop toxicity attributable to radiation after receiving at least one dose of radiation, the rest of the radiation treatment may be discontinued, and the AEs will be documented. Since the number of fractions are between 3-5 fractions, patients could receive at least 1 fraction up to 5 fractions. The initially prescribed dose per fraction will not change, but it is possible to simply reduce the total dose delivered. The patient will have a visit with the treating radiation oncologist at the end of every cycle of radiation treatment.

[0168] **PD-1 or PD-L1 Administration:** Subjects are given the same anti-PD-1/PD-L1 mAb on which they have failed in prior treatment. Anti-PD-1/PD-L1 mAb aredosed according to FDA recommendations as specified under Phase 1b and Phase 2 above. Anti-PD-1/PD-L1 mAb treatment cycle will define subject's treatment cycle for the study. The list of anti-PD-1/PD-L1 mAb approved to date for the following indications is provided here:

[0169] Merkel cell cancer: Avelumab, Pembrolizumab, Renal Cell Cancer: Pembrolizumab, Nivolumab, Bladder cancer: Durvalumab, MSI-H cancers (of any histology): Pembrolizumab, Nivolumab, Non-small cell lung cancer: Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab, Small Cell lung cancer: Pembrolizumab, Nivolumab, Atezolizumab, Melanoma: Nivolumab or Pembrolizumab single agent.

[0170] Any approved anti-PD-1/PD-L1 mAb can be used for the study. Anti-PD-1/PD-L1 mAb dose and administration route: Avelumab 800mg IV over 1 hr on Day 1 and Day 15 in Q4W, Atezolizumab 1200 mg Q3W IV 1 hr in 1st dose, may infuse over 30 min in subsequent doses if tolerated well, Durvalumab 10 mg/kg IV over 1 hr on Day 1 and Day 15 in Q4W, Nivolumab 240 mg IV over 30-60 min on Day 1 and Day 15 in Q4W, Pembrolizumab 200 mg Q3W IV over 30 min. Anti-PD-1/PD-L1 mAb will be administered after the rest period (at least 3 hours, but no later than 12 hours) of RT, if applicable, and before plinabulin infusion. The FDA product insert will be followed for the instructions of treatment dosing and toxicity management of each approved anti-PD-1 or PD-L1 mAb.

[0171] **Plinabulin Administration**. Plinabulin will be administered on Day 1 and Day 4 in Cycle 1 intravenously, and if optional RT is given in Cycle 2, Plinabulin will also be given on Day 1 and Day 4 of Cycle 2. Optional RT will always be given in Cycle 2 on Day 1. Plinabulin will always be given on day 1 of Cycle 3 and after.

[0172] Two plinabulin dose levels may be explored in phase 1b trial. Plinabulin dose level at 30 mg/m^2 will be first tested in phase 1b trial. If it is not deemed tolerable, then the dose at 20 mg/m^2 will be explored.

[0173] For plinabulin at 30 mg/m^2 dose level a 60 -minute infusion through IV with ± 10 min window is recommended. For plinabulin at 20 mg/m^2 dose level a 30-minute infusion through IV with ± 5 min window is recommended. For patients with a body surface area (BSA) greater than 2.4 m^2, dosing is calculated using the maximum BSA of 2.4 m^2 for Plinabulin.

[0174] Plinabulin is administered at 1-2 hours after completion of anti-PD-1 or PD-L1 mAb infusion when applicable, or at least 3 hours (but not longer than 12 hours) after the radiotherapy.

[0175] **Safety & Efficacy Assessments**. Safety and tolerability are assessed throughout the study according to NCI-CTCAE version 5.0. Vital signs, physical examination, and safety lab test result review (hematology, chemistry & urinalysis) will have to be performed prior to the study treatment to make sure the study treatment is safe to be administered.

[0176] Tumor assessments will be performed by the investigators based on both immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) and modified

Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Treatment decisions by the investigator will be based on irRECIST.

[0177] Tumor assessments will be carried out during the Screening, and every 9 weeks (± 1 week) for 27 weeks (during Q3W dosing) or every 8 weeks (± 1 week) for 24 weeks (during Q4W dosing), then every 12 weeks during treatment cycles in the Treatment Phase regardless of treatment cycles and follow up period. Computed tomography (CT)/magnetic resonance imaging (MRI) scans of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1/ Day 1), at all tumor assessment time points, and as indicated clinically. RT treated lesions will not be used for response assessment. At least one measurable tumor lesion will be kept untreated by RT for disease response assessment across the treatment.

[0178] Subjects going off treatment without disease progression will also undergo tumor assessments per the Schedule of Procedures/Assessments until disease progression is documented or another anticancer therapy is initiated.

[0179] If the time point tumor assessment is progressive disease (PD), treatment will continue, and tumor assessments repeated at least 4 weeks later in order to confirm immune-related progressive disease (irPD).

[0180] **Study Population:** Advanced staged cancer subjects who are either unresponsive or relapsed following prior standard PD-1 or PD-L1 regimen +/- chemotherapy or anti-CTLA4, for one of the following seven cancers: non-small cell lung cancer, small cell lung cancer, renal cell cancer, bladder cancer, Merkle cell cancer, MSI-H cancer (any history), and melanoma.

[0181] **Treatment Duration:** Treatment will continue until disease progression, development of unacceptable toxicity (i.e., DLTs), withdrawal from study treatment, or discontinuation of this study.

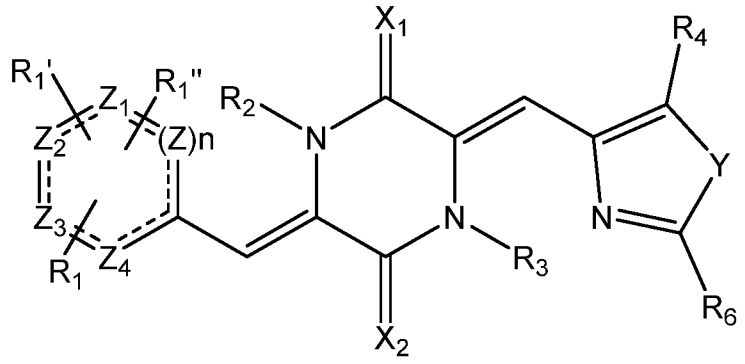
[0189] **Duration of Study**: Screen period: up to 28 days. Treatment period: Study treatment continues until disease progression (estimate 2-6 months), development of unacceptable toxicity, withdrawal from study treatment, or discontinuation of this study. Follow-up period: Study Follow-up consists of the End of Treatment Visit and the Follow-up Visits. The End of Treatment Visit will occur within 30 days following the last dose of study treatment, then transit to the Follow-up visit period. The Follow-up Visit at every 12 weeks

(±1 week) continue as long as the study subject is alive unless the subject withdraws consent or until the sponsor terminates the study. In the Follow-up Period, Subjects who discontinued for reasons other than progression of disease (and withdrawal from study treatment) will continue to visit the clinic for study assessments and evaluation of their disease by CT, MRI, or positron emission tomography (PET)/CT scan approximately every 12 weeks until progression of disease is determined, the patient receives additional anti-neoplastic medication, or for a maximum of 5 years Subjects who stopped treatment due to disease progression will be followed up for survival status.

WHAT IS CLAIMED IS:

1. A method of treating cancer in a subject, the method comprising:

administering to the subject a compound of Formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R_1, R_4, and R_6, are each separately selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1,-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups, hydroxy, carboxy, —CO—O—R_7,cyano, alkylthio, halogenated alkyl including polyhalogenated alkyl, halogenated carbonyl, and carbonyl —CH_2CO—R_7, wherein R_7 is selected from a hydrogen atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups;

R_1' and R_1'' are each independently selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups, hydroxy, carboxy, —CO—O—R_7, cyano, alkylthio, halogenated alkyl including polyhalogenated alkyl, halogenated carbonyl, and carbonyl —CH_2CO—R_7, wherein R_7 is selected from a hydrogen atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted

aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups;

R, R_1' and R_1'' are either covalently bound to one another or are not covalently bound to one another;

R_2, R_3, and R_5 are each separately selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1-C_{12} alkyl, unsaturated C_1-C_{12} alkenyl, acyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, and substituted nitro groups, sulfonyl and substituted sulfonyl groups;

m is an integer equal to zero, one or two;

X_1 and X_2 are separately selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, and

Y is selected from the group consisting of a NR_5, an oxygen atom, a sulfur atom, a oxidized sulfur atom, a methylene group and a substituted methylene group;

Z, for each separate n, if non-zero, and Z_1, Z_2, Z_3 and Z_4 are each separately selected from a carbon atom, a sulfur atom, a nitrogen atom or an oxygen atom;

the dashed bonds may be either single or double bonds,

wherein the cancer was resistant to a prior treatment with one or more immune checkpoint inhibitor.

2. The method of claim 1, wherein the cancer was a tumor that was resistant to the one or more immune checkpoint inhibitors.

3. The method of claim 2, wherein the tumor progressed after the prior treatment with the one or more immune checkpoint inhibitors.

4. The method of claim 2, wherein the tumor did not respond to an initial treatment regimen of the one or more immune checkpoint inhibitors.

5. The method of any one of claims 1 to 4, further comprising administering an additional chemotherapy agent.

6. The method of claim 5, wherein the additional chemotherapy agent is administered before administering the compound of formula (I) to the subject.

7. The method of claim 5, wherein the additional chemotherapy agent is a taxane.

8. The method of claim 7, wherein the taxane is docetaxel.

9. The method of any one of claims 1 to 8, wherein the one or more immune checkpoint inhibitor to which the cancer was resistant is a PD-1 inhibitor, PD-L1 inhibitor, a CTLA-4 inhibitor, or a combination thereof.

10. The method of claim 9, wherein the one or more immune checkpoint inhibitor to which the subject was resistant is a PD-1 inhibitor.

11. The method of claim 9, wherein the one or more immune checkpoint inhibitor to which the subject was resistant is a PD-L1 inhibitor.

12. The method of claim 9, wherein the one or more immune checkpoint inhibitor to which the subject was resistant is a CTLA-4 inhibitor.

13. The method of any one of claims 1 to 9, wherein the one or more immune checkpoint inhibitor to which the subject was resistant is pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, pembrolizumab, pidilizumab, ipilimumab, BMS 936559, durvalumab, spartalizumab, or any combinations thereof.

14. The method of claim 13, wherein the one or more immune checkpoint inhibitor to which the cancer was resistant is nivolumab and ipilimumab.

15. The method of any one of claims 1 to 14, wherein the cancer is selected from a breast cancer, a bladder cancer, a glioma, a glioblastoma, a head and neck cancer, a non-small cell lung cancer, a small cell lung cancer, recurrent small cell lung cancer (SCLC), a colorectal cancer, a gastrointestinal stromal tumor, a gastroesophageal carcinoma, a renal cell cancer, a prostate cancer, a liver cancer, a colon cancer, a pancreatic cancer, an ovarian

cancer, a lymphoma, or a cutaneous T-cell lymphoma, metastatic melanoma, hepatocellular carcinoma, malignant pleural mesothelioma, urothelial carcinoma, esophageal cancer, Merkel cell cancer, endometrial cancer, basal cell carcinoma, or a melanoma.

16. The method of claim 15, wherein the cancer is recurrent small cell lung cancer (SCLC).

17. The method of any one of claims 1 to 16, further comprising co-administering to the subject an immune checkpoint inhibitor.

18. The method of claim 17, wherein the co-administered one or more immune checkpoint inhibitor is a PD-1 inhibitor, PD-L1 inhibitor, a CTLA-4 inhibitor, or a combination thereof.

19. The method of claim 17, wherein the co-administered one or more immune checkpoint inhibitor is pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, pembrolizumab, pidilizumab, ipilimumab, BMS 936559, durvalumab, spartalizumab, or any combinations thereof.

20. The method of claim 18, comprising administering a PD-1 antibody and a CTLA-4 antibody.

21. The method of claim 20, wherein the PD-1 antibody is nivolumab and the CTLA-4 antibody is ipilimumab.

22. The method of claim 21, wherein the nivolumab is administered first followed by administering ipilimumab.

23. The method of claim 21, wherein the nivolumab is administered on the same day as ipilimumab.

24. The method of claim 21, wherein the nivolumab and the ipilmumab are administered on the same day every two weeks.

25. The method of claim 21, wherein the nivolumab and the ipilmumab are administered on the same day every three weeks.

26. The method of claim 21, wherein the nivolumab and the ipilmumab are administered on the same day every three weeks for four doses.

27. The method of any one of claims 21 to 26, wherein the nivolumab is administered at a range from about 100 mg to 600 mg.

28. The method of any one of claims 21 to 26, wherein the nivolumab is administered at a range from about 240 mg to 480 mg.

29. The method of any one of claims 17 to 28, wherein the co-administered one or more immune checkpoint inhibitor and the compound of Formula (I) is administered during four dosing cycles.

30. The method of any one of claims 17 to 28, wherein the subject receives the co-administered one or more immune checkpoint inhibitor and a compound of Formula (I) every 21-days.

31. The method of any one of claims 1 to 30, further comprising administering radiation to the subject.

32. The method of claim 31, wherein the radiation is administered before administering the compound of Formula (I) to the subject.

33. The method of claim 1, further comprising administering a PD-1 or PD-L1 inhibitor and an additional chemotherapy agent to the subject.

34. The method of claim 1, further comprising administering a PD-1 or PD-L1 inhibitor and radiation to the subject.

35. The method of claim 1, further comprising administering a PD-1 or PD-L1 inhibitor and a CTLA-4 inhibitor to the subject.

36. The method of claim 1, further comprising administering a CTLA-4 inhibitor and radiation to the subject.

37. The method of any one of claims 1 to 36, wherein the compound of Formula (I) is administered at a dose from about 5 mg/m^2 to 150 mg/m^2.

38. The method of claim 37, wherein the compound of Formula (I) is administered at a dose of about 20 mg/m^2 to about 30 mg/m^2.

39. The method of any one of claims 1 to 38, wherein the compound of formula (I) is administered orally, sublingually, buccally, subcutaneously, intravenously, intranasally, intratumorally, topically, transdermally, intradermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, or intraocularly.

40. The method of any one of claims 1 to 39, wherein the compound of Formula (I) is administered on day 1 of a 14 day dosing cycle.

41. The method of any one of claims 1 to 39, wherein the compound of Formula (I) is administered on day 1 of a 21 day dosing cycle.

42. The method of any one of claims 1 to 41, wherein the compound of Formula (I) is selected from plinabulin, (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-d-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(phenylmethylene-d)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenylmethylene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(phenyl-2,3,4,5,6-d_5)-methylene-d-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(4-Fluoro-(phenyl-2,3,5,6-d_4))-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene)piperazine-2,5-dione; (3Z,6Z)-3-(4-Fluoro-(phenyl-2,3,5,6-d_4))-methylene-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-fluorobenzylidene)-6-((5-

(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-benzoylbenzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(4-fluorobenzoyl)benzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(4-methoxybenzoyl)benzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-methoxybenzylidene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; (3Z,6Z)-3-(3-(trifluoromethyenzydene)-6-((5-(tert-butyl)-1H-imidazol-4-yl)methylene-d)piperazine-2,5-dione; and a pharmaceutically acceptable salt thereof.

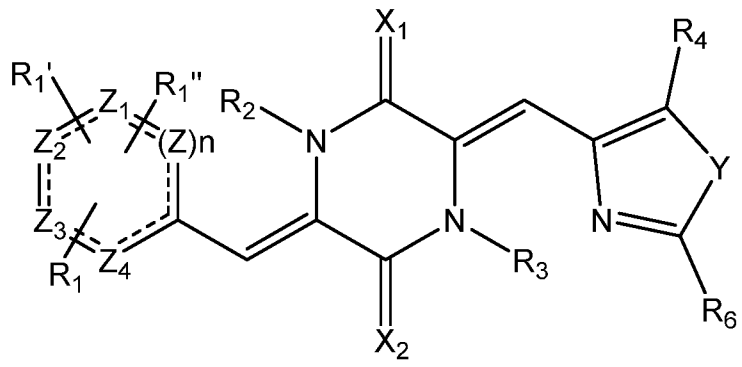
43. The method of any one of claims 1 to 42, wherein the compound of Formula (I) is plinabulin or a pharmaceutically acceptable salt thereof.

44. The method of any one of claims 2 to 4, wherein a mass of the tumor is reduced from about 50% to about 100%.

45. The method of claim 44, wherein the tumor mass is reduced from about 50% to about 70%.

46. A method of halting or reversing progressive cancer in a subject, the method comprising:

administering a compound of Formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R_1, R_4, and R_6, are each separately selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1,-C_{24} alkyl, unsaturated C_1-

C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups, hydroxy, carboxy, —CO—O—R_7,cyano, alkylthio, halogenated alkyl including polyhalogenated alkyl, halogenated carbonyl, and carbonyl —CH_2CO—R_7, wherein R_7 is selected from a hydrogen atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups;

R_1' and R_1'' are each independently selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups, hydroxy, carboxy, —CO—O—R_7, cyano, alkylthio, halogenated alkyl including polyhalogenated alkyl, halogenated carbonyl, and carbonyl —CH_2CO—R_7, wherein R_7 is selected from a hydrogen atom, a halogen atom, and saturated C_1-C_{24} alkyl, unsaturated C_1-C_{24} alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, azido, substituted nitro, phenyl, and substituted phenyl groups;

R, R_1' and R_1'' are either covalently bound to one another or are not covalently bound to one another;

R_2, R_3, and R_5 are each separately selected from the group consisting of a hydrogen atom, a deuterium atom, a halogen atom, and saturated C_1-C_{12} alkyl, unsaturated C_1-C_{12} alkenyl, acyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, amino, substituted amino, nitro, and substituted nitro groups, sulfonyl and substituted sulfonyl groups;

m is an integer equal to zero, one or two;

X_1 and X_2 are separately selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, and

Y is selected from the group consisting NR_5, an oxygen atom, a sulfur atom, a oxidized sulfur atom, a methylene group and a substituted methylene group;

Z, for each separate n, if non-zero, and Z_1, Z_2, Z_3 and Z_4 are each separately selected from a carbon atom, a sulfur atom, a nitrogen atom or an oxygen atom;

the dashed bonds may be either single or double bonds,

wherein the subject was resistant to prior treatment with one or more immune checkpoint inhibitors.

47. A method of treating cancer in a subject who exhibited resistance to checkpoint inhibitor therapy, the method comprising:

identifying a subject with a cancer that has shown resistance to one or more immune checkpoint inhibitors; and

co-administering to the subject plinabulin and one or more immune checkpoint inhibitors,

wherein the one or more immune checkpoint inhibitors is an inhibitor of PD-1, PD-L1 or CTLA-4.

48. The method of claim 47, wherein the inhibitor of PD-1 is nivolumab and is administered at 1 mg/kg.

49. The method of claim 47, wherein the inhibitor CTLA-4 is ipilimumab and is administered at 3 mg/kg.

50. The method of claim 47, wherein the plinabulin is administered at a dose from about 13.5 mg/m^2 to about 30 mg/m^2 on day 1 of a 21 day cycle.

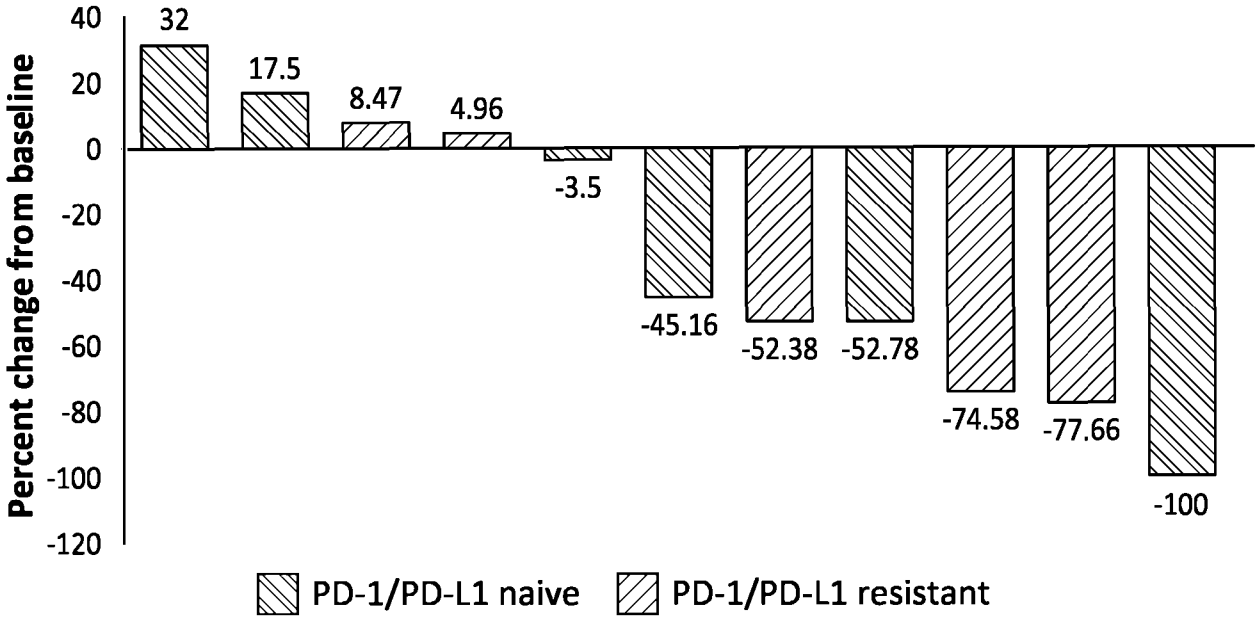

Percent change from baseline
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20
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-20
-40
-60
-80
-100
-120
32
17.5
8.47
4.96
-3.5
-45.16
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-74.58
-77.66
-100
PD-1/PD-L1 naive
PD-1/PD-L1 resistant

FIG. 1

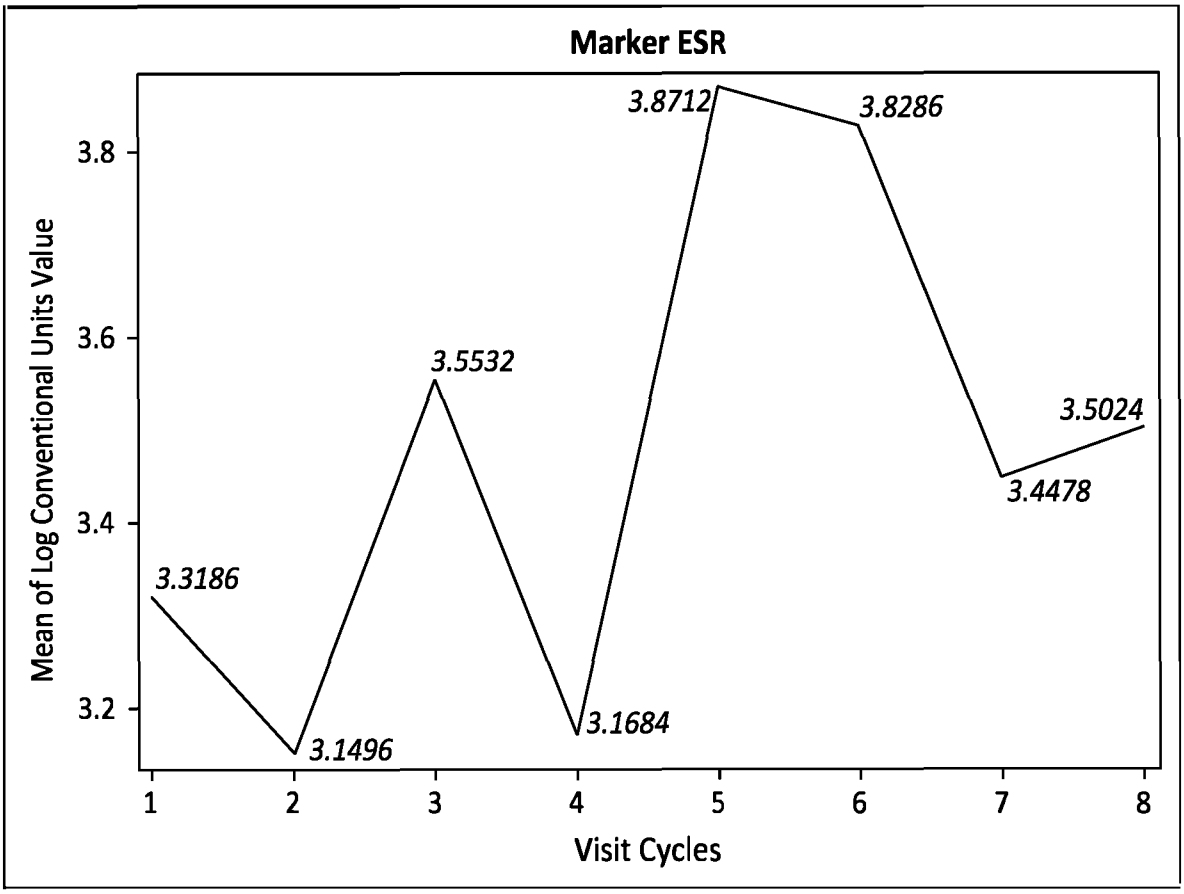

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3.6
3.4
3.2
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3.1496
3.5532
3.1684
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6
7
8
Visit Cycles

FIG. 2A

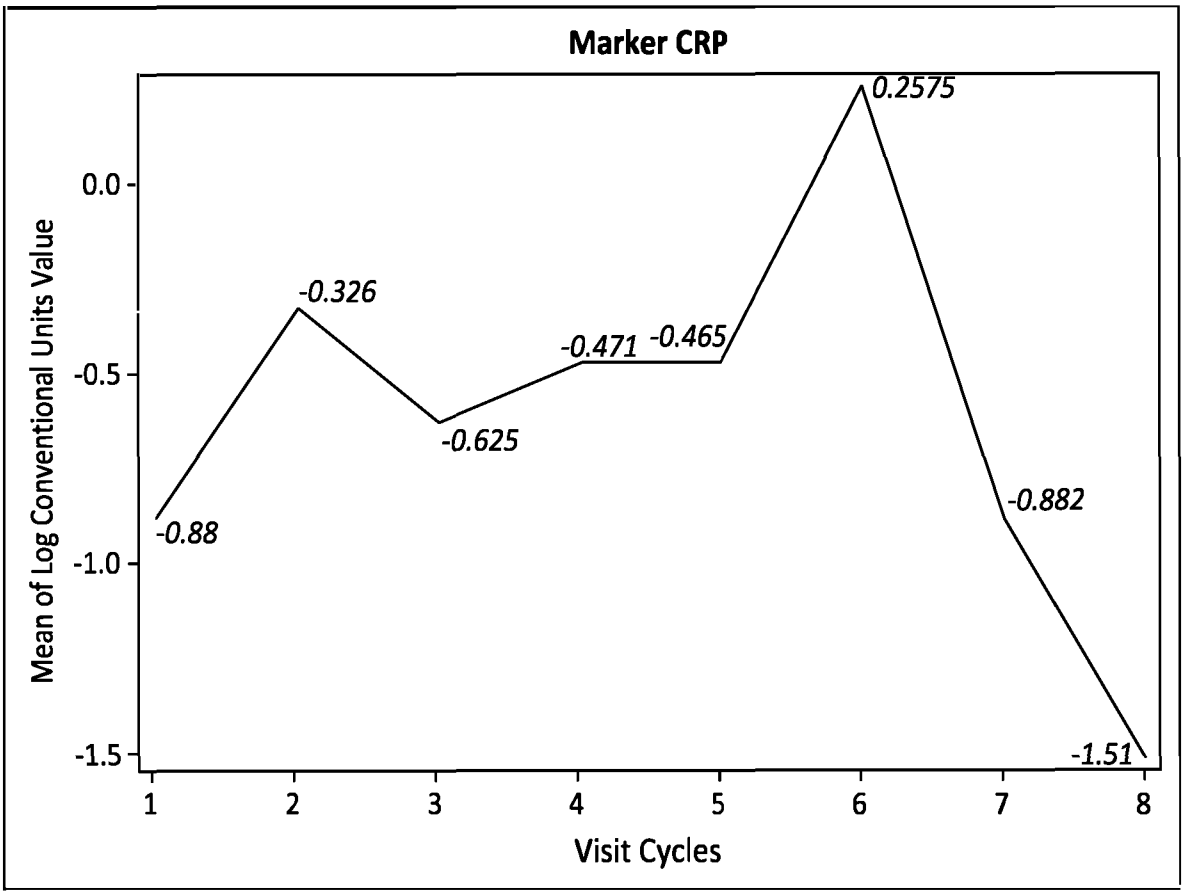

Marker CRP
Mean of Log Conventional Units Value
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-0.5
-1.0
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0.2575
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-1.51
1
2
3
4
5
6
7
8
Visit Cycles

FIG. 2B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/023793

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/496 (2006.01) ***A61K 31/337 (2006.01)*** ***A61P 25/00 (2006.01)*** ***A61P 35/00 (2006.01)*** ***A61K 39/395 (2006.01)*** ***C07K 16/28 (2006.01)***

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

EPOQUE – Database: PATENW; STN – Databases: REGISTRY, HCAPLUS, MEDLINE, BIOSIS, EMBASE; INTERNET – Espacenet, Pubmed, ClinicalTrials.gov

Keywords: cancer, plinabulin, immune checkpoint inhibitors, nivolumab, cemiplimab, atezolizumab, avelumab, pembrolizumab, pidilizumab, ipilimumab, BMS936559, durvalumab, spartalizumab and other similar terms searched.

Substructure search of Formula (I) carried out in STN

Espacenet, Auspat and Internal Databases: Applicant/Inventors names searched.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2022	21 June 2022

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Telephone No. +61262832949

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/US2022/023793
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2018/140600 A1 (MARINE BIOMEDICAL RESEARCH INSTITUTE OF QINGDAO CO., LTD) 24 May 2018 See [0012]-[0016] and Example 14	1-50
X	US 2007/0078138 A1 (PALLANDINO et al.) 05 April 2007 See [0010]-[0020], [0023]-[0032] and Examples	1-50
X	CN 110240592 A (MARINE BIOMEDICAL RESEARCH INSTITUTE OF QINGDAO CO., LTD) 17 September 2017 & English Translation retrieved from Espacenet See [0008]-[0016] and Example 16	1-50
X	WO 2016/144635 A1 (BEYONDSPRING PHARMACEUTICALS, INC.) 15 September 2016 See [0005]-[0010], [0018], [0054] and Examples	1-50
X	WO 2016/144636 A1 (BEYONDSPRING PHARMACEUTICALS, INC.) 15 September 2016 See [0005]-[0008], [0013], [0049]-[0051] and Examples	1-50
X	Mita, M., M., *et al.*, "Phase 1 First-in-Human Trial of the Vascular Disrupting Agent Plinabulin (NPI-2358) in Patients with Solid Tumors or Lymphomas", Clinical Cancer Research, 2010 Dec 1, Vol 16, No. 23, pp. 5892-99 See Abstract and Results	1-50
X	WO 2015/051543 A1 (BEYONDSPRING PHARMACEUTICALS, INC.) 16 April 2015 See pg 2 ln 5-14, pg 6 ln 5-11 and Examples	1-50
X	Nereus Pharmaceuticals, Inc., "Phase 1/2 Study of Vascular Disrupting Agent NPI-2358 + Docetaxel in Patients With Advanced Non-Small Cell Lung Cancer", ClinicalTrials.gov, NCT00630110, 16 Aug 2011, <URL: https://www.clinicaltrials.gov/ct2/show/NCT00630110> [retrieved online 1 June 2022] See Study Description	1-50
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X	Bazhenova, L., "Nivolumab in Combination With Plinabulin in Patients With Metastatic Non-Small Cell Lung Cancer (NSCLC)", ClinicalTrials.gov, NCT02812667 version 7, 21 Feb 2021, <URL: https://clinicaltrials.gov/ct2/history/NCT02812667?V_7=View#StudyPageTop> [retrieved online 1 June 2022] See Study Description	1-50
X	Malhotra, J., "A Phase I/II Study of Nivolumab, Ipilimumab and Plinabulin in Patients With Recurrent Small Cell Lung Cancer", ClinicalTrials.gov, NCT03575793 version 9, 15 Apr 2020, <URL: https://clinicaltrials.gov/ct2/history/NCT03575793?V_9=View#StudyPageTop> [retrieved online 1 June 2022] See Study Description	1-50
	Malhotra, J., Abstract 8570: "A phase I trial of plinabulin in combination with nivolumab and ipilimumab in patients with relapsed small cell lung cancer (SCLC): Big Ten Cancer Research Consortium (BTCRC-LUN17-127) study", Journal of Clinical Oncology, vol. 39, no. 15, 28 May 2021, DOI: 10.1200/JCO.2021.39.15_suppl.8570	

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2022/023793**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	See Abstract	1-50

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2022/023793**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2022/023793**

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2022/023793**

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2022/023793**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2022/023793**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

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This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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