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(54) Title: COMBINATION THERAPY WITH A VINCA ALKALOID N-OXIDE AND AN IMMUNE CHECKPOINT INHIBITOR

(57) Abstract: The present disclosure provides therapeutic methods of treating a cancer patient with a vinca alkaloide N-oxide and an immune checkpoint inhibitor.

COMBINATION THERAPY WITH A VINCA ALKALOID N-OXIDE AND AN IMMUNE CHECKPOINT INHIBITOR

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides therapeutic methods of treating a cancer patient with a vinca alkaloid N-oxide and an immune checkpoint inhibitor.

Background

[0002] Vinca alkaloids are a class of chemotherapeutic agents originally discovered in the Madagascar periwinkle. Representative vinca alkaloids include vinblastine, vincristine, vindesine, vinorelbine, and vinflunine. N-oxides of vinca alkaloids function as prodrugs that are activated under the hypoxic conditions found in cancer tumors and other hypoxic environments. *See* U.S. Patent Nos. 8,048,872 and 8,883,775.

[0003] Hypoxia is a common phenomenon in solid neoplasms. It arises when tissue oxygen demands exceed the oxygen supply from the vasculature. Hypoxic regions develop within solid tumors due to aberrant blood vessel formation, fluctuations in blood flow, and increasing oxygen demands from rapid tumor expansion. Hypoxia may limit tumor cell response to radiation, chemotherapy, and/or immunotherapy. Le and Courter, *Cancer Metastasis Rev. 27*:351–362 (2008). Thus, new combination therapies are needed to overcome hypoxia-mediated resistance to current cancer therapies. In particular, new combination therapies are needed to overcome resistance to cancer immunotherapies. Sharma *et al.*, *Cell 168*(4): 707–723 (2017).

BRIEF SUMMARY OF THE INVENTION

[0004] In one aspect, the present disclosure provides therapeutic methods of treating a cancer patient, the methods comprising administering to the patient therapeutically effective amounts of a vinca alkaloid N-oxide, e.g., vinblastine $N_{b'}$-oxide, vincristine $N_{b'}$-oxide, vindesine $N_{b'}$-oxide, vinorelbine $N_{b'}$-oxide, or vinflunine $N_{b'}$-oxide, and an immune checkpoint inhibitor, e.g., a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4

inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, a VISTA inhibitor, a TIGIT inhibitor, or a cd47 inhibitor.

[0005] In another aspect, the present disclosure provides therapeutic methods of treating a cancer patient, the methods comprising administering to the patient therapeutically effective amounts of a vinca alkaloid N-oxide and an immune checkpoint inhibitor, wherein one or more cancer biomarker proteins or genes is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0006] In another aspect, the present disclosure provides kits comprising a vinca alkaloid N-oxide and an immune checkpoint inhibitor.

[0007] In another aspect, the present disclosure provides lyophilized pharmaceutical compositions comprising a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt, encapsulated in a liposome.

[0008] In another aspect, the present disclosure provides kits comprising lyophilized pharmaceutical compositions comprising a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt, encapsulated in a liposome, and an immune checkpoint inhibitor.

DETAILED DESCRIPTION OF DRAWINGS

[0009] Fig. 1 is a line graph showing the mean tumor volume of Group 1-9 treated animals in the CT26.WT murine colon carcinoma model.

[0010] Fig. 2 is a line graph showing the mean body weight change in Group 1-9 treated animals in the CT26.WT murine colon carcinoma model.

DETAILED DESCRIPTION OF THE INVENTION

[0011] In one embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient a therapeutically effective amount of a vinca alkaloid N-oxide, e.g., vinblastine $N_{b'}$-oxide, vincristine $N_{b'}$-oxide, vindesine $N_{b'}$-oxide, vinorelbine $N_{b'}$-oxide, or vinflunine $N_{b'}$-oxide, and an immune checkpoint inhibitor, e.g., a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, a VISTA inhibitor, a TIGIT inhibitor, or a cd47 inhibitor.

[0012] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient a therapeutically effective amount of a vinca alkaloid N-oxide and an immune checkpoint inhibitor, wherein one or more of the genes listed in Table 1, see below, is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status. In another embodiment, HIF overexpression is differentially present in a sample taken from the patient.

[0013] In another embodiment, a vinca alkaloid N-oxide is administered to the patient before the immune checkpoint inhibitor.

[0014] In another embodiment, a vinca alkaloid N-oxide is administered to the patient after the immune checkpoint inhibitor.

[0015] In another embodiment, a vinca alkaloid N-oxide is administered to the patient at the same time as an immune checkpoint inhibitor.

[0016] In another embodiment, the present disclosure provides kits comprising a vinca alkaloid N-oxide and an immune checkpoint inhibitor, and instructions for administering a vinca alkaloid N-oxide and the immune checkpoint inhibitor to a patient having cancer.

[0017] In another embodiment, the kit is packaged in a manner that facilitates its use to practice methods of the present disclosure.

[0018] In another embodiment, the kit includes a vinca alkaloid N-oxide (or a composition comprising a vinca alkaloid N-oxide) packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of a vinca alkaloid N-oxide or composition to practice the method of the disclosure. In one embodiment, a vinca alkaloid N-oxide is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

[0019] The disclosure provides various therapeutic methods, kits, and compositions relating to the treatment of cancer. In one embodiment, the cancer is a solid tumor. In another embodiment, the cancer is a hematological malignancy. In another embodiment, the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma,

adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed

Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0020] In another embodiment, the cancer is selected from the group consisting of squamous cell carcinoma of the head and neck, adenocarcinoma squamous cell carcinoma of the esophagus, adenocarcinoma of the stomach, adenocarcinoma of the colon, hepatocellular carcinoma, cholangiocarcinoma of the biliary system, adenocarcinoma of gall bladder, adenocarcinoma of the pancreas, ductal carcinoma in situ of the breast, adenocarcinoma of the breast, adenocarcinoma of the lungs, squamous cell carcinoma of the lungs, transitional cell carcinoma of the bladder, squamous cell carcinoma of the bladder, squamous cell carcinoma of the cervix, adenocarcinoma of the cervix, endometrial carcinoma, penile squamous cell carcinoma, and squamous cell carcinoma of the skin.

[0021] In another embodiment, a precancerous tumor is selected from the group consisting of leukoplakia of the head and neck, Barrett's esophagus, metaplasia of the

stomach, adenoma of the colon, chronic hepatitis, bile duct hyperplasia, pancreatic intraepithelial neoplasia, atypical adenomatous hyperplasia of the lungs, dysplasia of the bladder, cervical initraepithelial neoplasia, penile intraepithelial neoplasia, and actinic keratosis of the skin.

[0022] In another embodiment, the patient has tumors that overexpress HIF. The tumors may be determined to overexpress HIF by methods known in the art.

[0023] In another embodiment, the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0024] In another embodiment, the cancer is selected from the group consisting of glioblastoma, hepatocellular carcinoma, non-small cell and small-cell lung cancer, head and neck cancer, colorectal carcinoma, and triple-negative breast cancer.

[0025] In another embodiment, the cancer has become resistant to conventional cancer treatments. The term "conventional cancer treatments" as used herein refers to any cancer drugs, biologics, or radiotherapy, or combination of cancer drugs and/or biologics and/or radiotherapy that have been tested and/or approved for therapeutic use in humans by the U.S. Food and Drug Administration, European Medicines Agency, or similar regulatory agency.

[0026] In another embodiment, the patient has been treated previously with an immune checkpoint inhibitor without a vinca alkaloid N-oxide. For example, the previous immune checkpoint therapy may be an anti-PD-1 therapy.

[0027] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, the method comprising administering to the patient a therapeutically effective amount of a vinca alkaloid N-oxide and an immune checkpoint inhibitor, wherein the phenotypic status of the patient is overexpression of HIF. In another embodiment, the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0028] In another embodiment, the present disclosure provides therapeutic methods of treating a patient having cancer, comprising administering to the patient therapeutically effective amounts of a vinca alkaloid N-oxide, an immune checkpoint inhibitor, and a third therapeutic agent.

[0029] In another embodiment, the present disclosure provides personalized medicine for cancer patients, and encompasses the selection of treatment options with the highest likelihood of successful outcome for individual cancer patients. In another aspect, the disclosure relates to the use of an assay(s) to predict the treatment outcome, *e.g.*, the likelihood of favorable responses or treatment success, in patients having cancer.

[0030] In another embodiment, the present disclosure provides methods of selecting a patient, *e.g.*, a human subject for treatment of cancer with a vinca alkaloid N-oxide and, optionally, an immune checkpoint inhibitor comprising obtaining a biological sample, *e.g.*, blood cells, from the patient, testing a biological sample from the patient for the presence of a biomarker, *e.g.*, overexpression of HIF, and selecting the patient for treatment if the biological sample contains that biomarker. In another embodiment, the methods further comprise administering a therapeutically effective amount of a vinca alkaloid N-oxide and, optionally, an immune checkpoint inhibitor, to the patient if the biological sample contains the biomarker. Examples of cancer biomarkers are provided in Table 1 and Table 2. In another embodiment, the cancer is a solid tumor. In another embodiment, the cancer is a hematological malignancy. In another embodiment, the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0031] In another embodiment, the present disclosure provides methods of predicting treatment outcomes in a patient having cancer, comprising obtaining a biological sample, from the patient, testing the biological sample from the patient for the presence of a biomarker, e.g., overexpression of HIF, wherein the detection of the biomarker indicates the patient will respond favorably to administration of a therapeutically effective amount of a vinca alkaloid N-oxide and, optionally, an immune checkpoint inhibitor. Favorable responses include, but are not limited to, a decrease in tumor size and an increase in progression-free or overall survival.

[0032] In another embodiment, the present disclosure provides methods of treating cancer, comprising administering a therapeutically effective amount of a vinca alkaloid N-oxide and, optionally, an immune checkpoint inhibitor to a patient, *e.g.*, a human subject, with cancer in whom the patient's cells contain a biomarker. In another embodiment, the patient is selected for treatment with a vinca alkaloid N-oxide and,

optionally, an immune checkpoint inhibitor after the patient's cells have been determined to contain an overexpression of HIF.

[0033] In another embodiment, the method of treating a patient having cancer comprises obtaining a biological sample from the patient, determining whether the biological sample contains a biomarker, *e.g.*, overexpression of HIF, and administering to the patient a therapeutically effective amount of a vinca alkaloid N-oxide and, optionally, an immune checkpoint inhibitor if the biological sample contains the biomarker. In another embodiment, the methods provided herein comprise determining whether the patient's cells contain an overexpression of HIF.

I. Vinca alkaloid N-Oxides

[0034] Vinca alkaloids are well-known chemotherapeutic agents originally isolated from the Madagascar periwinkle plant. Non-limiting exemplary vinca alkaloids include vinblastine, vincristine, vindesine, vinorelbine, and vinflunine.

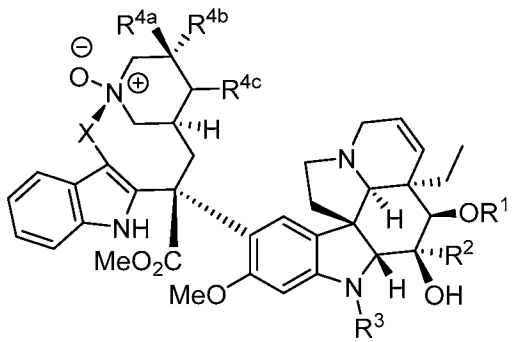
[0035] The term "vinca alkaloid N-oxide" as used herein refers to a N_b-oxide or $N_{b'}$-oxide of a vinca alkaloid, and the pharmaceutically acceptable salts or solvates thereof. *See* Barnett *et al.*, *J. Med. Chem. 21*:88-96 (1978) for discussion of the N_b and $N_{b'}$ positions of the vinca alkaloid skeleton.

[0036] In one embodiment, the vinca alkaloid N-oxide is described in U.S. Patent No. 8,048,872.

[0037] In another embodiment, the vinca alkaloid N-oxide is a vinca alkaloid N_b-oxide.

[0038] In another embodiment, the vinca alkaloid N-oxide is a vinca alkaloid $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0039] In another embodiment, the vinca alkaloid $N_{b'}$-oxide is represented by a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein

[0040] R^1 is selected from the group consisting of hydrogen and -C(=O)CH_3;

[0041] R^2 is selected from the group consisting of -C(=O)OCH_3 and -C(=O)NH_2;

[0042] R^3 is selected from the group consisting of -CH_3 and -CHO;

[0043] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0044] R^{4b} is selected from the group consisting of -CH_2CH_3 and -CF_2CH_3;

[0045] R^{4c} is hydrogen; or

[0046] R^{4a} and R^{4c} taken together form a double bond; and

[0047] X is selected from the group consisting of -CH_2- and -CH_2CH_2-.

[0048] In another embodiment, the vinca alkaloid N_b'-oxide is selected from the group consisting of vinblastine N_b'-oxide, vincristine N_b'-oxide, vindesine N_b'-oxide, vinorelbine N_b'-oxide, and vinflunine N_b'-oxide, and the pharmaceutically acceptable salts and solvates thereof.

[0049] In another embodiment, the vinca alkaloid N_b'-oxide is vinblastine N_b'-oxide, or a pharmaceutically acceptable salt or solvate thereof.

II. Immune checkpoint inhibitors

[0050] Immune checkpoint inhibitors are therapies that blockade immune system inhibitor checkpoints. Immune checkpoints can be stimulatory or inhibitory. Blockade of inhibitory immune checkpoint activates immune system function and can be used for cancer immunotherapy. Pardoll, *Nature Reviews. Cancer 12:*252-64 (2012). Tumor cells turn off activated T cells when they attach to specific T-cell receptors. Immune checkpoint inhibitors prevent tumor cells from attaching to T cells, which results in T cells remaining activated. In effect, the coordinated action by cellular and soluble components combats pathogens and injuries by cancers. The modulation of immune system pathways may involve changing the expression or the functional activity of at least one component of the pathway to then modulate the response by the immune system. U.S. 2015/0250853. Examples of immune checkpoint inhibitors include PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, LAG3 inhibitors, TIM3 inhibitors, cd47 inhibitors, VISTA inhibitors, TIGIT inhibitors, and B7-H1 inhibitors. Thus, in one embodiment, the immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, a VISTA inhibitor, a TIGIT inhibitor, and a cd47 inhibitor. In another embodiment, the immune checkpoint inhibitor is a CTLA-4 inhibitor.

[0051] In another embodiment, the immune checkpoint inhibitor is a programmed cell death (PD-1) inhibitor. PD-1 is a T-cell coinhibitory receptor that plays a pivotal role in the ability of tumor cells to evade the host's immune system. Blockage of interactions between PD-1 and PD-L1, a ligand of PD-1, enhances immune function and mediates antitumor activity. Examples of PD-1 inhibitors include antibodies that specifically bind to PD-1. Particular anti-PD-1 antibodies include, but are not limited to nivolumab, pembrolizumab, STI-A1014, and pidilzumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies of anti-PD-1 antibodies, see U.S. 2013/0309250, U.S. 6,808,710, U.S. 7,595,048, U.S. 8,008,449, U.S. 8,728,474, U.S. 8,779,105, U.S. 8,952,136, U.S. 8,900,587, U.S. 9,073,994, U.S. 9,084,776, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0052] In another embodiment, the immune checkpoint inhibitor is a PD-L1 (also known as B7-H1 or CD274) inhibitor. Examples of PD-L1 inhibitors include antibodies that specifically bind to PD-L1. Particular anti-PD-L1 antibodies include, but are not limited to, avelumab, atezolizumab, durvalumab, and BMS-936559. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 8,217,149, U.S. 2014/0341917, U.S. 2013/0071403, WO 2015036499, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0053] In another embodiment, the immune checkpoint inhibitor is a CTLA-4 inhibitor. CTLA-4, also known as cytotoxic T-lymphocyte antigen 4, is a protein receptor that downregulates the immune system. CTLA-4 is characterized as a "brake" that binds costimulatory molecules on antigen-presenting cells, which prevents interaction with CD28 on T cells and also generates an overtly inhibitory signal that constrains T cell activation. Examples of CTLA-4 inhibitors include antibodies that specifically bind to CTLA-4. Particular anti-CTLA-4 antibodies include, but are not limited to, ipilimumab and tremelimumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 6,984,720, U.S. 6,207,156, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0054] In another embodiment, the immune checkpoint inhibitor is a LAG3 inhibitor. LAG3, Lymphocyte Activation Gene 3, is a negative co-simulatory receptor that modulates T cell homeostatis, proliferation, and activation. In addition, LAG3 has been reported to participate in regulatory T cells (Tregs) suppressive function. A large

proportion of LAG3 molecules are retained in the cell close to the microtubule-organizing center, and only induced following antigen specific T cell activation. U.S. 2014/0286935. Examples of LAG3 inhibitors include antibodies that specifically bind to LAG3. Particular anti-LAG3 antibodies include, but are not limited to, GSK2831781. For a general discussion of the availability, methods of production, mechanism of action, and studies, see, U.S. 2011/0150892, U.S. 2014/0093511, U.S. 20150259420, and Huang *et al.*, *Immunity* 21:503-13 (2004).

[0055] In another embodiment, the immune checkpoint inhibitor is a TIM3 inhibitor. TIM3, T-cell immunoglobulin and mucin domain 3, is an immune checkpoint receptor that functions to limit the duration and magnitude of T_H1 and T_C1 T-cell responses. The TIM3 pathway is considered a target for anticancer immunotherapy due to its expression on dysfunctional $CD8^+$ T cells and Tregs, which are two reported immune cell populations that constitute immunosuppression in tumor tissue. Anderson, *Cancer Immunology Research 2:*393-98 (2014). Examples of TIM3 inhibitors include antibodies that specifically bind to TIM3. For a general discussion of the availability, methods of production, mechanism of action, and studies of TIM3 inhibitors, see U.S. 20150225457, U.S. 20130022623, U.S. 8,522,156, Ngiow *et al.*, *Cancer Res 71:* 6567-71 (2011), Ngiow, *et al.*, *Cancer Res 71:*3540-51 (2011), and *Anderson*, *Cancer Immunology Res* 2:393-98 (2014).

[0056] In another embodiment, the immune checkpoint inhibitor is a cd47 inhibitor. *See* Unanue, E.R., *PNAS* 110:10886-87 (2013).

[0057] In another embodiment, the immune checkpoint inhibitor is a VISTA inhibitor. *See* Hernandez-Martinez et al., *Journal of Thoracic Disease* 10:6378-6382 (2018).

[0058] In another embodiment, the immune checkpoint inhibitor is a TIGIT inhibitor. T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) is an inhibitory receptor expressed on several immune cell types, including $CD8^+$ T cells, natural killer, or NK, cells, T regulatory cells, or Tregs, and follicular T helper cells. TIGIT interacts with CD155 expressed on antigen-presenting cells or tumor cells to down-regulate T cell and natural killer (NK) cell functions. *See, e.g.*, Harjunpaa, *Clinical Experimental Immunology* 200(2):108-19 (2020). TIGIT has been shown to be a mediator of resistance to existing checkpoint inhibitors, including anti-PD-1. TIGIT also directly suppresses the antitumor effector function on CD8 T cells. TIGIT inhibitors may include antibodies and

small molecules. Non-limiting exemplary TIGIT inhibitor antibodies include vibostolimab (MK-7684), tiragolumab (RG6058), EOS_448, BMS-986207, BGB-A1217, MTIG7192A, AB154, ASP8374, and MK-7684.

[0059] The term "antibody" is meant to include intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity. In another embodiment, "antibody" is meant to include soluble receptors that do not possess the Fc portion of the antibody. In one embodiment, the antibodies are humanized monoclonal antibodies and fragments thereof made by means of recombinant genetic engineering.

[0060] In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody.

[0061] In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody.

[0062] In one embodiment, the CTLA-4 inhibitor is an anti-CTLA-4 antibody.

[0063] In one embodiment, the LAG3 inhibitor is an anti-LAG3 antibody.

[0064] In one embodiment, the TIM3 inhibitor is an anti-TIM3 antibody.

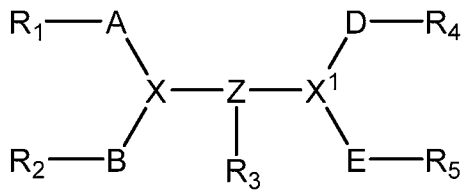
[0065] In one embodiment, the VISTA inhibitor is an anti-VISTA antibody.

[0066] In one embodiment, the TIGIT inhibitor is an anti-TIGIT antibody.

[0067] In one embodiment, the cd47 inhibitor is an anti-cd47 antibody.

[0068] Another class of immune checkpoint inhibitors include polypeptides that bind to and block PD-1 receptors on T-cells without triggering inhibitor signal transduction. Such peptides include B7-DC polypeptides, B7-H1 polypeptides, B7-1 polypeptides and B7-2 polypeptides, and soluble fragments thereof, as disclosed in U.S. Pat. 8,114,845.

[0069] Another class of immune checkpoint inhibitors include compounds with peptide moieties that inhibit PD-1 signaling. Examples of such compounds are disclosed in U.S. Pat. 8,907,053 and have the structure:



or a pharmaceutically acceptable salt thereof, wherein the compound comprises at least 5 amino acids useful as therapeutic agents capable of inhibiting the PD-1 signaling pathway.

[0070] Another class of immune checkpoint inhibitors include inhibitors of certain metabolic enzymes, such as indoleamine 2,3 dioxygenase (IDO), which is expressed by infiltrating myeloid cells and tumor cells. The IDO enzyme inhibits immune responses by depleting amino acids that are necessary for anabolic functions in T cells or through the synthesis of particular natural ligands for cytosolic receptors that are able to alter lymphocyte functions. Pardoll, *Nature Reviews. Cancer 12:*252-64 (2012); Löb, *Cancer Immunol Immunother 58:*153-57 (2009). Particular IDO blocking agents include, but are not limited to levo-1-methyl typtophan (L-1MT) and 1-methyl-tryptophan (1MT). Qian *et al., Cancer Res 69:*5498-504 (2009); and Löb *et al., Cancer Immunol Immunother 58:*153-7 (2009).

[0071] In one embodiment, the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, STI-A1110, avelumab, atezolizumab, durvalumab, STI-A1014, ipilimumab, tremelimumab, GSK2831781, BMS-936559 or MED14736.

III. Optional Therapeutic agents

[0072] In certain therapeutic methods of the disclosure, a third therapeutic agent is administered to a cancer patient in combination with the vinca alkaloid N-oxide and the immune checkpoint inhibitor. The third therapeutic agent used in the therapeutic methods of the present disclosure are referred to as "optional therapeutic agents." Such optional therapeutic agents useful in the treatment of cancer patients are known in the art.

[0073] Optional therapeutic agents are administered in an amount to provide their desired therapeutic effect. The effective dosage range for each optional therapeutic agent is known in the art, and the optional therapeutic agent is administered to an individual in need thereof within such established ranges.

[0074] A vinca alkaloid N-oxide, immune checkpoint inhibitor, and/or the optional therapeutic agent can be administered together as a single-unit dose or separately as multi-unit doses, and in any order, e.g., wherein a vinca alkaloid N-oxide is administered before the immune checkpoint inhibitor and/or the optional therapeutic agent, or vice versa. One or more doses of a vinca alkaloid N-oxide, the immune checkpoint inhibitor, and/or the optional therapeutic agent can be administered to the patient.

[0075] In one embodiment, the optional therapeutic agent is an epigenetic drug. As used herein, the term "epigenetic drug" refers to a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include the histone lysine

methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, but are not limited to, vorinostat.

[0076] In another embodiment, the optional therapeutic agent is a chemotherapeutic agent or other anti-proliferative agent that can be administered in combination with a vinca alkaloid N-oxide to treat cancer. Examples of conventional therapies and anticancer agents that can be used in combination with a vinca alkaloid N-oxide include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, a biologic response modifier (e.g., an interferon, an interleukin, tumor necrosis factor (TNF), hyperthermia and cryotherapy, an agent to attenuate any adverse effect (e.g., an antiemetic), and any other approved biologic therapy or chemotherapy, e.g., a treatment regimen that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated.

[0077] Nonlimiting exemplary antiproliferative compounds include an aromatase inhibitor; an anti-estrogen; an anti-androgen; a gonadorelin agonist; a topoisomerase I inhibitor; a topoisomerase II inhibitor; a microtubule active agent; an alkylating agent, e.g., temozolomide; a retinoid, a carontenoid, or a tocopherol; a cyclooxygenase inhibitor; an MMP inhibitor; an mTOR inhibitor; an antimetabolite; a platin compound; a methionine aminopeptidase inhibitor; a bisphosphonate; an antiproliferative antibody; a heparanase inhibitor; an inhibitor of Ras oncogenic isoforms; a telomerase inhibitor; a proteasome inhibitor; a compound used in the treatment of hematologic malignancies; a Flt-3 inhibitor; an Hsp90 inhibitor; a kinesin spindle protein inhibitor; a MEK inhibitor; an antitumor antibiotic; a nitrosourea; a compound targeting/decreasing protein or lipid kinase activity, a compound targeting/decreasing protein or lipid phosphatase activity, or any further anti-angiogenic compound.

[0078] Nonlimiting exemplary aromatase inhibitors include steroids, such as atamestane, exemestane, and formestane, and non-steroids, such as aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole, and letrozole.

[0079] Nonlimiting anti-estrogens include tamoxifen, fulvestrant, raloxifene, and raloxifene hydrochloride. Anti-androgens include, but are not limited to, bicalutamide. Gonadorelin agonists include, but are not limited to, abarelix, goserelin, and goserelin acetate.

[0080] Nonlimiting exemplary topoisomerase I inhibitors include topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin, and the macromolecular camptothecin conjugate PNU-166148. Topoisomerase II inhibitors include, but are not limited to, anthracyclines, such as doxorubicin, daunorubicin, epirubicin, idarubicin, and nemorubicin; anthraquinones, such as mitoxantrone and losoxantrone; and podophillotoxines, such as etoposide and teniposide.

[0081] Microtubule active agents include microtubule stabilizing, microtubule destabilizing compounds, and microtubulin polymerization inhibitors including, but not limited to, taxanes, such as paclitaxel and docetaxel; discodermolides; cochicine and epothilones and derivatives thereof.

[0082] Nonlimiting exemplary alkylating agents include cyclophosphamide, ifosfamide, melphalan, and nitrosoureas, such as carmustine and lomustine.

[0083] Nonlimiting exemplary matrix metalloproteinase inhibitors ("MMP inhibitors") include collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, batimastat, marimastat, prinomastat, metastat, BMS-279251, BAY 12-9566, TAA211, MMI270B, and AAJ996.

[0084] Nonlimiting exemplary mTOR inhibitors include compounds that inhibit the mammalian target of rapamycin (mTOR) and possess antiproliferative activity such as sirolimus, everolimus, CCI-779, and ABT578.

[0085] Nonlimiting exemplary antimetabolites include 5-fluorouracil (5-FU), capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists, such as pemetrexed.

[0086] Nonlimiting exemplary platin compounds include carboplatin, cis-platin, cisplatinum, and oxaliplatin.

[0087] Nonlimiting exemplary methionine aminopeptidase inhibitors include bengamide or a derivative thereof and PPI-2458.

[0088] Nonlimiting exemplary bisphosphonates include etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, and zoledronic acid.

[0089] Nonlimiting exemplary heparanase inhibitors include compounds that target, decrease, or inhibit heparin sulfate degradation, such as PI-88 and OGT2115.

[0090] Nonlimiting exemplary compounds which target, decrease, or inhibit the oncogenic activity of Ras include farnesyl transferase inhibitors, such as L-744832, DK8G557, tipifarnib, and lonafarnib.

[0091] Nonlimiting exemplary telomerase inhibitors include compounds that target, decrease, or inhibit the activity of telomerase, such as compounds that inhibit the telomerase receptor, such as telomestatin.

[0092] Nonlimiting exemplary proteasome inhibitors include compounds that target, decrease, or inhibit the activity of the proteasome including, but not limited to, bortezomib. In some embodiments, the proteasome inhibitor is carfilzomib.

[0093] Nonlimiting exemplary FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R) include interferon, I-β-D-arabinofuransylcytosine (ara-c), and bisulfan; and ALK inhibitors, which are compounds which target, decrease, or inhibit anaplastic lymphoma kinase.

[0094] Nonlimiting exemplary Flt-3 inhibitors include PKC412, midostaurin, a staurosporine derivative, SU11248, and MLN518.

[0095] Nonlimiting exemplary HSP90 inhibitors include compounds targeting, decreasing, or inhibiting the intrinsic ATPase activity of HSP90; or degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins, or antibodies that inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[0096] Nonlimiting exemplary protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, include a) a compound targeting, decreasing, or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as a compound that targets, decreases, or inhibits the activity of PDGFR, such as an

N-phenyl-2-pyrimidine-amine derivatives, such as imatinib, SUlOl, SU6668, and GFB-111; b) a compound targeting, decreasing, or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) a compound targeting, decreasing, or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as a compound that targets, decreases, or inhibits the activity of IGF-IR; d) a compound targeting, decreasing, or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) a compound targeting, decreasing, or inhibiting the activity of the Axl receptor tyrosine kinase family; f) a compound targeting, decreasing, or inhibiting the activity of the Ret receptor tyrosine kinase; g) a compound targeting, decreasing, or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) a compound targeting, decreasing, or inhibiting the activity of the c-Kit receptor tyrosine kinases, such as imatinib; i) a compound targeting, decreasing, or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. Bcr-Abl kinase) and mutants, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib; PD180970; AG957; NSC 680410; PD173955; or dasatinib; j) a compound targeting, decreasing, or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK), such as a staurosporine derivative disclosed in U.S. Patent No. 5,093,330, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, bryostatin 1, perifosine; ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521 ; LY333531/LY379196; a isochinoline compound; a farnesyl transferase inhibitor; PD184352 or QAN697, or AT7519; k) a compound targeting, decreasing or inhibiting the activity of a protein-tyrosine kinase, such as imatinib mesylate or a tyrphostin, such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); 1) a compound targeting, decreasing, or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as CP 358774, ZD 1839, ZM 105180; trastuzumab, cetuximab, gefitinib, erlotinib, OSI-774, Cl-1033, EKB-569, GW-

2016, antibodies El.l, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; and m) a compound targeting, decreasing, or inhibiting the activity of the c-Met receptor.

[0097] Nonlimiting exemplary compounds that target, decrease, or inhibit the activity of a protein or lipid phosphatase include inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[0098] Further anti-angiogenic compounds include compounds having another mechanism for their activity unrelated to protein or lipid kinase inhibition, e.g., thalidomide and TNP-470.

[0099] Additional, nonlimiting, exemplary chemotherapeutic compounds, one or more of which may be used in combination with a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt thereof, include: avastin, daunorubicin, adriamycin, Ara-C, VP-16, teniposide, mitoxantrone, idarubicin, carboplatinum, PKC412, 6-mercaptopurine (6-MP), fludarabine phosphate, octreotide, SOM230, FTY720, 6-thioguanine, cladribine, 6-mercaptopurine, pentostatin, hydroxyurea, 2-hydroxy-lH-isoindole-l,3-dione derivatives, l-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate, angiostatin, endostatin, anthranilic acid amides, ZD4190, ZD6474, SU5416, SU6668, bevacizumab, rhuMAb, rhuFab, macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, RPI 4610, bevacizumab, porfimer sodium, anecortave, triamcinolone, hydrocortisone, 11-a-epihydrocotisol, cortex olone, 17a-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone, dexamethasone, fluocinolone, a plant alkaloid, a hormonal compound and/or antagonist, a biological response modifier, such as a lymphokine or interferon, an antisense oligonucleotide or oligonucleotide derivative, shRNA, and siRNA.

[0100] A number of suitable optional therapeutic, e.g., anticancer, agents are contemplated for use in the therapeutic methods provided herein. Indeed, the methods provided herein can include, but are not limited to, administration of numerous optional therapeutic agents such as: agents that induce apoptosis; polynucleotides (*e.g.*, anti-sense, ribozymes, siRNA); polypeptides (*e.g.*, enzymes and antibodies); biological mimetics (*e.g.*, gossypol or BH3 mimetics); agents that bind (*e.g.*, oligomerize or complex) with a Bcl-2 family protein such as Bax; alkaloids; alkylating agents; antitumor antibiotics;

antimetabolites; hormones; platinum compounds; monoclonal or polyclonal antibodies (*e.g.*, antibodies conjugated with anticancer drugs, toxins, defensins), toxins; radionuclides; biological response modifiers (*e.g.*, interferons (*e.g.*, IFN-α) and interleukins (*e.g.*, IL-2)); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (*e.g.*, all-trans-retinoic acid); gene therapy reagents (*e.g.*, antisense therapy reagents and nucleotides); tumor vaccines; angiogenesis inhibitors; proteosome inhibitors: NF-KB modulators; anti-CDK compounds; HDAC inhibitors; and the like. Numerous other examples of optional therapeutic agents such as chemotherapeutic compounds and anticancer therapies suitable for co-administration with the disclosed compounds are known to those skilled in the art.

[0101] In certain embodiments, anticancer agents comprise agents that induce or stimulate apoptosis. Agents that induce or stimulate apoptosis include, for example, agents that interact with or modify DNA, such as by intercalating, cross-linking, alkylating, or otherwise damaging or chemically modifying DNA. Agents that induce apoptosis include, but are not limited to, radiation (*e.g.*, X-rays, gamma rays, UV); tumor necrosis factor (TNF)-related factors (*e.g.*, TNF family receptor proteins, TNF family ligands, TRAIL, antibodies to TRAIL-R1 or TRAIL-R2); kinase inhibitors (*e.g.*, epidermal growth factor receptor (EGFR) kinase inhibitor. Additional anticancer agents include: vascular growth factor receptor (VGFR) kinase inhibitor, fibroblast growth factor receptor (FGFR) kinase inhibitor, platelet-derived growth factor receptor (PDGFR) kinase inhibitor, and Bcr-Abl kinase inhibitors (such as GLEEVEC)); antisense molecules; antibodies (*e.g.*, HERCEPTIN, RITUXAN, ZEVALIN, and AVASTIN); anti-estrogens (*e.g.*, raloxifene and tamoxifen); anti-androgens (*e.g.*, flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids); cyclooxygenase 2 (COX-2) inhibitors (*e.g.*, celecoxib, meloxicam, NS-398, and non-steroidal anti-inflammatory drugs (NSAIDs)); anti-inflammatory drugs (*e.g.*, butazolidin, DECADRON, DELTASONE, dexamethasone, dexamethasone intensol, DEXONE, HEXADROL, hydroxychloroquine, METICORTEN, ORADEXON, ORASONE, oxyphenbutazone, PEDIAPRED, phenylbutazone, PLAQUENIL, prednisolone, prednisone, PRELONE, and TANDEARIL); and cancer chemotherapeutic drugs (*e.g.*, irinotecan (CAMPTOSAR), CPT-11, fludarabine (FLUDARA), dacarbazine (DTIC), dexamethasone, mitoxantrone, MYLOTARG, VP-16, cisplatin, carboplatin, oxaliplatin,

5-FU, doxorubicin, gemcitabine, bortezomib, gefitinib, bevacizumab, TAXOTERE or TAXOL); cellular signaling molecules; ceramides and cytokines; staurosporine, and the like.

[0102] In still other embodiments, the therapeutic methods provided herein include administering to a cancer patient therapeutically effective amounts of a vinca alkaloid N-oxide and an immune checkpoint inhibitor and at least one additional anti-hyperproliferative or antineoplastic agent selected from alkylating agents, antimetabolites, and natural products (*e.g.*, herbs and other plant and/or animal derived compounds).

[0103] Alkylating agents suitable for use in the present methods include, but are not limited to: 1) nitrogen mustards (*e.g.*, mechlorethamine, cyclophosphamide, ifosfamide, melphalan (L-sarcolysin); and chlorambucil); 2) ethylenimines and methylmelamines (*e.g.*, hexamethylmelamine and thiotepa); 3) alkyl sulfonates (*e.g.*, busulfan); 4) nitrosoureas (*e.g.*, carmustine (BCNU); lomustine (CCNU); semustine (methyl-CCNU); and streptozocin (streptozotocin)); and 5) triazenes (*e.g.*, dacarbazine (DTIC; dimethyltriazenoimid-azolecarboxamide).

[0104] In some embodiments, antimetabolites suitable for use in the present methods include, but are not limited to: 1) folic acid analogs (*e.g.*, methotrexate (amethopterin)); 2) pyrimidine analogs (*e.g.*, fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorode-oxyuridine; FudR), and cytarabine (cytosine arabinoside)); and 3) purine analogs (*e.g.*, mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG), and pentostatin (2'-deoxycoformycin)).

[0105] In still further embodiments, chemotherapeutic agents suitable for use in the methods of the present disclosure include, but are not limited to: 1) vinca alkaloids (*e.g.*, vinblastine (VLB), vincristine); 2) epipodophyllotoxins (*e.g.*, etoposide and teniposide); 3) antibiotics (*e.g.*, dactinomycin (actinomycin D), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin), and mitomycin (mitomycin C)); 4) enzymes (*e.g.*, L-asparaginase); 5) biological response modifiers (*e.g.*, interferon-alfa); 6) platinum coordinating complexes (*e.g.*, cisplatin (cis-DDP) and carboplatin); 7) anthracenediones (*e.g.*, mitoxantrone); 8) substituted ureas (*e.g.*, hydroxyurea); 9) methylhydrazine derivatives (*e.g.*, procarbazine (N-methylhydrazine; MIH)); 10) adrenocortical suppressants (*e.g.*, mitotane (o,p'–DDD) and aminoglutethimide); 11) adrenocorticosteroids (*e.g.*, prednisone); 12) progestins (*e.g.*,

hydroxyprogesterone caproate, medroxyprogesterone acetate, and megestrol acetate); 13) estrogens (*e.g.*, diethylstilbestrol and ethinyl estradiol); 14) antiestrogens (*e.g.*, tamoxifen); 15) androgens (*e.g.*, testosterone propionate and fluoxymesterone); 16) antiandrogens (*e.g.*, flutamide): and 17) gonadotropin-releasing hormone analogs (*e.g.*, leuprolide).

[0106] Any oncolytic agent that is routinely used in a cancer therapy context finds use in the therapeutic methods of the present disclosure. For example, the U.S. Food and Drug Administration (FDA) maintains a formulary of oncolytic agents approved for use in the United States. International counterpart agencies to the FDA maintain similar formularies. Those skilled in the art will appreciate that the "product labels" required on all U.S. approved chemotherapeutics describe approved indications, dosing information, toxicity data, and the like, for the exemplary agents.

[0107] Anticancer agents further include compounds which have been identified to have anticancer activity. Examples include, but are not limited to, 3-AP, 12-O-tetradecanoylphorbol-13-acetate, 17AAG, 852A, ABI-007, ABR-217620, ABT-751, ADI-PEG 20, AE-941, AG-013736, AGRO100, alanosine, AMG 706, antibody G250, antineoplastons, AP23573, apaziquone, APC8015, atiprimod, ATN-161, atrasenten, azacitidine, BB-10901, BCX-1777, bevacizumab, BG00001, bicalutamide, BMS 247550, bortezomib, bryostatin-1, buserelin, calcitriol, CCI-779, CDB-2914, cefixime, cetuximab, CG0070, cilengitide, clofarabine, combretastatin A4 phosphate, CP-675,206, CP-724,714, CpG 7909, curcumin, decitabine, DENSPM, doxercalciferol, E7070, E7389, ecteinascidin 743, efaproxiral, eflornithine, EKB-569, enzastaurin, erlotinib, exisulind, fenretinide, flavopiridol, fludarabine, flutamide, fotemustine, FR901228, G17DT, galiximab, gefitinib, genistein, glufosfamide, GTI-2040, histrelin, HKI-272, homoharringtonine, HSPPC-96, hu14.18-interleukin-2 fusion protein, HuMax-CD4, iloprost, imiquimod, infliximab, interleukin-12, IPI-504, irofulven, ixabepilone, lapatinib, lenalidomide, lestaurtinib, leuprolide, LMB-9 immunotoxin, lonafarnib, luniliximab, mafosfamide, MB07133, MDX-010, MLN2704, monoclonal antibody 3F8, monoclonal antibody J591, motexafin, MS-275, MVA-MUC1-IL2, nilutamide, nitrocamptothecin, nolatrexed dihydrochloride, nolvadex, NS-9, O6-benzylguanine, oblimersen sodium, ONYX-015, oregovomab, OSI-774, panitumumab, paraplatin, PD-0325901, pemetrexed, PHY906, pioglitazone, pirfenidone, pixantrone, PS-341, PSC 833, PXD101,

pyrazoloacridine, R115777, RAD001, ranpirnase, rebeccamycin analogue, rhuAngiostatin protein, rhuMab 2C4, rosiglitazone, rubitecan, S-1, S-8184, satraplatin, SB-, 15992, SGN-0010, SGN-40, sorafenib, SR31747A, ST1571, SU011248, suberoylanilide hydroxamic acid, suramin, talabostat, talampanel, tariquidar, temsirolimus, TGFa-PE38 immunotoxin, thalidomide, thymalfasin, tipifarnib, tirapazamine, TLK286, trabectedin, trimetrexate glucuronate, TroVax, UCN-1, valproic acid, vinflunine, VNP40101M, volociximab, vorinostat, VX-680, ZD1839, ZD6474, zileuton, and zosuquidar trihydrochloride.

[0108] For a more detailed description of anticancer agents and other optional therapeutic agents, those skilled in the art are referred to any number of instructive manuals including, but not limited to, the Physician's Desk Reference and to Goodman and Gilman's "Pharmaceutical Basis of Therapeutics" tenth edition, Eds. Hardman *et al.*, 2002.

[0109] In some embodiments, methods provided herein comprise administering a vinca alkaloid N-oxide and an immune checkpoint inhibitor to a cancer patient in combination with radiation therapy. The methods provided herein are not limited by the types, amounts, or delivery and administration systems used to deliver the therapeutic dose of radiation to a patient. For example, the patient may receive photon radiotherapy, particle beam radiation therapy, other types of radiotherapies, and combinations thereof. In some embodiments, the radiation is delivered to the patient using a linear accelerator. In still other embodiments, the radiation is delivered using a gamma knife.

[0110] The source of radiation can be external or internal to the patient. External radiation therapy is most common and involves directing a beam of high-energy radiation to a tumor site through the skin using, for instance, a linear accelerator. While the beam of radiation is localized to the tumor site, it is nearly impossible to avoid exposure of normal, healthy tissue. However, external radiation is usually well tolerated by patients. Internal radiation therapy involves implanting a radiation-emitting source, such as beads, wires, pellets, capsules, particles, and the like, inside the body at or near the tumor site including the use of delivery systems that specifically target cancer cells (*e.g.*, using particles attached to cancer cell binding ligands). Such implants can be removed following treatment, or left in the body inactive. Types of internal radiation therapy

include, but are not limited to, brachytherapy, interstitial irradiation, intracavity irradiation, radioimmunotherapy, and the like.

[0111] The patient may optionally receive radiosensitizers (*e.g.*, metronidazole, misonidazole, intra-arterial Budr, intravenous iododeoxyuridine (IudR), nitroimidazole, 5-substituted-4-nitroimidazoles, 2H-isoindolediones, [[(2-bromoethyl)-amino]methyl]-nitro-1H-imidazole-1-ethanol, nitroaniline derivatives, DNA-affinic hypoxia selective cytotoxins, halogenated DNA ligand, 1,2,4 benzotriazine oxides, 2-nitroimidazole derivatives, fluorine-containing nitroazole derivatives, benzamide, nicotinamide, acridine-intercalator, 5-thiotretrazole derivative, 3-nitro-1,2,4-triazole, 4,5-dinitroimidazole derivative, hydroxylated texaphrins, cisplatin, mitomycin, tiripazamine, nitrosourea, mercaptopurine, methotrexate, fluorouracil, bleomycin, vincristine, carboplatin, epirubicin, doxorubicin, cyclophosphamide, vindesine, etoposide, paclitaxel, heat (hyperthermia), and the like), radioprotectors (*e.g.*, cysteamine, aminoalkyl dihydrogen phosphorothioates, amifostine (WR 2721), IL-1, IL-6, and the like). Radiosensitizers enhance the killing of tumor cells. Radioprotectors protect healthy tissue from the harmful effects of radiation.

[0112] Any type of radiation can be administered to an patient, so long as the dose of radiation is tolerated by the patient without unacceptable negative side-effects. Suitable types of radiotherapy include, for example, ionizing (electromagnetic) radiotherapy (*e.g.*, X-rays or gamma rays) or particle beam radiation therapy (*e.g.*, high linear energy radiation). Ionizing radiation is defined as radiation comprising particles or photons that have sufficient energy to produce ionization, *i.e.*, gain or loss of electrons (as described in, for example, U.S. 5,770,581 incorporated herein by reference in its entirety). The effects of radiation can be at least partially controlled by the clinician. In one embodiment, the dose of radiation is fractionated for maximal target cell exposure and reduced toxicity.

[0113] In one embodiment, the total dose of radiation administered to a patient is about .01 Gray (Gy) to about 100 Gy. In another embodiment, about 10 Gy to about 65 Gy (*e.g.*, about 15 Gy, 20 Gy, 25 Gy, 30 Gy, 35 Gy, 40 Gy, 45 Gy, 50 Gy, 55 Gy, or 60 Gy) are administered over the course of treatment. While in some embodiments a complete dose of radiation can be administered over the course of one day, the total dose is ideally fractionated and administered over several days. Desirably, radiotherapy is administered

over the course of at least about 3 days, *e.g.*, at least 5, 7, 10, 14, 17, 21, 25, 28, 32, 35, 38, 42, 46, 52, or 56 days (about 1-8 weeks). Accordingly, a daily dose of radiation will comprise approximately 1-5 Gy (*e.g.*, about 1 Gy, 1.5 Gy, 1.8 Gy, 2 Gy, 2.5 Gy, 2.8 Gy, 3 Gy, 3.2 Gy, 3.5 Gy, 3.8 Gy, 4 Gy, 4.2 Gy, or 4.5 Gy), or 1-2 Gy (*e.g.*, 1.5-2 Gy). The daily dose of radiation should be sufficient to induce destruction of the targeted cells. If stretched over a period, in one embodiment, radiation is not administered every day, thereby allowing the animal to rest and the effects of the therapy to be realized. For example, radiation desirably is administered on 5 consecutive days, and not administered on 2 days, for each week of treatment, thereby allowing 2 days of rest per week. However, radiation can be administered 1 day/week, 2 days/week, 3 days/week, 4 days/week, 5 days/week, 6 days/week, or all 7 days/week, depending on the animal's responsiveness and any potential side effects. Radiation therapy can be initiated at any time in the therapeutic period. In one embodiment, radiation is initiated in week 1 or week 2, and is administered for the remaining duration of the therapeutic period. For example, radiation is administered in weeks 1-6 or in weeks 2-6 of a therapeutic period comprising 6 weeks for treating, for instance, a solid tumor. Alternatively, radiation is administered in weeks 1-5 or weeks 2-5 of a therapeutic period comprising 5 weeks. These exemplary radiotherapy administration schedules are not intended, however, to limit the methods provided herein.

IV. Therapeutic methods

[0114] In the therapeutic methods provided herein, a vinca alkaloid N-oxide and an immune checkpoint inhibitor may be administered to a cancer patient under one or more of the following conditions: at different periodicities, at different durations, at different concentrations, by different administration routes, *etc.* An optional therapeutic, e.g., anticancer, agent may also be administered to the cancer patient.

[0115] In some embodiments, the vinca alkaloid N-oxide is administered prior to the immune checkpoint inhibitor, *e.g.*, 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 3, or 4 weeks prior to the administration of the immune checkpoint inhibitor.

[0116] In some embodiments, the vinca alkaloid N-oxide is administered after the immune checkpoint inhibitor, *e.g.*, 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 3, or 4 weeks after the administration of the immune checkpoint inhibitor.

[0117] In some embodiments, the vinca alkaloid N-oxide and the immune checkpoint inhibitor are administered concurrently but on different schedules, *e.g.*, the vinca alkaloid N-oxide is administered daily while the immune checkpoint inhibitor is administered once a week, once every two weeks, once every three weeks, or once every four weeks. In other embodiments, the vinca alkaloid N-oxide is administered once a day while the immune checkpoint inhibitor is administered once a week, once every two weeks, once every three weeks, or once every four weeks.

[0118] The therapeutic methods provided herein comprise administering the vinca alkaloid N-oxide to a cancer patient in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the vinca alkaloid N-oxide may be administered in an amount from about 0.05 mg/kg to about 500 mg/kg, about 0.05 mg/kg to about 100 mg/kg, about 0.05 mg/kg to about 50 mg/kg, or about 0.05 mg/kg to about 10 mg/kg. The dosage of a composition can be at any dosage including, but not limited to, about 0.05 mg/week to about 25 mg/week. Particular doses include 0.05, 1, 2, 5, 10, 20, 500, and 100 mg/kg once weekly. In one embodiment, the vinca alkaloid N-oxide is administed once a week. These dosages are exemplary, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this disclosure. In practice, the physician determines the actual dosing regimen that is most suitable for an individual patient, which can vary with the age, weight, and response of the particular patient.

[0119] The unit oral dose of the vinca alkaloid N-oxide may comprise from about 0.01 to about 1000 mg, e.g., about 0.01 to about 100 mg of the vinca alkaloid N-oxide. In one embodiment, the unit oral dose of the vinca alkaloid N-oxide is 0.05 mg, 1 mg, 3 mg, 5 mg, 7 mg, 9 mg, 10 mg 12 mg, 14 mg, 15 mg, 17 mg, 20 mg, 22 mg, 25 mg, 27 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg. The unit dose may be administered one or more times daily, e.g., as one or more tablets or capsules. The unit does may also be administered by IV once a week. In practice, the physician determines the actual dosing regimen that is most suitable for an individual patient, which can vary with the age, weight, and response of the particular patient.

[0120] In addition to administering the vinca alkaloid N-oxide as a raw chemical, it may be administered as part of a pharmaceutical preparation or composition. In some embodiments, the pharmaceutical preparation or composition can include one or more pharmaceutically acceptable carriers, excipients, and/or auxiliaries. In some embodiments, the one or more carriers, excipients, and auxiliaries facilitate processing of the vinca alkaloid N-oxide into a preparation or composition which can be used pharmaceutically. The preparations, particularly those preparations which can be administered orally or topically and which can be used for one type of administration, such as tablets, dragees, slow release lozenges and capsules, mouth rinses and mouth washes, gels, liquid suspensions, hair rinses, hair gels, shampoos and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by intravenous infusion, injection, topically or orally, contain from about 0.01 to 99 percent, in one embodiment from about 0.25 to 75 percent of active compound(s), together with the one or more carriers, excipients, and/or auxiliaries.

[0121] The pharmaceutical compositions of provided herein may be administered to any patient which may experience the beneficial effects of the vinca alkaloid N-oxide. Foremost among such patients are mammals, *e.g.*, humans, although the methods and compositions provided herein are not intended to be so limited. Other patients include veterinary animals (cows, sheep, pigs, horses, dogs, cats and the like).

[0122] The pharmaceutical preparations provided herein are manufactured by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0123] Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch,

cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries can be suitable flow-regulating agents and lubricants. Suitable auxiliaries include, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[0124] Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are in one embodiment dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

[0125] Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

[0126] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400. Aqueous injection suspensions may contain

substances which increase the viscosity of the suspension including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

[0127] The present disclosure encompasses the use of solvates of the vinca alkaloid N-oxide. Solvates typically do not significantly alter the physiological activity or toxicity of a compound, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a vinca alkaloid N-oxide with a solvent molecule such as, *e.g.*, a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to vinca alkaloid N-oxide is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. The vinca alkaloid N-oxide can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the disclosure includes both solvated and unsolvated forms of the vinca alkaloid N-oxide. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate involves dissolving a vinca alkaloid N-oxide in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.*, filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

[0128] Therapeutically effective amounts of the vinca alkaloid N-oxide and the immune checkpoint inhibitor formulated in accordance with standard pharmaceutical practices, are administered to a human patient in need thereof. Whether such a treatment is indicated

depends on the individual case and is subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

[0129] The vinca alkaloid N-oxide and the immune checkpoint inhibitor can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, intracisternal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site) administration. Parenteral administration can be accomplished using a needle and syringe or using a high pressure technique.

[0130] Pharmaceutical compositions include those wherein the vinca alkaloid N-oxide and the immune checkpoint inhibitor are administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by an individual physician in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of the vinca alkaloid N-oxide and the immune checkpoint inhibitor that is sufficient to maintain therapeutic effects.

[0131] Toxicity and therapeutic efficacy of the vinca alkaloid N-oxide and the immune checkpoint inhibitor can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) of a compound, which defines as the highest dose that causes no toxicity in a patient. The dose ratio between the maximum tolerated dose and therapeutic effects (e.g. inhibiting of tumor growth) is the therapeutic index. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0132] A therapeutically effective amount of the vinca alkaloid N-oxide and the immune checkpoint inhibitor required for use in therapy varies with the nature of the condition being treated, the length of time that activity is desired, and the age and the condition of the patient, and ultimately is determined by the attendant physician. For example, dosage amounts and intervals can be adjusted individually to provide plasma levels of the vinca

alkaloid N-oxide and immune checkpoint inhibitor that are sufficient to maintain the desired therapeutic effects. The desired dose conveniently can be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four or more subdoses per day. Multiple doses often are desired, or required. For example, the vinca alkaloid N-oxide and immune checkpoint inhibitor can be administered at a frequency of: one dose per day; four doses delivered as one dose per day at four-day intervals (q4d x 4); four doses delivered as one dose per day at three-day intervals (q3d x 4); one dose delivered per day at five-day intervals (qd x 5); one dose per week for three weeks (qwk3); five daily doses, with two days rest, and another five daily doses (5/2/5); or, any dose regimen determined to be appropriate for the circumstance.

[0133] The immune checkpoint inhibitor is administered in therapeutically effective amounts. When the immune checkpoint inhibitor is a monoclonal antibody, 1-20 mg/kg is administered as an intravenous infusion every 2-4 weeks. For example, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg and 2000 mg of the antibody may be administered.

[0134] For example, when the immune checkpoint inhibitor is the anti-PD-1 antibody nivolumab, 3 mg/kg may be administered by intravenous infusion over 60 minutes every two weeks. When the immune checkpoint inhibitor is the anti-PD-1 antibody pembrolizumab, 2 mg/kg may be administered by intravenous infusion over 30 minutes every two or three weeks. When the immune checkpoint inhibitor is the anti-PD-L1 antibody avelumab, 10 mg/kg may be administered by intravenous infusion as frequently as every 2 weeks. Disis *et al.*, *J. Clin Oncol. 33* (2015) (suppl; abstr 5509). When the immune checkpoint inhibitor is the anti-PD-L1 antibody MPDL3280A, 20 mg/kg may be administered by intravenous infusion every 3 weeks. Herbst *et al.*, *Nature 515:*563-80 (2014). When the immune checkpoint inhibitor is the anti-CTLA-4 antibody ipilumumab, 3 mg/kg may be administered by intravenous infusion over 90 minutes every 3 weeks. When the immune checkpoint inhibitor is the anti-CTLA-4 antibody tremelimumab, 15 mg/kg may be administered by intravenous infusion every 12 weeks. Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014); *Drugs R D, 10:*123-32 (2010). When the immune checkpoint inhibitor is the anti-LAG3 antibody GSK2831781, 1.5 to 5 mg/kg may be administered by intravenous infusion over 120 minutes every 2-4 weeks. When

the immune checkpoint inhibitor is an anti-TIM3 antibody, 1-5 mg/kg may be administered by intravenous infusion over 30-90 minutes every 2-4 weeks. When an inhibitor of indoleamine 2,3-dioxygenase (IDO) pathway is inhibitor indoximod in combination with temozolomide, 18.5 mg/kg/dose BID with an escalation to 27.7 mg/kg/dose BID of indoximod with 200 mg/m^2 every 5 days of temozolomide.

[0135] In one embodiment, the immune checkpoint inhibitor is an antibody and 1-20 mg/kg is administered by intravenous infusion every 2-4 weeks. In another embodiment, 50-2000 mg of the antibody is administered by intravenous infusion every 2-4 weeks. In another embodiment, the vinca alkaloid N-oxide is administered prior to administration of the antibody. In another embodiment, the vinca alkaloid N-oxide is administered 3-7 days prior to the day of administration of the antibody. In another embodiment, the vinca alkaloid N-oxide is also administered the day the antibody is administered and on consecutive days thereafter until disease progression or until the vinca alkaloid N-oxide administration is no longer beneficial.

[0136] In one embodiment, the cancer patient receives 2 mg/kg pembrolizumab administered by intravenous infusion every three weeks and about 0.1 to 100 mg of the vinca alkaloid N-oxide administered for 1-7 days prior to pembrolizumab administration, optionally, on the day of pembrolizumab administration, and, optionally, thereafter until disease progression or until there is no therapeutic benefit. In another embodiment, the cancer patient has tumors with a biomarker, e.g., overexpression of HIF.

[0137] In another embodiment, the cancer patient receives 3 mg/kg nivolumab administered by intravenous infusion every 2 weeks and about 0.1 to 100 mg of the vinca alkaloid N-oxide administered for 1-7 days prior to nivolumab administration, optionally, on the day of nivolumab administration, and, optionally, thereafter until disease progression or until there is no therapeutic benefit. In another embodiment, the cancer patient has tumors with a biomarker, e.g., overexpression of HIF.

[0138] In another embodiment, the cancer patient receives 3 mg/kg nivolumab administered by intravenous infusion every 2 weeks and about 0.1 to 100 mg of the vinca alkaloid N-oxide administered for 1-7 days prior to nivolumab administration, optionally, on the day of nivolumab administration, and, optionally, thereafter until disease progression or until there is no therapeutic benefit. In another embodiment, the cancer patient has tumors with a biomarker, e.g., overexpression of HIF.

[0139] Representative dosing regimens for certain immune checkpoint inhibitors to treat certain cancers are provided in Table 6.

Table 6

Drug	Body-Weight-Based Dose	Flat Dose	Clinical Applications
Ipilimumab	3 mg/kg Q3W 10 mg/kg Q3W		Metastatic melanoma Cutaneous melanoma Advanced renal cell carcinoma
Nivolumab	3 mg/kg Q2W	240 mg Q2W 480 mg Q4W	Metastatic melanoma Metastatic NSCLC Hodgkin lymphoma Advanced renal cell carcinoma Advanced or metastatic urothelial carcinoma Metastatic colorectal cancer Hepatocellular carcinoma
Pembrolizumab	2 mg/kg Q3W	200 mg Q3W 400 mg Q6W	Melanoma NSCLC Head and neck squamous cell cancer Classical Hodgkin lymphoma Primary mediastinal large b-cell lymphoma Urothelial carcinoma Microsatellite instability-high cancer Gastric cancer Cervical cancer Hepatocellular carcinoma Merkel cell carcinoma
Cemiplimab		350 mg Q3W	Metastatic CSCC Locally advanced CSCC
Atezolizumab		840 mg Q2W 1200 mg Q3W 1680 mg Q4W	Urothelical Carcinoma NSCLC TNBC Metastatic treatment of TNBC
Avelumab	10 mg/kg Q2W	800 mg Q2W	Metastatic Merkel cell carcinoma Advanced or metastatic urothelial carcinoma Advanced renal cell carcinoma (+ axitinib)
Durvalumab	10 mg/kg Q2W	750 mg Q2W 1500 mg Q4W	Locally advanced or metastatic urothelical carcinoma Unresectable stage III NSCLC

[0140] In one embodiment, the one or more optional immune checkpoint inhibitors is an antibody, and 1-20 mg/kg is administered to the subject by intravenous infusion every 2-4 weeks. In another embodiment, 20-2000 mg of the antibody is administered to the subject by intravenous infusion every 2-4 weeks. In another embodiment, the vinca alkaloid N-oxide is administered prior to administration of the antibody. In another embodiment, the vinca alkaloid N-oxide is administered to the subject 1, 2, 3, 4, 5, 6, or 7 days prior to the day of administration of the antibody. In another embodiment, the vinca alkaloid N-oxide is administered to the subject the day the antibody is administered. In another embodiment, the vinca alkaloid N-oxide is administered to the subject 1, 2, 3, 4, 5, 6, or 7 days after the day of administration of the antibody.

[0141] For example, the subject receives pembrolizumab administered by intravenous infusion every three weeks and vinblastine $N_{b'}$-oxide adminstered three times a week by intravenous or two times a week by subcutaneous infusion, wherein the first dose of vinblastine $N_{b'}$-oxide is administered prior to the first dose of pembrolizumab, the first dose of vinblastine $N_{b'}$-oxide is administered on the same day as the first dose of pembrolizumab, or the first dose of vinblastine $N_{b'}$-oxide is administered after to the first dose of pembrolizumab, e.g., until disease progression or until there is no therapeutic benefit.

[0142] For example, the subject receives nivolumab administered by intravenous infusion every two weeks and vinblastine $N_{b'}$-oxide adminstered three times a week by intravenous or two times a week by subcutaneous infusion, wherein the first dose of vinblastine $N_{b'}$-oxide is administered prior to the first dose of nivolumab, the first dose of vinblastine $N_{b'}$-oxide is administered on the same day as the first dose of nivolumab, or the first dose vinblastine $N_{b'}$-oxide is administered after to the first dose of nivolumab, e.g., until disease progression or until there is no therapeutic benefit.

[0143] In another embodiment, the treatment of the cancer patient with a vinca alkaloid N-oxide and an immune checkpoint inhibitor induces anti-proliferative response faster than when the immune checkpoint inhibitor is administered alone.

V. Biomarkers

[0144] The term "biomarker" as used herein refers to any biological compound, such as a gene, a protein, a fragment of a protein, a peptide, a polypeptide, a nucleic acid, etc., that

can be detected and/or quantified in a cancer patient *in vivo* or in a biological sample obtained from a cancer patient. A biomarker can be the entire intact molecule, or it can be a portion or fragment thereof. In one embodiment, the expression level of the biomarker is measured. The expression level of the biomarker can be measured, for example, by detecting the protein or RNA, e.g., mRNA, level of the biomarker. In some embodiments, portions or fragments of biomarkers can be detected or measured, for example, by an antibody or other specific binding agent. In some embodiments, a measurable aspect of the biomarker is associated with a given state of the patient, such as a particular stage of cancer. For biomarkers that are detected at the protein or RNA level, such measurable aspects may include, for example, the presence, absence, or concentration, i.e., expression level, of the biomarker in a cancer patient, or biological sample obtained from the cancer patient. For biomarkers that are detected at the nucleic acid level, such measurable aspects may include, for example, allelic versions of the biomarker or type, rate, and/or degree of mutation of the biomarker, also referred to herein as mutation status.

[0145] For biomarkers that are detected based on expression level of protein or RNA, expression level measured between different phenotypic statuses can be considered different, for example, if the mean or median expression level of the biomarker in the different groups is calculated to be statistically significant. Common tests for statistical significance include, among others, t-test, ANOVA, Kruskal-Wallis, Wilcoxon, Mann-Whitney, Significance Analysis of Microarrays, odds ratio, etc. Biomarkers, alone or in combination, provide measures of relative likelihood that a subject belongs to one phenotypic status or another. Therefore, they are useful, inter alia, as markers for disease and as indicators that particular therapeutic treatment regimens will likely result in beneficial patient outcomes.

[0146] Biomarkers include, but are not limited, the genes listed in Table 1 and/or Table 2. *See, e.g.*, Le and Courter, *Cancer Metastasis Rev. 27*:351–362 (2008). In one embodiment, the measurable aspect of the biomarker is its expression status. In one embodiment, the measurable aspect of the biomarker is its mutation status.

Table 1

Gene	Gene synonym	Gene description
A2M	CPAMD5, FWP007, S863-7	Alpha-2-macroglobulin

ABCB1	ABC20, CD243, CLCS, GP170, MDR1, P-gp, PGY1	ATP-binding cassette, sub-family B (MDR/TAP), member 1
ABCC1	GS-X, MRP, MRP1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1
ABCC2	CMOAT, cMRP, DJS, MRP2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2
ABCC3	cMOAT2, EST90757, MLP2, MOAT-D, MRP3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3
ABCC5	EST277145, MOAT-C, MRP5, SMRP	ATP-binding cassette, sub-family C (CFTR/MRP), member 5
ABCC6	ARA, EST349056, MLP1, MRP6, PXE, URG7	ATP-binding cassette, sub-family C (CFTR/MRP), member 6
ABCG2	ABCP, BCRP, CD338, EST157481, MXR	ATP-binding cassette, sub-family G (WHITE), member 2 (Junior blood group)
ABL1	ABL, c-ABL, JTK7, p150	ABL proto-oncogene 1, non-receptor tyrosine kinase
ABL2	ABLL, ARG	ABL proto-oncogene 2, non-receptor tyrosine kinase
ACAP1	CENTB1, KIAA0050	ArfGAP with coiled-coil, ankyrin repeat and PH domains 1
ACLY	ACL, ATPCL, CLATP	ATP citrate lyase
ACPP	ACP-3, ACP3	Acid phosphatase, prostate
ACVR1B	ActRIB, ACVRLK4, ALK4, SKR2	Activin A receptor, type IB
ACVR2A	ACTRII, ACVR2	Activin A receptor, type IIA
ACVR2B	ActR-IIB	Activin A receptor, type IIB
ADAM9	CORD9, KIAA0021, MCMP, MDC9, Mltng	ADAM metallopeptidase domain 9
ADAMTS1	C3-C5, KIAA1346, METH1	ADAM metallopeptidase with thrombospondin type 1 motif, 1
ADAMTS14		ADAM metallopeptidase with thrombospondin type 1 motif, 14
ADAMTS18	ADAMTS21	ADAM metallopeptidase with thrombospondin type 1 motif, 18
ADAMTS20	GON-1	ADAM metallopeptidase with thrombospondin type 1 motif, 20
ADAMTS3	ADAMTS-4, KIAA0366	ADAM metallopeptidase with thrombospondin type 1 motif, 3
ADAMTS4	ADAMTS-2, ADMP-1, KIAA0688	ADAM metallopeptidase with thrombospondin type 1 motif, 4
ADAMTS5	ADAMTS11, ADMP-2	ADAM metallopeptidase with thrombospondin type 1 motif, 5
ADAMTS6	ADAM-TS6	ADAM metallopeptidase with thrombospondin type 1 motif, 6
ADAMTS8	ADAM-TS8, FLJ41712, METH2	ADAM metallopeptidase with thrombospondin type 1 motif, 8
ADAMTS9	KIAA1312	ADAM metallopeptidase with thrombospondin type 1 motif, 9

ADM	AM	Adrenomedullin
ADRA1B		Adrenoceptor alpha 1B
AFP	FETA, HPAFP	Alpha-fetoprotein
AGER	RAGE	Advanced glycosylation end product-specific receptor
AHR	bHLHe76	Aryl hydrocarbon receptor
AHSG	A2HS, FETUA, HSGA	Alpha-2-HS-glycoprotein
AKAP12	AKAP250, SSeCKS	A kinase (PRKA) anchor protein 12
AKR1B1	ALDR1, AR	Aldo-keto reductase family 1, member B1 (aldose reductase)
AKT1	AKT, PKB, PRKBA, RAC	V-akt murine thymoma viral oncogene homolog 1
AKT2		V-akt murine thymoma viral oncogene homolog 2
AKT3	PKBG, PRKBG, RAC-gamma	V-akt murine thymoma viral oncogene homolog 3
ALB		Albumin
ALCAM	CD166, MEMD	Activated leukocyte cell adhesion molecule
ALDOA		Aldolase A, fructose-bisphosphate
ALDOB		Aldolase B, fructose-bisphosphate
ALDOC		Aldolase C, fructose-bisphosphate
ALPL	HOPS, TNSALP	Alkaline phosphatase, liver/bone/kidney
ALPP		Alkaline phosphatase, placental
ANG	RNASE5	Angiogenin, ribonuclease, RNase A family, 5
ANGPT1	Ang1, KIAA0003	Angiopoietin 1
ANGPT2	Ang2	Angiopoietin 2
ANXA1	ANX1, LPC1	Annexin A1
ANXA11	ANX11	Annexin A11
ANXA2	ANX2, ANX2L4, CAL1H, LIP2, LPC2D	Annexin A2
ANXA4	ANX4	Annexin A4
ANXA7	ANX7	Annexin A7
AOC3	HPAO, VAP-1, VAP1	Amine oxidase, copper containing 3
AP2B1	ADTB2, CLAPB1	Adaptor-related protein complex 2, beta 1 subunit
APAF1	APAF-1, CED4	Apoptotic peptidase activating factor 1
APEX1	APE, APE-1, APEN, APEX, APX, HAP1, REF-1, REF1	APEX nuclease (multifunctional DNA repair enzyme) 1
APOA1		Apolipoprotein A-I
APOA2		Apolipoprotein A-II
APOC1		Apolipoprotein C-I
APOC3		Apolipoprotein C-III
APOD		Apolipoprotein D
APOE	AD2	Apolipoprotein E
APPBP2	Hs.84084, KIAA0228, PAT1	Amyloid beta precursor protein (cytoplasmic tail) binding protein 2

AR	AIS, DHTR, HUMARA, NR3C4, SBMA, SMAX1	Androgen receptor
AREG	AREGB, SDGF	Amphiregulin
ARG2		Arginase 2
ARNT	bHLHe2, HIF-1beta	Aryl hydrocarbon receptor nuclear translocator
ASPH	BAH, CASQ2BP1, HAAH, JCTN	Aspartate beta-hydroxylase
ATM	ATA, ATC, ATD, ATDC, TEL1, TELO1	ATM serine/threonine kinase
ATOH1	bHLHa14, HATH1, MATH-1, Math1	Atonal homolog 1 (Drosophila)
ATP7B	WND	ATPase, Cu++ transporting, beta polypeptide
AURKA	AIK, ARK1, AurA, BTAK, PPP1R47, STK15, STK6, STK7	Aurora kinase A
AURKB	Aik2, AIM-1, ARK2, AurB, IPL1, PPP1R48, STK12, STK5	Aurora kinase B
AZGP1	ZA2G, ZAG	Alpha-2-glycoprotein 1, zinc-binding
B2M		Beta-2-microglobulin
BAD	BBC2, BCL2L8	BCL2-associated agonist of cell death
BAG1		BCL2-associated athanogene
BAI1		Brain-specific angiogenesis inhibitor 1
BAX	BCL2L4	BCL2-associated X protein
BCL11A	BCL11A-L, BCL11A-S, BCL11A-XL, CTIP1, EVI9, HBFQTL5, ZNF856	B-cell CLL/lymphoma 11A (zinc finger protein)
BCL2	Bcl-2, PPP1R50	B-cell CLL/lymphoma 2
BCL2A1	ACC-1, ACC-2, BCL2L5, BFL1, GRS, HBPA1	BCL2-related protein A1
BCL2L1	Bcl-X, bcl-xL, bcl-xS, BCL2L, BCLX, PPP1R52	BCL2-like 1
BCL2L2	BCL-W, KIAA0271, PPP1R51	BCL2-like 2
BCL2L2-PABPN1		BCL2L2-PABPN1 readthrough
BCL3	BCL4, D19S37	B-cell CLL/lymphoma 3
BCL6	BCL5, BCL6A, LAZ3, ZBTB27, ZNF51	B-cell CLL/lymphoma 6
BDNF		Brain-derived neurotrophic factor
BIRC2	API1, c-IAP1, cIAP1, hiap-2, MIHB, RNF48	Baculoviral IAP repeat containing 2
BIRC3	API2, c-IAP2, cIAP2, hiap-1, MALT2, MIHC, RNF49	Baculoviral IAP repeat containing 3
BIRC5	API4, EPR-1, survivin	Baculoviral IAP repeat containing 5
BIRC6	BRUCE	Baculoviral IAP repeat containing 6
BLK	MGC10442	BLK proto-oncogene, Src family tyrosine kinase

BLMH	BH	Bleomycin hydrolase
BMI1	PCGF4, RNF51	BMI1 proto-oncogene, polycomb ring finger
BMP2	BMP2A	Bone morphogenetic protein 2
BMP4	BMP2B	Bone morphogenetic protein 4
BNIP3	Nip3	BCL2/adenovirus E1B 19kDa interacting protein 3
BNIP3L	BNIP3a, Nix	BCL2/adenovirus E1B 19kDa interacting protein 3-like
BRCA1	BRCC1, PPP1R53, RNF53	Breast cancer 1, early onset
BRCA2	BRCC2, FACD, FAD, FAD1, FANCD, FANCD1	Breast cancer 2, early onset
BRMS1	DKFZP564A063	Breast cancer metastasis suppressor 1
BTG2	MGC126063, MGC126064, PC3, TIS21	BTG family, member 2
C18orf8	HsT2591, MIC-1, MIC1	Chromosome 18 open reading frame 8
C1QBP	gC1Q-R, gC1qR, HABP1, p32, SF2p32	Complement component 1, q subcomponent binding protein
C6		Complement component 6
C7		Complement component 7
CA8	CALS, CARP	Carbonic anhydrase VIII
CALCA	CALC1	Calcitonin-related polypeptide alpha
CALM1	CALML2, CAMI, DD132, PHKD	Calmodulin 1 (phosphorylase kinase, delta)
CALM2	CAMII, PHKD	Calmodulin 2 (phosphorylase kinase, delta)
CALM3	PHKD	Calmodulin 3 (phosphorylase kinase, delta)
CALR	cC1qR, CRT, FLJ26680, RO, SSA	Calreticulin
CANX	CNX, IP90, P90	Calnexin
CAPN6	CalpM, CANPX, CAPNX	Calpain 6
CASC3	BTZ, MLN51	Cancer susceptibility candidate 3
CASP1	ICE, IL1BC	Caspase 1, apoptosis-related cysteine peptidase
CASP10	MCH4	Caspase 10, apoptosis-related cysteine peptidase
CASP2	ICH1, MGC2181, NEDD2, PPP1R57	Caspase 2, apoptosis-related cysteine peptidase
CASP3	apopain, CPP32, CPP32B, Yama	Caspase 3, apoptosis-related cysteine peptidase
CASP4	ICE(rel)II, ICH-2, TX	Caspase 4, apoptosis-related cysteine peptidase
CASP5	ICE(rel)III	Caspase 5, apoptosis-related cysteine peptidase
CASP6	MCH2	Caspase 6, apoptosis-related cysteine peptidase
CASP7	CMH-1, ICE-LAP3, MCH3	Caspase 7, apoptosis-related cysteine peptidase

CASP8	Casp-8, FLICE, MACH, MCH5	Caspase 8, apoptosis-related cysteine peptidase
CASP9	APAF-3, ICE-LAP6, MCH6, PPP1R56	Caspase 9, apoptosis-related cysteine peptidase
CAT		Catalase
CAV1	CAV	Caveolin 1, caveolae protein, 22kDa
CBL	c-Cbl, CBL2, RNF55	Cbl proto-oncogene, E3 ubiquitin protein ligase
CCKBR		Cholecystokinin B receptor
CCL11	eotaxin, MGC22554, SCYA11	Chemokine (C-C motif) ligand 11
CCL13	CKb10, MCP-4, MGC17134, NCC-1, SCYA13, SCYL1	Chemokine (C-C motif) ligand 13
CCL14	CKb1, HCC-1, HCC-3, MCIF, NCC-2, SCYA14, SCYL2	Chemokine (C-C motif) ligand 14
CCL16	CKb12, HCC-4, LCC-1, LEC, LMC, Mtn-1, NCC-4, SCYA16, SCYL4	Chemokine (C-C motif) ligand 16
CCL18	AMAC-1, CKb7, DC-CK1, DCCK1, MIP-4, PARC, SCYA18	Chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)
CCL19	CKb11, ELC, exodus-3, MIP-3b, SCYA19	Chemokine (C-C motif) ligand 19
CCL2	GDCF-2, HC11, MCAF, MCP-1, MCP1, MGC9434, SCYA2, SMC-CF	Chemokine (C-C motif) ligand 2
CCL21	6Ckine, CKb9, ECL, exodus-2, SCYA21, SLC, TCA4	Chemokine (C-C motif) ligand 21
CCL23	Ckb-8, CKb8, MIP-3, MPIF-1, SCYA23	Chemokine (C-C motif) ligand 23
CCL3	G0S19-1, LD78ALPHA, MIP-1-alpha, SCYA3	Chemokine (C-C motif) ligand 3
CCL4	Act-2, AT744.1, LAG1, MIP-1-beta, SCYA4	Chemokine (C-C motif) ligand 4
CCL5	D17S136E, MGC17164, RANTES, SCYA5, SISd, TCP228	Chemokine (C-C motif) ligand 5
CCL7	FIC, MARC, MCP-3, MCP3, NC28, SCYA6, SCYA7	Chemokine (C-C motif) ligand 7
CCL8	HC14, MCP-2, SCYA8	Chemokine (C-C motif) ligand 8
CCNA1	CT146	Cyclin A1
CCNA2	CCN1, CCNA	Cyclin A2
CCNB1	CCNB	Cyclin B1
CCNB2	HsT17299	Cyclin B2
CCND1	BCL1, D11S287E, PRAD1, U21B31	Cyclin D1
CCND2		Cyclin D2
CCNE1	CCNE	Cyclin E1

CCNE2	CYCE2	Cyclin E2
CCNG1	CCNG	Cyclin G1
CCNG2		Cyclin G2
CCNH	CycH, p34, p37	Cyclin H
CCR10	GPR2	Chemokine (C-C motif) receptor 10
CCR7	BLR2, CD197, CDw197, CMKBR7, EBI1	Chemokine (C-C motif) receptor 7
CD14		CD14 molecule
CD27	S152, TNFRSF7, Tp55	CD27 molecule
CD36	FAT, GP3B, GP4, GPIV, SCARB3	CD36 molecule (thrombospondin receptor)
CD38		CD38 molecule
CD40	Bp50, p50, TNFRSF5	CD40 molecule, TNF receptor superfamily member 5
CD40LG	CD154, CD40L, gp39, hCD40L, HIGM1, IMD3, TNFSF5, TRAP	CD40 ligand
CD44	CD44R, CSPG8, HCELL, IN, MC56, MDU2, MDU3, MIC4, Pgp1	CD44 molecule (Indian blood group)
CD46	MCP, MGC26544, MIC10, TLX, TRA2.10	CD46 molecule, complement regulatory protein
CD52	CDW52	CD52 molecule
CD59	16.3A5, EJ16, EJ30, EL32, G344, MIC11, MIN1, MIN2, MIN3, MSK21, p18-20	CD59 molecule, complement regulatory protein
CD70	CD27L, CD27LG, TNFSF7	CD70 molecule
CD74	DHLAG	CD74 molecule, major histocompatibility complex, class II invariant chain
CD82	IA4, KAI1, R2, ST6, TSPAN27	CD82 molecule
CD9	BA2, MIC3, MRP-1, P24, TSPAN29	CD9 molecule
CDC16	ANAPC6, APC6, CUT9	Cell division cycle 16
CDC20	CDC20A, p55CDC	Cell division cycle 20
CDC25A		Cell division cycle 25A
CDC25B		Cell division cycle 25B
CDC25C	CDC25, PPP1R60	Cell division cycle 25C
CDC34	E2-CDC34, UBC3, UBE2R1	Cell division cycle 34
CDC37	P50CDC37	Cell division cycle 37
CDC6	CDC18L	Cell division cycle 6
CDH1	CD324, UVO, uvomorulin	Cadherin 1, type 1, E-cadherin (epithelial)
CDH17	cadherin, HPT-1	Cadherin 17, LI cadherin (liver-intestine)
CDH5	7B4, CD144	Cadherin 5, type 2 (vascular endothelium)
CDK1	CDC2, CDC28A	Cyclin-dependent kinase 1
CDK2		Cyclin-dependent kinase 2
CDK4	PSK-J3	Cyclin-dependent kinase 4
CDK6	PLSTIRE	Cyclin-dependent kinase 6
CDK7	CAK, CAK1, CDKN7, MO15,	Cyclin-dependent kinase 7

	STK1	
CDKN1A	CAP20, CDKN1, CIP1, P21, p21CIP1, p21Cip1/Waf1, SDI1, WAF1	Cyclin-dependent kinase inhibitor 1A (p21, Cip1)
CDKN1C	BWCR, BWS, KIP2, P57	Cyclin-dependent kinase inhibitor 1C (p57, Kip2)
CDKN2A	ARF, CDK4I, CDKN2, CMM2, INK4, INK4a, MLM, MTS1, p14, p14ARF, p16, p16INK4a, p19, p19Arf	Cyclin-dependent kinase inhibitor 2A
CEACAM5	CD66e, CEA	Carcinoembryonic antigen-related cell adhesion molecule 5
CEACAM6	CD66c, NCA	Carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)
CENPF	hcp-1	Centromere protein F, 350/400kDa
CFHR1	CFHL, CFHL1, CFHL1P, CFHR1P, FHR1, H36-1, H36-2, HFL1, HFL2	Complement factor H-related 1
CFLAR	c-FLIP, CASH, CASP8AP1, Casper, CLARP, FLAME, FLIP, I-FLICE, MRIT	CASP8 and FADD-like apoptosis regulator
CFTR	ABC35, ABCC7, CF, CFTR/MRP, dJ760C5.1, MRP7, TNR-CFTR	Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)
CGA	FSHA, GPHa, GPHA1, HCG, LHA, TSHA	Glycoprotein hormones, alpha polypeptide
CGB	CGB3	Chorionic gonadotropin, beta polypeptide
CGB5	HCG	Chorionic gonadotropin, beta polypeptide 5
CGB7	CG-beta-a	Chorionic gonadotropin, beta polypeptide 7
CGB8		Chorionic gonadotropin, beta polypeptide 8
CHD7	CRG, FLJ20357, FLJ20361, KIAA1416	Chromodomain helicase DNA binding protein 7
CHEK1	CHK1	Checkpoint kinase 1
CHEK2	bA444G7, CDS1, CHK2, HuCds1, PP1425, RAD53	Checkpoint kinase 2
CHFR	FLJ10796, RNF196	Checkpoint with forkhead and ring finger domains, E3 ubiquitin protein ligase
CHGA		Chromogranin A (parathyroid secretory protein 1)
CHI3L1	GP39, YKL40	Chitinase 3-like 1 (cartilage glycoprotein-39)
CHP2		Calcineurin-like EF-hand protein 2
CIB2	DFNB48, KIP2, USH1J	Calcium and integrin binding family member 2
CKB	CKBB	Creatine kinase, brain
CKS1B	CKS1, ckshs1	CDC28 protein kinase regulatory subunit 1B

CKS2		CDC28 protein kinase regulatory subunit 2
CLDN3	C7orf1, CPE-R2, CPETR2, HRVP1, RVP1	Claudin 3
CLDN4	CPE-R, CPETR, CPETR1, hCPE-R, WBSCR8	Claudin 4
CLDN7	CEPTRL2, CPETRL2, Hs.84359	Claudin 7
CLEC3B	TN, TNA	C-type lectin domain family 3, member B
CLIC1	NCC27, p64CLCP	Chloride intracellular channel 1
CLIP1	CLIP, CLIP-170, CLIP170, CYLN1, RSN	CAP-GLY domain containing linker protein 1
CLSTN1	CDHR12, CSTN1, KIAA0911	Calsyntenin 1
CLU	APOJ, CLI, CLU1, CLU2, KUB1, SGP-2, SP-40, TRPM-2	Clusterin
CNN1	Sm-Calp, SMCC	Calponin 1, basic, smooth muscle
CNTF	HCNTF	Ciliary neurotrophic factor
COL11A1	CO11A1, COLL6, STL2	Collagen, type XI, alpha 1
COL17A1	BP180, BPAG2	Collagen, type XVII, alpha 1
COL18A1	KNO, KNO1, KS	Collagen, type XVIII, alpha 1
COL1A1	OI4	Collagen, type I, alpha 1
COL1A2	OI4	Collagen, type I, alpha 2
COL4A2	DKFZp686I14213, FLJ22259	Collagen, type IV, alpha 2
COL4A3		Collagen, type IV, alpha 3 (Goodpasture antigen)
COL4A4	CA44	Collagen, type IV, alpha 4
COL4A5	ASLN, ATS	Collagen, type IV, alpha 5
COL6A1		Collagen, type VI, alpha 1
COX17		COX17 cytochrome c oxidase copper chaperone
CP		Ceruloplasmin (ferroxidase)
CRABP1	CRABP, CRABP-I, CRABPI, RBP5	Cellular retinoic acid binding protein 1
CRADD	RAIDD	CASP2 and RIPK1 domain containing adaptor with death domain
CREBBP	CBP, KAT3A, RSTS, RTS	CREB binding protein
CRP	PTX1	C-reactive protein, pentraxin-related
CRYAB	CRYA2, HSPB5	Crystallin, alpha B
CSE1L	CAS, CSE1, XPO2	CSE1 chromosome segregation 1-like (yeast)
CSF1	M-CSF, MCSF, MGC31930	Colony stimulating factor 1 (macrophage)
CSF1R	C-FMS, CD115, CSFR, FMS	Colony stimulating factor 1 receptor
CSF2	GM-CSF, GMCSF	Colony stimulating factor 2 (granulocyte-macrophage)
CSF2RA	CD116, CSF2R	Colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)
CSF3	C17orf33, G-CSF, GCSF, MGC45931	Colony stimulating factor 3 (granulocyte)
CSN1S1	CASA, CSN1	Casein alpha s1

CSNK1E	CKIE, CKIepsilon, HCKIE	Casein kinase 1, epsilon
CSNK2A1		Casein kinase 2, alpha 1 polypeptide
CSNK2A2	CSNK2A1	Casein kinase 2, alpha prime polypeptide
CSNK2B		Casein kinase 2, beta polypeptide
CST3		Cystatin C
CST6		Cystatin E/M
CSTA	STF1, STFA	Cystatin A (stefin A)
CSTB	CST6, EPM1, PME, STFB	Cystatin B (stefin B)
CTAG1A	ESO1, LAGE2A	Cancer/testis antigen 1A
CTAG1B	CT6.1, CTAG, CTAG1, ESO1, LAGE2A, LAGE2B, NY-ESO-1	Cancer/testis antigen 1B
CTAG2	CAMEL, CT6.2a, CT6.2b, ESO2, LAGE-1, LAGE-1a, LAGE-1b, LAGE1, MGC138724, MGC3803	Cancer/testis antigen 2
CTGF	CCN2, IGFBP8	Connective tissue growth factor
CTNNB1	armadillo, beta-catenin, CTNNB	Catenin (cadherin-associated protein), beta 1, 88kDa
CTNNBL1	C20orf33, FLJ21108, NAP, NYD-SP19, P14, P14L	Catenin, beta like 1
CTSB		Cathepsin B
CTSD	CLN10, CPSD	Cathepsin D
CTSH	ACC-4, ACC-5, CPSB	Cathepsin H
CTSL	CTSL1, FLJ31037	Cathepsin L
CUL2		Cullin 2
CUL5	VACM-1	Cullin 5
CXCL1	FSP, GRO1, GROa, MGSA, MGSA-a, NAP-3, SCYB1	Chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)
CXCL10	C7, crg-2, gIP-10, IFI10, INP10, IP-10, mob-1, SCYB10	Chemokine (C-X-C motif) ligand 10
CXCL13	ANGIE, ANGIE2, BCA-1, BLC, BLR1L, SCYB13	Chemokine (C-X-C motif) ligand 13
CXCL2	CINC-2a, GRO2, GROb, MGSA-b, MIP-2a, SCYB2	Chemokine (C-X-C motif) ligand 2
CXCL5	ENA-78, SCYB5	Chemokine (C-X-C motif) ligand 5
CXCL8	3-10C, AMCF-I, b-ENAP, GCP-1, GCP1, IL-8, IL8, K60, LECT, LUCT, LYNAP, MDNCF, MONAP, NAF, NAP-1, NAP1, SCYB8, TSG-1	Chemokine (C-X-C motif) ligand 8
CXCL9	CMK, crg-10, Humig, MIG, SCYB9	Chemokine (C-X-C motif) ligand 9
CXCR1	CD181, CDw128a, CKR-1, CMKAR1, IL8RA	Chemokine (C-X-C motif) receptor 1
CXCR2	CD182, CMKAR2, IL8RB	Chemokine (C-X-C motif) receptor 2
CXCR4	CD184, D2S201E, fusin, HM89,	Chemokine (C-X-C motif) receptor 4

	HSY3RR, LESTR, NPY3R, NPYR, NPYY3R	
CYB5R3	DIA1	Cytochrome b5 reductase 3
CYP19A1	ARO, ARO1, aromatase, CPV1, CYAR, CYP19, P-450AROM	Cytochrome P450, family 19, subfamily A, polypeptide 1
CYP1A2	CP12, P3-450	Cytochrome P450, family 1, subfamily A, polypeptide 2
CYP2C19	CPCJ, CYP2C, P450IIC19	Cytochrome P450, family 2, subfamily C, polypeptide 19
CYP2E1	CYP2E	Cytochrome P450, family 2, subfamily E, polypeptide 1
CYP3A4	CYP3A3	Cytochrome P450, family 3, subfamily A, polypeptide 4
CYP3A5	CP35, P450PCN3, PCN3	Cytochrome P450, family 3, subfamily A, polypeptide 5
DAD1	OST2	Defender against cell death 1
DAPK1	DAPK	Death-associated protein kinase 1
DAXX	DAP6	Death-domain associated protein
DBI	ACBD1, ACBP	Diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)
DCC	IGDCC1, NTN1R1	DCC netrin 1 receptor
DCDC1		Doublecortin domain containing 1
DCN	DSPG2, SLRR1B	Decorin
DDB2	DDBB, FLJ34321, UV-DDB2	Damage-specific DNA binding protein 2, 48kDa
DDIT3	CHOP, CHOP10, GADD153	DNA-damage-inducible transcript 3
DEFA1	DEF1, DEFA2, HNP-1, MRS	Defensin, alpha 1
DEFA1B		Defensin, alpha 1B
DEFA3	DEF3, HNP-3	Defensin, alpha 3, neutrophil-specific
DEK	D6S231E	DEK proto-oncogene
DES	CMD1I, CSM1, CSM2	Desmin
DHFR		Dihydrofolate reductase
DIAPH3	AN, AUNA1, DRF3, FLJ34705, NSDAN	Diaphanous-related formin 3
DLC1	ARHGAP7, DLC-1, HP, p122-RhoGAP, STARD12	DLC1 Rho GTPase activating protein
DNAJC2	MPHOSPH11, MPP11, ZRF1, ZUO1, zuotin	DnaJ (Hsp40) homolog, subfamily C, member 2
DST	BP240, BPA, BPAG1, CATX-15, FLJ13425, FLJ21489, FLJ30627, FLJ32235, KIAA0728, MACF2	Dystonin
DUSP1	CL100, HVH1, MKP-1, PTPN10	Dual specificity phosphatase 1
DUSP14	MKP-L, MKP6	Dual specificity phosphatase 14
DUSP4	HVH2, MKP-2, TYP	Dual specificity phosphatase 4
DVL3	KIAA0208	Dishevelled segment polarity protein 3

DYNLL1	DLC1, DLC8, DNCL1, hdlc1, LC8, PIN	Dynein, light chain, LC8-type 1
DYRK2		Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2
E2F1	RBBP3, RBP3	E2F transcription factor 1
E2F3		E2F transcription factor 3
E2F5		E2F transcription factor 5, p130-binding
EBAG9	EB9, RCAS1	Estrogen receptor binding site associated, antigen, 9
EDN1	ET1	Endothelin 1
EEF2	EEF-2, EF2	Eukaryotic translation elongation factor 2
EFNA1	ECKLG, EPLG1, LERK1, TNFAIP4	Ephrin-A1
EFNA2	ELF-1, EPLG6, LERK6	Ephrin-A2
EFNA5	AF1, EPLG7, LERK7	Ephrin-A5
EFNB1	CFNS, Elk-L, EPLG2, LERK2	Ephrin-B1
EFNB2	EPLG5, Htk-L, HTKL, LERK5, MGC126226, MGC126227, MGC126228	Ephrin-B2
EFNB3	EPLG8, LERK-8	Ephrin-B3
EGF		Epidermal growth factor
EGFR	ERBB, ERBB1	Epidermal growth factor receptor
EGR1	AT225, G0S30, KROX-24, NGFI-A, TIS8, ZIF-268, ZNF225	Early growth response 1
EI24	EPG4, PIG8, TP53I8	Etoposide induced 2.4
EIF3H	eIF3-gamma, eIF3-p40, eIF3h, EIF3S3	Eukaryotic translation initiation factor 3, subunit H
EIF4E	EIF4E1, EIF4EL1, EIF4F	Eukaryotic translation initiation factor 4E
EIF4EBP1	4E-BP1, PHAS-I	Eukaryotic translation initiation factor 4E binding protein 1
EIF4G1	EIF4F, EIF4G, p220, PARK18	Eukaryotic translation initiation factor 4 gamma, 1
EIF4H	KIAA0038, WBSCR1, WSCR1	Eukaryotic translation initiation factor 4H
EIF5A	EIF-5A, EIF5A1, MGC104255, MGC99547	Eukaryotic translation initiation factor 5A
ELANE	ELA2, HLE, HNE, NE	Elastase, neutrophil expressed
ELK3	ERP, NET, SAP2	ELK3, ETS-domain protein (SRF accessory protein 2)
ENC1	ENC-1, KLHL37, NRPB, PIG10, TP53I10	Ectodermal-neural cortex 1 (with BTB domain)
ENG	CD105, END, HHT1, ORW, ORW1	Endoglin
ENO1	ENO1L1, MBP-1, MPB1, PPH	Enolase 1, (alpha)
ENO2		Enolase 2 (gamma, neuronal)
ENPP2	ATX, PD-IALPHA, PDNP2	Ectonucleotide pyrophosphatase/phosphodiesterase 2

EPAS1	bHLHe73, HIF2A, HLF, MOP2, PASD2	Endothelial PAS domain protein 1
EPCAM	17-1A, 323/A3, CD326, CO-17A, EGP-2, EGP34, EGP40, Ep-CAM, ESA, GA733-2, HEA125, KS1/4, KSA, Ly74, M4S1, MH99, MIC18, MK-1, MOC31, TACST-1, TACSTD1, TROP1	Epithelial cell adhesion molecule
EPHA1	EPH, EPHT, EPHT1	EPH receptor A1
EPHA2	ECK	EPH receptor A2
EPHA3	ETK, ETK1, HEK, HEK4, TYRO4	EPH receptor A3
EPHA4	Hek8, TYRO1	EPH receptor A4
EPHA7	Hek11	EPH receptor A7
EPHA8	EEK, Hek3	EPH receptor A8
EPHB2	DRT, EPHT3, ERK, Hek5, Tyro5	EPH receptor B2
EPHB3	ETK2, Hek2, Tyro6	EPH receptor B3
EPHB4	HTK, Tyro11	EPH receptor B4
EPHX1	EPHX	Epoxide hydrolase 1, microsomal (xenobiotic)
EPO	EP	Erythropoietin
EPOR		Erythropoietin receptor
ERBB2	CD340, HER-2, HER2, NEU, NGL	V-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2
ERBB3	HER3, LCCS2	V-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3
ERBB4	ALS19	V-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4
ERCC1	RAD10	Excision repair cross-complementation group 1
ERCC2	EM9, MAG, MGC102762, MGC126218, MGC126219, TFIIH, XPD	Excision repair cross-complementation group 2
ERCC3	BTF2, GTF2H, RAD25, TFIIH, XPB	Excision repair cross-complementation group 3
ERCC4	FANCQ, RAD1, XPF	Excision repair cross-complementation group 4
ERCC5	ERCM2, XPGC	Excision repair cross-complementation group 5
ERCC6	ARMD5, CKN2, CSB, RAD26	Excision repair cross-complementation group 6
ESR1	Era, ESR, NR3A1	Estrogen receptor 1
ESR2	Erb, NR3A2	Estrogen receptor 2 (ER beta)
ETHE1	HSCO, YF13H12	Ethylmalonic encephalopathy 1
ETV4	E1A-F, E1AF, PEA3	Ets variant 4

ETV5	ERM	Ets variant 5
EXT1	LGCR, LGS, ttv	Exostosin glycosyltransferase 1
EZH2	ENX-1, EZH1, KMT6, KMT6A	Enhancer of zeste 2 polycomb repressive complex 2 subunit
EZR	VIL2	Ezrin
F13A1	F13A	Coagulation factor XIII, A1 polypeptide
F13B	FXIIIB	Coagulation factor XIII, B polypeptide
F2		Coagulation factor II (thrombin)
F3	CD142	Coagulation factor III (thromboplastin, tissue factor)
FABP1	L-FABP	Fatty acid binding protein 1, liver
FABP2	I-FABP	Fatty acid binding protein 2, intestinal
FABP4	A-FABP, aP2	Fatty acid binding protein 4, adipocyte
FABP5	E-FABP, KFABP, PA-FABP	Fatty acid binding protein 5 (psoriasis-associated)
FADD	GIG3, MORT1	Fas (TNFRSF6)-associated via death domain
FAF1	CGI-03, hFAF1, HFAF1s, UBXD12, UBXN3A	Fas (TNFRSF6) associated factor 1
FAM129A	C1orf24, GIG39, NIBAN	Family with sequence similarity 129, member A
FAP	DPPIV	Fibroblast activation protein, alpha
FAS	APO-1, APT1, CD95, FAS1, TNFRSF6	Fas cell surface death receptor
FASLG	APT1LG1, CD178, FasL, TNFSF6	Fas ligand (TNF superfamily, member 6)
FASN	FAS, SDR27X1	Fatty acid synthase
FBXO6	FBG2, FBS2, FBX6, Fbx6b	F-box protein 6
FCER2	CD23, CD23A, CLEC4J, FCE2	Fc fragment of IgE, low affinity II, receptor for (CD23)
FEN1	FEN-1, MF1, RAD2	Flap structure-specific endonuclease 1
FES	FPS	FES proto-oncogene, tyrosine kinase
FGA		Fibrinogen alpha chain
FGB		Fibrinogen beta chain
FGF1	AFGF, ECGF, ECGF-beta, ECGFA, ECGFB, FGF-alpha, FGFA, GLIO703, HBGF1	Fibroblast growth factor 1 (acidic)
FGF17	FGF-13	Fibroblast growth factor 17
FGF18	FGF-18, ZFGF5	Fibroblast growth factor 18
FGF19		Fibroblast growth factor 19
FGF2	FGFB	Fibroblast growth factor 2 (basic)
FGF23		Fibroblast growth factor 23
FGF3	HBGF-3, INT2	Fibroblast growth factor 3
FGF4	HBGF-4, HST, HST-1, HSTF1, K-FGF, KFGF	Fibroblast growth factor 4
FGF6		Fibroblast growth factor 6
FGF7	KGF	Fibroblast growth factor 7

FGF8	AIGF	Fibroblast growth factor 8 (androgen-induced)
FGF9		Fibroblast growth factor 9
FGFR1	BFGFR, CD331, CEK, FLG, FLT2, H2, H3, H4, H5, KAL2, N-SAM	Fibroblast growth factor receptor 1
FGFR2	BEK, CD332, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25	Fibroblast growth factor receptor 2
FGFR3	ACH, CD333, CEK2, JTK4	Fibroblast growth factor receptor 3
FGFR4	CD334, JTK2	Fibroblast growth factor receptor 4
FGG		Fibrinogen gamma chain
FHIT	AP3Aase, FRA3B	Fragile histidine triad
FIGF	VEGF-D, VEGFD	C-fos induced growth factor (vascular endothelial growth factor D)
FKBP5	FKBP51, FKBP54, P54, PPIase, Ptg-10	FK506 binding protein 5
FKBP8	FKBP38, FKBPr38	FK506 binding protein 8, 38kDa
FLT1	FLT, VEGFR1	Fms-related tyrosine kinase 1
FLT4	PCL, VEGFR3	Fms-related tyrosine kinase 4
FMO5		Flavin containing monooxygenase 5
FN1	CIG, FINC, GFND2, LETS, MSF	Fibronectin 1
FOLH1	FOLH, GCP2, GCPII, NAALAD1, NAALAdase, PSM, PSMA	Folate hydrolase (prostate-specific membrane antigen) 1
FOS	AP-1, c-fos	FBJ murine osteosarcoma viral oncogene homolog
FOSL1	fra-1	FOS-like antigen 1
FOXJ1	FKHL13, HFH-4, HFH4	Forkhead box J1
FOXM1	FKHL16, HFH-11, HNF-3, INS-1, MPHOSPH2, MPP2, TGT3, trident	Forkhead box M1
FOXO1	FKH1, FKHR, FOXO1A	Forkhead box O1
FOXO3	AF6q21, FKHRL1, FOXO2, FOXO3A	Forkhead box O3
FOXQ1	HFH1	Forkhead box Q1
FSCN1	FLJ38511, p55, SNL	Fascin actin-bundling protein 1
FSHB		Follicle stimulating hormone, beta polypeptide
FST	FS	Follistatin
FTH1	FHC, FTH, FTHL6, PIG15, PLIF	Ferritin, heavy polypeptide 1
FTL	MGC71996, NBIA3	Ferritin, light polypeptide
FZD1	DKFZp564G072	Frizzled class receptor 1
FZD2		Frizzled class receptor 2
G6PD	G6PD1	Glucose-6-phosphate dehydrogenase

GADD45A	DDIT1, GADD45	Growth arrest and DNA-damage-inducible, alpha
GADD45G	CR6, DDIT2, GADD45gamma, GRP17	Growth arrest and DNA-damage-inducible, gamma
GAS1		Growth arrest-specific 1
GAST	GAS	Gastrin
GATA3	HDR	GATA binding protein 3
GCLM	GLCLR	Glutamate-cysteine ligase, modifier subunit
GDF15	MIC-1, MIC1, NAG-1, PDF, PLAB, PTGFB	Growth differentiation factor 15
GDNF	ATF1, ATF2, HFB1-GDNF	Glial cell derived neurotrophic factor
GH1	GH, GH-N, GHN, hGH-N	Growth hormone 1
GH2	GH-V , GH2, GHL, GHV, hGH-V	Growth hormone 2
GJA1	CX43, GJAL, ODD, ODDD, ODOD, SDTY3	Gap junction protein, alpha 1, 43kDa
GJB5	CX31.1	Gap junction protein, beta 5, 31.1kDa
GLO1	GLOD1	Glyoxalase I
GMNN	Gem	Geminin, DNA replication inhibitor
GNAS	GNAS1, GNASXL, GPSA, NESP, NESP55, SCG6	GNAS complex locus
GPA33	A33	Glycoprotein A33 (transmembrane)
GPC3	DGSX, OCI-5, SDYS, SGB, SGBS, SGBS1	Glypican 3
GPI	AMF, NLK	Glucose-6-phosphate isomerase
GPX1		Glutathione peroxidase 1
GPX2	GSHPX-GI	Glutathione peroxidase 2 (gastrointestinal)
GRB10		Growth factor receptor-bound protein 10
GRB2	NCKAP2	Growth factor receptor-bound protein 2
GRB7		Growth factor receptor-bound protein 7
GSK3A		Glycogen synthase kinase 3 alpha
GSN	DKFZp313L0718	Gelsolin
GSR		Glutathione reductase
GSTM1	GST1, H-B, MU	Glutathione S-transferase mu 1
GSTM3	GST5	Glutathione S-transferase mu 3 (brain)
GSTP1	FAEES3, GST3, GSTP	Glutathione S-transferase pi 1
HDAC10	DKFZP761B039	Histone deacetylase 10
HDAC2	RPD3, YAF1	Histone deacetylase 2
HDAC5	FLJ90614, KIAA0600, NY-CO-9	Histone deacetylase 5
HGF	DFNB39, F-TCF, HGFB, HPTA, SF	Hepatocyte growth factor (hepapoietin A; scatter factor)
HGFAC	HGFA, HGFAP	HGF activator
HIF1A	bHLHe78, HIF-1alpha, HIF1, MOP1, PASD8	Hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)
HIP1R	FLJ14000, HIP12, HIP3, ILWEQ, KIAA0655	Huntingtin interacting protein 1 related

HIST1H2AC	H2AFL	Histone cluster 1, H2ac
HK1		Hexokinase 1
HK2		Hexokinase 2
HLA-G		Major histocompatibility complex, class I, G
HMGA1	HMGIY	High mobility group AT-hook 1
HMGA2	BABL, HMGIC, LIPO	High mobility group AT-hook 2
HMOX1	bK286B10, HO-1	Heme oxygenase (decycling) 1
HOXA5	HOX1, HOX1C	Homeobox A5
HOXA9	HOX1, HOX1G	Homeobox A9
HP		Haptoglobin
HPGD	SDR36C1	Hydroxyprostaglandin dehydrogenase 15-(NAD)
HPN	TMPRSS1	Hepsin
HRAS	HRAS1	Harvey rat sarcoma viral oncogene homolog
HSF1	HSTF1	Heat shock transcription factor 1
HSP90AA1	FLJ31884, Hsp89, Hsp90, HSP90N, HSPC1, HSPCA	Heat shock protein 90kDa alpha (cytosolic), class A member 1
HSP90AB1	HSPC2, HSPCB	Heat shock protein 90kDa alpha (cytosolic), class B member 1
HSP90B1	GP96, GRP94, TRA1	Heat shock protein 90kDa beta (Grp94), member 1
HSPA1A	HSP70-1, HSPA1	Heat shock 70kDa protein 1A
HSPA1B	HSP70-2	Heat shock 70kDa protein 1B
HSPA1L	HSP70-HOM, hum70t	Heat shock 70kDa protein 1-like
HSPA2		Heat shock 70kDa protein 2
HSPA4	HS24/P52, HSPH2	Heat shock 70kDa protein 4
HSPA8	HSC70, HSC71, HSP73, HSPA10	Heat shock 70kDa protein 8
HSPB1	Hs.76067, Hsp25, HSP27, HSP28	Heat shock 27kDa protein 1
HSPD1	GROEL, HSP60, SPG13	Heat shock 60kDa protein 1 (chaperonin)
HSPE1	CPN10, GROES	Heat shock 10kDa protein 1
HSPH1	HSP105A, HSP105B, KIAA0201, NY-CO-25	Heat shock 105kDa/110kDa protein 1
IBSP	BSP, BSP-II, SP-II	Integrin-binding sialoprotein
ICAM1	BB2, CD54	Intercellular adhesion molecule 1
ID1	bHLHb24, dJ857M17.1.2	Inhibitor of DNA binding 1, dominant negative helix-loop-helix protein
ID2	bHLHb26, GIG8	Inhibitor of DNA binding 2, dominant negative helix-loop-helix protein
ID3	bHLHb25, HEIR-1	Inhibitor of DNA binding 3, dominant negative helix-loop-helix protein
IDO1	IDO, INDO	Indoleamine 2,3-dioxygenase 1
IFNA1	IFL, IFN, IFN-ALPHA, IFN-alphaD, IFNA13, IFNA@	Interferon, alpha 1

IFNA13		Interferon, alpha 13
IFNAR1	IFNAR, IFRC	Interferon (alpha, beta and omega) receptor 1
IFNAR2	IFNABR	Interferon (alpha, beta and omega) receptor 2
IFNB1	IFB, IFF, IFNB	Interferon, beta 1, fibroblast
IFNG		Interferon, gamma
IGF1	IGF-I, IGF1A, IGFI	Insulin-like growth factor 1 (somatomedin C)
IGF1R	CD221, IGFIR, IGFR, JTK13, MGC18216	Insulin-like growth factor 1 receptor
IGF2	C11orf43, FLJ44734, IGF-II	Insulin-like growth factor 2
IGF2R	CD222, CIMPR, M6P-R, MPR1, MPRI	Insulin-like growth factor 2 receptor
IGFBP2	IBP2	Insulin-like growth factor binding protein 2, 36kDa
IGFBP3	BP-53, IBP3	Insulin-like growth factor binding protein 3
IL10	CSIF, IL-10, IL10A, TGIF	Interleukin 10
IL11	AGIF, IL-11	Interleukin 11
IL12A	CLMF, IL-12A, NFSK, NKSF1, p35	Interleukin 12A
IL13	ALRH, BHR1, IL-13, MGC116786, MGC116788, MGC116789, P600	Interleukin 13
IL13RA2	CD213a2, CT19, IL-13R, IL13BP	Interleukin 13 receptor, alpha 2
IL15	IL-15, MGC9721	Interleukin 15
IL16	FLJ16806, FLJ42735, HsT19289, IL-16, LCF, prIL-16	Interleukin 16
IL17A	CTLA8, IL-17, IL-17A, IL17	Interleukin 17A
IL17B	IL-17B, IL-20, MGC138900, MGC138901, NIRF, ZCYTO7	Interleukin 17B
IL18	IGIF, IL-18, IL-1g, IL1F4	Interleukin 18
IL1A	IL-1A, IL1, IL1-ALPHA, IL1F1	Interleukin 1, alpha
IL1B	IL-1B, IL1-BETA, IL1F2	Interleukin 1, beta
IL1R1	CD121A, D2S1473, IL1R, IL1RA	Interleukin 1 receptor, type I
IL1R2	CD121b, IL1RB	Interleukin 1 receptor, type II
IL1RN	ICIL-1RA, IL-1RN, IL1F3, IL1RA, IRAP, MGC10430	Interleukin 1 receptor antagonist
IL2	IL-2, TCGF	Interleukin 2
IL24	C49A, FISP, IL-24, IL10B, mda-7, Mob-5, ST16	Interleukin 24
IL2RA	CD25, IDDM10, IL2R	Interleukin 2 receptor, alpha
IL2RB	CD122, IL15RB	Interleukin 2 receptor, beta
IL2RG	CD132, CIDX, IMD4, SCIDX1	Interleukin 2 receptor, gamma
IL4	BCGF-1, BCGF1, BSF1, IL-4,	Interleukin 4

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IL4R	CD124	Interleukin 4 receptor
IL5	EDF, IL-5, TRF	Interleukin 5
IL6	BSF2, HGF, HSF, IFNB2, IL-6	Interleukin 6
IL6R	CD126	Interleukin 6 receptor
IL6ST	CD130, GP130	Interleukin 6 signal transducer
IL7	IL-7	Interleukin 7
IL9	HP40, IL-9, P40	Interleukin 9
ILF3	DRBP76, MPHOSPH4, MPP4, NF90, NFAR-1	Interleukin enhancer binding factor 3, 90kDa
ILK		Integrin-linked kinase
INHBA		Inhibin, beta A
INHBB		Inhibin, beta B
INS	IDDM1, IDDM2	Insulin
IRF1	MAR	Interferon regulatory factor 1
IRF4	LSIRF, MUM1	Interferon regulatory factor 4
ITGA1	CD49a, VLA1	Integrin, alpha 1
ITGA2	CD49B	Integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)
ITGA2B	CD41, CD41B, GP2B, PPP1R93	Integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41)
ITGA3	CD49c, GAP-B3, MSK18, VCA-2, VLA3a	Integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)
ITGA4	CD49D	Integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)
ITGA5	CD49e, FNRA	Integrin, alpha 5 (fibronectin receptor, alpha polypeptide)
ITGA6	CD49f	Integrin, alpha 6
ITGAM	CD11B, CR3A, MAC-1	Integrin, alpha M (complement component 3 receptor 3 subunit)
ITGAV	CD51, MSK8, VNRA, VTNR	Integrin, alpha V
ITGB1	CD29, FNRB, GPIIA, MDF2, MSK12	Integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)
ITGB3	CD61, GP3A, GPIIIa	Integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)
ITGB4	CD104	Integrin, beta 4
ITGB5		Integrin, beta 5
ITGB6		Integrin, beta 6
ITGB8		Integrin, beta 8
ITIH4	H4P, IHRP, ITIHL1	Inter-alpha-trypsin inhibitor heavy chain family, member 4
JKAMP	C14orf100, CDA06, HSPC213, HSPC327, JAMP	JNK1/MAPK8-associated membrane protein
JTB	hJT	Jumping translocation breakpoint
JUN	AP-1, c-Jun	Jun proto-oncogene
JUND	AP-1	Jun D proto-oncogene

JUP	CTNNG, DP3, DPIII, PDGB, PKGB	Junction plakoglobin
KAT2B	GCN5, GCN5L, P/CAF, PCAF	K(lysine) acetyltransferase 2B
KDR	CD309, FLK1, VEGFR, VEGFR2	Kinase insert domain receptor (a type III receptor tyrosine kinase)
KIF2A	HK2, KIF2	Kinesin heavy chain member 2A
KIF2C	CT139, KNSL6, MCAK	Kinesin family member 2C
KISS1		KiSS-1 metastasis-suppressor
KIT	C-Kit, CD117, PBT, SCFR	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
KITLG	FPH2, Kitl, KL-1, MGF, SCF, SF	KIT ligand
KLF4	EZF, GKLF	Kruppel-like factor 4 (gut)
KLF5	BTEB2, CKLF, IKLF	Kruppel-like factor 5 (intestinal)
KLK10	NES1, PRSSL1	Kallikrein-related peptidase 10
KLK11	PRSS20, TLSP	Kallikrein-related peptidase 11
KLK13	KLK-L4	Kallikrein-related peptidase 13
KLK14	KLK-L6	Kallikrein-related peptidase 14
KLK15	ACO, HSRNASPH, prostinogen	Kallikrein-related peptidase 15
KLK2		Kallikrein-related peptidase 2
KLK3	APS, PSA	Kallikrein-related peptidase 3
KLK4	EMSP, EMSP1, KLK-L1, PRSS17, PSTS	Kallikrein-related peptidase 4
KLK5	KLK-L2, SCTE	Kallikrein-related peptidase 5
KLK6	Bssp, Klk7, neurosin, PRSS18, PRSS9	Kallikrein-related peptidase 6
KLK7	PRSS6, SCCE	Kallikrein-related peptidase 7
KLK8	HNP, neuropsin, ovasin, PRSS19, TADG14	Kallikrein-related peptidase 8
KLRK1	CD314, D12S2489E, KLR, NKG2-D, NKG2D	Killer cell lectin-like receptor subfamily K, member 1
KRAS	KRAS1, KRAS2	Kirsten rat sarcoma viral oncogene homolog
KRT13	CK13, K13, MGC161462, MGC3781	Keratin 13
KRT14	EBS3, EBS4	Keratin 14
KRT15	CK15, K15, K1CO	Keratin 15
KRT17	PCHC1	Keratin 17
KRT18		Keratin 18
KRT19	CK19, K19, K1CS, MGC15366	Keratin 19
KRT4	CK4, CYK4, K4	Keratin 4
KRT8	CARD2, CK8, CYK8, K2C8, K8, KO	Keratin 8
LALBA	LYZL7	Lactalbumin, alpha-
LAMB1	CLM	Laminin, beta 1
LAMC1	LAMB2	Laminin, gamma 1 (formerly LAMB2)
LCN1	MGC71975, PMFA, TLC, TP,	Lipocalin 1

	VEGP	
LDHA		Lactate dehydrogenase A
LEP	OB, OBS	Leptin
LGALS3	GALIG, LGALS2, MAC-2	Lectin, galactoside-binding, soluble, 3
LGALS3BP	90K, BTBD17B, CyCAP, gp90, M2BP, MAC-2-BP, TANGO10B	Lectin, galactoside-binding, soluble, 3 binding protein
LGALS4	GAL4	Lectin, galactoside-binding, soluble, 4
LGI1	EPITEMPIN, EPT, ETL1, IB1099	Leucine-rich, glioma inactivated 1
LGMN	LGMN1, PRSC1	Legumain
LHB	CGB4, hLHB, LSH-B	Luteinizing hormone beta polypeptide
LHX1	LIM-1, LIM1	LIM homeobox 1
LIF	CDF, DIA, HILDA	Leukemia inhibitory factor
LIG4		Ligase IV, DNA, ATP-dependent
LIMK1	LIMK	LIM domain kinase 1
LMNA	CMD1A, HGPS, LGMD1B, LMN1, LMNL1, PRO1	Lamin A/C
LRP1B	LRP-DIT, LRPDIT	Low density lipoprotein receptor-related protein 1B
LRP6	ADCAD2	Low density lipoprotein receptor-related protein 6
LTA	LT, TNFB, TNFSF1	Lymphotoxin alpha
LTA4H		Leukotriene A4 hydrolase
LTB	p33, TNFC, TNFSF3	Lymphotoxin beta (TNF superfamily, member 3)
LTBR	D12S370, TNF-R-III, TNFCR, TNFR-RP, TNFR2-RP, TNFRSF3	Lymphotoxin beta receptor (TNFR superfamily, member 3)
LTF	HLF2	Lactotransferrin
MAD2L1	HSMAD2, MAD2	MAD2 mitotic arrest deficient-like 1 (yeast)
MAD2L2	MAD2B, POLZ2, REV7	MAD2 mitotic arrest deficient-like 2 (yeast)
MAGEA3	CT1.3, HIP8, HYPD, MAGE3, MGC14613	Melanoma antigen family A, 3
MAGEA4	CT1.4, MAGE-41, MAGE-X2, MAGE4, MAGE4A, MAGE4B, MGC21336	Melanoma antigen family A, 4
MAGEA6	CT1.6, MAGE6	Melanoma antigen family A, 6
MAGEB5	CT3.3, MAGE-B5	Melanoma antigen family B, 5
MAGEB6	CT3.4, FLJ40242, MAGE-B6, MAGEB6A	Melanoma antigen family B, 6
MAGEC1	CT7, CT7.1, MAGE-C1, MGC39366	Melanoma antigen family C, 1
MAGEC2	CT10, MAGE-C2, MAGEE1	Melanoma antigen family C, 2
MAGEC3	CT7.2, HCA2, MAGE-C3	Melanoma antigen family C, 3

MAGED1	DLXIN-1, NRAGE	Melanoma antigen family D, 1
MAGED2	11B6, BCG1, HCA10, JCL-1, MAGE-D2, MAGED, MGC8386	Melanoma antigen family D, 2
MAGI1	AIP3, BAIAP1, BAP1, MAGI-1, TNRC19, WWP3	Membrane associated guanylate kinase, WW and PDZ domain containing 1
MAP2K1	MAPKK1, MEK1, PRKMK1	Mitogen-activated protein kinase kinase 1
MAP2K2	MEK2, PRKMK2	Mitogen-activated protein kinase kinase 2
MAP2K4	JNKK1, MEK4, MKK4, PRKMK4, SERK1	Mitogen-activated protein kinase kinase 4
MAPK1	ERK, ERK2, MAPK2, p41mapk, PRKM1, PRKM2	Mitogen-activated protein kinase 1
MAPK14	CSBP1, CSBP2, CSPB1, Mxi2, p38, PRKM14, PRKM15	Mitogen-activated protein kinase 14
MAPK3	ERK1, p44erk1, p44mapk, PRKM3	Mitogen-activated protein kinase 3
MAPK7	BMK1, ERK5, PRKM7	Mitogen-activated protein kinase 7
MAPK8	JNK, JNK1, PRKM8, SAPK1	Mitogen-activated protein kinase 8
MAPKAPK2		Mitogen-activated protein kinase-activated protein kinase 2
MBD1	CXXC3, PCM1	Methyl-CpG binding domain protein 1
MBD2		Methyl-CpG binding domain protein 2
MBD4	MED1	Methyl-CpG binding domain protein 4
MCL1	BCL2L3, Mcl-1	Myeloid cell leukemia 1
MCM2	BM28, CCNL1, cdc19, CDCL1, D3S3194, KIAA0030	Minichromosome maintenance complex component 2
MCM3		Minichromosome maintenance complex component 3
MCM5	CDC46	Minichromosome maintenance complex component 5
MCM7	CDC47, MCM2, PPP1R104	Minichromosome maintenance complex component 7
MDH1		Malate dehydrogenase 1, NAD (soluble)
MDK	FLJ27379, MK, NEGF2	Midkine (neurite growth-promoting factor 2)
MDM2	HDM2, MGC5370	MDM2 proto-oncogene, E3 ubiquitin protein ligase
MECP2	MRX16, MRX79, RTT	Methyl CpG binding protein 2
MED1	CRSP1, CRSP200, DRIP230, PBP, PPARBP, PPARGBP, RB18A, TRAP220, TRIP2	Mediator complex subunit 1
MET	HGFR, RCCP2	MET proto-oncogene, receptor tyrosine kinase
MFGE8	BA46, EDIL1, hP47, HsT19888, MFG-E8, OAcGD3S, SED1, SPAG10	Milk fat globule-EGF factor 8 protein
MGMT		O-6-methylguanine-DNA methyltransferase

MIA	CD-RAP	Melanoma inhibitory activity
MIF	GIF, GLIF	Macrophage migration inhibitory factor (glycosylation-inhibiting factor)
MKI67	MIB-, PPP1R105	Marker of proliferation Ki-67
MLH1	COCA2, FCC2, HNPCC, HNPCC2	MutL homolog 1
MLLT11	AF1Q	Myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11
MME	CALLA, CD10, NEP	Membrane metallo-endopeptidase
MMP1	CLG	Matrix metallopeptidase 1 (interstitial collagenase)
MMP10	STMY2	Matrix metallopeptidase 10 (stromelysin 2)
MMP11	STMY3	Matrix metallopeptidase 11 (stromelysin 3)
MMP12	HME	Matrix metallopeptidase 12 (macrophage elastase)
MMP13	CLG3	Matrix metallopeptidase 13 (collagenase 3)
MMP14	MT1-MMP	Matrix metallopeptidase 14 (membrane-inserted)
MMP15	MT2-MMP, MTMMP2, SMCP-2	Matrix metallopeptidase 15 (membrane-inserted)
MMP16	C8orf57, DKFZp761D112, MT3-MMP	Matrix metallopeptidase 16 (membrane-inserted)
MMP2	CLG4, CLG4A, TBE-1	Matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)
MMP3	STMY, STMY1	Matrix metallopeptidase 3 (stromelysin 1, progelatinase)
MMP7	MPSL1, PUMP-1	Matrix metallopeptidase 7 (matrilysin, uterine)
MMP8	CLG1	Matrix metallopeptidase 8 (neutrophil collagenase)
MMP9	CLG4B	Matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)
MPO		Myeloperoxidase
MRE11A	ATLD, MRE11	MRE11 meiotic recombination 11 homolog A (S. cerevisiae)
MSH6	GTBP	MutS homolog 6
MSLN	CAK1, MPF	Mesothelin
MSMB	IGBF, MSP, MSPB, PN44, PRPS, PSP, PSP-94, PSP57, PSP94	Microseminoprotein, beta-
MSR1	CD204, SCARA1	Macrophage scavenger receptor 1
MT1A	MT1, MT1S	Metallothionein 1A
MT1G	MT1, MT1K	Metallothionein 1G
MTA1		Metastasis associated 1

MUC1	ADMCKD, ADMCKD1, CD227, MCD, MCKD, MCKD1, PEM, PUM	Mucin 1, cell surface associated
MUTYH	MYH	MutY homolog
MVP	LRP, VAULT1	Major vault protein
MXI1	bHLHc11, MAD2, MXD2, MXI	MAX interactor 1, dimerization protein
MYBL2	B-MYB, BMYB	V-myb avian myeloblastosis viral oncogene homolog-like 2
MYC	bHLHe39, c-Myc, MYCC	V-myc avian myelocytomatosis viral oncogene homolog
MYOCD	MYCD	Myocardin
MYOD1	bHLHc1, MYF3, MYOD, PUM	Myogenic differentiation 1
MYOG	bHLHc3, MYF4	Myogenin (myogenic factor 4)
NAGA	D22S674	N-acetylgalactosaminidase, alpha-
NAIP	BIRC1, NLRB1	NLR family, apoptosis inhibitory protein
NAMPT	PBEF, PBEF1	Nicotinamide phosphoribosyltransferase
NAT2	AAC2	N-acetyltransferase 2 (arylamine N-acetyltransferase)
NCAM1	CD56, NCAM	Neural cell adhesion molecule 1
NCOA3	ACTR, AIB1, bHLHe42, CAGH16, KAT13B, p/CIP, RAC3, SRC-3, SRC3, TNRC16, TRAM-1	Nuclear receptor coactivator 3
NDRG1	CAP43, DRG1, NDR1, RTP, TDD5	N-myc downstream regulated 1
NEDD8	Nedd-8	Neural precursor cell expressed, developmentally down-regulated 8
NEO1	HsT17534, IGDCC2, NGN, NTN1R2	Neogenin 1
NFKB1	KBF1, NF-kappaB, NF-kB1, NFkappaB, NFKB-p50, p105, p50	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1
NFKB2	LYT-10, NF-kB2, p105, p52	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)
NFKBIA	IkappaBalpha, IKBA, MAD-3, NFKBI	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
NFKBIE	IKBE	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon
NGF	NGFB	Nerve growth factor (beta polypeptide)
NGFR	CD271, p75NTR, TNFRSF16	Nerve growth factor receptor
NKX3-1	BAPX2, NKX3.1, NKX3A	NK3 homeobox 1
NME1	NDPKA, NM23, NM23-H1	NME/NM23 nucleoside diphosphate kinase 1
NME2	NDPKB, NM23-H2	NME/NM23 nucleoside diphosphate kinase 2
NOS1	nNOS, NOS	Nitric oxide synthase 1 (neuronal)
NOS2	HEP-NOS, iNOS, NOS, NOS2A	Nitric oxide synthase 2, inducible

NOS3	ECNOS, eNOS	Nitric oxide synthase 3 (endothelial cell)
NOTCH1	TAN1	Notch 1
NOTCH2		Notch 2
NOTCH3	CADASIL, CASIL	Notch 3
NQO1	DHQU, DIA4, DTD, NMOR1, QR1	NAD(P)H dehydrogenase, quinone 1
NR0B1	AHC, AHCH, DAX1, DSS, NR0B1	Nuclear receptor subfamily 0, group B, member 1
NRG1	GGF, HGL, HRG, NDF, NRG1-IT2	Neuregulin 1
NRG2	Don-1, HRG2, NTAK	Neuregulin 2
NRG3		Neuregulin 3
NRP1	CD304, NRP, VEGF165R	Neuropilin 1
NRP2	VEGF165R2	Neuropilin 2
NTF3	NGF2	Neurotrophin 3
NTF4	GLC1O, NT-4/5, NTF5	Neurotrophin 4
NTHL1	NTH1, OCTS3	Nth endonuclease III-like 1 (E. coli)
NTN1	NTN1L	Netrin 1
NTRK1	MTC, TRK, TRKA	Neurotrophic tyrosine kinase, receptor, type 1
NTRK2	TRKB	Neurotrophic tyrosine kinase, receptor, type 2
NTRK3	TRKC	Neurotrophic tyrosine kinase, receptor, type 3
NUDT1	MTH1	Nudix (nucleoside diphosphate linked moiety X)-type motif 1
NUMB	C14orf41	Numb homolog (Drosophila)
OGG1	HMMH, HOGG1, MUTM, OGH1	8-oxoguanine DNA glycosylase
OR51E2	PSGR	Olfactory receptor, family 51, subfamily E, member 2
ORM1		Orosomucoid 1
OSM	MGC20461	Oncostatin M
PAGE4	CT16.7, GAGEC1, PAGE-4	P antigen family, member 4 (prostate associated)
PAPPA	ASBABP2, DIPLA1, IGFBP-4ase, PAPA, PAPP-A, PAPPA1	Pregnancy-associated plasma protein A, pappalysin 1
PARP1	ADPRT, PARP, PPOL	Poly (ADP-ribose) polymerase 1
PARVB	CGI-56	Parvin, beta
PAX5	BSAP	Paired box 5
PAX8		Paired box 8
PCNA		Proliferating cell nuclear antigen
PDGFA	PDGF-A, PDGF1	Platelet-derived growth factor alpha polypeptide
PDGFB	SIS, SSV	Platelet-derived growth factor beta polypeptide
PDGFRA	CD140a, PDGFR2	Platelet-derived growth factor receptor,

		alpha polypeptide
PDGFRB	CD140b, JTK12, PDGFR, PDGFR1	Platelet-derived growth factor receptor, beta polypeptide
PDZD4	FLJ34125, KIAA1444, LU1, PDZK4, PDZRN4L	PDZ domain containing 4
PF4	CXCL4, SCYB4	Platelet factor 4
PGC		Progastricsin (pepsinogen C)
PGF	D12S1900, PGFL, PLGF, PlGF-2, SHGC-10760	Placental growth factor
PGR	NR3C3, PR	Progesterone receptor
PHF20	C20orf104, dJ1121G12.1, TDRD20A	PHD finger protein 20
PIGR		Polymeric immunoglobulin receptor
PIK3CA	PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PIK3R1	GRB1, p85, p85-ALPHA	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha)
PIK3R2	p85, P85B	Phosphoinositide-3-kinase, regulatory subunit 2 (beta)
PIK3R3	p55	Phosphoinositide-3-kinase, regulatory subunit 3 (gamma)
PIM1	PIM	Pim-1 proto-oncogene, serine/threonine kinase
PIM2		Pim-2 proto-oncogene, serine/threonine kinase
PIM3		Pim-3 proto-oncogene, serine/threonine kinase
PIN1	dod	Peptidylprolyl cis/trans isomerase, NIMA-interacting 1
PIP4K2B	PIP5K2B, PIP5KIIB, PIP5KIIbeta	Phosphatidylinositol-5-phosphate 4-kinase, type II, beta
PKM	OIP3, PK3, PKM2, THBP1	Pyruvate kinase, muscle
PLAT		Plasminogen activator, tissue
PLAU	UPA, URK	Plasminogen activator, urokinase
PLAUR	CD87, UPAR, URKR	Plasminogen activator, urokinase receptor
PLG		Plasminogen
PLK1	PLK	Polo-like kinase 1
PLP1	GPM6C, PLP, SPG2	Proteolipid protein 1
PMEPA1	STAG1, TMEPAI	Prostate transmembrane protein, androgen induced 1
PML	MYL, RNF71, TRIM19	Promyelocytic leukemia
PMP22	GAS-3, HNPP, Sp110	Peripheral myelin protein 22
PNMT	PENT	Phenylethanolamine N-methyltransferase
POMC	ACTH, CLIP, LPH, MSH, NPP, POC	Proopiomelanocortin
PON1	ESA, PON	Paraoxonase 1
POSTN	OSF-2, periostin, PN	Periostin, osteoblast specific factor

POU2F2	OCT2, OTF2	POU class 2 homeobox 2
PPA2	FLJ20459	Pyrophosphatase (inorganic) 2
PPARG	NR1C3, PPARG1, PPARG2, PPARgamma	Peroxisome proliferator-activated receptor gamma
PPARGC1A	PGC1, PGC1A, PPARGC1	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha
PPM1D	PP2C-DELTA, Wip1	Protein phosphatase, Mg2+/Mn2+ dependent, 1D
PPP1R15A	GADD34	Protein phosphatase 1, regulatory subunit 15A
PPY	PNP	Pancreatic polypeptide
PRDM13		PR domain containing 13
PRDM16	KIAA1675, MEL1, MGC166915, PFM13	PR domain containing 16
PRDX2	MGC4104, NKEFB, PRP, PRX2, PRXII, TDPX1, TSA	Peroxiredoxin 2
PRDX4	AOE37-2	Peroxiredoxin 4
PRKCA	PKCA	Protein kinase C, alpha
PRKCB	PKCB, PRKCB1, PRKCB2	Protein kinase C, beta
PRKCE		Protein kinase C, epsilon
PRKCH	PKC-L, PKCL, PRKCL	Protein kinase C, eta
PRKCI	DXS1179E, PKCI	Protein kinase C, iota
PRKCQ		Protein kinase C, theta
PRKDC	DNA-PKcs, DNAPK, DNPK1, HYRC, HYRC1, p350, XRCC7	Protein kinase, DNA-activated, catalytic polypeptide
PRL		Prolactin
PROC		Protein C (inactivator of coagulation factors Va and VIIIa)
PRSS1	TRY1	Protease, serine, 1 (trypsin 1)
PSCA		Prostate stem cell antigen
PSMD4	AF, AF-1, Rpn10, S5A	Proteasome (prosome, macropain) 26S subunit, non-ATPase, 4
PTCH1	BCNS, NBCCS, PTCH	Patched 1
PTCH2		Patched 2
PTGS1	COX1, PGHS-1, PTGHS	Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)
PTGS2	COX2	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)
PTH	PTH1	Parathyroid hormone
PTHLH	HHM, PLP, PTHR, PTHRP	Parathyroid hormone-like hormone
PTK2	FADK, FAK, FAK1, PPP1R71	Protein tyrosine kinase 2
PTN	HBGF8, HBNF, NEGF1	Pleiotrophin
PTPRO	GLEPP1, NPHS6, PTP-oc, PTP-U2, PTPU2	Protein tyrosine phosphatase, receptor type, O
PTTG1	EAP1, HPTTG, PTTG, securin,	Pituitary tumor-transforming 1

	TUTR1	
PURA	PUR-ALPHA, PUR1, PURALPHA	Purine-rich element binding protein A
PZP	CPAMD6	Pregnancy-zone protein
RAB11FIP3	eferin, KIAA0665, Rab11-FIP3	RAB11 family interacting protein 3 (class II)
RAB18		RAB18, member RAS oncogene family
RAB25	CATX-8	RAB25, member RAS oncogene family
RAC1	p21-Rac1, Rac-1, TC-25	Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)
RAD23A	HHR23A, MGC111083	RAD23 homolog A (S. cerevisiae)
RAD23B	HHR23B, HR23B, P58	RAD23 homolog B (S. cerevisiae)
RAD51	BRCC5, HsRad51, HsT16930, RAD51A, RECA	RAD51 recombinase
RAD51D	HsTRAD, R51H3, RAD51L3, Trad	RAD51 paralog D
RAD52		RAD52 homolog (S. cerevisiae)
RAD54B	RDH54	RAD54 homolog B (S. cerevisiae)
RAF1	c-Raf, CRAF, Raf-1	Raf-1 proto-oncogene, serine/threonine kinase
RARA	NR1B1, RAR	Retinoic acid receptor, alpha
RARB	HAP, NR1B2, RRB2	Retinoic acid receptor, beta
RARG	NR1B3, RARC	Retinoic acid receptor, gamma
RASA1	CM-AVM, GAP, p120GAP, p120RASGAP, RASA	RAS p21 protein activator (GTPase activating protein) 1
RB1	OSRC, PPP1R130, RB	Retinoblastoma 1
RBBP4	lin-53, NURF55, RbAp48	Retinoblastoma binding protein 4
RBL1	cp107, p107, PRB1	Retinoblastoma-like 1
RBL2	p130, Rb2	Retinoblastoma-like 2
RBM6	3G2, DEF-3, DEF3, g16, NY-LU-12	RNA binding motif protein 6
RBP4		Retinol binding protein 4, plasma
REL	c-Rel, I-Rel	V-rel avian reticuloendotheliosis viral oncogene homolog
RELA	NFKB3, p65	V-rel avian reticuloendotheliosis viral oncogene homolog A
RELB	REL-B	V-rel avian reticuloendotheliosis viral oncogene homolog B
RET	CDHF12, CDHR16, HSCR1, MEN2A, MEN2B, MTC1, PTC, RET51	Ret proto-oncogene
RHOA	ARH12, ARHA, Rho12, RhoA, RHOH12	Ras homolog family member A
RHOB	ARH6, ARHB, MST081, RhoB, RHOH6	Ras homolog family member B
RHOC	ARH9, ARHC, RhoC	Ras homolog family member C

RPA2		Replication protein A2, 32kDa
RPL27	L27	Ribosomal protein L27
RPS3	FLJ26283, FLJ27450, MGC87870, S3	Ribosomal protein S3
RPS6KA1	HU-1, RSK, RSK1	Ribosomal protein S6 kinase, 90kDa, polypeptide 1
RPS6KA3	CLS, HU-3, MRX19, RSK, RSK2	Ribosomal protein S6 kinase, 90kDa, polypeptide 3
RXRA	NR2B1	Retinoid X receptor, alpha
RXRB	H-2RIIBP, NR2B2, RCoR-1	Retinoid X receptor, beta
RXRG	NR2B3	Retinoid X receptor, gamma
S100A1	S100-alpha, S100A	S100 calcium binding protein A1
S100A2	CAN19, S100L	S100 calcium binding protein A2
S100A4	18A2, 42A, CAPL, FSP1, MTS1, P9KA, PEL98	S100 calcium binding protein A4
S100A6	2A9, CABP, CACY, PRA	S100 calcium binding protein A6
S100A7	PSOR1, S100A7c	S100 calcium binding protein A7
S100A8	60B8AG, CAGA, CFAG, CGLA, MRP8, P8	S100 calcium binding protein A8
S100A9	60B8AG, CAGB, CFAG, CGLB, LIAG, MAC387, MIF, MRP14, NIF, P14	S100 calcium binding protein A9
S100B	S100beta	S100 calcium binding protein B
S1PR1	CD363, D1S3362, edg-1, EDG1	Sphingosine-1-phosphate receptor 1
SAA1	PIG4, SAA, TP53I4	Serum amyloid A1
SAA2		Serum amyloid A2
SART1	Ara1, SNRNP110, Snu66	Squamous cell carcinoma antigen recognized by T cells
SCGB1A1	CC10, CC16, CCSP, UGB	Secretoglobin, family 1A, member 1 (uteroglobin)
SCGB1D2	LIPB, LPHB	Secretoglobin, family 1D, member 2
SCGB2A1	LPHC, MGB2, MGC71973, UGB3	Secretoglobin, family 2A, member 1
SCGB2A2	MGB1, MGC71974, UGB2	Secretoglobin, family 2A, member 2
SDC1	CD138, SDC, SYND1, syndecan	Syndecan 1
SELE	CD62E, ELAM, ELAM1, ESEL	Selectin E
SELL	CD62L, hLHRc, LAM-1, LAM1, Leu-8, LNHR, LSEL, Lyam-1, LYAM1, PLNHR	Selectin L
SELP	CD62, CD62P, GMP140, GRMP, PADGEM, PSEL	Selectin P (granule membrane protein 140kDa, antigen CD62)
SEMA3B	LUCA-1, SemA, sema5, SEMAA, semaV	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3B
2-Sep	DIFF6, hNedd5, KIAA0158, NEDD5, Pnutl3	Septin 2
SERPINA1	A1A, A1AT, AAT, alpha-1-	Serpin peptidase inhibitor, clade A (alpha-1

	antitrypsin, alpha1AT, PI, PI1	antiproteinase, antitrypsin), member 1
SERPINA3	AACT, ACT, alpha-1-antichymotrypsin	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3
SERPINA5	PAI3, PCI, PLANH3, PROCI	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5
SERPINB2	HsT1201, PAI2, PLANH2	Serpin peptidase inhibitor, clade B (ovalbumin), member 2
SERPINB3	HsT1196, SCC, SCCA1, T4-A	Serpin peptidase inhibitor, clade B (ovalbumin), member 3
SERPINB4	LEUPIN, PI11, SCCA-2, SCCA1, SCCA2	Serpin peptidase inhibitor, clade B (ovalbumin), member 4
SERPINE1	PAI, PAI1, PLANH1	Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1
SERPINF1	EPC-1, PEDF, PIG35	Serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member 1
SFN	YWHAS	Stratifin
SHBG	ABP, MGC126834, MGC138391, TEBG	Sex hormone-binding globulin
SIRT2	SIR2L	Sirtuin 2
SKP2	FBL1, FBXL1, p45	S-phase kinase-associated protein 2, E3 ubiquitin protein ligase
SLC19A1	FOLT	Solute carrier family 19 (folate transporter), member 1
SLC2A1	DYT18, GLUT, GLUT1, HTLVR	Solute carrier family 2 (facilitated glucose transporter), member 1
SLC3A2	4F2, 4F2HC, 4T2HC, CD98, CD98HC, MDU1, NACAE	Solute carrier family 3 (amino acid transporter heavy chain), member 2
SLPI	ALK1, ALP, BLPI, HUSI, HUSI-I, WAP4, WFDC4	Secretory leukocyte peptidase inhibitor
SMAD1	JV4-1, MADH1, MADR1	SMAD family member 1
SMAD2	JV18-1, MADH2, MADR2	SMAD family member 2
SMAD3	HsT17436, JV15-2, MADH3	SMAD family member 3
SMAD4	DPC4, MADH4	SMAD family member 4
SMYD3	KMT3E, ZMYND1, ZNFN3A1	SET and MYND domain containing 3
SOD1	ALS, ALS1, IPOA	Superoxide dismutase 1, soluble
SOD2		Superoxide dismutase 2, mitochondrial
SOX1		SRY (sex determining region Y)-box 1
SOX9	CMD1, CMPD1, SRA1	SRY (sex determining region Y)-box 9
SP1		Sp1 transcription factor
SPARC	ON	Secreted protein, acidic, cysteine-rich (osteonectin)
SPARCL1	MAST9	SPARC-like 1 (hevin)
SPINK1	PCTT, PSTI, Spink3, TATI	Serine peptidase inhibitor, Kazal type 1
SPINT1	HAI, MANSC2	Serine peptidase inhibitor, Kunitz type 1
SPINT2	HAI-2, Kop	Serine peptidase inhibitor, Kunitz type, 2

SPP1	BNSP, BSPI, ETA-1, OPN	Secreted phosphoprotein 1
SPRR1B	GADD33, SPRR1	Small proline-rich protein 1B
SPRR3		Small proline-rich protein 3
SPRY1	hSPRY1	Sprouty homolog 1, antagonist of FGF signaling (Drosophila)
SRC	ASV, c-src, SRC1	SRC proto-oncogene, non-receptor tyrosine kinase
SRD5A1		Steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)
SRD5A2		Steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2)
SST	SMST	Somatostatin
SSX2	CT5.2a, HD21, HOM-MEL-40, MGC119055, MGC15364, MGC3884, SSX	Synovial sarcoma, X breakpoint 2
SSX2B	CT5.2b	Synovial sarcoma, X breakpoint 2B
ST14	HAI, MT-SP1, PRSS14, SNC19, TMPRSS14	Suppression of tumorigenicity 14 (colon carcinoma)
STARD3	es64, MLN64	StAR-related lipid transfer (START) domain containing 3
STAT4		Signal transducer and activator of transcription 4
STAT5A	MGF, STAT5	Signal transducer and activator of transcription 5A
STEAP1	PRSS24, STEAP	Six transmembrane epithelial antigen of the prostate 1
STMN1	C1orf215, FLJ32206, Lag, LAP18, OP18, PP17, PP19, PR22, SMN	Stathmin 1
STRAP	MAWD, pt-wd, UNRIP	Serine/threonine kinase receptor associated protein
STT3A	ITM1, MGC9042, STT3-A, TMC	STT3A, subunit of the oligosaccharyltransferase complex (catalytic)
SULT1E1	EST, STE	Sulfotransferase family 1E, estrogen-preferring, member 1
TAGLN	DKFZp686P11128, SM22, SMCC, TAGLN1, WS3-10	Transgelin
TDRD6	bA446F17.4, CT41.2, NY-CO-45, SPATA36	Tudor domain containing 6
TEK	CD202b, TIE-2, TIE2, VMCM, VMCM1	TEK tyrosine kinase, endothelial
TERT	EST2, hEST2, TCS1, TP2, TRT	Telomerase reverse transcriptase
TF	PRO1557, PRO2086	Transferrin
TFAP2B	AP2-B	Transcription factor AP-2 beta (activating enhancer binding protein 2 beta)

TFDP1	Dp-1, DP1, DRTF1	Transcription factor Dp-1
TFDP2	Dp-2	Transcription factor Dp-2 (E2F dimerization partner 2)
TFF1	BCEI, D21S21, HP1.A, HPS2, pNR-2, pS2	Trefoil factor 1
TFF2	SML1	Trefoil factor 2
TFF3	HITF, ITF	Trefoil factor 3 (intestinal)
TFRC	CD71, p90, TFR1	Transferrin receptor
TG	AITD3, TGN	Thyroglobulin
TGFA		Transforming growth factor, alpha
TGFB1	CED, DPD1, TGFB, TGFbeta	Transforming growth factor, beta 1
TGFB2		Transforming growth factor, beta 2
TGFB3	ARVD, ARVD1	Transforming growth factor, beta 3
TGFBR3	betaglycan, BGCAN	Transforming growth factor, beta receptor III
TGM4	TGP	Transglutaminase 4
TGM7	TGMZ	Transglutaminase 7
THBS1	THBS, THBS-1, TSP, TSP-1, TSP1	Thrombospondin 1
THBS2	TSP2	Thrombospondin 2
THBS4		Thrombospondin 4
THPO	MGDF, MPLLG, TPO	Thrombopoietin
THRA	AR7, EAR-7.1/EAR-7.2, ERBA, ERBA1, NR1A1, THRA1, THRA2, THRA3	Thyroid hormone receptor, alpha
THRB	ERBA-BETA, ERBA2, GRTH, NR1A2, PRTH, THR1, THRB1, THRB2	Thyroid hormone receptor, beta
TIE1	JTK14, TIE	Tyrosine kinase with immunoglobulin-like and EGF-like domains 1
TIMP1	CLGI, EPO, TIMP	TIMP metallopeptidase inhibitor 1
TIMP2	CSC-21K	TIMP metallopeptidase inhibitor 2
TIMP3	SFD	TIMP metallopeptidase inhibitor 3
TK1		Thymidine kinase 1, soluble
TMF1	ARA160, TMF	TATA element modulatory factor 1
TMPRSS2	PRSS10	Transmembrane protease, serine 2
TMPRSS3	DFNB10, DFNB8	Transmembrane protease, serine 3
TNC	DFNA56, HXB, MGC167029, TN	Tenascin C
TNF	DIF, TNF-alpha, TNFA, TNFSF2	Tumor necrosis factor
TNFAIP2	B94, EXOC3L3	Tumor necrosis factor, alpha-induced protein 2
TNFAIP3	A20, OTUD7C	Tumor necrosis factor, alpha-induced protein 3
TNFRSF10A	Apo2, CD261, DR4, TRAILR-1	Tumor necrosis factor receptor superfamily, member 10a

TNFRSF10B	CD262, DR5, KILLER, TRAIL-R2, TRICK2A, TRICKB	Tumor necrosis factor receptor superfamily, member 10b
TNFRSF10C	CD263, DcR1, LIT, TRAILR3, TRID	Tumor necrosis factor receptor superfamily, member 10c, decoy without an intracellular domain
TNFRSF10D	CD264, DcR2, TRAILR4, TRUNDD	Tumor necrosis factor receptor superfamily, member 10d, decoy with truncated death domain
TNFRSF11B	OCIF, OPG, TR1	Tumor necrosis factor receptor superfamily, member 11b
TNFRSF12A	CD266, FN14, TweakR	Tumor necrosis factor receptor superfamily, member 12A
TNFRSF14	ATAR, CD270, HVEA, HVEM, LIGHTR, TR2	Tumor necrosis factor receptor superfamily, member 14
TNFRSF1A	CD120a, TNF-R, TNF-R-I, TNF-R55, TNFAR, TNFR1, TNFR60	Tumor necrosis factor receptor superfamily, member 1A
TNFRSF1B	CD120b, p75, TNF-R-II, TNF-R75, TNFBR, TNFR2, TNFR80	Tumor necrosis factor receptor superfamily, member 1B
TNFRSF4	ACT35, CD134, OX40, TXGP1L	Tumor necrosis factor receptor superfamily, member 4
TNFRSF8	CD30, D1S166E, KI-1	Tumor necrosis factor receptor superfamily, member 8
TNFRSF9	4-1BB, CD137, ILA	Tumor necrosis factor receptor superfamily, member 9
TNFSF10	Apo-2L, CD253, TL2, TRAIL	Tumor necrosis factor (ligand) superfamily, member 10
TNFSF11	CD254, ODF, OPGL, RANKL, TRANCE	Tumor necrosis factor (ligand) superfamily, member 11
TNFSF13	APRIL, CD256	Tumor necrosis factor (ligand) superfamily, member 13
TNFSF13B	BAFF, BLYS, CD257, TALL-1, TALL1, THANK, TNFSF20	Tumor necrosis factor (ligand) superfamily, member 13b
TNFSF4	CD252, gp34, OX-40L, TXGP1	Tumor necrosis factor (ligand) superfamily, member 4
TNFSF8	CD153, CD30LG	Tumor necrosis factor (ligand) superfamily, member 8
TNK2	ACK, ACK1, p21cdc42Hs	Tyrosine kinase, non-receptor, 2
TOP2A	TOP2	Topoisomerase (DNA) II alpha 170kDa
TP53	LFS1, p53	Tumor protein p53
TP53BP2	53BP2, ASPP2, PPP1R13A	Tumor protein p53 binding protein 2
TPD52	D52, hD52, N8L	Tumor protein D52
TPI1		Triosephosphate isomerase 1
TPM1	C15orf13, CMH3	Tropomyosin 1 (alpha)
TPM2	AMCD1, DA1, NEM4	Tropomyosin 2 (beta)
TPX2	C20orf1, C20orf2, DIL-2, p100	TPX2, microtubule-associated
TRAF1	EBI6	TNF receptor-associated factor 1

TRAF2	TRAP3	TNF receptor-associated factor 2
TRAF4	CART1, MLN62, RNF83	TNF receptor-associated factor 4
TRIM25	EFP, RNF147, ZNF147	Tripartite motif containing 25
TRIP4	HsT17391, ZC2HC5	Thyroid hormone receptor interactor 4
TRO	KIAA1114, MAGE-D3, MAGED3	Trophinin
TSG101	TSG10, VPS23	Tumor susceptibility 101
TSPAN8	CO-029, TM4SF3	Tetraspanin 8
TSPO	BZRP, DBI, IBP, MBR, mDRC, PBR, pk18, PKBS	Translocator protein (18kDa)
TTR	CTS, CTS1, HsT2651, PALB	Transthyretin
TUSC2	C3orf11, FUS1, PAP, PDAP2	Tumor suppressor candidate 2
TWIST1	ACS3, bHLHa38, BPES2, BPES3, CRS, CRS1, H-twist, SCS, TWIST	Twist family bHLH transcription factor 1
TXLNA	DKFZp451J0118	Taxilin alpha
TYMP	ECGF1, MNGIE	Thymidine phosphorylase
TYMS	HsT422, TMS, TS, Tsase	Thymidylate synthetase
TYRO3	Brt, Dtk, RSE, Sky, Tif	TYRO3 protein tyrosine kinase
UBA1	A1S9T, CFAP124, GXP1, POC20, UBE1, UBE1X	Ubiquitin-like modifier activating enzyme 1
UBE2C	UBCH10	Ubiquitin-conjugating enzyme E2C
UBE2I	UBC9	Ubiquitin-conjugating enzyme E2I
UBE2N	MGC8489, UBC13, UbcH-ben	Ubiquitin-conjugating enzyme E2N
UGT1A10	UGT1J	UDP glucuronosyltransferase 1 family, polypeptide A10
UGT1A3	UGT1C	UDP glucuronosyltransferase 1 family, polypeptide A3
UGT1A4	HUG-BR2, UGT1D	UDP glucuronosyltransferase 1 family, polypeptide A4
UGT1A8	UGT1H	UDP glucuronosyltransferase 1 family, polypeptide A8
UGT1A9	HLUGP4, LUGP4, UGT1AI	UDP glucuronosyltransferase 1 family, polypeptide A9
USH1C	AIE-75, DFNB18, harmonin, NY-CO-37, NY-CO-38, PDZ-73, PDZ73, PDZD7C	Usher syndrome 1C (autosomal recessive, severe)
VAMP3	CEB	Vesicle-associated membrane protein 3
VCAM1	CD106	Vascular cell adhesion molecule 1
VEGFA	VEGF, VEGF-A, VPF	Vascular endothelial growth factor A
VEGFB	VEGFL, VRF	Vascular endothelial growth factor B
VEGFC	VRP	Vascular endothelial growth factor C
VHL	VHL1	Von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase
VIL1	D2S1471, VIL	Villin 1
VIP		Vasoactive intestinal peptide
VTN	VN	Vitronectin

VWF	F8VWF	Von Willebrand factor
WEE1		WEE1 G2 checkpoint kinase
WFDC2	dJ461P17.6, EDDM4, HE4, WAP5	WAP four-disulfide core domain 2
WISP1	CCN4	WNT1 inducible signaling pathway protein 1
WNT1	INT1	Wingless-type MMTV integration site family, member 1
WNT2	INT1L1, IRP	Wingless-type MMTV integration site family member 2
WRN	RECQ3, RECQL2	Werner syndrome, RecQ helicase-like
WT1	AWT1, GUD, WAGR, WIT-2	Wilms tumor 1
XBP1	XBP2	X-box binding protein 1
XIAP	API3, BIRC4, hILP	X-linked inhibitor of apoptosis
XPA	XP1, XPAC	Xeroderma pigmentosum, complementation group A
XPC	RAD4, XPCC	Xeroderma pigmentosum, complementation group C
XRCC2		X-ray repair complementing defective repair in Chinese hamster cells 2
XRCC3		X-ray repair complementing defective repair in Chinese hamster cells 3
XRCC4		X-ray repair complementing defective repair in Chinese hamster cells 4
XRCC5	KARP-1, KU80, Ku86, KUB2	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining)
XRCC6	D22S671, D22S731, G22P1, KU70, ML8	X-ray repair complementing defective repair in Chinese hamster cells 6
YBX1	BP-8, CSDA2, CSDB, DBPB, MDR-NF1, NSEP-1, NSEP1, YB-1, YB1	Y box binding protein 1
YWHAB	YWHAA	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta
YWHAE	FLJ45465	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon
YWHAH	YWHA1	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta
ZBTB16	PLZF, ZNF145	Zinc finger and BTB domain containing 16
ZMAT3	FLJ12296, MGC10613, PAG608, WIG-1, WIG1	Zinc finger, matrin-type 3

Table 2

Gene	**Gene synonym**	**Gene description**
HIF1A	HIF-1α	hypoxia-inducible factor 1, alpha subunit
ARNT	HIF-1β	aryl hydrocarbon receptor nuclear translocator

EPAS1	HIF-2α	endothelial PAS domain protein 1
ARNT2	HIF-2β	aryl-hydrocarbon receptor nuclear translocator 2
HIF3A	HIF-3α	hypoxia inducible factor 3, alpha subunit
ARNTL	HIF-3β	aryl-hydrocarbon receptor nuclear translocator 3
CA9	CA IX	Carbonic anhydrase 9
SLC2A1	GLUT-1, GLUT	Solute Carrier Family 2 Member 1

[0147] In one embodiment, the biomarker is a molecular marker for tumor hypoxia. In one embodiment, the molecular marker for tumor hypoxia is a hypoxia-inducible factor (HIF). In one embodiment, the measurable aspect of HIF is its expression status. In one embodiment, the biomarker is overexpression of HIF.

[0148] Thus, in certain aspects of the disclosure, the biomarker is HIF-1α which is differentially present in a subject of one phenotypic status, e.g., a patient having cancer, e.g., colon cancer, breast cancer, pancreatic cancer, kidney cancer, prostate cancer, brain cancer, bladder cancer, cervical cancer, non-small-cell lung carcinoma, oligodendroglioma, oropharyngeal cancer, ovarian cancer, endometrial cancer, esophageal cancer, head and neck cancer, and stomach cancer, as compared with another phenotypic status, e.g., a normal undiseased subject or a patient having cancer without overexpression HIF-1α. In one embodiment, the biomarker is overexpression of HIF-1α.

[0149] Biomarker standards can be predetermined, determined concurrently, or determined after a biological sample is obtained from the subject. Biomarker standards for use with the methods described herein can, for example, include data from samples from subjects without cancer; data from samples from subjects with cancer, e.g., breast cancer, that is not metastatic; and data from samples from subjects with cancer, e.g., breast cancer, that metastatic. Comparisons can be made to establish predetermined threshold biomarker standards for differenct classes of subjects, e.g., diseased vs. non-diseased subjects. The standards can be run in the same assay or can be known standards from a previous assay.

[0150] A biomarker is differentially present between different phenotypic status groups if the mean or median expression or mutation levels of the biomarker is calculated to be different, i.e., higher or lower, between the groups. Thus, biomarkers provide an indication that a subject, e.g., a cancer patient, belongs to one phenotypic status or another.

[0151] In addition to individual biological compounds, e.g., HIF-1α or HIF-2α, the term "biomarker" as used herein is meant to include groups, sets, or arrays of multiple biological compounds. For example, the combination of HIF-1α and HIF-1α may comprise a biomarker. The term "biomarker" may comprise one, two, three, four, five, six, seven, eight, nine, ten, fifteen, twenty, twenty five, thirty, or more, biological compounds.

[0152] The determination of the expression level or mutation status of a biomarker in a patient can be performed using any of the many methods known in the art. Any method known in the art for quantitating specific proteins and/or detecting HIF expression, or the expression or mutation levels of any other biomarker in a patient or a biological sample may be used in the methods of the disclosure. Examples include, but are not limited to, PCR (polymerase chain reaction), or RT-PCR, Northern blot, Western blot, ELISA (enzyme linked immunosorbent assay), RIA (radioimmunoassay), gene chip analysis of RNA expression, immunohistochemistry or immunofluorescence. *See, e.g.*, Slagle et al. Cancer 83:1401 (1998). Certain embodiments of the disclosure include methods wherein biomarker RNA expression (transcription) is determined. Other embodiments of the disclosure include methods wherein protein expression in the biological sample is determined. See, for example, Harlow *et al.*, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, (1988) and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York 3rd Edition, (1995). For northern blot or RT-PCR analysis, RNA is isolated from the tumor tissue sample using RNAse free techniques. Such techniques are commonly known in the art.

[0153] In one embodiment of the disclosure, a biological sample is obtained from the patient and cells in the biopsy are assayed for determination of biomarker expression or mutation status.

[0154] In one embodiment of the disclosure, PET imaging is used to determine biomarker expression.

[0155] In another embodiment of the disclosure, Northern blot analysis of biomarker transcription in a tumor cell sample is performed. Northern analysis is a standard method for detection and/or quantitation of mRNA levels in a sample. Initially, RNA is isolated from a sample to be assayed using Northern blot analysis. In the analysis, the RNA samples are first separated by size via electrophoresis in an agarose gel under denaturing

conditions. The RNA is then transferred to a membrane, crosslinked and hybridized with a labeled probe. Typically, Northern hybridization involves polymerizing radiolabeled or nonisotopically labeled DNA, in vitro, or generation of oligonucleotides as hybridization probes. Typically, the membrane holding the RNA sample is prehybridized or blocked prior to probe hybridization to prevent the probe from coating the membrane and, thus, to reduce non-specific background signal. After hybridization, typically, unhybridized probe is removed by washing in several changes of buffer. Stringency of the wash and hybridization conditions can be designed, selected and implemented by any practitioner of ordinary skill in the art. Detection is accomplished using detectably labeled probes and a suitable detection method. Radiolabeled and non-radiolabled probes and their use are well known in the art. The presence and or relative levels of expression of the biomarker being assayed can be quantified using, for example, densitometry.

[0156] In another embodiment of the disclosure, biomarker expression and/or mutation status is determined using RT-PCR. RT-PCR allows detection of the progress of a PCR amplification of a target gene in real time. Design of the primers and probes required to detect expression and/or mutation status of a biomarker of the disclosure is within the skill of a practitioner of ordinary skill in the art. RT-PCR can be used to determine the level of RNA encoding a biomarker of the disclosure in a tumor tissue sample. In an embodiment of the disclosure, RNA from the biological sample is isolated, under RNAse free conditions, than converted to DNA by treatment with reverse transcriptase. Methods for reverse transcriptase conversion of RNA to DNA are well known in the art. A description of PCR is provided in the following references: Mullis et al., *Cold Spring Harbor Symp. Quant. Biol. 51*:263 (1986); EP 50,424; EP 84,796; EP 258,017; EP 237,362; EP 201,184; U.S. Patent Nos. 4,683,202; 4,582,788; 4,683,194.

[0157] RT-PCR probes depend on the 5'-3' nuclease activity of the DNA polymerase used for PCR to hydrolyze an oligonucleotide that is hybridized to the target amplicon (biomarker gene). RT-PCR probes are oligonucleotides that have a fluorescent reporter dye attached to the 5, end and a quencher moiety coupled to the 3' end (or vice versa). These probes are designed to hybridize to an internal region of a PCR product. In the unhybridized state, the proximity of the fluor and the quench molecules prevents the detection of fluorescent signal from the probe. During PCR amplification, when the polymerase replicates a template on which an RT-PCR probe is bound, the 5'-3' nuclease

activity of the polymerase cleaves the probe. This decouples the fluorescent and quenching dyes and FRET no longer occurs. Thus, fluorescence increases in each cycle, in a manner proportional to the amount of probe cleavage. Fluorescence signal emitted from the reaction can be measured or followed over time using equipment which is commercially available using routine and conventional techniques.

[0158] In another embodiment of the disclosure, expression of proteins encoded by biomarkers are detected by western blot analysis. A western blot (also known as an immunoblot) is a method for protein detection in a given sample of tissue homogenate or extract. It uses gel electrophoresis to separate denatured proteins by mass. The proteins are then transferred out of the gel and onto a membrane (*e.g.*, nitrocellulose or polyvinylidene fluoride (PVDF)), where they are detected using a primary antibodythat specifically bind to the protein. The bound antibody can then detected by a secondary antibody that is conjugated with a detectable label (*e.g.*, biotin, horseradish peroxidase or alkaline phosphatase). Detection of the secondary label signal indicates the presence of the protein.

[0159] In another embodiment of the disclosure, the expression of a protein encoded by a biomarker is detected by enzyme-linked immunosorbent assay (ELISA). In one embodiment of the disclosure, "sandwich ELISA" comprises coating a plate with a capture antibody; adding sample wherein any antigen present binds to the capture antibody; adding a detecting antibody which also binds the antigen; adding an enzyme-linked secondary antibody which binds to detecting antibody; and adding substrate which is converted by an enzyme on the secondary antibody to a detectable form. Detection of the signal from the secondary antibody indicates presence of the biomarker antigen protein.

[0160] In another embodiment of the disclosure, the expression of a biomarker is evaluated by use of a gene chip or microarray. Such techniques are within ordinary skill held in the art.

VI. Definitions

[0161] The vinca alkaloid N-oxides of the present disclosure may exist as pharmaceutically acceptable salts. Nonlimiting examples of salts of vinca alkaloid N-oxides include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate,

adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphsphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, paratoluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulfonate, and p-toluenesulfonate salts.

[0162] The term "biological sample" as used herein refers any tissue or fluid from a patient that is suitable for detecting a biomarker, such as HIF-1α expression status. Examples of useful biological samples include, but are not limited to, biopsied tissues and/or cells, *e.g.*, solid tumor, lymph gland, inflamed tissue, tissue and/or cells involved in a condition or disease, blood, plasma, serous fluid, cerebrospinal fluid, saliva, urine, lymph, cerebral spinal fluid, and the like. Other suitable biological samples will be familiar to those of ordinary skill in the relevant arts. A biological sample can be analyzed for biomarker expression and/or mutation using any technique known in the art and can be obtained using techniques that are well within the scope of ordinary knowledge of a clinical practioner. In one embodiment of the disclosure, the biological sample comprises blood cells.

[0163] The term hypoxia-inducible factor or "HIF" as used herein refers to proteins that sense and respond to oxygen deficiency by acting as transcription factors. The HIF signaling cascade mediates the effects of hypoxia, the state of low oxygen concentration, on the cell. Wilkins *et al.*, *ChemMedChem 11*:773-786 (2016). The following are memberes of the human HIF family:

member	gene	protein
HIF-1α	HIF1A	hypoxia-inducible factor 1, alpha subunit
HIF-1β	ARNT	aryl hydrocarbon receptor nuclear translocator
HIF-2α	EPAS1	endothelial PAS domain protein 1
HIF-2β	ARNT2	aryl-hydrocarbon receptor nuclear translocator 2
HIF-3α	HIF3A	hypoxia inducible factor 3, alpha subunit
HIF-3β	ARNTL	aryl-hydrocarbon receptor nuclear translocator 3

[0164] HIF proteins are overexpressed in many human cancers. Zhong *et al.*, *Cancer Research 59*:5830-5835 (1999). Talks *et al.*, *The American Journal of Pathology. 157*:411–21 (2000). Wigerup *et al.*, *Pharmacology & Therapeutics 164*:152–169 (2016).

HIF overexpression is implicated in promoting tumor growth and metastasis through its role in initiating angiogenesis and regulating cellular metabolism to overcome hypoxia. Hypoxia promotes apoptosis in both normal and tumor cells. But hypoxic conditions in cancer tumors, along with accumulation of genetic alternations, often contribute to HIF overexpression. Semenza, *Nature Reviews. Cancer 3*:721–32 (2003).

[0165] Significant HIF expression has been noted in most solid tumors including cancers of the colon, breast, pancreas, kidneys, prostate, ovary, brain, and bladder. Clinically, elevated HIF levels in a number of cancers, including cervical cancer, non-small-cell lung carcinoma, breast cancer (LV-positive and negative), oligodendroglioma, oropharyngeal cancer, ovarian cancer, endometrial cancer, esophageal cancer, head and neck cancer, and stomach cancer, have been associated with aggressive tumor progression, and thus has been implicated as a predictive and prognostic marker for resistance to radiation treatment, chemotherapy, and increased mortality.

[0166] HIFIA (or HIF-1α) expression may also regulate breast tumor progression. *Bos et al., Journal of the National Cancer Institute 93:309–14 (2001).* Elevated HIFIA levels may be detected in early cancer development, and have been found in early ductal carcinoma *in situ*, a pre-invasive stage in breast cancer development, and is also associated with increased microvasculature density in tumor lesions. Moreover, despite histologically-determined low-grade, lymph-node negative breast tumor in a subset of patients examined, detection of significant HIF1A expression was able to independently predict poor response to therapy. Bos *et al.*, *Cancer 97*:1573–81 (2003). Similar findings have been reported in brain cancer and ovarian cancer studies as well, and suggest at regulatory role of HIF-1α in initiating angiogenesis through interactions with pro-angiogenic factors such as VEGF. Studies of glioblastoma multiforme show striking similarity between HIF1A expression pattern and that of VEGF gene transcription level. In addition, high-grade glioblastoma multiform tumors with high VEGF expression pattern, similar to breast cancer with HIF1A overexpression, display significant signs of tumor neovascularization. This further suggests the regulatory role of HIF-1α in promoting tumor progression, likely through hypoxia-induced VEGF expression pathways. Powis and Kirkpatrick, *Molecular Cancer Therapeutics 3*:647–54 (2004).

[0167] HIF1A overexpression in tumors may also occur in a hypoxia-independent pathway. In hemagioblastoma, HIF1A expression is found in most cells sampled from the

well-vascularized tumor. Although in both renal carcinoma and hemagioblastoma, the von Hippel-Lindau gene is inactivated, HIF1A is still expressed at high levels. In addition to VEGF overexpression in response elevated HIF1A levels, the PI3K/AKT pathway is also involved in tumor growth. In prostate cancers, the commonly occurring PTEN mutation is associated with tumor progression toward aggressive stage, increased vascular density and angiogenesis.

[0168] During hypoxia, tumor suppressor p53 overexpression may be associated with HIF1A-dependent pathway to initiate apoptosis. Moreover, p53-independent pathway may also induce apoptosis through the Bcl-2 pathway. However, overexpression of HIF1A is cancer- and individual-specific, and depends on the accompanying genetic alternations and levels of pro- and anti-apoptotic factors present. One study on epithelial ovarian cancer shows HIF1A and nonfunctional tumor suppressor p53 is correlated with low levels of tumor cell apoptosis and poor prognosis. Further, early-stage esophageal cancer patients with demonstrated overexpression of HIF1 and absence of BCL2 expression also failed photodynamic therapy. Studies of glioblastoma multiforme show striking similarity between HIF1A protein expression pattern and that of VEGF gene transcription level.

[0169] The term "liposome" refers to microscopic lipid vesicles composed of a bilayer of phospholipids or any similar amphipathic lipids encapsulating an internal aqueous medium. Bozzuto and Molinari, *International Journal of Nanomedicine 10*:975–999 (2015). Liposomes of the present disclosure can be unilamellar vesicles such as small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs), and smaller multilamellar vesicles (MLV), typically varying in size, e.g., from 50 nm to 500 nm. No particular limitation is imposed on the liposomal membrane structure in the present disclosure. The term liposomal membrane refers to the bilayer of phospholipids separating the internal aqueous medium from the external aqueous medium.

[0170] Exemplary liposomal membranes useful in the current disclosure may be formed from a variety of vesicle-forming lipids, typically including dialiphatic chain lipids, such as phospholipids, diglycerides, dialiphatic glycolipids, egg sphingomyelin and glycosphingolipid, cholesterol, and derivatives thereof, and combinations thereof. Phospholipids are amphiphilic agents having hydrophobic groups formed of long-chain alkyl chains, and a hydrophilic group containing a phosphate moiety. The group of

phospholipids includes phosphatidic acid, phosphatidyl glycerols, phosphatidylcholines, phosphatidylethanolamines, phosphatidylinositols, phosphatidylserines, and mixtures thereof. In some embodiments, the phospholipids are chosen from egg yolk phosphatidylcholine (EYPC), soy phosphatidylcholine (SPC), palmitoyl-oleoyl phosphatidylcholine, dioleyl phosphatidylcholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-dimyristoyl-sn-phosphatidylcholine (DMPC), hydrogenated soy phosphatidylcholine (HSPC), distearoyl phosphatidylcholine (DSPC), or hydrogenated egg yolk phosphatidylcholine (HEPC), egg phosphatidylglycerol, distearoylphosphatidylglycerol (DSPG), sterol modified lipids, cationic lipids and zwitterlipids.

[0171] Liposomes can be prepared by any of the techniques known in the art. *See*, *e.g.*, Shah *et al.*, *Journal of Controlled Release 253*:37–45 (2017). For example, the liposomes can be formed by the conventional technique for preparing multilamellar lipid vesicles (MLVs), that is, by depositing one or more selected lipids on the inside walls of a suitable vessel by dissolving the lipids in chloroform and then evaporating the chloroform, and by then adding the aqueous solution which is to be encapsulated to the vessel, allowing the aqueous solution to hydrate the lipid, and swirling or vortexing the resulting lipid suspension. This process engenders a mixture including the desired liposomes. Alternatively, techniques used for producing large unilamellar lipid vesicles (LUVs), such as reverse-phase evaporation, infusion procedures, and detergent dilution, can be used to produce the liposomes. A review of these and other methods for producing lipid vesicles can be found in: Liposome Technology: Liposome preparation and related Techniques, 3rd addition, 2006, G. Gregoriadis, ed.). For example, the lipid-containing particles can be in the form of steroidal lipid vesicles, stable plurilamellar lipid vesicles (SPLVs), monophasic vesicles (MPVs), or lipid matrix carriers (LMCs). In the case of MLVs, if desired, the liposomes can be subjected to multiple (five or more) freeze-thaw cycles to enhance their trapped volumes and trapping efficiencies and to provide a more uniform interlamellar distribution of solute.

[0172] Following liposome preparation, the liposomes are optionally sized to achieve a desired size range and relatively narrow distribution of liposome sizes. A size range of from about 30 to about 200 nanometers allows the liposome suspension to be sterilized by filtration through a conventional sterile filter, typically a 0.22 micron or 0.4 micron filter.

The filter sterilization method can be carried out on a high throughput basis if the liposomes have been sized down to about 20-300 nanometers. Several techniques are available for sizing liposomes to a desired size. Sonicating a liposome suspension either by bath or probe sonication produces a progressive size reduction down to small unilamellar vesicles less than about 50 nanometer in size. Homogenization is another method which relies on shearing energy to fragment large liposomes into smaller ones. In a typical homogenization procedure, multilamellar vesicles are recirculated through a standard emulsion homogenizer until selected liposome sizes, typically between about 50 and 500 nanometers, are observed. In both methods, the particle size distribution can be monitored by conventional laser-beam particle size determination. Extrusion of liposome through a small-pore polycarbonate membrane or an asymmetric ceramic membrane is also an effective method for reducing liposome sizes to a relatively well-defined size distribution. Typically, the suspension is cycled through the membrane one or more times until the desired liposome size distribution is achieved. The liposomes may be extruded through successively smaller-pore membranes, to achieve a gradual reduction in liposome size. Other useful sizing methods such as sonication, solvent vaporization or reverse phase evaporation are known to those of skill in the art.

[0173] Exemplary liposomes for use in various embodiments of the disclosure have a size of from about 30 nm to about 300 nm, e.g., from about 50 nm to about 250 nm.

[0174] The internal aqueous medium, as referred to herein, typically is the original medium in which the liposomes were prepared and which initially becomes encapsulated upon formation of the liposome. In accordance with the present disclosure, freshly prepared liposomes encapsulating the original aqueous medium can be used directly for active loading. Embodiments are also envisaged however wherein the liposomes, after preparation, are dehydrated, e.g. for storage. In such embodiments the present process may involve addition of the dehydrated liposomes directly to the external aqueous medium used to create the transmembrane gradients. However it is also possible to hydrate the liposomes in another external medium first, as will be understood by those skilled in the art. Liposomes are optionally dehydrated under reduced pressure using standard freeze-drying equipment or equivalent apparatus. In various embodiments, the liposomes and their surrounding medium are frozen in liquid nitrogen before being dehydrated and placed under reduced pressure. To ensure that the liposomes will survive

the dehydration process without losing a substantial portion of their internal contents, one or more protective sugars are typically employed to interact with the lipid vesicle membranes and keep them intact as the water in the system is removed. A variety of sugars can be used, including such sugars as trehalose, maltose, sucrose, glucose, lactose, and dextran. In general, disaccharide sugars have been found to work better than monosaccharide sugars, with the disaccharide sugars trehalose and sucrose being most effective. Typically, one or more sugars are included as part of either the internal or external media of the lipid vesicles. Most preferably, the sugars are included in both the internal and external media so that they can interact with both the inside and outside surfaces of the liposomes' membranes. Inclusion in the internal medium is accomplished by adding the sugar or sugars to the buffer which becomes encapsulated in the lipid vesicles during the liposome formation process. In addition to the sugars, a co-lyophilization agent such as glycine, betaine or carnitine, can be included to further increase the stability of the lyophilized liposome chelators. In these embodiments the external medium used during the active loading process should also preferably include one or more of the protective sugars.

[0175] As is generally known to those skilled in the art, polyethylene glycol (PEG)-lipid conjugates have been used extensively to improve circulation times for liposome-encapsulated functional compounds, to avoid or reduce premature leakage of the functional compound from the liposomal composition and to avoid detection of liposomes by the body's immune system. Attachment of PEG-derived lipids onto liposomes is called PEGylation. Hence, in one embodiment of the disclosure, the liposomes are PEGylated liposomes. Suitable PEG-derived lipids according to the disclosure, include conjugates of DSPE-PEG, functionalized with one of carboxylic acids, glutathione (GSH), maleimides (MAL), 3-(2-pyridyldithio) propionic acid (PDP), cyanur, azides, amines, biotin or folate, in which the molecular weight of PEG is between 2000 and 5000 g/mol. Other suitable PEG-derived lipids are mPEGs conjugated with ceramide, having either C_8- or C_{16}-tails, in which the molecular weight of mPEG is between 750 and 5000 daltons. Still other appropriate ligands are mPEGs or functionalized PEGs conjugated with glycerophospholipds like 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE), 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine

(DSPE), and the like. PEGylation of liposomes is a technique generally known by those skilled in the art.

[0176] In various embodiments, the liposomes are PEGylated with DSPE-mPEG conjugates (wherein the molecular weight of PEG is typically within the range of 750-5000 daltons, e.g. 2000 daltons). The phospholipid composition of an exemplary PEGylated lipsome of the disclosure may comprise up to, e.g., 0.8-20 mol % of PEG-lipid conjugates.

[0177] The terms "a", "an", "the", and similar referents in the context of describing the disclosure (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein merely are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use of any and all examples, or exemplary language, e.g., "such as," provided herein, is intended to better illustrate the disclosure and is not a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosure.

[0178] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

[0179] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. However, in one embodiment, administration of avinca alkaloid N-oxide and an immune checkpoint inhibitor leads to remission of the cancer.

[0180] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to result in amelioration of one or more symptoms of a disorder, or prevent advancement of a disorder, or cause regression of the disorder. For example, with respect to the treatment of cancer, in one embodiment, a therapeutically effective amount will refer to the amount of a therapeutic agent that causes a therapeutic response, *e.g.*, normalization of blood counts, decrease in the rate of tumor growth,

decrease in tumor mass, decrease in the number of metastases, increase in time to tumor progression, and/or increase patient survival time by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100%, or more.

[0181] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" encompasses any of the standard pharmaceutical carriers, solvents, surfactants, or vehicles. Suitable pharmaceutically acceptable vehicles include aqueous vehicles and nonaqueous vehicles. Standard pharmaceutical carriers and their formulations are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995.

[0182] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0183] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0184] "Concurrent administration," "administered in combination," "simultaneous administration," and similar phrases mean that two or more agents are administered concurrently to the subject being treated. By "concurrently," it is meant that each agent is administered either simultaneously or sequentially in any order at different points in time. However, if not administered simultaneously, it is meant that they are administered to an individual in a sequence and sufficiently close in time so as to provide the desired therapeutic effect and can act in concert. For example, the vinca alkaloid N-oxide can be administered at the same time or sequentially in any order at different points in time as the immune checkpoint inhibitor. The vinca alkaloid N-oxide and the immune checkpoint inhibitor can be administered separately, in any appropriate form and by any suitable route, e.g., by IV injection. When the vinca alkaloid N-oxide and the immune checkpoint inhibitor are not administered concurrently, it is understood that they can be

administered in any order to a patient in need thereof. For example, the vinca alkaloid N-oxide can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the immune checkpoint inhibitor. In various embodiments, vinca alkaloid N-oxide and the immune checkpoint inhibitor are administered 1 minute apart, 10 minutes apart, 30 minutes apart, less than 1 hour apart, 1 hour apart, 1 hour to 2 hours apart, 2 hours to 3 hours apart, 3 hours to 4 hours apart, 4 hours to 5 hours apart, 5 hours to 6 hours apart, 6 hours to 7 hours apart, 7 hours to 8 hours apart, 8 hours to 9 hours apart, 9 hours to 10 hours apart, 10 hours to 11 hours apart, 11 hours to 12 hours apart, no more than 24 hours apart, no more than 48 hours apart, no more than 3 days apart, or no more than 1 week apart. In one embodiument, the vinca alkaloid N-oxide is administered 1-14 days prior to the day the immune checkpoint inhibitor is administered. In one embodiument, the vinca alkaloid N-oxide is administered 1-7 days prior to the day the immune checkpoint inhibitor is administered. In another embodiment, the vinca alkaloid N-oxide is also administered on the day the immune checkpoint inhibitor is administered.

VII. Particular Embodiments

[0185] The disclosure provides the following particular embodiments.

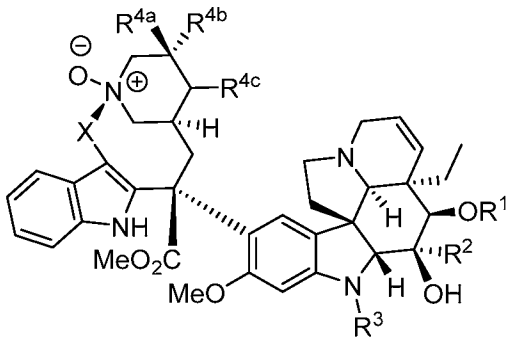
[0186] Embodiment 1. A method of treating a patient having cancer, the method comprising administering to the patient in need thereof a therapeutically effective amount of:

[0187] (a) a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0188] (b) an immune checkpoint inhibitor.

[0189] Embodiment 2. The method of Embodiment 1, wherein the vinca alkaloid N-oxide is a $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0190] Embodiment 3. The method of Embodiment 2, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0191] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0192] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0193] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0194] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0195] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0196] R^{4c} is hydrogen; or

[0197] R^{4a} and R^{4c} taken together form a double bond; and

[0198] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0199] Embodiment 4. The method of Embodiment 3, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0200] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0201] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0202] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0203] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0204] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0205] Embodiment 5. The method of any one of Embodiments 1-4, wherein the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, is administered to the patient encapsulated in a liposome.

[0206] Embodiment 6. The method of Embodiment 5, wherein the liposome comprises sphingomyelin and cholesterol.

[0207] Embodiment 7. The method of Embodiment 5, wherein the liposome comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

[0208] Embodiment 8. The method of any one of Embodiments 1-7, wherein immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIGTI inhibitor, and a TIM3 inhibitor.

[0209] Embodiment 9. The method of Embodiment 8, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.

[0210] Embodiment 10. The method of Embodiment 9, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

[0211] Embodiment 11. The method of Embodiment 10, wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, STI-A1110, PDR001, MEDI-0680, AGEN2034, BGB-A317, AB122, TSR-042, PF-06801591, cemiplimab, SYM021, JNJ-63723283, HLX10, LZM009, and MGA012.

[0212] Embodiment 12. The method of Embodiment 8, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.

[0213] Embodiment 13. The method of Embodiment 12, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody.

[0214] Embodiment 14. The method of Embodiment 13, wherein the anti-PD-L1 antibody is selected from the group consisting of avelumab, atezolizumab, durvalumab, and STI-A1014.

[0215] Embodiment 15. The method of Embodiment 8, wherein the immune checkpoint inhibitor is an anti-CTLA-4 inhibitor.

[0216] Embodiment 16. The method of Embodiment 15, wherein the anti-CTLA-4 inhibitor is an anti-CTLA-4 antibody.

[0217] Embodiment 17. The method of Embodiment 16, wherein the anti-CTLA-4 antibody is selected from the group consisting of ipilimumab and tremelimumab.

[0218] Embodiment 18. The method of Embodiment 8, wherein the immune checkpoint inhibitor is a LAG3 inhibitor.

[0219] Embodiment 19. The method of Embodiment 18, wherein the LAG3 inhibitor is an anti-LAG3 antibody.

[0220] Embodiment 20. The method of Embodiment 19, wherein the anti-LAG3 antibody is GSK2831781.

[0221] Embodiment 21. The method of Embodiment 8, wherein the immune checkpoint inhibitor is a TIM3 inhibitor.

[0222] Embodiment 22. The method of Embodiment 21, wherein the TIM3 inhibitor is an anti-TIM3 antibody.

[0223] Embodiment 23. The method of any one of Embodiments1-22, wherein the vinca alkaloid N-oxide is administered to the patient before the immune checkpoint inhibitor.

[0224] Embodiment 24. The method of any one of Embodiments 1-22, wherein the vinca alkaloid N-oxide is administered to the patient after the immune checkpoint inhibitor.

[0225] Embodiment 25. The method of any one of Embodiments 1-22, wherein the vinca alkaloid N-oxide is administered to the patient at the same time as the immune checkpoint inhibitor.

[0226] Embodiment 26. The method of any one of Embodiments 1-25, wherein the cancer is a solid tumor.

[0227] Embodiment 27. The method of any one of Embodiments 1-25, wherein the cancer is a hematological malignancy.

[0228] Embodiment 28. The method of any one of Embodiments 1-25, wherein the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma,

chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma,

rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0229] Embodiment 29. The method of Embodiment 28, wherein the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0230] Embodiment 30. The method of Embodiment 28, wherein the cancer is selected from the group consisting of non-small cell lung cancer, bladder cancer, head and neck cancer, cvarian cancer, and triple negative breast cancer.

[0231] Embodiment 31. The method of any one of Embodiments 1-30, wherein the cancer has become resistant to one or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0232] Embodiment 32. The method of Embodiment 31, wherein the cancer has become resistant to two or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0233] Embodiment 33. The method of Embodiments 31 or 32, wherein the cancer has become resistant to treatment with at least one immune checkpoint inhibitor.

[0234] Embodiment 34. The method of any one of Embodiments 1-33, wherein one or more of the biomarkers listed in Table 1 or Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0235] Embodiment 35. The method of Embodiment 34, wherein one or more of the biomarkers listed in Table 2 is differentially present in a biological sample taken from the

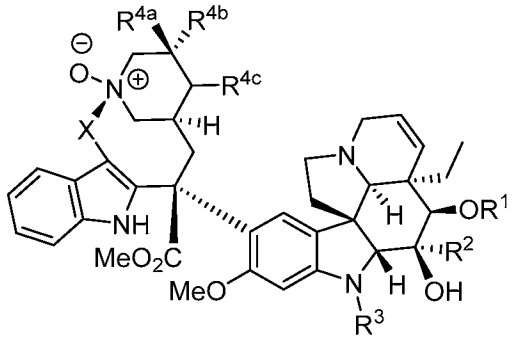
patient as compared with a biological sample taken from a subject of another phenotypic status.

[0236] Embodiment 36. The method of Embodiment 35, wherein HIF-1α expression is differentially present in a sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0237] Embodiment 37. A kit comprising a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, together with an immune checkpoint inhibitor to a patient having cancer.

[0238] Embodiment 38. The kit of Embodiment 37, wherein the vinca alkaloid N-oxide is a N_b'-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0239] Embodiment 39. The kit of Embodiment 38, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0240] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0241] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0242] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0243] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0244] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0245] R^{4c} is hydrogen; or

[0246] R^{4a} and R^{4c} taken together form a double bond; and

[0247] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0248] Embodiment 40. The kit of Embodiment 39, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0249] (a) vinblastine N_b'-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0250] (b) vincristine N_b'-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0251] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

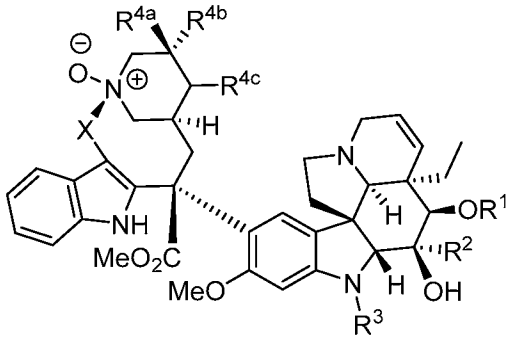
[0252] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0253] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0254] Embodiment 41. A lyophilized pharmaceutical composition comprising a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, encapsulated in a liposome.

[0255] Embodiment 42. The lyophilized pharmaceutical composition of Embodiment 41, wherein the vinca alkaloid N-oxide is a $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0256] Embodiment 43. The lyophilized pharmaceutical composition of Embodiment 42, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0257] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0258] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0259] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0260] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0261] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0262] R^{4c} is hydrogen; or

[0263] R^{4a} and R^{4c} taken together form a double bond; and

[0264] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0265] Embodiment 44. The lyophilized pharmaceutical composition of Embodiment 43, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0266] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0267] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0268] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0269] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0270] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0271] Embodiment 45. The lyophilized pharmaceutical composition of any one of Embodiments 41-44, wherein the liposome comprises sphingomyelin and cholesterol.

[0272] Embodiment 46. The lyophilized pharmaceutical composition of any one of Embodiments 41-44, wherein the liposome formulation comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

[0273] Embodiment 47. The lyophilized pharmaceutical composition of any one of Embodiments 41-46, wherein the composition is reconstituted in a sterile aqueous solution for parenteral administration to a patient.

[0274] Embodiment 48. The lyophilized pharmaceutical composition of Embodiment 47, wherein the sterile aqueous solution is water, saline, or 5% dextrose in water.

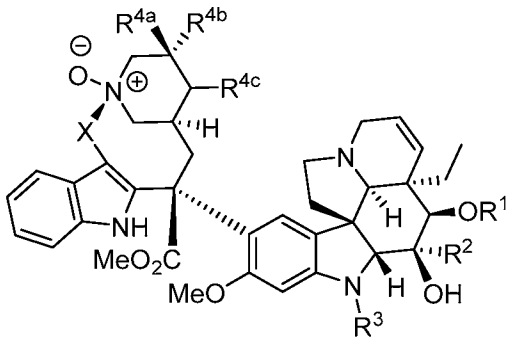
[0275] Embodiment 49. A kit comprising the lyophilized pharmaceutical composition of any one of Embodiments 41-46, and instructions for reconstituting the lyophilized pharmaceutical composition in a sterile aqueous solution for parenteral administration together with an immune checkpoint inhibitor to a patient having cancer.

[0276] Embodiment 50. The method of any one of claims 1-36, wherein the vinca alkaloid N-oxide and the immune checkpoint inhibitor are administered to the patient as separate pharmaceutical compositions.

[0277] Embodiment 51. A vinca alkaloid N-oxide, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, in combination with an immune checkpoint inhibitor.

[0278] Embodiment 52. The vinca alkaloid N-oxide for use of Embodiment 51, wherein the vinca alkaloid N-oxide is a $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0279] Embodiment 53. The vinca alkaloid N-oxide for use of Embodiment 52, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0280] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0281] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0282] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0283] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0284] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0285] R^{4c} is hydrogen; or

[0286] R^{4a} and R^{4c} taken together form a double bond; and

[0287] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0288] Embodiment 54. The vinca alkaloid N-oxide for use of Embodiment 53, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0289] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0290] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0291] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0292] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0293] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0294] Embodiment 55. The vinca alkaloid N-oxide for use of any one of Embodiments 51-54, wherein the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, is administered to the patient encapsulated in a liposome.

[0295] Embodiment 56. The vinca alkaloid N-oxide for use of Embodiment 55, wherein the liposome comprises sphingomyelin and cholesterol.

[0296] Embodiment 57. The vinca alkaloid N-oxide for use of Embodiment 55, wherein the liposome comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

[0297] Embodiment 58. The vinca alkaloid N-oxide for use of any one of Embodiments 51-57, wherein immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIGIT inhibitor, and a TIM3 inhibitor.

[0298] Embodiment 59. The vinca alkaloid N-oxide for use of Embodiment 58, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.

[0299] Embodiment 60. The vinca alkaloid N-oxide for use of Embodiment 59, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

[0300] Embodiment 61. The vinca alkaloid N-oxide for use of Embodiment 60, wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, STI-A1110, PDR001, MEDI-0680, AGEN2034, BGB-A317, AB122, TSR-042, PF-06801591, cemiplimab, SYM021, JNJ-63723283, HLX10, LZM009, and MGA012.

[0301] Embodiment 62. The vinca alkaloid N-oxide for use of Embodiment 58, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.

[0302] Embodiment 63. The vinca alkaloid N-oxide for use of Embodiment 62, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody.

[0303] Embodiment 64. The vinca alkaloid N-oxide for use of Embodiment 63, wherein the anti-PD-L1 antibody is selected from the group consisting of avelumab, atezolizumab, durvalumab, and STI-A1014.

[0304] Embodiment 65. The vinca alkaloid N-oxide for use of Embodiment 58, wherein the immune checkpoint inhibitor is an anti-CTLA-4 inhibitor.

[0305] Embodiment 66. The vinca alkaloid N-oxide for use of Embodiment 65, wherein the anti-CTLA-4 inhibitor is an anti-CTLA-4 antibody.

[0306] Embodiment 67. The vinca alkaloid N-oxide for use of Embodiment 66, wherein the anti-CTLA-4 antibody is selected from the group consisting of ipilimumab and tremelimumab.

[0307] Embodiment 68. The vinca alkaloid N-oxide for use of Embodiment 58, wherein the immune checkpoint inhibitor is a LAG3 inhibitor.

[0308] Embodiment 69. The vinca alkaloid N-oxide for use of Embodiment 68, wherein the LAG3 inhibitor is an anti-LAG3 antibody.

[0309] Embodiment 70. The vinca alkaloid N-oxide for use of Embodiment 69, wherein the anti-LAG3 antibody is GSK2831781.

[0310] Embodiment 71. The vinca alkaloid N-oxide for use of Embodiment 58, wherein the immune checkpoint inhibitor is a TIM3 inhibitor.

[0311] Embodiment 72. The vinca alkaloid N-oxide for use of Embodiment 71, wherein the TIM3 inhibitor is an anti-TIM3 antibody.

[0312] Embodiment 73. The vinca alkaloid N-oxide for use of any one of Embodiments 51-72, wherein the vinca alkaloid N-oxide is administered to the patient before the immune checkpoint inhibitor.

[0313] Embodiment 74. The vinca alkaloid N-oxide for use of any one of Embodiment 51-72, wherein the vinca alkaloid N-oxide is administered to the patient after the immune checkpoint inhibitor.

[0314] Embodiment 75. The vinca alkaloid N-oxide for use of any one of Embodiments 51-72, wherein the vinca alkaloid N-oxide is administered to the patient at the same time as the immune checkpoint inhibitor.

[0315] Embodiment 76. The vinca alkaloid N-oxide for use of any one of Embodiments 51-75, wherein the cancer is a solid tumor.

[0316] Embodiment 77. The vinca alkaloid N-oxide for use of any one of Embodiments 51-75, wherein the cancer is a hematological malignancy.

[0317] Embodiment 78. The vinca alkaloid N-oxide for use of any one of Embodiments 51-75, wherein the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma,

bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central

nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0318] Embodiment 79. The vinca alkaloid N-oxide for use of Embodiment 78, wherein the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0319] Embodiment 80. The vinca alkaloid N-oxide for use of Embodiment 78, wherein the cancer is selected from the group consisting of non-small cell lung cancer, bladder cancer, head and neck cancer, cvarian cancer, and triple negative breast cancer.

[0320] Embodiment 81. The vinca alkaloid N-oxide for use of any one of Embodiments 51-80, wherein the cancer has become resistant to one or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0321] Embodiment 82. The vinca alkaloid N-oxide for use of Embodiment 81, wherein the cancer has become resistant to two or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0322] Embodiment 83. The vinca alkaloid N-oxide for use of Embodiments 81 or 82, wherein the cancer has become resistant to treatment with at least one immune checkpoint inhibitor.

[0323] Embodiment 84. The vinca alkaloid N-oxide for use of any one of Embodiments 51-83, wherein one or more of the biomarkers listed in Table 1 or Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

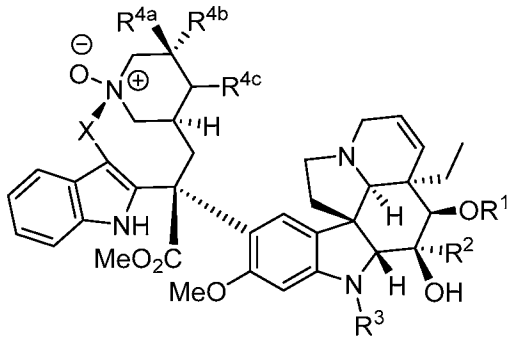
[0324] Embodiment 85. The vinca alkaloid N-oxide for use of Embodiment 84, wherein one or more of the biomarkers listed in Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0325] Embodiment 86. The vinca alkaloid N-oxide for use of Embodiment 85, wherein HIF-1α expression is differentially present in a sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0326] Embodiment 87. Use of a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt thereof, for the manufacture of medicament for use in combination therapy for treating cancer, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor.

[0327] Embodiment 88. The use of Embodiment 87, wherein the vinca alkaloid N-oxide is a $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0328] Embodiment 89. The use of Embodiment 88, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0329] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0330] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0331] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0332] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0333] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0334] R^{4c} is hydrogen; or

[0335] R^{4a} and R^{4c} taken together form a double bond; and

[0336] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0337] Embodiment 90. The use of Embodiment 89, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0338] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0339] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0340] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0341] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0342] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0343]

[0344] Embodiment 91. The use of any one of Embodiments 87-90, wherein the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, is administered to the patient encapsulated in a liposome.

[0345] Embodiment 92. The use of Embodiment 91, wherein the liposome comprises sphingomyelin and cholesterol.

[0346] Embodiment 93. The use of Embodiment 91, wherein the liposome comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

[0347] Embodiment 94. The use of any one of Embodiments 87-93, wherein immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIGIT inhibitor, and a TIM3 inhibitor.

[0348] Embodiment 95. The use of Embodiment 94, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.

[0349] Embodiment 96. The use of Embodiment 95, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

[0350] Embodiment 97. The use of Embodiment 96, wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, STI-A1110, PDR001, MEDI-0680, AGEN2034, BGB-A317, AB122, TSR-042, PF-06801591, cemiplimab, SYM021, JNJ-63723283, HLX10, LZM009, and MGA012.

[0351] Embodiment 98. The use of Embodiment 94, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.

[0352] Embodiment 99. The use of Embodiment 98, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody.

[0353] Embodiment 100. The use of Embodiment 99, wherein the anti-PD-L1 antibody is selected from the group consisting of avelumab, atezolizumab, durvalumab, and STI-A1014.

[0354] Embodiment 101. The use of Embodiment 94, wherein the immune checkpoint inhibitor is an anti-CTLA-4 inhibitor.

[0355] Embodiment 102. The use of Embodiment 101, wherein the anti-CTLA-4 inhibitor is an anti-CTLA-4 antibody.

[0356] Embodiment 103. The use of Embodiment 102, wherein the anti-CTLA-4 antibody is selected from the group consisting of ipilimumab and tremelimumab.

[0357] Embodiment 104. The use of Embodiment 94, wherein the immune checkpoint inhibitor is a LAG3 inhibitor.

[0358] Embodiment 105. The use of Embodiment 104, wherein the LAG3 inhibitor is an anti-LAG3 antibody.

[0359] Embodiment 106. The use of Embodiment 105, wherein the anti-LAG3 antibody is GSK2831781.

[0360] Embodiment 107. The use of Embodiment 94, wherein the immune checkpoint inhibitor is a TIM3 inhibitor.

[0361] Embodiment 108. The use of Embodiment 107, wherein the TIM3 inhibitor is an anti-TIM3 antibody.

[0362] Embodiment 109. The use of any one of Embodiments 87-108, wherein the vinca alkaloid N-oxide is administered to the patient before the immune checkpoint inhibitor.

[0363] Embodiment 110. The use of any one of Embodiment 87-108, wherein the vinca alkaloid N-oxide is administered to the patient after the immune checkpoint inhibitor.

[0364] Embodiment 111. The use of any one of Embodiments 87-108, wherein the vinca alkaloid N-oxide is administered to the patient at the same time as the immune checkpoint inhibitor.

[0365] Embodiment 112. The use of any one of Embodiments 87-111, wherein the cancer is a solid tumor.

[0366] Embodiment 113. The use of any one of Embodiments 87-111, wherein the cancer is a hematological malignancy.

[0367] Embodiment 114. The use of any one of Embodiments 87-111, wherein the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal

cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0368] Embodiment 115. The use of Embodiment 114, wherein the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0369] Embodiment 116. The use of Embodiment 114, wherein the cancer is selected from the group consisting of non-small cell lung cancer, bladder cancer, head and neck cancer, cvarian cancer, and triple negative breast cancer.

[0370] Embodiment 117. The use of any one of Embodiments 87-116, wherein the cancer has become resistant to one or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0371] Embodiment 118. The use of Embodiment 117, wherein the cancer has become resistant to two or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0372] Embodiment 119. The use of Embodiments 117 or 118, wherein the cancer has become resistant to treatment with at least one immune checkpoint inhibitor.

[0373] Embodiment 120. The use of any one of Embodiments 87-119, wherein one or more of the biomarkers listed in Table 1 or Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

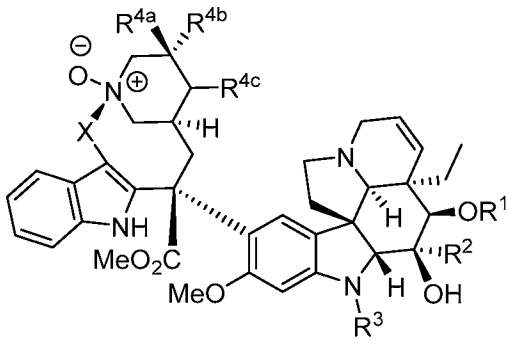
[0374] Embodiment 121. The use of Embodiment 120, wherein one or more of the biomarkers listed in Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0375] Embodiment 122. The use of Embodiment 121, wherein HIF-1α expression is differentially present in a sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0376] Embodiment 123. A pharmaceutical composition comprising a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt thereof, for the treatment of cancer in a patient, wherein the pharmaceutical composition is to be administered to the patient in combination with an immune checkpoint inhibitor.

[0377] Embodiment 124. The pharmaceutical composition of Embodiment 123, wherein the vinca alkaloid N-oxide is a $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0378] Embodiment 125. The pharmaceutical composition of Embodiment 124, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0379] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0380] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0381] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0382] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0383] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0384] R^{4c} is hydrogen; or

[0385] R^{4a} and R^{4c} taken together form a double bond; and

[0386] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0387] Embodiment 126. The pharmaceutical composition of Embodiment 125, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0388] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0389] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0390] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0391] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0392] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0393] Embodiment 127. The pharmaceutical composition of any one of Embodiments 123-126, wherein the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, is administered to the patient encapsulated in a liposome.

[0394] Embodiment 128. The pharmaceutical composition of Embodiment 127, wherein the liposome comprises sphingomyelin and cholesterol.

[0395] Embodiment 129. The pharmaceutical composition of Embodiment 127, wherein the liposome comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

[0396] Embodiment 130. The pharmaceutical composition of any one of Embodiments 123-129, wherein immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIGIT inhibitor, and a TIM3 inhibitor.

[0397] Embodiment 131. The pharmaceutical composition of Embodiment 130, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.

[0398] Embodiment 132. The pharmaceutical composition of Embodiment 131, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

[0399] Embodiment 133. The pharmaceutical composition of Embodiment 132, wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, STI-A1110, PDR001, MEDI-0680, AGEN2034, BGB-A317, AB122, TSR-042, PF-06801591, cemiplimab, SYM021, JNJ-63723283, HLX10, LZM009, and MGA012.

[0400] Embodiment 134. The pharmaceutical composition of Embodiment 130, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.

[0401] Embodiment 135. The pharmaceutical composition of Embodiment 134, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody.

[0402] Embodiment 136. The pharmaceutical composition of Embodiment 135, wherein the anti-PD-L1 antibody is selected from the group consisting of avelumab, atezolizumab, durvalumab, and STI-A1014.

[0403] Embodiment 137. The pharmaceutical composition of Embodiment 136, wherein the immune checkpoint inhibitor is an anti-CTLA-4 inhibitor.

[0404] Embodiment 138. The pharmaceutical composition of Embodiment 137, wherein the anti-CTLA-4 inhibitor is an anti-CTLA-4 antibody.

[0405] Embodiment 139. The pharmaceutical composition of Embodiment 138, wherein the anti-CTLA-4 antibody is selected from the group consisting of ipilimumab and tremelimumab.

[0406] Embodiment 140. The pharmaceutical composition of Embodiment 130, wherein the immune checkpoint inhibitor is a LAG3 inhibitor.

[0407] Embodiment 141. The pharmaceutical composition of Embodiment 140, wherein the LAG3 inhibitor is an anti-LAG3 antibody.

[0408] Embodiment 142. The pharmaceutical composition of Embodiment 141, wherein the anti-LAG3 antibody is GSK2831781.

[0409] Embodiment 143. The pharmaceutical composition of Embodiment 130, wherein the immune checkpoint inhibitor is a TIM3 inhibitor.

[0410] Embodiment 144. The pharmaceutical composition of Embodiment 143, wherein the TIM3 inhibitor is an anti-TIM3 antibody.

[0411] Embodiment 145. The pharmaceutical composition of any one of Embodiments 123-144, wherein the vinca alkaloid N-oxide is administered to the patient before the immune checkpoint inhibitor.

[0412] Embodiment 146. The pharmaceutical composition of any one of Embodiment 123-144, wherein the vinca alkaloid N-oxide is administered to the patient after the immune checkpoint inhibitor.

[0413] Embodiment 147. The pharmaceutical composition of any one of Embodiments 123-144, wherein the vinca alkaloid N-oxide is administered to the patient at the same time as the immune checkpoint inhibitor.

[0414] Embodiment 148. The pharmaceutical composition of any one of Embodiments 123-147, wherein the cancer is a solid tumor.

[0415] Embodiment 149. The pharmaceutical composition of any one of Embodiments 123-147, wherein the cancer is a hematological malignancy.

[0416] Embodiment 150. The pharmaceutical composition of any one of Embodiments 123-147, wherein the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma,

bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central

nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0417] Embodiment 151. The pharmaceutical composition of Embodiment 150, wherein the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0418] Embodiment 152. The pharmaceutical composition of Embodiment 150, wherein the cancer is selected from the group consisting of non-small cell lung cancer, bladder cancer, head and neck cancer, cvarian cancer, and triple negative breast cancer.

[0419] Embodiment 153. The pharmaceutical composition of any one of Embodiments 123-152, wherein the cancer has become resistant to one or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0420] Embodiment 154. The pharmaceutical composition of Embodiment 153, wherein the cancer has become resistant to two or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0421] Embodiment 155. The pharmaceutical composition of Embodiments 153 or 154, wherein the cancer has become resistant to treatment with at least one immune checkpoint inhibitor.

[0422] Embodiment 156. The pharmaceutical composition of any one of Embodiments 123-155, wherein one or more of the biomarkers listed in Table 1 or Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

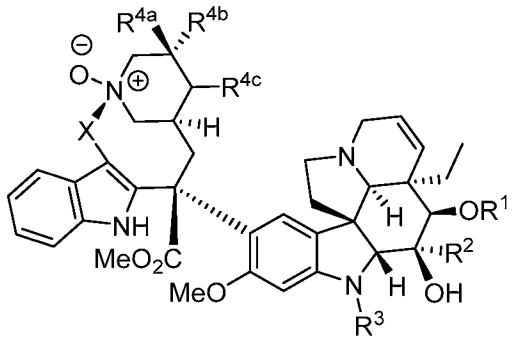
[0423] Embodiment 157. The pharmaceutical composition of Embodiment 156, wherein one or more of the biomarkers listed in Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0424] Embodiment 158. The pharmaceutical composition of Embodiment 157, wherein HIF-1α expression is differentially present in a sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0425] Embodiment 159. A method of treating a patient having cancer, the method comprising administering to the patient in need thereof a therapeutically effective amount of a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, wherein one or more of the biomarkers listed in Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0426] Embodiment 160. The method of Embodiment 159, wherein the vinca alkaloid N-oxide is a N_b-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0427] Embodiment 161. The method of Embodiment 160, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0428] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0429] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0430] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0431] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0432] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0433] R^{4c} is hydrogen; or

[0434] R^{4a} and R^{4c} taken together form a double bond; and

[0435] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0436] Embodiment 162. The method of Embodiment 161, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0437] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0438] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0439] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0440] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0441] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0442] Embodiment 163. The method of any one of Embodiments 159-162, wherein HIF-1α expression is differentially present in a sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0443] The disclosure provides the following particular embodiments.

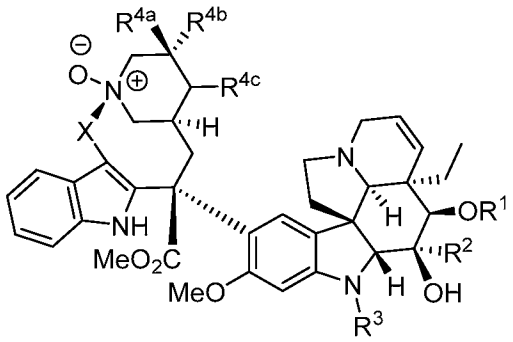
[0444] Embodiment A 1. A method of treating a patient having cancer, the method comprising administering to the patient in need thereof a therapeutically effective amount of:

[0445] (a) a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0446] (b) an immune checkpoint inhibitor.

[0447] Embodiment A 2. The method of Embodiment A 1, wherein the vinca alkaloid N-oxide is a $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0448] Embodiment A 3. The method of Embodiment A 2, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

[0449] or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0450] R^1 is selected from the group consisting of hydrogen and -C(=O)CH_3;

[0451] R^2 is selected from the group consisting of -C(=O)OCH_3 and -C(=O)NH_2;

[0452] R^3 is selected from the group consisting of -CH_3 and -CHO;

[0453] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0454] R^{4b} is selected from the group consisting of -CH_2CH_3 and -CF_2CH_3;

[0455] R^{4c} is hydrogen; or

[0456] R^{4a} and R^{4c} taken together form a double bond; and

[0457] X is selected from the group consisting of -CH_2- and -CH_2CH_2-.

[0458] Embodiment A 4. The method of Embodiment A 3, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0459] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0460] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0461] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0462] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0463] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0464] Embodiment A 5. The method of any one of Embodiments A 1-A 4, wherein the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, is administered to the patient encapsulated in a liposome.

[0465] Embodiment A 6. The method of Embodiment A 5, wherein the liposome comprises sphingomyelin and cholesterol.

[0466] Embodiment A 7. The method of Embodiment A 5, wherein the liposome comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

[0467] Embodiment A 8. The method of any one of Embodiments A 1-A 7, wherein immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, a VISTA inhibitor, a TIGIT inhibitor, and a cd47 inhibitor.

[0468] Embodiment A 9. The method of Embodiment A 8, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.

[0469] Embodiment A 10. The method of Embodiment A 9, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

[0470] Embodiment A 11. The method of Embodiment A 10, wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, STI-A1110, PDR001, MEDI-0680, AGEN2034, BGB-A317, AB122, TSR-042, PF-06801591, cemiplimab, SYM021, JNJ-63723283, HLX10, LZM009, and MGA012.

[0471] Embodiment A 12. The method of Embodiment A 8, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.

[0472] Embodiment A 13. The method of Embodiment A 12, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody.

[0473] Embodiment A 14. The method of Embodiment A 13, wherein the anti-PD-L1 antibody is selected from the group consisting of avelumab, atezolizumab, durvalumab, and STI-A1014.

[0474] Embodiment A 15. The method of Embodiment A 8, wherein the immune checkpoint inhibitor is an anti-CTLA-4 inhibitor.

[0475] Embodiment A 16. The method of Embodiment A 15, wherein the anti-CTLA-4 inhibitor is an anti-CTLA-4 antibody.

[0476] Embodiment A 17. The method of Embodiment A 16, wherein the anti-CTLA-4 antibody is selected from the group consisting of ipilimumab and tremelimumab.

[0477] Embodiment A 18. The method of Embodiment A 8, wherein the immune checkpoint inhibitor is a LAG3 inhibitor.

[0478] Embodiment A 19. The method of Embodiment A 18, wherein the LAG3 inhibitor is an anti-LAG3 antibody.

[0479] Embodiment A 20. The method of Embodiment A 19, wherein the anti-LAG3 antibody is GSK2831781.

[0480] Embodiment A 21. The method of Embodiment A 8, wherein the immune checkpoint inhibitor is a TIM3 inhibitor.

[0481] Embodiment A 22. The method of Embodiment A 21, wherein the TIM3 inhibitor is an anti-TIM3 antibody.

[0482] Embodiment A 23. The method of Embodiment A 8, wherein the immune checkpoint inhibitor is a VISTA inhibitor.

[0483] Embodiment A 24. The method of Embodiment A 23, wherein the VISTA inhibitor is an anti-VISTA antibody.

[0484] Embodiment A 25. The method of Embodiment A 8, wherein the immune checkpoint inhibitor is a cd47 inhibitor.

[0485] Embodiment A 26. The method of Embodiment A 25, wherein the cd47 inhibitor is an anti-cd47 antibody.

[0486] Embodiment A 27. The method of Embodiment A 8, wherein the immune checkpoint inhibitor is a TIGIT inhibitor.

[0487] Embodiment A 28. The method of Embodiment A 27, wherein the TIGIT inhibitor is an anti-TIGIT antibody.

[0488] Embodiment A 29. The method of any one of Embodiments A 1- A 28, wherein the vinca alkaloid N-oxide is administered to the patient before the immune checkpoint inhibitor.

[0489] Embodiment A 30. The method of any one of Embodiments A 1-A 28, wherein the vinca alkaloid N-oxide is administered to the patient after the immune checkpoint inhibitor.

[0490] Embodiment A 31. The method of any one of Embodiments A 1-A 28, wherein the vinca alkaloid N-oxide is administered to the patient at the same time as the immune checkpoint inhibitor.

[0491] Embodiment A 32. The method of any one of Embodiments A 1-A 31, wherein the cancer is a solid tumor.

[0492] Embodiment A 33. The method of any one of Embodiments A 1-A 31, wherein the cancer is a hematological malignancy.

[0493] Embodiment A 34. The method of any one of Embodiments A 1-A 31, wherein the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large

cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic

nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0494] Embodiment A 35. The method of Embodiment A 34, wherein the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0495] Embodiment A 36. The method of Embodiment A 34, wherein the cancer is selected from the group consisting of non-small cell lung cancer, bladder cancer, head and neck cancer, cvarian cancer, and triple negative breast cancer.

[0496] Embodiment A 37. The method of any one of Embodiments A 1-A 36, wherein the cancer has become resistant to one or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0497] Embodiment A 38. The method of Embodiment A 33, wherein the cancer has become resistant to two or more conventional cancer treatments selected from the group consisting of radiotherapy, chemotherapy, hormonal therapy, or biologic therapy.

[0498] Embodiment A 39. The method of Embodiments A 37 or A 38, wherein the cancer has become resistant to treatment with at least one immune checkpoint inhibitor.

[0499] Embodiment A 40. The method of any one of Embodiments A 1-A 39, wherein one or more of the biomarkers listed in Table 1 or Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

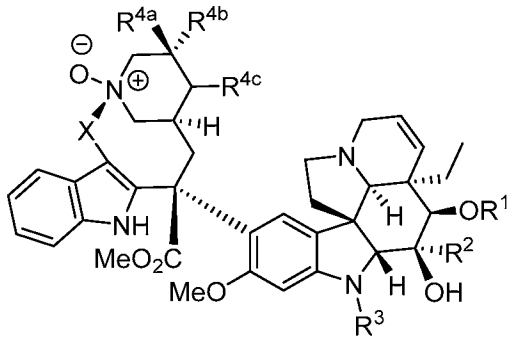
[0500] Embodiment A 41. The method of Embodiment A 40, wherein one or more of the biomarkers listed in Table 2 is differentially present in a biological sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0501] Embodiment A 42. The method of Embodiment A 41, wherein HIF-1α expression is differentially present in a sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

[0502] Embodiment A 43. A kit comprising a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, together with an immune checkpoint inhibitor to a patient having cancer.

[0503] Embodiment A 44. The kit of Embodiment A 43, wherein the vinca alkaloid N-oxide is a N_b-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0504] Embodiment A 45. The kit of Embodiment A 44, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

[0505] or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0506] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0507] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0508] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0509] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0510] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0511] R^{4c} is hydrogen; or

[0512] R^{4a} and R^{4c} taken together form a double bond; and

[0513] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0514] Embodiment A 46. The kit of Embodiment A 45, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0515] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0516] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0517] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

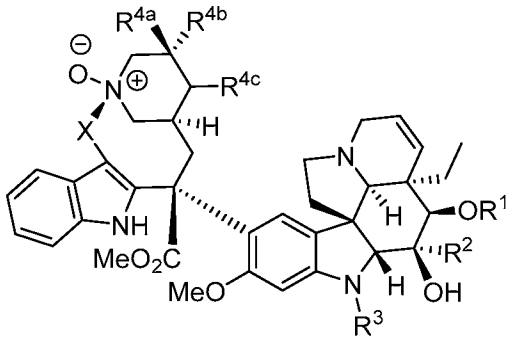
[0518] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0519] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0520] Embodiment A 47. A lyophilized pharmaceutical composition comprising a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, encapsulated in a liposome.

[0521] Embodiment A 48. The lyophilized pharmaceutical composition of Embodiment A 47, wherein the vinca alkaloid N-oxide is a $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0522] Embodiment A 49. The lyophilized pharmaceutical composition of Embodiment A 48, wherein the vinca alkaloid N-oxide is represented by a compound having Formula **I**:



I,

[0523] or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0524] R^1 is selected from the group consisting of hydrogen and $-C(=O)CH_3$;

[0525] R^2 is selected from the group consisting of $-C(=O)OCH_3$ and $-C(=O)NH_2$;

[0526] R^3 is selected from the group consisting of $-CH_3$ and -CHO;

[0527] R^{4a} is selected from the group consisting of hydrogen and -OH;

[0528] R^{4b} is selected from the group consisting of $-CH_2CH_3$ and $-CF_2CH_3$;

[0529] R^{4c} is hydrogen; or

[0530] R^{4a} and R^{4c} taken together form a double bond; and

[0531] X is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$.

[0532] Embodiment A 50. The lyophilized pharmaceutical composition of Embodiment A 49, wherein the vinca alkaloid N-oxide is selected from the group consisting of:

[0533] (a) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0534] (b) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0535] (c) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof;

[0536] (d) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

[0537] (e) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0538] Embodiment A 51. The lyophilized pharmaceutical composition of any one of Embodiments A 47-A 51, wherein the liposome comprises sphingomyelin and cholesterol.

[0539] Embodiment A 52. The lyophilized pharmaceutical composition of any one of Embodiments A 47-A 51, wherein the liposome comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

[0540] Embodiment A 53. The lyophilized pharmaceutical composition of any one of Embodiments A 47-A 52, wherein the composition is reconstituted in a sterile aqueous solution for parenteral administration to a patient.

[0541] Embodiment A 54. The lyophilized pharmaceutical composition of Embodiment A 53, wherein the sterile aqueous solution is water, saline, or 5% dextrose in water.

[0542] Embodiment A 55. A kit comprising the lyophilized pharmaceutical composition of any one of Embodiments A 47-A 52, and instructions for reconstituting the lyophilized pharmaceutical composition in a sterile aqueous solution for parenteral administration together with an immune checkpoint inhibitor to a patient having cancer.

[0543] Embodiment A 56. The method of any one of Embodiments A 1-A 42, wherein vinca alkaloid N-oxide is vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0544] Embodiment A 57. The kit of any one of Embodiments A 43-A 46, wherein vinca alkaloid N-oxide is vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0545] Embodiment A 58. The lyophilized pharmaceutical composition of any one of Embodiments A 47-A 54, wherein vinca alkaloid N-oxide is vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

[0546] Embodiment A 59. The kit of Embodiment A 55, wherein vinca alkaloid N-oxide is vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

EXAMPLES

EXAMPLE 1

Efficacy evaluation of vinblastine $N_{b'}$-oxide (CPD100 Li) alone or in combination with anti-mCTLA-4, anti-mPD-L1, or anti-mVISTA

[0547] The anti-cancer effects of CPD100 Li alone or in combination with anti-mCTLA-4, anti-mPD-L1, or anti-mVISTA against CT26.WT murine colon carcinoma in female BALB/c mice were evaluated. CPD100 Li is a liposomal formulation of vinblastine $N_{b'}$-oxide comprising sphingomyelin/cholesterol (55/45; mol/mol).

Test Agents and Vehicles

[0548] Isotype control (Clone MPC-11)

Supplier	BioXCell	Lot/ Cat #	645420M2/BP0086
Date received	NA	Physical description	Clear, colorless solution
Concentration	4.11 mg/mL	Storage	4°C
Mol. Formula	NA	Mol wt/Form wt	NA
Purity	NA	% Parent	NA
Vehicle	Dulbecco's Phosphate Buffered Saline (DPBS)	High Dose Formulation	1 mg/mL
Formulation pH	7.4	Stability	7 days
Form. Desc.	Clear, colorless solution	Storage	4°C
Dose volume	0.01 mL/g	Dose expressed as	Vendor indicated, uncorrected

[0549] CPD100Li

Supplier	Cascade Prodrug Inc.	Lot/ Cat #	CPD100
Date received	7/29/2020	Physical description	White powder
Concentration	NA	Storage	4°C
Mol. Formula	NA	Mol wt/Form wt	827/827 g/mole
Purity	100%	% Parent	100%
Vehicle	Saline	High Dose Formulation	3.75 mg/mL
Formulation pH	5.3	Stability	1 day
Form. Desc.	powder	Storage	4°C
Dose volume	0.008 mL/g	Dose expressed as	Bulk, uncorrected
Comment	CPD100Li is a liposomal formulation of vinblastine N_b-oxide comprising sphingomyelin/cholesterol (55/45; mol/mol). *See* Shah *et al.*, *Journal of Controlled Release 253*:37–45 (2017).		

[0550] Anti-mCTLa-4 (Clone 9D9)

Supplier	BioXCell	Lot/ Cat #	731719A2/BP0164
Date received	NA	Physical description	Clear, colorless solution
Concentration	8.50 mg/mL	Storage	4°C
Mol. Formula	NA	Mol wt/Form wt	NA
Purity	NA	% Parent	NA
Vehicle	DPBS	High Dose Formulation	1 mg/mL
Formulation pH	NA	Stability	7 days
Form. Desc.	Clear, colorless solution	Storage	4°C
Dose volume	0.01 mL/g	Dose expressed as	Vendor indicated, uncorrected

[0551] Anti-mPD-L1 (Clone 10F.9G2)

Supplier	BioXCell	Lot/ Cat #	720619J3/BP0101
Date received	NA	Physical description	Clear, colorless solution
Concentration	6.34 mg/mL	Storage	4°C
Mol. Formula	NA	Mol wt/Form wt	NA
Purity	NA	% Parent	NA
Vehicle	DPBS	High Dose Formulation	1.175 mg/mL
Formulation pH	7.1	Stability	7 days
Form. Desc.	Clear, colorless solution	Storage	4°C
Dose volume	0.01 mL/g	Dose expressed as	Vendor indicated, uncorrected

[0552] Anti-mVISTA (Clone 13F3)

Supplier	BioXCell	Lot/ Cat #	704218J3/BP0310
Date received	NA	Physical description	Clear, colorless solution
Concentration	6.93 mg/mL	Storage	4°C
Mol. Formula	NA	Mol wt/Form wt	NA
Purity	NA	% Parent	NA
Vehicle	DPBS	High Dose Formulation	1 mg/mL
Formulation pH	7.3	Stability	7 days
Form. Desc.	Clear, colorless solution	Storage	4°C
Dose volume	0.01 mL/g	Dose expressed as	Vendor indicated, uncorrected

Animals and Husbandry

[0553] All procedures carried out in this experiment were conducted in compliance with the applicable laws, regulations and guidelines of the National Institutes of Health (NIH).

Species	Mouse	Source	Envigo
Strain	BALB/c (BALB/cAnNHsd)	Sex	Female
Age at implant	7-8 weeks	On Study/Total	104/182
Diet	Teklad 2918.15 Rodent Diet	Water	Ad libitum
Supplements	Hydrogel added to the cage bottom when body weight loss exceeded 10%.	Acclimation	7 days
Housing	Innovive disposable ventilated caging with corn cob bedding inside Biobubble® Clean Rooms	Animals/cage	5 or less
Temp	70±2°F	Light cycle	12/12 hr
Humidity	30-70%	ID method	Ear punch
Measure freq	3/week	Weigh freq	3/week
Staged by	Calipers	Min individual weight (D7)	16.7 g
Overall mean body weight (D7)	19.1 g	Overall mean tumor burden (D7)	93 mm^3
Necropsy	Yes	Health Checks	Daily
Euthanasia criteria	Study termination, >2000mm^3 tumor burden, >20% body weight loss and severe clinical signs.		

Cell Preparation/Implantation

Model	CT26.WT	Histotype	Murine colon carcinoma
Source	ATCC	Implant type	Cells
Media	RPMI 1640 Medium, 1 mM Na Pyruvate, 10 mM HEPES buffer, 2.8 mL 45% glucose (1.25 g), 10% Non-Heat-Inactivated Fetal Bovine Serum (FBS) and 1% Penicillin/Streptomycin/L-Glutamine (PSG)	Dissociation solution	0.25% Trypsin/2.21 mM EDTA in HBSS
Route	Subcutaneous	Location	High right axilla
Inoculum	5.00E+05 trypan-excluding cells	Implant media	Serum-free RPMI 1640 Medium
Matrigel	0%	Inj. Volume	200 µL
Viability (pre)	80%	Viability (post)	78%

Treatment

[0554] All mice were sorted into study groups based on caliper estimation of tumor burden. The mice were distributed to ensure that the mean tumor burden for all groups was within 10% of the overall mean tumor burden for the study population. Study groups were treated according to the schedule set forth in Table 3

Table 3

Group	N	Treatment	Dose	ROA	Regimen	Days of Treatment
1	8	Vehicle	0.16 mL/20 g	IV	Q14Dx2	7, 21
		isotype control (Clone MPC-11)	10 mg/kg	IP	(Q3Dx2,10)(x2)	7, 10, 21, 24
2	8	CPD100 Li	30 mg/kg	IV	Q14Dx3	7, 21, 35
3	8	CPD100 Li	30 mg/kg	IV	Q14Dx3	7, 21, 35
		isotype control (Clone MPC-11)	10 mg/kg	IP	(Q3Dx2,10)(x2); QDx1 (D35)	7, 10, 21, 24, 35
4	8	anti-mCTLA-4 (Clone 9D9)	10 mg/kg	IP	(Q3Dx2,10)(x2)	7, 10, 21, 24
5	8	anti-mPD-L1 (Clone 10F.9G2)	10 mg/kg	IP	Q3Dx2; QDx1 (D21)	7, 10, 21
6	8	anti-mVISTA (Clone 13F3)	10 mg/kg	IP	Q3Dx2; QDx1 (D21)	7, 10, 21

7	8	CPD100 Li	30 mg/kg	IV	Q14Dx3	7, 21, 35
		anti-mCTLA-4 (Clone 9D9)	10 mg/kg	IP	(Q3Dx2,10)(x2); QDx1 (D35)	7, 10, 21, 24, 35
8	8	CPD100 Li	30 mg/kg	IV	Q14Dx2	7, 21
		anti-mPD-L1 (Clone 10F.9G2)	10 mg/kg	IP	Q3Dx2; QDx1 (D21)	7, 10, 21
9	8	CPD100 Li	30 mg/kg	IV	Q14Dx2	7, 21
		anti-mVISTA (Clone 13F3)	10 mg/kg	IP	Q3Dx2; QDx1 (D21)	7, 10, 21

Tumor Growth/General Observations/Controls

[0555] The mean estimated tumor burden for all groups in the experiment on the first day of treatment was 93 mm^3, and all groups in the experiment were well-matched. All animals weighed at least 16.7 g at the initiation of therapy. Mean group body weights at first treatment were also well-matched, with an overall mean body weight of 19.1 g. Control animals experienced a 3.4 g (18.1%) mean weight gain during the treatment regimen. The median tumor volume doubling time for the Control Group was 2.6 days. There were no regressions in the Control Group.

[0556] A tumor burden of 2000 mm^3 was chosen for evaluation of efficacy by time to progression. In the Control Group, the median time to progression was 14 days.

[0557] Efficacy evaluation was measured by median $\Delta T/\Delta C$ on Day 20.

[0558] All thioglycolate cultures of cells used for implantation of this study were negative for gross bacterial contamination. All of this information is consistent with historical norms and the experiment was judged to be technically satisfactory and the data appropriate for evaluation.

Miscellaneous

[0559] Day 0 – The day on which the tumors are implanted (standard) or the day of first treatment.

[0560] Treatment Window – Begins with the first delivered dose and ends 2 weeks after the last treatment for each individual group.

Efficacy

[0561] ΔC and ΔT – Are individual mouse endpoints that are calculated for each mouse as follows:

$$\Delta T = T_t - T_0 \text{ and } \Delta C = C_t - C_0,$$

[0562] Where T_t and T_0 are the tumor burdens of a treated mouse at time t or at the initiation of dosing, respectively. ΔC reflects similar calculations for the control mice.

[0563] Median ΔT/ΔC – Is a group endpoint. It is calculated for each day of treatment as:

$$Median\frac{\Delta T}{\Delta C} = \left(\frac{\Delta T_{med}}{\Delta C_{med}}\right) * 100 = \left(\frac{median(T_t - T_0)}{median(C_t - C_0)}\right) * 100$$

[0564] The results are presented as a %. When the median ΔT/ΔC is negative (the median treated tumor burden is regressing), the median ΔT/ΔC is not reported and the Median % Regression is reported instead.

[0565] Tumor Growth Inhibition (TGI) – TGI is a group endpoint. The convention established by the NCI many years ago for calculation of this endpoint was followed. Tumor growth inhibition is calculated only when the median tumor burden is increasing (positive median ΔT). When the median tumor burden is regressing (negative median ΔT), the percent regression is calculated instead. TGI is calculated as follows:

$$\%TGI = \left(1 - \frac{\Delta T_{med}}{\Delta C_{med}}\right) * 100$$

where ΔT_{med} is the median ΔT in the treated group, and ΔC_{med} is the median ΔC of the control group on any given day.

[0566] Time to Progression (TP) – Time to progression is an individual endpoint and can be used as a surrogate for lifespan or time on study. The selected tumor evaluation size is tumor model and study dependent. TP data is analyzed by Kaplan Meier methods just as traditional lifespan data. The Time to Progression for an individual animal is the number of days between initiation of treatment and death or the day that the animal reaches a selected evaluation size. The initiation of treatment is the day of first treatment in the study as a whole and is not specific to the group in question. Time to progression is a log-linear interpolation between the adjacent data points on either side of the selected tumor evaluation size. This normalizes the evaluation criteria for all animals.

[0567] If animals do not reach the selected evaluation size and is euthanized or found dead due to disease progression or lack of treatment tolerance, lifespan is reported instead

of Time to Progression. Animals euthanized or found dead for causes unrelated to disease progression (technical errors, etc.) are excluded from this calculation and reported as "NA". The median Time to Progression for a group is used to calculate the % Increase in Time to Progression (%ITP).

[0568] % Increase in Time to Progression (%ITP) – %ITP is a group endpoint. It is calculated as:

$$\%ITP = \left\{\frac{[(median\ Treated\ TP) - (median\ Control\ TP)]}{median\ Control\ TP}\right\} * 100$$

[0569] Tumor Doubling Time (Td) – Td is an individual and group parameter, typically expressed as the median Td of the group. It is measured in days. Td can be calculated from any type of volumetric data (caliper measurements, BLI signals, etc). For QC purposes it is calculated for the exponential portion of the tumor growth curve. Data points during any lag phase and in the Gompertzian advanced stage are not included. Typical tumor burden limits are between 100 and 1000mm^3, but actual selection is data driven. Td is calculated for each mouse from a least square best fit of a log/linear plot of tumor burden vs day as:

$$Td = \log 2 / slope$$

[0570] On rare occasions the median Td is used as a potential indicator of efficacy. As such it is calculated as the median for every group, over a specified range of days thought to reflect a period of response to therapy.

Tumor Regression

[0571] Complete Regression (CR) – An animal is credited a complete regression if its tumor burden is reduced to an immeasurable volume at any point after the first treatment. Our convention is to record any tumor volume measurement less than 63mm3 as a "0". The CR must be maintained for at least 2 consecutive measurements. This is in keeping with the convention of the NCI and reflects the inherent mechanical error in such measurements in addition to the biology of what is measured at those small sizes. (Individual efficacy parameter)

[0572] Partial Regression - An animal is credited with a partial regression if its tumor burden decreases to less than half of the tumor burden at first treatment. The PR must be maintained for at least 2 consecutive measurements for caliper driven studies. (For BLI

driven studies the required confirmation is waived because of the dynamic range of the measurements and typically longer intervals between imaging.) PRs are tabulated exclusive of CRs, thus an animal that achieves a CR is not also counted as a PR. (Individual efficacy parameter)

[0573] Tumor-Free Survivor (TFS) – A TFS is any animal that (1) survives until termination of the study, and (2) has no reliably measurable evidence of disease at study termination. Mice that are tumor–free at some point during the study but are then euthanized for sampling or other purposes prior to the end of the study are not considered TFS. They are excluded from calculation of the %TFS.

Results

[0574] The mean tumor volume curves of Groups 1-9 are provided in Fig. 1. The mean body weight change curves of Groups 1-9 are provided in Fig. 2. A summary of these results is provided in Table 4.

[0575] Combination treatment with CPD100 Li + anti-mCTLA-4 (Group 7) produced surprising anti-cancer activity in the CT26.WT (colon carcinoma) model, resulting in a Day 20 median $\Delta T/\Delta C$ value of 4%, an increase in time to progression of >207%, and a 62.5% incidence of complete tumor regressions with 25.0% remaining as tumor-free survivors at the end of the study.

Table 4

Group #	Weight Change in Treatment Window (%)	Deaths In Treatment Window (%)	Median ΔT/ ΔC Day 20 (%)	Increased Time to Progression (%)	Partial Regression (%)	Complete Regression (%)	Tumor Free Survivors (%)
1	18.1	0.0	NA	NA	0.0	0.0	0.0
2	-7.5	12.5	56	128	0.0	0.0	0.0
3	-8.5	37.5	60	71	0.0	0.0	0.0
4	13.0	0.0	55	35	0.0	0.0	0.0
5	12.1	25.0	54	42	0.0	0.0	0.0
6	8.1	25.0	59	21	0.0	0.0	0.0
7	-14.0	25.0	4	>207	0.0	62.5	25.0
8	-13.6	87.5	30	7	0.0	0.0	0.0
9	-8.7	87.5	29	7	0.0	0.0	0.0

EXAMPLE 2

[0576] A clinical study compares progression-free or overall survival using pembrolizumab or nivolumab to pembrolizumab or nivolumab in combination with vinblastine $N_{b'}$-oxide for participants with cancer who are untreated or have progressed after prior therapy. Participants will be randomized to receive either standard anti-PD-1 therapy plus placebo or standard anti-PD-1 therapy plus vinblastine $N_{b'}$-oxide.

[0577] Primary Outcome Measures: Progression-free-survival (PFS) and/or Overall survival (OS)

[0578] Secondary Outcome Measures: Overall response rate (ORR) and/or Response Duration

Eligibility

[0579] Ages Eligible for Study: Generally – 18 Years and older

[0580] Genders Eligible for Study: Both

Inclusion Criteria:

[0581] Histologically or cytologically confirmed diagnosis of cancer not amenable to local therapy

[0582] Must consent to allow correlative studies; must provide a newly obtained tissue/biopsy specimen (or specimen obtained within 60 days of consenting)

[0583] Radiographically measurable disease

[0584] Eastern Cooperative Oncology Group Performance Status of 0 or 1

[0585] Patient may have cancer with overexpressed HIF.

Exclusion criteria:

[0586] Chemotherapy, radiation therapy, or biological therapy within four weeks prior to the first dose of study drug, or not recovered from the AEs due to cancer therapies administered more than four weeks earlier

[0587] Participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of study drug

[0588] Expected to require any other form of systemic or localized antineoplastic therapy while on study

[0589] Chronic systemic steroid therapy within two weeks before the planned date for first dose randomized treatment or on any other form of immunosuppressive medication

[0590] Known history of any other than the current malignancy excepting adequately treated basal or squamous cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, breast cancer, or other in situ cancers

[0591] Known active central nervous system (CNS) metastases and/or carcinomatous meningitis

[0592] Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents

[0593] Prior treatment with any other anti-programmed cell death (PD) agent

[0594] Active infection requiring systemic therapy

[0595] Known history of Human Immunodeficiency Virus (HIV)

[0596] Active Hepatitis B or Hepatitis C

[0597] Regular user (including recreational use of) illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol)

[0598] Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

Protocols:

[0599] A first group of patients receive 2-10 mg/kg pembrolizumab (or flat dose equivalent) administered by intravenous infusion every three weeks and vinblastine $N_{b'}$-oxide administered orally or by IV at 0.01-100 mg once weekly. Vinblastine $N_{b'}$-oxide administration is started 1-14 days prior to initiating pembrolizumab therapy and, optionally, continues on the day of pembrolizumab administration, and, optionally, continues until disease progression or until vinblastine $N_{b'}$-oxide therapy is no longer beneficial. The control patients receive 2-10 mg/kg pembrolizumab (or flat dose equivalent) administered by intravenous infusion every three weeks.

[0600] A second group of patients receive 3 mg/kg nivolumab administered over 60 minutes by intravenous infusion every 2 weeks and vinblastine $N_{b'}$-oxide administered orally or by IV at 0.01-100 mg once weekly. Vinblastine $N_{b'}$-oxide administration is started 1-14 days prior to prior to initiating nivolumab therapy, continues on the day of nivolumab administration, and, optionally, continues until disease progression or until

vinblastine $N_{b'}$-oxide therapy is no longer beneficial. The control patients receive 3 mg/kg nivolumab administered over 60 minutes by intravenous infusion every 2 weeks.

EXAMPLE 3

Open label Phase 2 study assessing the combination of checkpoint blockade immunotherapy and vinblastine $N_{b'}$-oxide in patients relapsing from or refractory to standard anti-PD-1 therapy

[0601] Primary endpoint: ORR

[0602] Secondary endpoints: PFS, OS, Duration of Response, Safety

Inclusion criteria:

[0603] Histologically confirmed diagnosis of cancer not amenable to local therapy

[0604] Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

[0605] At least one measurable lesion

[0606] Adequate organ function

[0607] Prior therapy with an anti-PD-1 or anti-PD-L1 antibody

[0608] Patient has disease with overexpressed MYC and/or MCL1

Exclusion criteria:

[0609] Chemotherapy, targeted small molecule therapy, radiotherapy, or biological cancer therapy (including monoclonal antibodies) within 4 weeks prior to the first dose of trial treatment, or not recovered (<= Grade 1 or baseline) from adverse events due to a previously administered agent.

[0610] Expected to require any other form of systemic or localized antineoplastic therapy while in study.

[0611] Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

[0612] Documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.

[0613] Receiving systemic steroid therapy or any other form of immunosuppressive therapy within 1 week prior to the first dose of study treatment.

[0614] Received a live vaccine within 4 weeks prior to the first dose of trial treatment.

[0615] History or evidence of active pneumonitis.

[0616] Human immunodeficiency virus (HIV)-positive.

[0617] Active Hepatitis B or C.

[0618] Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial treatment through 120 days after the last dose of study medication.

Dosing protocol:

Table 5 Vinblastine N_b-oxide + CheckPoint Inhibitor Combination Dosing & Schedules

	Every 2 weeks	Every 3 weeks	Every 4 weeks
Pembrolizumab 2mg/kg	X	X	
Pembrolizumab 10mg/kg	X	X	
Pembrolizumab 200mg	X	X	
Pembrolizumab 300mg	X	X	
Nivolumab 3mg/kg	X	X	X
Nivolumab 1mg/kg	X	X	X
Pidilizumab 3mg/kg	X	X	X
Pidilizumab 1.5mg/kg	X	X	X
STI-A1110 2mg/kg	X	X	X
STI-A1110 2mg/kg	X	X	X
Durvalumab 10mg/kg	X	X	
Durvalumab 2mg/kg	X	X	
Durvalumab 15,g/kg		X	X
Avelumab 1200mg	X	X	X
Avelumab 10mg/kg	X	X	X
Avelumab 5mg/kg	X	X	X
Atezolizumab 1200mg		X	

STI-A1014 10mg/kg	X	X	X
STI-A1014 15mg/kg	X	X	X

* vinblastine $N_{b'}$-oxide is dosed weekly (0.1-100 mg/kg) starting 1-14 day prior to initiating checkpoint inhibitor therapy and continuing until disease progression or investigator decision

Results

[0619] Combining vinblastine $N_{b'}$-oxide with at least one checkpoint inhibitor in patients may reverse immune evasion and induce clinically relevant responses in patients previously nonresponding to or failing checkpoint inhibitor therapy or *de novo* cancer patients. Objective responses are associated with lack of tumor progression and extension of long term survival compared to historical controls using (the antibody) alone. In one embodiment, patients receiving vinblastine $N_{b'}$-oxide and an immune checkpoint inhibitor achieve an extension of time to progression (or progression-free survival) of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months. In another embodiment, at least some of the patients receiving vinblastine $N_{b'}$-oxide and an immune checkpoint inhibitor achieve an extension of duration of response of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months.

EXAMPLE 4

Placebo-controlled, randomized phase 2 study of pembrolizumab plus vinblastine $N_{b'}$-oxide vs. pembrolizumab + placebo in participants with previously-treated locally advanced unresectable or metastatic colorectal cancer

[0620] Primary Endpoint: PFS

[0621] Secondary Endpoint: ORR, Duration of Response

Inclusion criteria:

[0622] Histologically-proven locally advanced unresectable or metastatic high colorectal carcinoma

[0623] Previously treated with at least two lines of approved standard therapies, which must include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab

[0624] Eastern Cooperative Oncology Group performance status of 0 or 1

[0625] Patient has disease that, optionally, overexpresses HIF

[0626] Life expectancy of greater than 3 months

[0627] At least one measureable lesion

[0628] Female participants of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication

[0629] Male participants should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study medication

[0630] Adequate organ function

Exclusion criteria:

[0631] Currently participating in another study and receiving trial treatment, participated in a study of an investigational agent and received trial treatment within 4 weeks of the first dose of medication in this study, or used an investigational device within 4 weeks of the first dose of medication in this study

[0632] Active autoimmune disease that has required systemic treatment in past 2 years

[0633] Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication

[0634] Known active central nervous system (CNS) metastases and/or carcinomatous meningitis

[0635] Prior monoclonal antibody (mAb), chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or not recovered (i.e., $\leqslant$ Grade 1 or at baseline) from adverse events due to a previously administered agent

[0636] Prior therapy with an anti-programmed cell death (PD)-1, anti-PD-L1, or anti-PD-L2 agent, or participant has previously participated in Merck pembrolizumab (MK-3475) clinical trial

[0637] Known additional malignancy that is progressing or requires active treatment with the exception of basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer

[0638] Received a live vaccine within 30 days of planned start of study medication

[0639] Known history of human immunodeficiency virus (HIV)

[0640] Known active Hepatitis B or C

[0641] Known history or any evidence of interstitial lung disease or active, non-infectious pneumonitis

[0642] Active infection requiring systemic therapy

[0643] Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

[0644] Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial medication

Dosing protocol:

[0645] Patients receive 2-10 mg/kg pembrolizumab administered by intravenous infusion every three weeks and vinblastine $N_{b'}$-oxide administered orally or IV 1-7 days prior to pembrolizumab administration and, optionally, on the day of pembrolizumab administration, and, optionally, continuously thereafter until disease progression or until it is no longer beneficial. The control patients receive 2 mg/kg pembrolizumab administered by intravenous infusion every three weeks.

Results:

[0646] When used in patients with tumors overexpressing HIF, vinblastine $N_{b'}$-oxide combined with pembrolizumab provides better clinical activity than pembrolizumab alone in the same patients. Objective responses are associated with lack of tumor progression and extension of long term survival compared to historical controls using (the antibody) alone. In one embodiment, patients receiving vinblastine $N_{b'}$-oxide and pembrolizumab achieve an extension of time to progression (or progression-free survival) of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months. In another embodiment, at least some of the patients receiving vinblastine $N_{b'}$-oxide and pembrolizumab achieve an extension of duration of response of at least 2 months, at least 4 months, at least 6 months, at least 8 months, at least 10 months or at least 12 months.

[0647] Having now fully described the methods, compounds, and compositions herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without

affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A method of treating a patient having cancer, the method comprising administering to the patient in need thereof a therapeutically effective amount of:

(a) a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

(b) one or more immune checkpoint inhibitors;

wherein the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof is:

(i) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; (ii) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; (iii) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; (iv) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; or (v) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; and

the one or more immune checkpoint inhibitors comprise an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-LAG3 antibody, an anti-TIM3 antibody, an anti-VISTA antibody, an anti-TIGIT antibody, or an anti-cd47 antibody, or a combination thereof.

2. The method of claim 1, wherein the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, is administered to the patient encapsulated in a liposome.

3. The method of claim 2, wherein the liposome comprises sphingomyelin and cholesterol.

4. The method of claim 2, wherein the liposome comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

5. The method of any one of claims 1-4, wherein the immune checkpoint inhibitor is an anti-PD-1 antibody selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, STI-A1110, PDR001, MEDI-0680, AGEN2034, BGB-A317, AB122, TSR-

042, PF-06801591, cemiplimab, SYM021, JNJ-63723283, HLX10, LZM009, and MGA012.

6. The method of any one of claims 1-4, wherein the immune checkpoint inhibitor is an anti-PD-L1 antibody selected from the group consisting of avelumab, atezolizumab, durvalumab, and STI-A1014.

7. The method of any one of claims 1-4, wherein the immune checkpoint inhibitor is an anti-CTLA-4 antibody selected from the group consisting of ipilimumab and tremelimumab.

8. The method of any one of claims 1-4, wherein the immune checkpoint inhibitor is an anti-LAG3 antibody that is GSK2831781.

9. The method of any one of claims 1-4, wherein the immune checkpoint inhibitor is an anti-TIM3 antibody.

10. The method of any one of claims 1-4, wherein the immune checkpoint inhibitor is an anti-VISTA antibody.

11. The method of any one of claims 1-4, wherein the immune checkpoint inhibitor is an anti-cd47 antibody.

12. The method of any one of claims 1-4, wherein the immune checkpoint inhibitor is an anti-TIGIT antibody.

13. The method of any one of claims 1-12, wherein the cancer selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia,

AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatocellular carcinoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma,

neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

14. The method of any one of claims 1-13, wherein HIF-1α expression is differentially present in a sample taken from the patient as compared with a biological sample taken from a subject of another phenotypic status.

15. A lyophilized pharmaceutical composition comprising a vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof, encapsulated in a liposome, wherein the vinca alkaloid N-oxide, or a pharmaceutically acceptable salt or solvate thereof is (i) vinblastine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; (ii) vincristine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; (iii) vindesine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; (iv) vinorelbine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof; or (v) vinflunine $N_{b'}$-oxide, or a pharmaceutically acceptable salt or solvate thereof.

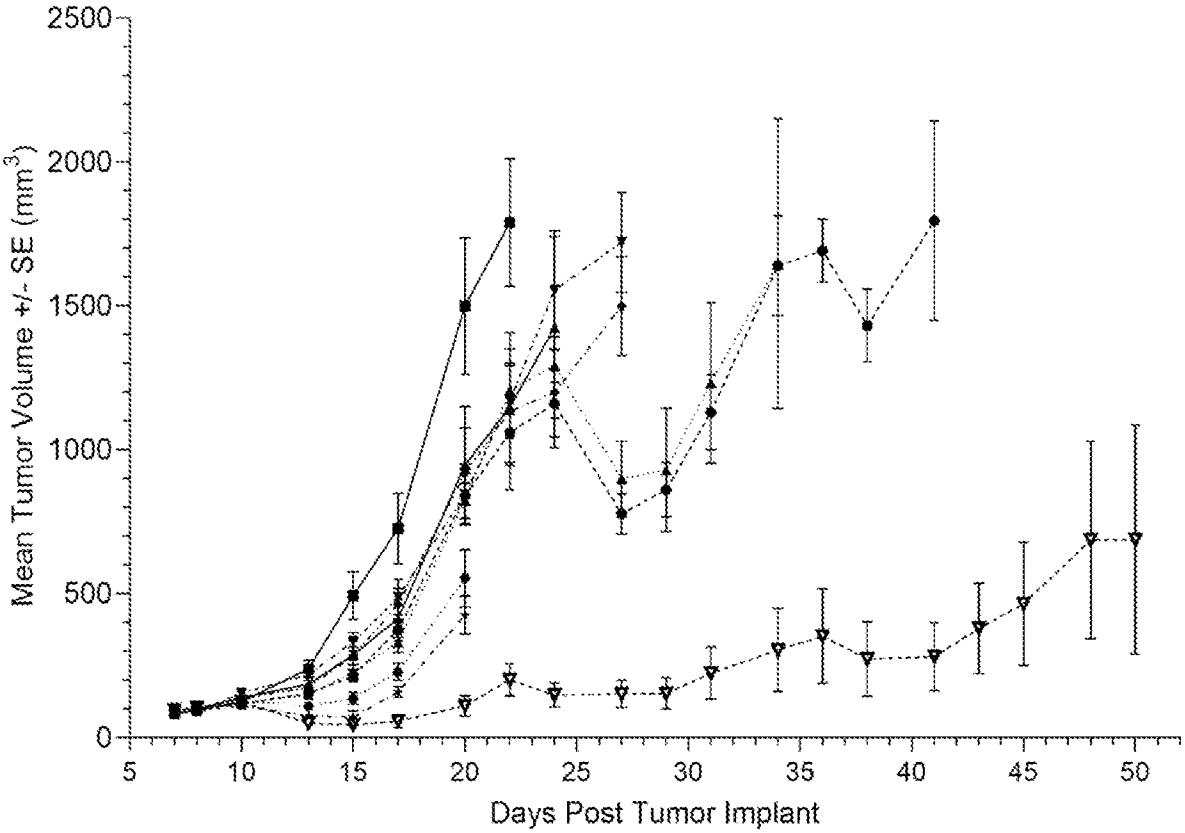
16. The lyophilized pharmaceutical composition of claim 15, wherein the liposome comprises sphingomyelin and cholesterol.

17. The lyophilized pharmaceutical composition of claim 15, wherein the liposome comprises sphingomyelin, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycerol)-2000].

18. The lyophilized pharmaceutical composition of any one of claims 15-17, wherein the composition is reconstituted in a sterile aqueous solution for parenteral administration to a patient.

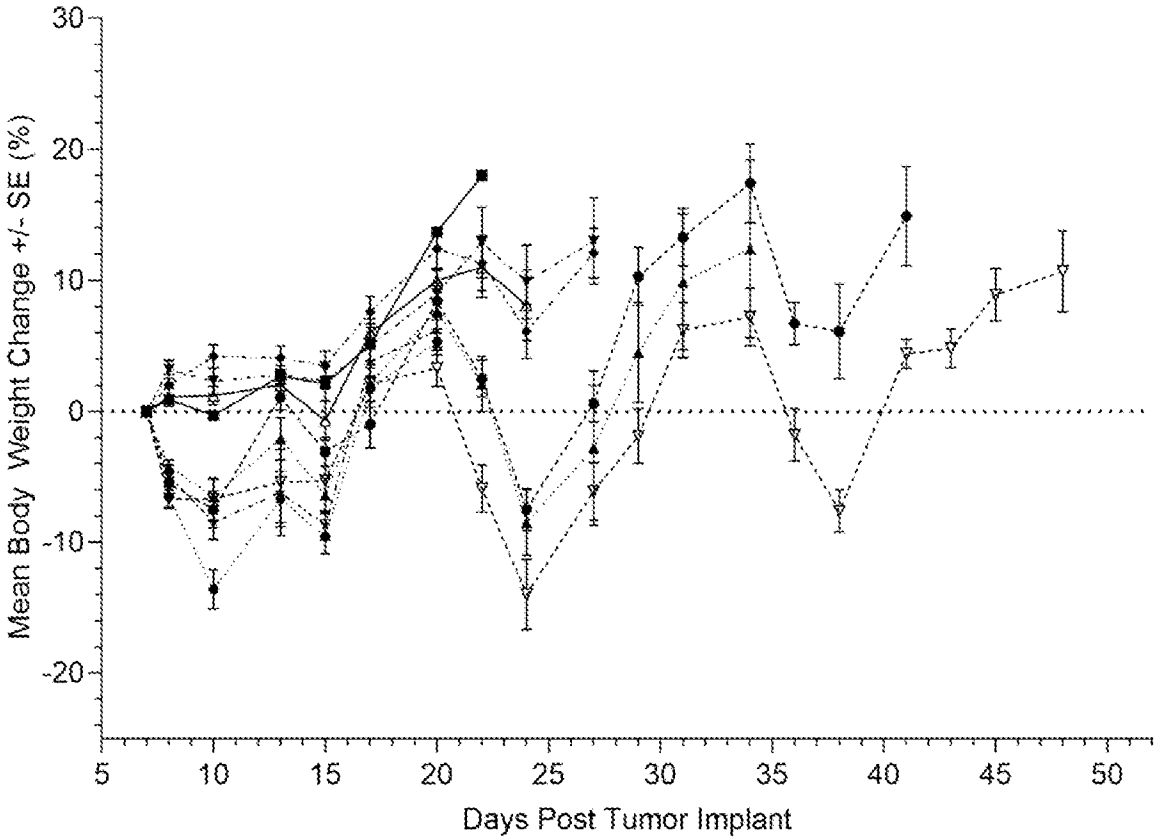
19. The lyophilized pharmaceutical composition of claim 18, wherein the sterile aqueous solution is water, saline, or 5% dextrose in water.

20. A kit comprising the lyophilized pharmaceutical composition of any one of claims 15-19, and instructions for reconstituting the lyophilized pharmaceutical composition in a sterile aqueous solution for parenteral administration together with an immune checkpoint inhibitor to a patient having cancer.



- G1 – Vehicle 0.16 mL/20 IV Q14Dx2, isotype control (Clone MPC-11) 10 mg/kg IP (Q3Dx2, 10)(x2)
- G2 – CPD100 Li 30 mg/kg IV Q14Dx3
- G3 – CPD100 Li 30 mg/kg IV Q14Dx3, isotype control (Clone MPC-11) 10 mg/kg IP (Q3Dx2, 10)(x2), isotype control (Clone MPC-11) 10 mg/kg IP QDx1
- G4 – anti-mCTLA-4 (Clone 9D9) 10 mg/kg IP (Q3Dx2, 10(x2)
- G5 – anti-mPD-L1 (Clone 10F.9G2) 10 mg/kg IP Q3Dx2, anti-mPD-L1 (Clone 10F.9G2) 10 mg/kg IPQDx1
- G6 – anti-mVISTA (Clone 13F3) 10 mg/kg IP Q3Dx2, anti-mVISTA (Clone 13F3) 10mg/kg IP QDx1
- G7 – CPD100 Li 30 mg/kg IV Q14Dx3, anti-mCTLA-4 (Clone 9D9) 10 mg/kg IP (Q3Dx2, 10)(x2), anti-mCTLA-4 (Clone 9D9) 10 mg/kg IP QDx1
- G8 – CPD100 Li 30 mg/kg IV Q14Dx2, anti-mPD-L1 (Clone 10F.9G2) 10 mg/kg IP Q3Dx2, anti-mPD-L1 (Clone 10F.9G2) 10 mg/kg IP QDx1
- G9 – CPD100 Li 30 mg/kg IV Q14Dx2, anti-mVISTA (Clone 13F3) 10 mg/kg IP Q3Dx2, anti-mVISTA (Clone 13F3) 10 mg/kg IP QDx1

Fig. 1



G1 – Vehicle 0.16 mL/20 IV Q14Dx2, isotype control (Clone MPC-11) 10 mg/kg IP (Q3Dx2, 10)(x2)

G2 – CPD100 Li 30 mg/kg IV Q14Dx3

G3 – CPD100 Li 30 mg/kg IV Q14Dx3, isotype control (Clone MPC-11) 10 mg/kg IP (Q3Dx2, 10)(x2), isotype control (Clone MPC-11) 10 mg/kg IP QDx1

G4 – anti-mCTLA-4 (Clone 9D9) 10 mg/kg IP (Q3Dx2, 10(x2)

G5 – anti-mPD-L1 (Clone 10F.9G2) 10 mg/kg IP Q3Dx2, anti-mPD-L1 (Clone 10F.9G2) 10 mg/kg IPQDx1

G6 – anti-mVISTA (Clone 13F3) 10 mg/kg IP Q3Dx2, anti-mVISTA (Clone 13F3) 10mg/kg IP QDx1

G7 – CPD100 Li 30 mg/kg IV Q14Dx3, anti-mCTLA-4 (Clone 9D9) 10 mg/kg IP (Q3Dx2, 10)(x2), anti-mCTLA-4 (Clone 9D9) 10 mg/kg IP QDx1

G8 – CPD100 Li 30 mg/kg IV Q14Dx2, anti-mPD-L1 (Clone 10F.9G2) 10 mg/kg IP Q3Dx2, anti-mPD-L1 (Clone 10F.9G2) 10 mg/kg IP QDx1

G9 – CPD100 Li 30 mg/kg IV Q14Dx2, anti-mVISTA (Clone 13F3) 10 mg/kg IP Q3Dx2, anti-mVISTA (Clone 13F3) 10 mg/kg IP QDx1

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/65059

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/435; A61K 31/55; C07D 519/04 (2022.01)

CPC - A61P 1/00; A61P 1/04; A61P 1/16

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2008/0305075 A1 (CURD et al.) 11 December 2008 (11.12.2008); para [0029], [0047], [0051], [0202], [0215], [0217]-[0222], [0272], [0274], [0306]; claim 50	15, (18-19)/15 --- 1-12, 16-17, (18-19)/(16-17)
Y	WO 2019/197583 A1 (AVACTA LIFE SCIENCES LIMITED) 17 October 2019 (17.10.2019); pg 19 para 8; pg 29 para 8-pg 30 para 1; pg 75 para 4; pg 76 para 3; pg 120 para 1; pg 139 para 4-5; pg 153 para 1-3; pg 154 para 3; pg 175 para 3; pg 176 para 3; pg 184 para 2	1-12
Y	US 2015/0209281 A1 (ONYX THERAPEUTICS, INC.) 30 July 2015 (30.07.2015); para [0002], [0009]-[0010], [0105], [0204]	4, (5-12)/4, 16-17, (18-19)/(16-17)
A	WO 2019/079596 A1 (EPIZYME, INC.) 25 April 2019 (25.04.2019); see entire document	1-12, 15-19
A	US 2005/0158375 A1 (KIMURA et al.) 21 July 2005 (21.07.2015); see entire document	1-12, 15-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
01 March 2022	MAR 24 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/65059

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

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

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

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

3. ☒ Claims Nos.: 13-14, 20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.