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(54) Title: COMBINATION OF CK2 INHIBITORS AND IMMUNE CHECKPOINT MODULATORS FOR CANCER TREATMENT

(57) Abstract: Compositions and methods are disclosed which are useful for the treatment and prevention of proliferative disorders.



COMBINATION OF CK2 INHIBITORS AND IMMUNE CHECKPOINT MODULATORS FOR CANCER TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims priority from U.S. Provisional Application No. 62/243,841 filed October 20, 2015, the disclosures of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

10 This invention relates to methods for treating cancer in a subject comprising administering to the subject a combination of a CK2 inhibitor and an immune checkpoint modulator.

BACKGROUND OF THE INVENTION

15 The National Cancer Institute has estimated that in the United States alone, 1 in 3 people will be struck with cancer during their lifetime. Moreover, approximately 50% to 60% of people contracting cancer will eventually succumb to the disease. The widespread occurrence of this disease underscores the need for improved anticancer regimens for the treatment of malignancy.

20 In recent years there has been a growing shift in the understanding of the biology and immunology of cancer, with the recognition that the immune system provides built-in defense mechanisms against not only infectious agents but cancers as well. It is increasingly appreciated that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors.

25 However, the immune system also exerts a major effort to avoid immune over-activation, which could harm healthy tissues. Cancer takes advantage of this ability to hide from the immune system by exploiting a series of immune escape mechanisms that were developed to avoid autoimmunity. Among these mechanisms are the hijacking of immune-cell-intrinsic checkpoints that are induced on T-cell activation (Pardoll et al., *Nat Rev Cancer*
30 2012, 12:252-64). A novel approach in immunotherapy of cancer has been to counteract these resistance mechanisms, activating and allowing the endogenous immune system to reject tumors. Blockade of one of these checkpoints, cytotoxic T-lymphocyte-associated

antigen 4 (CTLA-4), provided the first clinical evidence of improvement in overall survival for the treatment of patients with metastatic melanoma (Hodi et al., *N Engl J Med* 2010, 363:711-23. [Erratum, *N Engl J Med* 2010, 363:1290]; Robert et al., *N Engl J Med* 2011, 364:2517-26).

5 The Programmed Death 1 receptor (PD-1) is another key checkpoint receptor expressed by activated T and B cells and mediates immunosuppression. PD-1 is a member of the CD28 family of receptors, which includes CD28, CTLA-4, ICOS, PD-1, and BTLA. Two cell surface glycoprotein ligands for PD-1 have been identified, Programmed Death Ligand-1 (PD-L1) and Programmed Death Ligand-2 (PD-L2), that
10 are expressed on antigen-presenting cells as well as many human cancers and have been shown to down-regulate T cell activation and cytokine secretion upon binding to PD-1. Inhibition of the PD-1/PD-L1 interaction mediates potent antitumor activity in preclinical models (U.S. Patent Nos. 8,008,449 and 7,943,743), and the use of antibody inhibitors of the PD-1/PD-L1 interaction for treating cancer has entered clinical trials (Brahmer et al.,
15 2010, *J Clin Oncol* 28:3167-75; Topalian et al., 2012, *N Engl J Med* 366:2443-54; Topalian et al., 2014, *J Clin Oncol* 32(10):1020-30; Hamid et al., 2013, *N Engl J Med* 369:134-144; Brahmer et al., 2012, *N Engl J Med* 366:2455-65; Flies et al., 2011, *Yale J Biol Med* 84:409-21; Pardoll, 2012, *Nat Rev Cancer* 12:252-64; Hamid and Carvajal, 2013, *Expert Opin Biol Ther* 13(6):847-61).

20 Protein kinase CK2 (formerly known as casein kinase II) is a highly conserved serine/threonine kinase. Protein kinase CK2 is ubiquitously distributed and constitutively active in eukaryotes. In mammals, the enzyme exists in two isozymic forms due to variations in the catalytic subunits of the enzyme. The CK2 holoenzyme is a heterotetrameric complex composed of two catalytic α (CK2A1) subunits or α' (CK2A2)
25 subunits and two regulatory β -subunits. The formation of CK2 complexes containing the catalytic subunits requires dimerization of the regulatory β -subunits. CK2 interacts with a variety of cellular proteins and has been implicated in various cellular processes such as cell proliferation and differentiation, cellular survival, and tumorigenesis. With respect to tumorigenesis, protein kinase CK2 has been implicated in kidney tumors (Stalter et al.,
30 “Asymmetric expression of protein kinase CK2 subunits in human kidney tumors”, *Biochem. Biophys. Res. Commun.*, 202:141-147 (1994)), mammary gland tumors (Landesman-Bollag et al., “Protein kinase CK2 in mammary gland tumorigenesis”,

Oncology, 20:3247-3257 (2001)), lung carcinoma (Daya-Makin et al., "Activation of a tumor-associated protein kinase (p40TAK) and casein kinase II in human squamous cell carcinomas and adenocarcinomas of the lung", *Cancer Res.*, 54:2262-2268 (1994)), head and neck carcinoma (Faust et al., "Antisense oligonucleotides against protein kinase CK2- α inhibit growth of squamous cell carcinoma of the head and neck *in vitro*", *Head Neck*, 22:341-346 (2000)), and prostate cancer (Wang et al., "Role of protein kinase CK2 in the regulation of tumor necrosis factor-related apoptosis inducing ligand-induced apoptosis in prostate cancer cells", *Cancer Res.*, 66:2242-2249 (2006)).

The present inventors have discovered that CK2 inhibitors can act synergistically when used in combination with certain immune checkpoint modulators (ICMs) such as an anti-Programmed Death-1 (PD-1) antibody or an anti-Cytotoxic T-Lymphocyte-associated Antigen 4 (CTLA-4) antibody. It is an object of the invention to provide efficacious immunotherapeutic treatment regimens wherein CK2 inhibitors are combined with ICMs for the treatment of proliferative diseases.

SUMMARY OF THE INVENTION

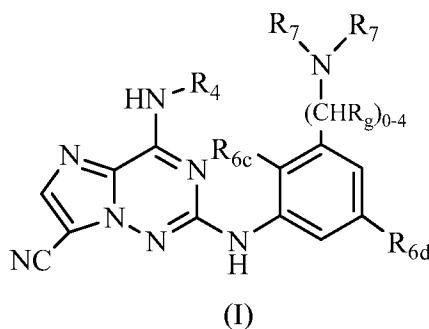
The present invention provides a method for the treatment of proliferative diseases, including cancer, which comprises administering to a subject in need thereof a synergistically, therapeutically effective amount of (1) a CK2 inhibitor and (2) an ICM.

In one embodiment, the ICM is selected from an antagonist of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4.

In another embodiment, the ICM is selected from an anti-CTLA-4 antibody, *i.e.*, ipilimumab (also referred to as Yervoy®) and an anti-PD-1 antibody, *i.e.* nivolumab (also referred to as Opdivo®).

In one embodiment, the CK2 inhibitor is selected from CX-4945 and CX-8184.

In another embodiment, the CK2 inhibitor is a compound of Formula (I):



including enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, prodrugs, hydrates, or solvates thereof, wherein

- 5 R_4 is selected from the group consisting of C_{1-4} alkyl substituted with 1-3 R_e , C_{3-6} cycloalkyl and heterocyclyl substituted with 1-3 R_e ;
- R_7 and R_7 together with the nitrogen atom to which they are both attached form a 4- to 7-membered monocyclic or 7- to 12-membered bicyclic heterocycle containing carbon atoms and additional 1-3 heteroatoms selected from the group consisting
- 10 of NR_{8a} , O, and $S(O)_2$ and substituted with 1-4 R_8 ;
- R_8 , at each occurrence, is independently selected from the group consisting of H, F, Cl, Br, C_{1-4} alkyl substituted with 1-4 R_e , =O, C_{2-4} alkenyl substituted with 1-5 R_e , -
 $(CHR_g)_rOR_b$, $-(CHR_g)_rS(O)_pR_c$, $-(CHR_g)_rC(=O)(CHR_g)_rR_d$, $-(CHR_g)_rNR_aR_a$, -
 $(CHR_g)_rC(=O)NR_aR_a$, $-(CHR_g)_rC(=O)NR_aS(O)_pR_c$, -
15 $(CHR_g)_rNR_a(CR_gR_g)_rC(=O)R_d$, $-(CHR_g)_rNR_aC(=O)OR_b$, -
 $(CHR_g)_rOC(=O)(CHR_g)_rR_d$, $-(CHR_g)_rOC(=O)(CHR_g)_rC(=O)OR_d$, -
 $(CHR_g)_rOC(=O)(CHR_g)_rC(=O)NR_aR_a$, $-(CHR_g)_rOC(=O)(CHR_g)_rNR_aC(=O)R_b$, -
 $(CHR_g)_rOC(=O)(CHR_g)_rNR_aR_a$, $-(CHR_g)_rNR_aC(=O)NR_aR_a$, -
 $(CHR_g)_rC(=O)(CH_2)_rOR_b$, $-(CHR_g)_rC(=O)(CHR_g)_rOC(=O)R_b$, -
20 $(CHR_g)_rS(O)_2NR_aR_a$, $-(CHR_g)_rNR_aS(O)_pNR_aR_a$, $-(CHR_g)_rNR_aS(O)_pR_c$, $-OPO_3H$, -
 $(CHR_g)_rC_{3-6}$ cycloalkyl substituted with 1-5 R_e , $-(CHR_g)_r$ -aryl substituted with 1-4 R_e and $-(CHR_g)_r$ -heterocyclyl substituted with 1-4 R_e ;
- R_{8a} is selected from the group consisting of H, C_{1-4} alkyl substituted with 1-5 R_e , C_{2-4} alkenyl substituted with 1-5 R_e , $-(CHR_g)_rOR_b$, $-(CHR_g)_rS(O)_pR_c$, -
25 $(CHR_g)_rC(=O)(CHR_g)_rR_d$, $-(CHR_g)_rNR_aR_a$, $-(CHR_g)_rC(=O)NR_aR_a$, -
 $(CHR_g)_rC(=O)NR_aS(O)_pR_c$, $-(CHR_g)_rNR_a(CR_gR_g)_rC(=O)R_d$, -
 $(CHR_g)_rNHC(=O)OR_b$, $-(CHR_g)_rOC(=O)(CHR_g)_rR_d$, -
 $(CHR_g)_rOC(=O)(CHR_g)_rC(=O)OR_d$, $-(CHR_g)_rOC(=O)(CHR_g)_rC(=O)NR_aR_a$, -

- $(\text{CHR}_g)_r\text{OC}(=\text{O})(\text{CHR}_g)_r\text{NR}_a\text{C}(=\text{O})\text{R}_b$, $-(\text{CHR}_g)_r\text{OC}(=\text{O})(\text{CHR}_g)_r\text{NR}_a\text{R}_a$, -
 $(\text{CHR}_g)_r\text{NR}_a(\text{CHR}_g)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CHR}_g)_r\text{C}(=\text{O})\text{OR}_b$, -
 $(\text{CHR}_g)_r\text{C}(=\text{O})(\text{CHR}_g)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CHR}_g)_r\text{S}(\text{O})_2\text{NR}_a\text{R}_a$, -
 $(\text{CHR}_g)_r\text{NR}_a\text{S}(\text{O})_p\text{NR}_a\text{R}_a$, $-(\text{CHR}_g)_r\text{NR}_a\text{S}(\text{O})_p\text{R}_c$, $-\text{OPO}_3\text{H}$, $-(\text{CHR}_g)_r\text{-C}_{3-6}$
 5 cycloalkyl substituted with 1-5 R_e , $-(\text{CHR}_g)_r$ -aryl substituted with 1-4 R_e and -
 $(\text{CHR}_g)_r$ -heterocyclyl substituted with 1-4 R_e ;
 R_a , at each occurrence, is independently selected from the group consisting of H, CN, C_{1-6}
 alkyl substituted with 1-5 R_e , C_{2-6} alkenyl substituted with 1-5 R_e , C_{2-6} alkynyl
 substituted with 1-5 R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl substituted with 1-5 R_e , and -
 10 $(\text{CH}_2)_r$ -heterocyclyl substituted with 1-5 R_e ; or R_a and R_a together with the
 nitrogen atom to which they are both attached form a heterocyclic ring substituted
 with 1-5 R_e ;
 R_b , at each occurrence, is independently selected from the group consisting of H, C_{1-6}
 alkyl substituted with 1-5 R_e , C_{2-6} alkenyl substituted with 1-5 R_e , C_{2-6} alkynyl
 15 substituted with 1-5 R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl substituted with 1-5 R_e , and -
 $(\text{CH}_2)_r$ -heterocyclyl substituted with 1-5 R_e ;
 R_c , at each occurrence, is independently selected from the group consisting of C_{1-6} alkyl
 substituted with 1-5 R_e , C_{2-6} alkenyl substituted with 1-5 R_e , C_{2-6} alkynyl
 substituted with 1-5 R_e , C_{3-6} carbocyclyl, and heterocyclyl;
 20 R_d , at each occurrence, is independently selected from the group consisting of H, OH, C_{1-6}
 alkyl substituted with 1-5 R_e , C_{2-6} alkenyl substituted with 1-5 R_e , C_{2-6} alkynyl
 substituted with 1-5 R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}$ carbocyclyl substituted with 1-5 R_e , and -
 $(\text{CH}_2)_r$ -heterocyclyl substituted with 1-5 R_e ;
 R_e , at each occurrence, is independently selected from the group consisting of H, N_3 , C_{1-6}
 25 C_{1-6} alkyl substituted with 1-5 R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(\text{CH}_2)_r\text{-C}_{3-6}$ cycloalkyl, -
 $(\text{CH}_2)_r$ -heterocyclyl, F, Cl, Br, $-(\text{CH}_2)_r\text{CN}$, NO_2 , $=\text{O}$, $-\text{OPO}_3\text{H}$, $-\text{OSi}(\text{C}_{1-4}\text{alkyl})_3$, -
 $(\text{CH}_2)_r\text{OC}_{1-5}$ alkyl, $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_r\text{OC}_{1-5}$ alkyl, $-(\text{CH}_2)_r\text{OH}$, $-(\text{CH}_2)_r\text{S}(\text{O})_2\text{C}_{1-5}$
 alkyl, $-(\text{CH}_2)_r\text{S}(\text{O})_2\text{R}_f$, $-(\text{CH}_2)_r\text{NHS}(\text{O})_2\text{C}_{1-5}\text{alkyl}$, $-\text{S}(\text{O})_2\text{NH}_2$, SH, $-(\text{CH}_2)_r\text{NR}_f\text{R}_f$, -
 $(\text{CH}_2)_r\text{NHC}(=\text{O})\text{OR}_f$, $-(\text{CH}_2)_r\text{NHC}(=\text{O})\text{R}_f$, $-(\text{CH}_2)_r\text{NHC}(=\text{NH})\text{NR}_f\text{R}_f$, -
 30 $(\text{CH}_2)_r\text{C}(=\text{O})(\text{CH}_2)_r\text{R}_f$, and $-(\text{CH}_2)_r\text{C}(=\text{O})\text{OR}_f$;
 R_f , at each occurrence, is independently selected from the group consisting of H, -
 $(\text{CH}_2)_r\text{OH}$, $-(\text{CH}_2)_r\text{OC}_{1-5}\text{alkyl}$, $\text{C}_{1-5}\text{alkyl}$ (optionally substituted with F, Cl, OH,

- NH₂), C₃₋₆ cycloalkyl optionally substituted with NH₂, -(CH₂)_rS(O)_pC₁₋₄alkyl, -NHC(=O)C₁₋₄alkyl, -C(=O)NH₂, -C(=O)OC₁₋₄alkyl, -C(=O)C₁₋₄alkyl, -(CH₂)_rphenyl, -(CH₂)_rheterocyclyl optionally substituted with alkyl and CN, or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with C₁₋₄alkyl;
- R_g, at each occurrence, is independently selected from the group consisting of H, F, OH, and C₁₋₅alkyl;
- p, at each occurrence, is independently selected from the group consisting of zero, 1, and 2; and
- r, at each occurrence, is independently selected from the group consisting of zero, 1, 2, 3, 4, and 5.

The present invention further provides a pharmaceutical composition for the synergistic treatment of cancer which comprises at least one CK2 inhibitor and an ICM, and a pharmaceutically acceptable carrier.

In a preferred embodiment of the invention the ICM is administered simultaneous with or before or after the administration of a compound of Formulas (I) and (II).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for the scheduled administration of CK2 inhibitors in synergistic combination(s) with immune checkpoint modulators (ICMs) for the treatment and prevention of proliferative diseases.

In one embodiment, the invention provides methods for treating cancer in a patient comprising the administration of a CK2 inhibitor of Formulas (I) and (II) in combination with an anti-PD-1 antibody or an anti-CTLA-4 antibody. Examples of anti-PD-1 antibodies include, but are not limited to, nivolumab, pembrolizumab, MEDI-0680, and pidilizumab. Examples of anti-CTLA-4 antibodies include, but are not limited to, ipilimumab and tremelimumab.

The CK2 inhibitors of Formulas (I) and (II) when used in combination with an anti-CTLA-4 antibody or anti-PD-1 antibody demonstrate superior cytotoxic activity.

I. Definitions

In order that the present disclosure may be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

5 When describing the compounds of the present invention, the phrase “alkyl” refers to an unsubstituted alkyl group of 1 to 6, preferably 1 to 4, carbon atoms.

 The term “aralkyl” refers to an aryl group bonded directly through a lower alkyl group. A preferred aralkyl group is benzyl.

 The term “aryl” refers to a monocyclic or bicyclic aromatic hydrocarbon group
10 having 6 to 12 carbon atoms in the ring portion. Exemplary of aryl herein are phenyl, naphthyl and biphenyl groups.

 The term “heterocyclo” or “heterocyclyl” refers to a fully saturated or unsaturated, aromatic or nonaromatic cyclic group which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system which has at least one
15 heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and sulfur where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclo group may be attached at any heteroatom or carbon atom.

20 Exemplary monocyclic heterocyclo groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazoliny, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazoliny, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperaziny, 2-oxopiperaziny, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepiny, azepiny, 4-
25 piperidonyl, pyridyl, N-oxo-pyridyl, pyraziny, pyrimidinyl, pyridaziny, tetrahydrothiopyranyl, tetrahydropyranyl, morpholiny, thiamorpholiny, thiamorpholiny sulfoxide, tetrahydrothiopyranylsulfone, thiamorpholiny sulfone, 1,3-dioxolane, tetrahydro-1,1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triaziny, triazolyl, and the like.

30 Exemplary bicyclic heterocyclo groups include benzothiazolyl, benzoxazolyl, benzothieryl, quinoliny, quinoliny-N-oxide, tetrahydroisoquinoliny, isoquinoliny, benzimidazolyl, benzopyranyl, indoliziny, benzofuryl, chromonyl, coumariny,

cinnoliny, quinoxaliny, indazolyl, pyrrolopyridyl, furopyridiny (such as furo[2,3-c]pyridiny, furo[3,1-b]pyridiny or furo[2,3-b]pyridiny), dihydroisoindolyl, dihydroquinazoliny (such as 3,4-dihydro-4-oxo-quinazoliny), benzisothiazolyl, benzisoxazolyl, benzodiazolyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, 5 benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothieryl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indoliny, isochromanyl, isoindoliny, naphthyridiny, phthalaziny, piperonyl, puriny, pyridopyridyl, quinazoliny, tetrahydroquinoliny, thienofuryl, thienopyridyl, thienothieryl, and the like.

When a group is referred to as being optionally substituted, it may be substituted 10 with one to five, preferably one to three, substituents such as F, Cl, Br, I, trifluoromethyl, trifluoromethoxy, hydroxy, lower alkoxy, cycloalkoxy, heterocycloxy, oxo, lower alkanoyl, aryloxy, lower alkanoyloxy, amino, lower alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the two amino substituents independently are selected from lower alkyl, aryl or aralkyl, lower 15 alkanoylamino, aroylamino, aralkanoylamino, substituted lower alkanoylamino, substituted arylamino, substituted aralkylanoylamino, thiol, lower alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, lower alkylthiono, arylthiono, aralkylthiono, lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamide (e.g., SO₂NH₂), substituted sulfonamide, nitro, cyano, carboxy, carbamyl (e.g., CONH₂), substituted 20 carbamyl (e.g., CONH-lower alkyl, CONH-aryl, CONH-aralkyl or cases where there are two substituents on the nitrogen independently selected from lower alkyl, aryl or aralkyl), lower alkoxy-carbonyl, aryl, substituted aryl, guanidino, and heterocyclos (e.g., indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like). Where noted above that the substituent is further substituted, it will be substituted with F, Cl, 25 Br, I, optionally substituted lower alkyl, hydroxy, optionally substituted lower alkoxy, optionally substituted aryl, or optionally substituted aralkyl.

All stereoisomers of the Formulas (I) and (II) compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of the formula I compounds embraces all possible stereoisomers and their 30 mixtures. The Formulas (I) and (II) definitions very particularly embrace the racemic forms and the isolated optical isomers having the specified activity.

“Administering” refers to the physical introduction of a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Preferred routes of administration for the anti-PD-1 antibody and/or the anti-CTLA4 antibody include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion.

The phrase “parenteral administration” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. The CK2 inhibitor is typically administered via a non-parenteral route, preferably orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

An “adverse event” (AE) as used herein is any unfavorable and generally unintended or undesirable sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a medical treatment. For example, an adverse event may be associated with activation of the immune system or expansion of immune system cells (*e.g.*, T cells) in response to a treatment. A medical treatment may have one or more associated AEs and each AE may have the same or different level of severity. Reference to methods capable of “altering adverse events” means a treatment regime that decreases the incidence and/or severity of one or more AEs associated with the use of a different treatment regime.

An “antibody” (Ab) shall include, without limitation, a glycoprotein immunoglobulin which binds specifically to an antigen and comprises at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen-binding portion thereof. Each H chain comprises a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region comprises three constant domains, C_{H1} , C_{H2} and C_{H3} . Each light chain comprises a

light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region comprises one constant domain, C_L . The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

An immunoglobulin may derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG and IgM. IgG subclasses are also well known to those in the art and include but are not limited to human IgG1, IgG2, IgG3 and IgG4. "Isotype" refers to the Ab class or subclass (*e.g.*, IgM or IgG1) that is encoded by the heavy chain constant region genes. The term "antibody" includes, by way of example, both naturally occurring and non-naturally occurring antibodies; monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human or nonhuman antibodies; wholly synthetic antibodies; and single chain antibodies. A nonhuman Ab may be humanized by recombinant methods to reduce its immunogenicity in man. Where not expressly stated, and unless the context indicates otherwise, the term "antibody" also includes an antigen-binding fragment or an antigen-binding portion of any of the aforementioned immunoglobulins, and includes a monovalent and a divalent fragment or portion, and a single chain Ab.

An "isolated antibody" refers to an Ab that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated Ab that binds specifically to PD-1 is substantially free of Abs that bind specifically to antigens other than PD-1). Moreover, an isolated Ab may be substantially free of other cellular material and/or chemicals.

The term "monoclonal antibody" ("mAb") refers to a non-naturally occurring preparation of Ab molecules of single molecular composition, *i.e.*, Ab molecules whose primary sequences are essentially identical, and which exhibits a single binding

specificity and affinity for a particular epitope. A mAb is an example of an isolated Ab. MAbs may be produced by hybridoma, recombinant, transgenic or other techniques known to those skilled in the art.

5 A “human” antibody (HuMAb) refers to an Ab having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the Ab contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human Abs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific
10 mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term “human antibody,” as used herein, is not intended to include Abs in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms “human” Abs and “fully human” Abs and are used synonymously.

15 A “humanized antibody” refers to an Ab in which some, most or all of the amino acids outside the CDR domains of a non-human Ab are replaced with corresponding amino acids derived from human immunoglobulins. In one embodiment of a humanized form of an Ab, some, most or all of the amino acids outside the CDR domains have been replaced with amino acids from human immunoglobulins, whereas some, most or all
20 amino acids within one or more CDR regions are unchanged. Small additions, deletions, insertions, substitutions or modifications of amino acids are permissible as long as they do not abrogate the ability of the Ab to bind to a particular antigen. A “humanized” Ab retains an antigenic specificity similar to that of the original Ab.

A “chimeric antibody” refers to an Ab in which the variable regions are derived
25 from one species and the constant regions are derived from another species, such as an Ab in which the variable regions are derived from a mouse Ab and the constant regions are derived from a human Ab.

An “anti-antigen” Ab refers to an Ab that binds specifically to the antigen. For example, an anti-PD-1 Ab binds specifically to PD-1 and an anti-CTLA4 Ab binds
30 specifically to CTLA4.

An “antigen-binding portion” of an Ab (also called an “antigen-binding fragment”) refers to one or more fragments of an Ab that retain the ability to bind specifically to the antigen bound by the whole Ab.

As used herein, the term “immune checkpoint modulator” or “ICM” refers to molecules that modulate one or more checkpoint proteins. Checkpoint proteins regulate T-cell activation or function. Numerous checkpoint proteins are known, such as CTLA-4 and its ligands CD80 and CD86; and PD1 with its ligands PDL1 and PDL2 (Pardoll, Nature Reviews Cancer 12: 252-264, 2012). These proteins are responsible for co-stimulatory or inhibitory interactions of T-cell responses. Immune checkpoint proteins regulate and maintain self-tolerance and the duration and amplitude of physiological immune responses. Immune checkpoint modulators include antibodies or are derived from antibodies.

A “cancer” refers a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth divide and grow results in the formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. The terms, “cancer,” “tumor,” and “neoplasm,” are used interchangeably herein.

The term “immunotherapy” refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response. “Treatment” or “therapy” of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down or preventing the onset, progression, development, severity or recurrence of a symptom, complication or condition, or biochemical indicia associated with a disease.

“Programmed Death-1 (PD-1)” refers to an immunoinhibitory receptor belonging to the CD28 family. PD-1 is expressed predominantly on previously activated T cells *in vivo*, and binds to two ligands, PD-L1 and PD-L2. The term “PD-1” as used herein includes human PD-1 (hPD-1), variants, isoforms, and species homologs of hPD-1, and analogs having at least one common epitope with hPD-1. The complete hPD-1 sequence can be found under GenBank Accession No. U64863.

The terms “cytotoxic T lymphocyte-associated antigen-4,” “CTLA-4,” “CTLA4,” “CTLA-4 antigen” and “CD152” (*see, e.g., Murata, Am. J. Pathol.* (1999) 155:453-460) are used interchangeably, and include variants, isoforms, species homologs of human CTLA-4, and analogs having at least one common epitope with CTLA-4 (*see, e.g.,*
5 Balzano (1992) *Int. J. Cancer Suppl.* 7:28-32). The complete CTLA-4 nucleic acid sequence can be found under GenBank Accession No. L15006.

A “subject” includes any human or nonhuman animal. The term “nonhuman animal” includes, but is not limited to, vertebrates such as nonhuman primates, sheep, dogs, and rodents such as mice, rats and guinea pigs. In preferred embodiments, the
10 subject is a human. The terms, “subject” and “patient” are used interchangeably herein.

A “therapeutically effective amount” or “therapeutically effective dosage” of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease
15 symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the
20 activity of the agent in *in vitro* assays.

By way of example, an “anti-cancer agent” promotes cancer regression in a subject. In preferred embodiments, a therapeutically effective amount of the drug promotes cancer regression to the point of eliminating the cancer. “Promoting cancer regression” means that administering an effective amount of the drug, alone or in
25 combination with an anti-neoplastic agent, results in a reduction in tumor growth or size, necrosis of the tumor, a decrease in severity of at least one disease symptom, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. In addition, the terms “effective” and “effectiveness” with regard to a treatment includes both pharmacological
30 effectiveness and physiological safety. Pharmacological effectiveness refers to the ability of the drug to promote cancer regression in the patient. Physiological safety

refers to the level of toxicity, or other adverse physiological effects at the cellular, organ and/or organism level (adverse effects) resulting from administration of the drug.

By way of example for the treatment of tumors, a therapeutically effective amount of an anti-cancer agent preferably inhibits cell growth or tumor growth by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. In other preferred embodiments of the invention, tumor regression may be observed and continue for a period of at least about 20 days, more preferably at least about 40 days, or even more preferably at least about 60 days. Notwithstanding these ultimate measurements of therapeutic effectiveness, evaluation of immunotherapeutic drugs must also make allowance for “immune-related” response patterns.

An “immune-related” response pattern refers to a clinical response pattern often observed in cancer patients treated with immunotherapeutic agents that produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. This response pattern is characterized by a beneficial therapeutic effect that follows an initial increase in tumor burden or the appearance of new lesions, which in the evaluation of traditional chemotherapeutic agents would be classified as disease progression and would be synonymous with drug failure. Accordingly, proper evaluation of immunotherapeutic agents may require long-term monitoring of the effects of these agents on the target disease.

A therapeutically effective amount of a drug includes a “prophylactically effective amount,” which is any amount of the drug that, when administered alone or in combination with an anti-neoplastic agent to a subject at risk of developing a cancer (*e.g.*, a subject having a pre-malignant condition) or of suffering a recurrence of cancer, inhibits the development or recurrence of the cancer. In preferred embodiments, the prophylactically effective amount prevents the development or recurrence of the cancer entirely. “Inhibiting” the development or recurrence of a cancer means either lessening the likelihood of the cancer’s development or recurrence, or preventing the development or recurrence of the cancer entirely.

The use of the alternative (*e.g.*, “or”) should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the indefinite

articles “a” or “an” should be understood to refer to “one or more” of any recited or enumerated component.

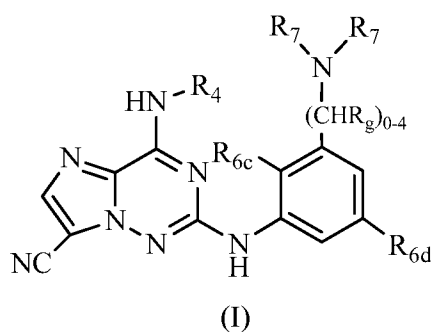
As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer within the recited
 5 range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

Various aspects of the invention are described in further detail in the following subsections.

10 II. CK2 Inhibitors

CK2 has been shown to be associated with acute and chronic myelogenous leukemia, lymphoma and multiple myeloma. In addition, enhanced CK2 activity has been observed in solid tumors of the colon, rectum and breast, squamous cell carcinomas of the lung and of the head and neck (SCCHN), adenocarcinomas of the lung, colon,
 15 rectum, kidney, breast, and prostate. Inhibition of CK2 by a small molecule is reported to induce apoptosis of pancreatic cancer cells, and hepatocellular carcinoma cells (HegG2, Hep3, HeLa cancer cell lines); and CK2 inhibitors dramatically sensitized RMS (Rhabdomyosarcoma) tumors toward apoptosis induced by TRAIL. Thus an inhibitor of CK2 alone, or in combination with another anti-cancer agent, would be useful to treat
 20 cancer.

In one embodiment, the CK2 inhibitor for use in the methods of the invention is a compound of Formula (I):



25 including enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, prodrugs, hydrates, or solvates thereof, wherein
 R₄ is selected from the group consisting of C₁₋₄alkyl substituted with 1-3 R_e, C₃₋₆cycloalkyl and heterocyclyl substituted with 1-3 R_e;

R₇ and R₇ together with the nitrogen atom to which they are both attached form a 4- to 7-membered monocyclic or 7- to 12-membered bicyclic heterocycle containing carbon atoms and additional 1-3 heteroatoms selected from the group consisting of NR_{8a}, O, and S(O)₂ and substituted with 1-4 R₈;

- 5 R₈, at each occurrence, is independently selected from the group consisting of H, F, Cl, Br, C₁₋₄alkyl substituted with 1-4 R_e, =O, C₂₋₄ alkenyl substituted with 1-5 R_e, - (CHR_g)_rOR_b, -(CHR_g)_rS(O)_pR_c, -(CHR_g)_rC(=O)(CHR_g)_rR_d, -(CHR_g)_rNR_aR_a, - (CHR_g)_rC(=O)NR_aR_a, -(CHR_g)_rC(=O)NR_aS(O)_pR_c, - (CHR_g)_rNR_a(CR_gR_g)_rC(=O)R_d, -(CHR_g)_rNR_aC(=O)OR_b, -
- 10 (CHR_g)_rOC(=O)(CHR_g)_rR_d, -(CHR_g)_rOC(=O)(CHR_g)_rC(=O)OR_d, - (CHR_g)_rOC(=O)(CHR_g)_rC(=O)NR_aR_a, -(CHR_g)_rOC(=O)(CHR_g)_rNR_aC(=O) R_b, - (CHR_g)_rOC(=O)(CHR_g)_rNR_aR_a, -(CHR_g)_rNR_aC(=O)NR_aR_a, - (CHR_g)_rC(=O)(CH₂)_rOR_b, -(CHR_g)_rC(=O)(CHR_g)_rOC(=O)R_b, - (CHR_g)_rS(O)₂NR_aR_a, -(CHR_g)_rNR_aS(O)_pNR_aR_a, -(CHR_g)_rNR_aS(O)_pR_c, -OPO₃H, -
- 15 (CHR_g)_r-C₃₋₆ cycloalkyl substituted with 1-5 R_e, -(CHR_g)_r-aryl substituted with 1-4 R_e and -(CHR_g)_r-heterocyclyl substituted with 1-4 R_e;

R_{8a} is selected from the group consisting of H, C₁₋₄alkyl substituted with 1-5 R_e, C₂₋₄

- alkenyl substituted with 1-5 R_e, -(CHR_g)_rOR_b, -(CHR_g)_rS(O)_pR_c, - (CHR_g)_rC(=O)(CHR_g)_rR_d, -(CHR_g)_rNR_aR_a, -(CHR_g)_rC(=O)NR_aR_a, -
- 20 (CHR_g)_rC(=O)NR_aS(O)_pR_c, -(CHR_g)_rNR_a(CR_gR_g)_rC(=O)R_d, - (CHR_g)_rNHC(=O)OR_b, -(CHR_g)_rOC(=O)(CHR_g)_rR_d, - (CHR_g)_rOC(=O)(CHR_g)_rC(=O)OR_d, -(CHR_g)_rOC(=O)(CHR_g)_rC(=O)NR_aR_a, - (CHR_g)_rOC(=O)(CHR_g)_rNR_aC(=O) R_b, -(CHR_g)_rOC(=O)(CHR_g)_rNR_aR_a, - (CHR_g)_rNR_a(CHR_g)_rC(=O)NR_aR_a, -(CHR_g)_rC(=O)OR_b, -
- 25 (CHR_g)_rC(=O)(CHR_g)_rOC(=O)R_b, -(CHR_g)_rS(O)₂NR_aR_a, - (CHR_g)_rNR_aS(O)_pNR_aR_a, -(CHR_g)_rNR_aS(O)_pR_c, -OPO₃H, -(CHR_g)_r-C₃₋₆ cycloalkyl substituted with 1-5 R_e, -(CHR_g)_r-aryl substituted with 1-4 R_e and - (CHR_g)_r-heterocyclyl substituted with 1-4 R_e;

R_a, at each occurrence, is independently selected from the group consisting of H, CN, C₁₋₆

- 30 alkyl substituted with 1-5 R_e, C₂₋₆ alkenyl substituted with 1-5 R_e, C₂₋₆ alkynyl substituted with 1-5 R_e, -(CH₂)_r-C₃₋₁₀carbocyclyl substituted with 1-5 R_e, and - (CH₂)_r-heterocyclyl substituted with 1-5 R_e; or R_a and R_a together with the

nitrogen atom to which they are both attached form a heterocyclic ring substituted with 1-5 R_e;

5 R_b, at each occurrence, is independently selected from the group consisting of H, C₁₋₆ alkyl substituted with 1-5 R_e, C₂₋₆ alkenyl substituted with 1-5 R_e, C₂₋₆ alkynyl substituted with 1-5 R_e, -(CH₂)_r-C₃₋₁₀carbocyclyl substituted with 1-5 R_e, and - (CH₂)_r-heterocyclyl substituted with 1-5 R_e;

R_c, at each occurrence, is independently selected from the group consisting of C₁₋₆ alkyl substituted with 1-5 R_e, C₂₋₆alkenyl substituted with 1-5 R_e, C₂₋₆alkynyl substituted with 1-5 R_e, C₃₋₆carbocyclyl, and heterocyclyl;

10 R_d, at each occurrence, is independently selected from the group consisting of H, OH, C₁₋₆ alkyl substituted with 1-5 R_e, C₂₋₆alkenyl substituted with 1-5 R_e, C₂₋₆alkynyl substituted with 1-5 R_e, -(CH₂)_r-C₃₋₁₀carbocyclyl substituted with 1-5 R_e, and - (CH₂)_r-heterocyclyl substituted with 1-5 R_e;

15 R_e, at each occurrence, is independently selected from the group consisting of H, N₃, C₁₋₆alkyl substituted with 1-5 R_f, C₂₋₆alkenyl, C₂₋₆alkynyl, -(CH₂)_r-C₃₋₆ cycloalkyl, - (CH₂)_r-heterocyclyl, F, Cl, Br, -(CH₂)_rCN, NO₂, =O, -OPO₃H, -OSi(C₁₋₄alkyl)₃, - (CH₂)_rOC₁₋₅ alkyl, -(CH₂)_rO(CH₂)_rOC₁₋₅ alkyl, -(CH₂)_rOH, -(CH₂)_rS(O)₂C₁₋₅alkyl, -(CH₂)_rS(O)₂R_f, -(CH₂)_rNHS(O)₂C₁₋₅alkyl, -S(O)₂NH₂, SH, -(CH₂)_rNR_fR_f, - (CH₂)_rNHC(=O)OR_f, -(CH₂)_rNHC(=O)R_f, -(CH₂)_rNHC(=NH)NR_fR_f, -
20 (CH₂)_rC(=O)(CH₂)_rR_f, and -(CH₂)_rC(=O)OR_f;

R_f, at each occurrence, is independently selected from the group consisting of H, - (CH₂)_rOH, -(CH₂)_rOC₁₋₅alkyl, C₁₋₅alkyl (optionally substituted with F, Cl, OH, NH₂), C₃₋₆ cycloalkyl optionally substituted with NH₂, -(CH₂)_rS(O)_pC₁₋₄alkyl, - NHC(=O)C₁₋₄alkyl, -C(=O)NH₂, -C(=O)OC₁₋₄alkyl, -C(=O)C₁₋₄alkyl, -
25 (CH₂)_rphenyl, -(CH₂)_rheterocyclyl optionally substituted with alkyl and CN, or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with C₁₋₄alkyl;

R_g, at each occurrence, is independently selected from the group consisting of H, F, OH, and C₁₋₅alkyl;

30 p, at each occurrence, is independently selected from the group consisting of zero, 1, and 2; and

r, at each occurrence, is independently selected from the group consisting of zero, 1, 2, 3, 4, and 5.

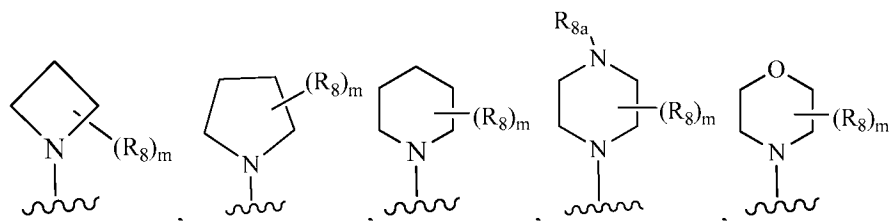
In another embodiment, the CK2 inhibitor for use in the methods of the invention is a compound of Formula (I) including enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, prodrugs, hydrates, or solvates thereof, wherein

R₄ is selected from the group consisting of C₁₋₄alkyl, C₃₋₆cycloalkyl, and heterocyclyl, each substituted with 1-3 R_e;

R_{6c} is selected from the group consisting of F and Cl; and

R_{6d} is selected from the group consisting of CN, -NHC(=O)O(C₁₋₄alkyl), and CHF₂;

NR₇R₇ is selected from the group consisting of



R₈ is selected from the group consisting of F, C₁₋₄alkyl substituted with 1-4 R_e, -OH, -O(C₁₋₄alkyl), -NR_aR_a, -NR_aC(=O)R_b, -NR_aC(=O)OR_b, -OC(=O)(CH₂)_rNH₂, -NHC(=O)NR_aR_a, and -NHS(O)₂(C₁₋₄alkyl); and

R_{8a} is selected from the group consisting of H, C₁₋₄alkyl, S(O)₂C₁₋₄alkyl, and 5- to 6-membered heterocyclyl substituted with 1-4 R_e.

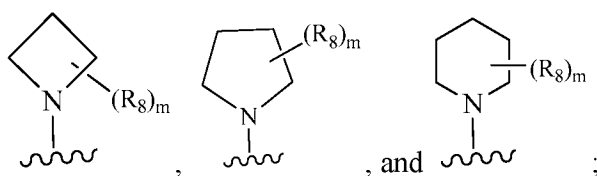
In another embodiment, the CK2 inhibitor for use in the methods of the invention is a compound of Formula (I) including enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, prodrugs, hydrates, or solvates thereof, wherein

R₄ is selected from the group consisting of methyl, ethyl, propyl, and cyclopropyl;

R_{6c} is Cl;

R_{6d} is selected from the group consisting of CN, OCHF₂, and CHF₂;

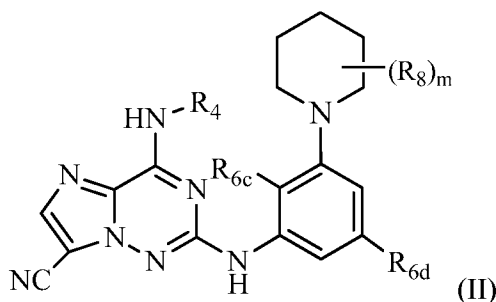
NR₇R₇ is selected from the group consisting of



R_8 is selected from the group consisting of F, C_{1-4} alkyl substituted with 1-4 R_e , -OH, $-O(C_{1-4}alkyl)$, $-NHC(=O)C_{1-4}alkyl$, $-NHC(=O)OC_{1-4}alkyl$, and $-NHS(O)_2(C_{1-4}alkyl)$; and

5 m , at each occurrence, is independently selected from the group consisting of zero, 1, and 2.

In another embodiment, the CK2 inhibitor for use in the methods of the invention is a compound of Formula (II):



10

including enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, prodrugs, hydrates, or solvates thereof, wherein

R_4 is selected from the group consisting of methyl, ethyl, propyl, and cyclopropyl;

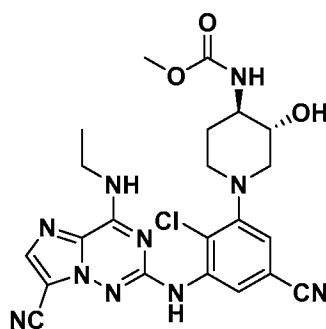
R_{6c} is Cl;

15 R_{6d} is selected from the group consisting of CN, $OCHF_2$, and CHF_2 ; and m , at each occurrence, is independently selected from the group consisting of zero, 1, and 2.

R_8 is selected from the group consisting of F, C_{1-4} alkyl substituted with 1-4 R_e , -OH, $-O(C_{1-4}alkyl)$, $-NR_aR_a$, $-NR_aC(=O)R_b$, $-NR_aC(=O)OR_b$, $-OC(=O)(CH_2)_rNH_2$, $-NHC(=O)NR_aR_a$, and $-NHS(O)_2(C_{1-4}alkyl)$; and

20 m , at each occurrence, is independently selected from the group consisting of zero, 1, and 2.

In another embodiment, the CK2 inhibitor of Formulas (I) and (II) for use in the methods of the invention is Compound 1:



Compound 1

or enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, prodrugs, hydrates, or solvates thereof.

5

III. Anti-PD-1 and Anti-CTLA4 Antibodies

HuMAbs that bind specifically to PD-1 with high affinity have been disclosed in U.S. Patent No. 8,008,449. Other anti-PD-1 mAbs have been described in, for example, U.S. Patent Nos. 6,808,710, 7,488,802, 8,168,757 and 8,354,509, and PCT Publication
 10 No. WO 2012/145493. Each of the anti-PD-1 HuMAbs disclosed in U.S. Patent No. 8,008,449 has been demonstrated to exhibit one or more of the following characteristics: (a) binds to human PD-1 with a K_D of 1×10^{-7} M or less, as determined by surface plasmon resonance using a Biacore biosensor system; (b) does not substantially bind to human CD28, CTLA-4 or ICOS; (c) increases T-cell proliferation in a Mixed
 15 Lymphocyte Reaction (MLR) assay; (d) increases interferon- γ production in an MLR assay; (e) increases IL-2 secretion in an MLR assay; (f) binds to human PD-1 and cynomolgus monkey PD-1; (g) inhibits the binding of PD-L1 and/or PD-L2 to PD-1; (h) stimulates antigen-specific memory responses; (i) stimulates Ab responses; and (j) inhibits tumor cell growth *in vivo*. Anti-PD-1 Abs usable in the present invention include
 20 mAbs that bind specifically to human PD-1 and exhibit at least one, preferably at least five, of the preceding characteristics.

A preferred anti-PD-1 Ab is nivolumab. Nivolumab is a fully human IgG4 anti-PD-1 monoclonal antibody disclosed as 5C4 in WO 2006/121168. Nivolumab is known to augment cellular immune responses against tumors (Brahmer, JR et al., 2010, *J Clin*
 25 *Oncol* 28:3167-3175). Another anti-PD-1 Ab usable in the present methods is pembrolizumab (Hamid et al., 2013, *New England Journal of Medicine* 369 (2): 134–44).

Anti-PD-1 Abs usable in the disclosed methods also include isolated Abs that bind specifically to human PD-1 and cross-compete for binding to human PD-1 with nivolumab (*see, e.g.*, U.S. Patent No. 8,008,449; WO 2013/173223). The ability of Abs to cross-compete for binding to an antigen indicates that these Abs bind to the same
5 epitope region of the antigen and sterically hinder the binding of other cross-competing Abs to that particular epitope region. These cross-competing Abs are expected to have functional properties very similar those of nivolumab by virtue of their binding to the same epitope region of PD-1. Cross-competing Abs can be readily identified based on their ability to cross-compete with nivolumab in standard PD-1 binding assays such as
10 Biacore analysis, ELISA assays or flow cytometry (*see, e.g.*, WO 2013/173223).

For administration to human subjects, these anti-PD-1 Abs are preferably chimeric Abs, or more preferably humanized or human Abs. Such chimeric, humanized or human mAbs can be prepared and isolated by methods well known in the art. Anti-PD-1 Abs usable in the methods of the disclosed invention also include antigen-binding portions of
15 the above Abs. It has been amply demonstrated that the antigen-binding function of an Ab can be performed by fragments of a full-length Ab. Examples of binding fragments encompassed within the term “antigen-binding portion” of an Ab include (i) a Fab fragment, a monovalent fragment consisting of the V_L , V_H , C_L and C_{H1} domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide
20 bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; and (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an Ab. Anti-PD-1 antibodies (or V_H and/or V_L domains derived therefrom) suitable for use in the invention can be generated using methods well known in the art.

An exemplary anti-PD-1 antibody is nivolumab comprising heavy and light chains
25 comprising the sequences shown in SEQ ID NOs: 11 and 12, respectively, or antigen binding fragments and variants thereof.

In other embodiments, the antibody has heavy and light chain CDRs or variable regions of nivolumab. Accordingly, in one embodiment, the antibody comprises CDR1, CDR2, and CDR3 domains of the V_H of nivolumab having the sequence set forth in SEQ
30 ID NO: 13, and CDR1, CDR2 and CDR3 domains of the V_L of nivolumab having the sequence set forth in SEQ ID NO: 14. In another embodiment, the antibody comprises CDR1, CDR2 and CDR3 domains comprising the sequences set forth in SEQ ID NOs:

15, 16, and 17, respectively, and CDR1, CDR2 and CDR3 domains comprising the sequences set forth in SEQ ID NOs: 18, 19, and 20, respectively. In another embodiment, the antibody comprises VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NO: 13 and/or SEQ ID NO: 14, respectively. In another embodiment, the antibody competes for binding with and/or binds to the same epitope on PD-1 as the above-mentioned antibodies. In another embodiment, the antibody has at least about 90% variable region amino acid sequence identity with the above-mentioned antibodies (*e.g.*, at least about 90%, 95% or 99% variable region identity with SEQ ID NO: 13 or SEQ ID NO: 14).

Anti-CTLA-4 antibodies of the instant invention can bind to an epitope on human CTLA-4 so as to inhibit CTLA-4 from interacting with a human B7 counterreceptor. Because interaction of human CTLA-4 with human B7 transduces a signal leading to inactivation of T-cells bearing the human CTLA-4 receptor, antagonism of the interaction effectively induces, augments or prolongs the activation of T cells bearing the human CTLA-4 receptor, thereby prolonging or augmenting an immune response. Anti-CTLA-4 antibodies are described in U.S. Patent Nos. 5,811,097; 5,855,887; 6,051,227; in PCT Application Publication Nos. WO 01/14424 and WO 00/37504; and in U.S. Patent Publication No. 2002/0039581. Each of these references is specifically incorporated herein by reference for purposes of description of anti-CTLA-4 antibodies. An exemplary clinical anti-CTLA-4 antibody is ipilimumab or human monoclonal antibody 10D1 as disclosed in WO 01/14424 and U.S. Patent Application No. 09/644,668. Antibody 10D1 has been administered in single and multiple doses, alone or in combination with a vaccine, chemotherapy, or interleukin-2 to more than 500 patients diagnosed with metastatic melanoma, prostate cancer, lymphoma, renal cell cancer, breast cancer, ovarian cancer, and HIV. Other anti-CTLA-4 antibodies encompassed by the methods of the present invention include, for example, those disclosed in: WO 98/42752; WO 00/37504; U.S. Patent No. 6,207,156; Hurwitz *et al.* (1998) *Proc. Natl. Acad. Sci. USA* 95(17):10067-10071; Camacho *et al.* (2004) *J. Clin. Oncology* 22(145): Abstract No. 2505 (antibody CP-675206); and Mokyr *et al.* (1998) *Cancer Res.* 58:5301-5304. In certain embodiments, the methods of the instant invention comprise use of an anti-CTLA-4 antibody that is a human sequence antibody, preferably a monoclonal antibody and in another embodiment is monoclonal antibody 10D1.

In certain embodiments, the anti-CTLA-4 antibody binds to human CTLA-4 with a K_D of 5×10^{-8} M or less, binds to human CTLA-4 with a K_D of 1×10^{-8} M or less, binds to human CTLA-4 with a K_D of 5×10^{-9} M or less, or binds to human CTLA-4 with a K_D of between 1×10^{-8} M and 1×10^{-10} M or less.

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IV. Pharmaceutical Compositions

The present invention encompasses pharmaceutical compositions of CK2 inhibitors of Formulas (I) and (II) useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compositions of this invention, with or without pharmaceutically acceptable carriers or diluents. As used herein, a “pharmaceutically acceptable carrier” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. “Pharmaceutically acceptable” means approved by a government regulatory agency or listed in the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, particularly in humans. The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered.

In one embodiment, the pharmaceutical compositions of this invention comprise at least a compound of Formulas (I) and (II) and a pharmaceutically acceptable carrier. The compositions of the present invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

The compounds of Formulas (I) and (II) and the compositions of the present invention may be administered orally or parenterally including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use, the compounds of Formulas (I) and (II) may be administered, for example, in the form of tablets or capsules, powders, dispersible granules, or cachets, or as aqueous solutions or suspensions. In the case of tablets for oral use, carriers which are commonly used include lactose, corn starch, magnesium carbonate, talc, and sugar, and lubricating agents such as magnesium stearate are commonly added. For oral administration in capsule form, useful carriers include lactose, corn starch, magnesium

carbonate, talc, and sugar. When aqueous suspensions are used for oral administration, emulsifying and/or suspending agents are commonly added.

In addition, sweetening and/or flavoring agents may be added to the oral compositions. For intramuscular, intraperitoneal, subcutaneous and intravenous use, 5 sterile solutions of the active ingredient(s) are usually employed, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of the solute(s) should be controlled in order to render the preparation isotonic.

For preparing suppositories according to the invention, a low melting wax such as 10 a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously in the wax, for example by stirring. The molten homogeneous mixture is then poured into conveniently sized molds and allowed to cool and thereby solidify.

Liquid preparations include solutions, suspensions and emulsions. Such 15 preparations are exemplified by water or water/propylene glycol solutions for parenteral injection. Liquid preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

20 Also included are solid preparations which are intended for conversion, shortly before use, to liquid preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of Formulas (I) and (II) may also be delivered transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions 25 and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The present invention encompasses pharmaceutical compositions of anti-PD-1 antibodies or anti-CTLA4 antibodies useful in the treatment of cancer. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of 30 petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, glycerol polyethylene glycol ricinoleate, and the like. Water or aqueous solution saline and aqueous dextrose and glycerol solutions may be employed as carriers,

particularly for injectable solutions (e.g., comprising an anti-PD-1 antibody). Preferably, the carrier for a composition containing an Ab is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion). A pharmaceutical composition of the invention may include one or more
5 pharmaceutically acceptable salts, anti-oxidant, aqueous and non-aqueous carriers, and/or adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents.

Liquid compositions for parenteral administration can be formulated for administration by injection or continuous infusion. Routes of administration by injection or infusion include intravenous, intraperitoneal, intramuscular, intrathecal and
10 subcutaneous. In one embodiment, the anti-CTLA4 antibody or the anti-PD-1 antibody are administered intravenously.

When formulating the pharmaceutical compositions of the invention the clinician may utilize preferred dosages as warranted by the condition of the patient being treated. The actual dosage employed may be varied depending upon the requirements of the
15 patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and
20 administered in portions during the day if desired. Intermittent therapy (e.g., one week out of three weeks or three out of four weeks) may also be used.

V. Combination Therapies

The present invention provides combination therapies involving administration of a
25 CK2 inhibitor and an ICM to treat subjects having cancer (e.g., a solid tumor or a B cell lymphoma). The particular choice of a CK2 inhibitor and an ICM will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol. In a particular embodiment, the CK2 inhibitor is a compound of Formulas (I) and (II) and the ICM is an anti-PD-1 antibody, e.g., nivolumab
30 or anti-CTLA4 antibody, e.g., ipilimumab.

The present invention is based, in part, on the following experimental data. Mouse tumor models (MC38 colon carcinoma and 4T1 breast carcinoma) were used to

examine the *in vivo* effect of treating a tumor by combining a CK2 inhibitor of Formulas (I) and (II) and an anti-CTLA-4 antibody or an anti-PD-1 antibody. The immunotherapeutic combination was provided either simultaneous with the implant of tumor cells or after the tumor cells were implanted for a time sufficient to become an established tumor. Regardless of the timing of antibody treatment, it was found that CK2 treatment alone, anti-CTLA-4 treatment alone, or anti-PD-1 treatment alone had a modest effect on reducing tumor growth in the MC38 tumor. Nonetheless, the combination treatment of a CK2 inhibitor, *i.e.*, Compound 1, and an anti-CTLA-4 antibody or an anti-PD-1 antibody showed an unexpected, significantly greater effect on reducing tumor growth as compared to treatment with either the CK2 inhibitor, or the anti-CTLA-4 antibody/anti-PD-1 antibody alone (*see, e.g.*, Tables 1 and 2).

In one embodiment, the present invention provides a method for treating a hyperproliferative disease, comprising administering a CK2 inhibitor of Formulas (I) and (II) and a PD-1 antibody or a CTLA-4 antibody to a subject. In further embodiments, the anti-PD-1 antibody or the anti-CTLA-4 antibody is administered at a subtherapeutic dose. In another embodiment, the present invention provides a method for altering an adverse event associated with treatment of a hyperproliferative disease, comprising administering a CK2 inhibitor of Formulas (I) and (II) and a subtherapeutic dose of anti-CTLA-4 antibody to a subject. In another embodiment, the present invention provides a method for altering an adverse event associated with treatment of a hyperproliferative disease, comprising administering a CK2 inhibitor of Formulas (I) and (II) and a subtherapeutic dose of anti-PD-1 antibody to a subject. In certain embodiments, the subject is human. In certain embodiments, the anti-CTLA-4 antibody is ipilimumab or human sequence monoclonal antibody 10D1 and the anti-PD-1 antibody is nivolumab or human sequence monoclonal antibody, such as 17D8, 2D3, 4H1, 5C4 and 4A11. Human sequence monoclonal antibodies 17D8, 2D3, 4H1, 5C4 and 4A11 have been isolated and structurally characterized, as described in U.S. Provisional Patent No. 60/679,466 (WO 2006/121,168).

The anti-CTLA-4 antibody and anti-PD-1 monoclonal antibodies (mAbs) and the human sequence antibodies of the invention can be produced by a variety of techniques, including conventional monoclonal antibody methodology, *e.g.*, the standard somatic cell hybridization technique of Kohler and Milstein (1975) *Nature* 256:495. Any technique

for producing monoclonal antibody can be employed, *e.g.*, viral or oncogenic transformation of B lymphocytes. One animal system for preparing hybridomas is the murine system. Hybridoma production in the mouse is a very well-established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion
5 are known in the art. Fusion partners (*e.g.*, murine myeloma cells) and fusion procedures are also known (*see, e.g.*, Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor New York).

The combination of CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 or anti-CTLA-4 antibodies is useful for enhancement of an immune response against a
10 hyperproliferative disease by both inhibition of CK2 and blockade of PD-1 and CTLA-4. In a preferred embodiment, the antibodies of the present invention are human antibodies. For example, these molecules can be administered to cells in culture, *in vitro* or *ex vivo*, or to human subjects, *e.g.*, *in vivo*, to enhance immunity in a variety of situations. Accordingly, in one aspect, the invention provides a method of modifying an immune
15 response in a subject comprising administering to the subject an anti-CTLA-4 antibody or an anti-PD-1 antibody or an antigen-binding portions thereof, such that the immune response in the subject is modified in addition to a CK2 inhibitor of Formulas (I) and (II). Preferably, the response is enhanced, stimulated or up-regulated. In another embodiment, the instant disclosure provides a method of altering adverse events associated with
20 treatment of a hyperproliferative disease with an immunostimulatory therapeutic agent, comprising administering a subtherapeutic dose of anti-CTLA-4 antibody or anti-PD-1 antibody in addition to a CK2 inhibitor of Formulas (I) and (II) to a subject.

Blockade of PD-1 and CTLA-4 by antibodies in addition to CK2 inhibition can enhance the immune response to cancerous cells in the patient. Cancers whose growth
25 may be inhibited using the antibodies of the instant disclosure include cancers typically responsive to immunotherapy. Representative examples of cancers for treatment with the combination therapy of the instant disclosure include melanoma (*e.g.*, metastatic malignant melanoma), renal cancer, prostate cancer, breast cancer, colon cancer and lung cancer. Examples of other cancers that may be treated using the methods of the instant
30 disclosure include bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer,

carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers. The present invention is also useful for treatment of metastatic cancers.

Methods for the safe and effective administration of chemotherapeutic agents such as CK2 inhibitors are known to those skilled in the art. In addition, their administration is described in the standard literature.

For example, the administration of many of the chemotherapeutic agents is described in the "2015 Physicians' Desk Reference" (PDR), *e.g.*, 69th edition), the disclosure of which is incorporated herein by reference thereto.

As used herein, adjunctive or combined administration (co-administration) includes simultaneous administration of a CK2 compound of Formulas (I) and (II) and the anti-CTLA4 or anti-PD-1 antibodies in the same or different dosage form, or separate administration of the compounds and antibodies (*e.g.*, sequential administration). Thus, the CK2 inhibitor of Formulas (I) and (II) and the anti-CTLA4 or anti-PD-1 antibodies can be formulated for separate administration and are administered concurrently or sequentially.

For example, a CK2 inhibitor of Formulas (I) and (II) can be administered first followed by (*e.g.*, immediately followed by) the administration of the anti-CTLA4 antibody or anti-PD-1 antibody, or vice versa. In one embodiment, the CK2 inhibitor of Formulas (I) and (II) is administered prior to administration of the anti-CTLA4 antibody or anti-PD-1 antibody. In another embodiment, the CK2 inhibitor of Formulas (I) and (II) is administered after administration of the anti-CTLA4 antibody or anti-PD-1 antibody. In

another embodiment, the CK2 inhibitor of Formulas (I) and (II) and the anti-CTLA4 antibody or anti-PD-1 antibody are administered concurrently. Such concurrent or sequential administration preferably results in the CK2 inhibitor of Formulas (I) and (II) and the anti-CTLA4 antibody and anti-PD-1 antibody being simultaneously present in
5 treated patients.

In one embodiment, the doses of the CK2 inhibitor of Formulas (I) and (II) and the anti-CTLA4 or anti-PD-1 antibody are calculated per body weight, *e.g.*, mg/kg body weight. In another embodiment, the doses of the CK2 inhibitor of Formulas (I) and (II) and anti-CTLA4 or anti-PD-1 antibody are varied over time. For example, the CK2
10 inhibitor of Formulas (I) and (II) and the anti-CTLA4 antibody or anti-PD-1 antibody may be initially administered at a high dose and may be lowered over time. In another embodiment, the CK2 inhibitor of Formulas (I) and (II) and the anti-CTLA4 antibody or anti-PD-1 antibody are initially administered at a low dose and increased over time.

In another embodiment, the amount of the CK2 inhibitors of Formulas (I) and (II) and anti-CTLA4 or anti-PD-1 antibodies administered is constant for each dose. In
15 another embodiment, the amount of the CK2 inhibitor of Formulas (I) and (II) and antibody administered varies with each dose. For example, the maintenance (or follow-on) dose of the antibody can be higher or the same as the loading dose which is first administered. In another embodiment, the maintenance dose of the antibody can be lower
20 or the same as the loading dose.

In another embodiment, the CK2 inhibitor of Formulas (I) and (II) and the anti-PD-1 antibody or anti-CTLA4 antibody are administered as a first line of treatment (*e.g.*, the initial or first treatment). In another embodiment, the CK2 inhibitor of Formulas (I) and (II) and the anti-PD-1 antibody or anti-CTLA4 antibody are administered as a second
25 line of treatment (*e.g.*, after the initial or first treatment, including after relapse and/or where the first treatment has failed).

In certain embodiments, the combination is administered to the subject orally for the CK2 inhibitor and intravenously for the anti-PD-1 antibody or an anti-CTLA-4 antibody. The antibody can be administrated intravenously in an induction phase,
30 followed by a maintenance phase.

Dosage and frequency vary depending on the half-life of the antibody in the subject. In general, human Abs show the longest half-life, followed by humanized

antibodies, chimeric antibodies, and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is typically administered at relatively infrequent intervals over a long period of time. Some patients
5 continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

10 A composition of the present invention can be administered via one or more routes of administration using one or more of a variety of methods well known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In general, the CK2 inhibitor of Formulas (I) and (II) and anti-CTLA-4 antibody or anti-PD-1 antibody do not have to be administered
15 in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the CK2 inhibitor of Formulas (I) and (II) may be administered orally to generate and maintain good blood levels thereof, while the anti-CTLA-4 antibody or anti-PD-1 antibody may be administered intravenously. The determination of the mode of
20 administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

25 Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being unduly toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the
30 activity of the particular compositions of the present invention employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or

materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts. Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component of the treatment according to the individual patient's needs, as the treatment proceeds.

In certain embodiments, the anti-PD-1 antibody or is administered at a dose ranging from about 0.1 to 10.0 mg/kg body weight once every 1, 2, 3 or 4 weeks. For example, the anti-PD-1 antibody is administered at a dose of 1 or 3 mg/kg body weight once every 2 weeks. In certain embodiments, the anti-CTLA4 antibody is administered at a dose ranging from about 1 to 10 mg (equivalent to about 0.01 to 0.1 mg/kg body weight) once every 4 or 8 weeks. For example, the anti-CTLA4 antibody is administered at a dose of 3 or 8 mg (equivalent to about 0.03 or 0.1 mg/kg body weight) once every 4 or 8 weeks.

In certain embodiments, the method comprises at least one treatment cycle (e.g., a treatment cycle consisting of four weeks). To illustrate, in an four-week cycle, the CK2 inhibitor is administered on Days 7-14 and anti-CTLA4 antibody or anti-PD-1 antibody is administered on Days 7, 14, 21 and 28. In one embodiment, the CK2 inhibitor is administered prior to administration of the anti-CTLA4 antibody or anti-PD-1 antibody. In another embodiment, the CK2 inhibitor is administered after administration of the anti-CTLA4 antibody or anti-PD-1 antibody. Optionally, the treatment cycle can be repeated up to 12 cycles (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 cycles), or as long as a clinical benefit is observed or until there is a complete response, confirmed progressive disease or unmanageable toxicity.

Patients treated according to the methods disclosed herein preferably experience improvement in at least one sign of cancer. In one embodiment, improvement is measured by a reduction in the quantity and/or size of measurable tumor lesions. Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan and lesions can be measured on chest x-rays or CT or MRI films. Successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. In another embodiment, cytology or histology can be used to evaluate responsiveness to a therapy.

In one embodiment, the patient treated exhibits a complete response (CR), a partial response (PR), stable disease (SD), immune-related complete disease (irCR), immune-related partial response (irPR), or immune-related stable disease (irSD). In another embodiment, the patient treated experiences tumor shrinkage and/or decrease in growth rate, *i.e.*, suppression of tumor growth. In another embodiment, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: the number of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent.

In other embodiments, administration of effective amounts of the CK2 inhibitor of Formulas (I) and (II) and the anti-CTLA4 antibody or the anti-PD-1 antibody according to any of the methods provided herein produces at least one therapeutic effect selected from the group consisting of reduction in size of a tumor, reduction in number of metastatic lesions appearing over time, complete remission, partial remission, or stable disease. In still other embodiments, the methods of treatment produce a comparable clinical benefit rate ($CBR = CR + PR + SD \geq 6 \text{ months}$) better than that achieved by a CK2 inhibitor, an anti-CTLA4 antibody, or an anti-PD-1 antibody alone. In other embodiments, the improvement of clinical benefit rate is about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or more compared to a CK2 inhibitor, an anti-CTLA4 antibody, or an anti-PD-1 antibody alone.

The combination of CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 and anti-CTLA-4 antibodies can be further combined with an immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines (He *et al.* (2004) *J. Immunol.* 173:4919-28). Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MART1 and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF (discussed further below).

The combination of CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 or anti-CTLA-4 antibodies can be further combined with a vaccination protocol. Many

experimental strategies for vaccination against tumors have been devised (*see* Rosenberg, S. (2000) Development of Cancer Vaccines, ASCO Educational Book Spring: 60-62; Logothetis, C., 2000, ASCO Educational Book Spring: 300-302; Khayat, D. (2000) ASCO Educational Book Spring: 414-428; Foon, K. (2000) ASCO Educational Book Spring: 730-738; see also Restifo and Sznol, Cancer Vaccines, Ch. 61, pp. 3023-3043 in DeVita *et al.* (eds.), 1997, Cancer: Principles and Practice of Oncology. Fifth Edition). In one of these strategies, a vaccine is prepared using autologous or allogeneic tumor cells. These cellular vaccines have been shown to be most effective when the tumor cells are transduced to express GM-CSF. GM-CSF has been shown to be a potent activator of antigen presentation for tumor vaccination (Dranoff *et al.* (1993) *Proc. Natl. Acad. Sci U.S.A.* 90: 3539-43).

The study of gene expression and large scale gene expression patterns in various tumors has led to the definition of so called tumor specific antigens (Rosenberg (1999) *Immunity* 10:281-7). In many cases, these tumor specific antigens are differentiation antigens expressed in the tumors and in the cell from which the tumor arose, for example melanocyte antigens gp100, MAGE antigens, and Trp-2. More importantly, many of these antigens can be shown to be the targets of tumor specific T cells found in the host. In certain embodiments, a combined CK2 inhibition and PD-1 or CTLA-4 blockade using the antibody compositions described herein may be used in conjunction with a collection of recombinant proteins and/or peptides expressed in a tumor in order to generate an immune response to these proteins. These proteins are normally viewed by the immune system as self-antigens and are, therefore, tolerant to them. The tumor antigen may also include the protein telomerase, which is required for the synthesis of telomeres of chromosomes and which is expressed in more than 85% of human cancers and in only a limited number of somatic tissues (Kim *et al.* (1994) *Science* 266: 2011-2013). (These somatic tissues may be protected from immune attack by various means). Tumor antigen may also be "neo-antigens" expressed in cancer cells because of somatic mutations that alter protein sequence or create fusion proteins between two unrelated sequences (*i.e.*, bcr-abl in the Philadelphia chromosome), or idiotype from B cell tumors.

Other tumor vaccines may include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). Another form of tumor specific antigen which

may be used in conjunction with PD-1 blockade is purified heat shock proteins (HSP) isolated from the tumor tissue itself. These heat shock proteins contain fragments of proteins from the tumor cells and these HSPs are highly efficient at delivery to antigen presenting cells for eliciting tumor immunity (Suot & Srivastava (1995) *Science*

5 269:1585-1588; Tamura *et al.* (1997) *Science* 278:117-120).

Dendritic cells (DC) are potent antigen presenting cells that can be used to prime antigen-specific responses. DC's can be produced *ex vivo* and loaded with various protein and peptide antigens as well as tumor cell extracts (Nestle *et al.* (1998) *Nature Medicine* 4: 328-332). DCs may also be transduced by genetic means to express these tumor

10 antigens as well. DCs have also been fused directly to tumor cells for the purposes of immunization (Kugler *et al.* (2000) *Nature Medicine* 6:332-336). As a method of vaccination, DC immunization may be effectively further combined with a combined PD-1 and CTLA-4 blockade to activate more potent anti-tumor responses.

The combination of CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 or anti-

15 CTLA-4 antibodies may also be further combined with standard cancer treatments. For example, it may be effectively combined with chemotherapeutic regimes. In these instances, it may be possible to reduce the dose of other chemotherapeutic reagent administered with the combination of the instant disclosure (Mokyr *et al.* (1998) *Cancer Research* 58: 5301-5304). The scientific rationale behind the combined use of PD-1 or

20 CTLA-4 blockade with chemotherapy is that cell death, which is a consequence of the cytotoxic action of most chemotherapeutic compounds, should result in increased levels of tumor antigen in the antigen presentation pathway. Other combination therapies that may result in synergy with a combined CK2 inhibition and PD-1 or CTLA-4 blockade through cell death include radiation, surgery, or hormone deprivation. Each of these

25 protocols creates a source of tumor antigen in the host. Angiogenesis inhibitors may also be combined with a combined CK2 inhibition and PD-1 or CTLA-4 blockade. Inhibition of angiogenesis leads to tumor cell death, which may also be a source of tumor antigen to be fed into host antigen presentation pathways.

In another example, the combination of CK2 inhibitors of Formulas (I) and (II)

30 and anti-PD-1 and anti-CTLA-4 antibodies can be used in conjunction with anti-neoplastic antibodies, such as Rituxan[®] (rituximab), Herceptin[®] (trastuzumab), Bexxar[®] (tositumomab), Zevalin[®] (ibritumomab), Campath[®] (alemtuzumab), Lymphocide[®]

(eprtezumab), Avastin® (bevacizumab), and Tarceva® (erlotinib), and the like. By way of example and not wishing to be bound by theory, treatment with an anti-cancer antibody or an anti-cancer antibody conjugated to a toxin can lead to cancer cell death (*e.g.*, tumor cells) which would potentiate an immune response mediated by CTLA-4 or PD-1. In an exemplary embodiment, a treatment of a hyperproliferative disease (*e.g.*, a cancer tumor) may include an anti-cancer antibody in combination with CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 or anti-CTLA-4 antibodies, concurrently or sequentially or any combination thereof, which may potentiate an anti-tumor immune responses by the host.

Tumors evade host immune surveillance by a large variety of mechanisms. Many of these mechanisms may be overcome by the inactivation of proteins, which are expressed by the tumors and which are immunosuppressive. These include, among others, TGF- β (Kehrl, J. *et al.* (1986) *J. Exp. Med.* 163: 1037-1050), IL-10 (Howard, M. & O'Garra, A. (1992) *Immunology Today* 13: 198-200), and Fas ligand (Hahne, M. *et al.* (1996) *Science* 274: 1363-1365). In another example, antibodies to each of these entities may be further combined with a CK2 inhibitor of Formulas (I) and (II) and an anti-PD-1 or anti-CTLA-4 combination to counteract the effects of immunosuppressive agents and favor anti-tumor immune responses by the host.

Other antibodies that may be used to activate host immune responsiveness can be further used in a CK2 inhibitor of Formulas (I) and (II) and anti-PD-1 or anti-CTLA-4 antibody combination. These include molecules on the surface of dendritic cells that activate DC function and antigen presentation. Anti-CD40 antibodies are able to substitute effectively for T cell helper activity (Ridge, J. *et al.* (1998) *Nature* 393: 474-478) and can be used in conjunction with an anti-PD-1 and anti-CTLA-4 combination (Ito, N. *et al.* (2000) *Immunobiology* 201 (5) 527-40). Activating antibodies to T cell costimulatory molecules, such as OX-40 (Weinberg, A. *et al.* (2000) *Immunol* 164: 2160-2169), 4-1BB (Melero, I. *et al.* (1997) *Nature Medicine* 3: 682-685 (1997), and ICOS (Hutloff, A. *et al.* (1999) *Nature* 397: 262-266) may also provide for increased levels of T cell activation.

There are also several experimental treatment protocols that involve *ex vivo* activation and expansion of antigen specific T cells and adoptive transfer of these cells into recipients in order to antigen-specific T cells against tumor (Greenberg, R. & Riddell, S. (1999) *Science* 285: 546-51). These methods may also be used to activate T cell

responses to infectious agents such as CMV. *Ex vivo* activation in the presence of CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 or anti-CTLA-4 antibodies may be expected to increase the frequency and activity of the adoptively transferred T cells.

In one aspect, the invention features any of the aforementioned embodiments,
5 wherein the anti-PD-1 antibody is replaced by, or combined with, an anti-PD-L1 or anti-PD-L2 antibody.

As set forth herein, organs can exhibit immune-related adverse events following immunostimulatory therapeutic antibody therapy, such as the GI tract (diarrhea and colitis) and the skin (rash and pruritis) after treatment with anti-CTLA-4 antibody. For
10 example, non-colonic gastrointestinal immune-related adverse events have also been observed in the esophagus (esophagitis), duodenum (duodenitis), and ileum (ileitis) after anti-CTLA-4 antibody treatment.

In certain embodiments, the present invention provides a method for altering an adverse event associated with treatment of a hyperproliferative disease with an
15 immunostimulatory agent, comprising administering a CK2 inhibitor of Formulas (I) and (II) and a subtherapeutic dose of anti-CTLA-4 antibody to a subject or a CK2 inhibitor of Formulas (I) and (II) and a subtherapeutic dose of anti-PD-1 antibody to a subject. For example, the methods of the present invention provide for a method of reducing the incidence of immunostimulatory therapeutic antibody-induced colitis or diarrhea by
20 administering a non-absorbable steroid to the patient. Because any patient who will receive an immunostimulatory therapeutic antibody is at risk for developing colitis or diarrhea induced by such an antibody, this entire patient population is suitable for therapy according to the methods of the present invention. Although steroids have been administered to treat inflammatory bowel disease (IBD) and prevent exacerbations of
25 IBD, they have not been used to prevent (decrease the incidence of) IBD in patients who have not been diagnosed with IBD. The significant side effects associated with steroids, even non-absorbable steroids, have discouraged prophylactic use.

In further embodiments, the combination of CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 and anti-CTLA-4 antibodies can be further combined with the use of
30 any non-absorbable steroid. As used herein, a “non-absorbable steroid” is a glucocorticoid that exhibits extensive first pass metabolism such that, following metabolism in the liver, the bioavailability of the steroid is low, *i.e.*, less than about 20%.

In one embodiment of the invention, the non-absorbable steroid is budesonide.

Budesonide is a locally-acting glucocorticosteroid, which is extensively metabolized, primarily by the liver, following oral administration. ENTOCORT EC[®] (Astra-Zeneca) is a pH- and time-dependent oral formulation of budesonide developed to optimize drug
5 delivery to the ileum and throughout the colon. ENTOCORT EC[®] is approved in the U.S. for the treatment of mild to moderate Crohn's disease involving the ileum and/or ascending colon. The usual oral dosage of ENTOCORT EC[®] for the treatment of Crohn's disease is 6 to 9 mg/day. ENTOCORT EC[®] is released in the intestines before being absorbed and retained in the gut mucosa. Once it passes through the gut mucosa
10 target tissue, ENTOCORT EC[®] is extensively metabolized by the cytochrome P450 system in the liver to metabolites with negligible glucocorticoid activity. Therefore, the bioavailability is low (about 10%). The low bioavailability of budesonide results in an improved therapeutic ratio compared to other glucocorticoids with less extensive first-pass metabolism. Budesonide results in fewer adverse effects, including less
15 hypothalamic-pituitary suppression, than systemically-acting corticosteroids. However, chronic administration of ENTOCORT EC[®] can result in systemic glucocorticoid effects such as hypercorticism and adrenal suppression. *See* PDR 58th ed. 2004; 608-610.

In still further embodiments, the combination of CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 or anti-CTLA-4 antibodies in conjunction with a non-absorbable
20 steroid can be further combined with a salicylate. Salicylates include 5-ASA agents such as, for example: sulfasalazine (AZULFIDINE[®], Pharmacia & UpJohn); olsalazine (DIPENTUM[®], Pharmacia & UpJohn); balsalazide (COLAZAL[®], Salix Pharmaceuticals, Inc.); and mesalamine (ASACOL[®], Procter & Gamble Pharmaceuticals; PENTASA[®], Shire US; CANASA[®], Axcan Scandipharm, Inc.; ROWASA[®], Solvay).

25 In accordance with the methods of the present invention, a salicylate administered in combination with CK2 inhibitors of Formulas (I) and (II) and anti-PD-1 or anti-CTLA-4 antibodies and a non-absorbable steroid can include any overlapping or sequential administration of the salicylate and the non-absorbable steroid for the purpose of decreasing the incidence of colitis induced by the immunostimulatory antibodies.

30 Thus, for example, methods for reducing the incidence of colitis induced by the immunostimulatory antibodies according to the present invention encompass administering a salicylate and a non-absorbable concurrently or sequentially (*e.g.*, a

salicylate is administered 6 hours after a non-absorbable steroid), or any combination thereof. Further, according to the present invention, a salicylate and a non-absorbable steroid can be administered by the same route (*e.g.*, both are administered orally) or by different routes (*e.g.*, a salicylate is administered orally and a non-absorbable steroid is administered rectally), which may differ from the route(s) used to administer the anti-PD-1 or anti-CTLA-4 antibodies.

When employing the methods or compositions of the present invention, other agents used in the modulation of tumor growth or metastasis in a clinical setting, such as antiemetics, can also be administered as desired.

The combinations of the instant invention may also be co-administered with other well-known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Combinations of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a multiple combination formulation is inappropriate.

VI. Kits and Unit Dosage Forms

Also provided herein are kits which include a pharmaceutical composition containing a CK2 inhibitor such the compounds of Formulas (I) and (II) and an ICM such as the anti-CTLA4 antibody or an anti-PD-1 antibody, and a pharmaceutically-acceptable carrier, in a therapeutically effective amount adapted for use in the preceding methods. The kits optionally can also include instructions, *e.g.*, comprising administration schedules, to allow a practitioner (*e.g.*, a physician, nurse, or patient) to administer the composition contained therein to administer the composition to a patient having a cancer (*e.g.*, a solid tumor or B cell lymphoma). The kit can also include a syringe.

Optionally, the kits include multiple packages of the single-dose pharmaceutical compositions each containing an effective amount of the CK2 inhibitor and the anti-CTLA4 antibody or the anti-PD-1 antibody in accordance with the methods provided above. Instruments or devices necessary for administering the pharmaceutical composition(s) also may be included in the kits. For instance, a kit may provide an amount of a CK2 inhibitor as tablets and one or more pre-filled syringes containing an amount of the anti-CTLA4 antibody or the anti-PD-1 antibody.

In one embodiment, the present invention provides a kit for treating a cancer (e.g., a solid tumor or B cell lymphoma) in a human patient, the kit comprising: (a) a dosage ranging from 0.1 to 50 mg/kg body weight of a CK2 inhibitor (b) a dosage ranging from 1 to 10 mg of an anti-CTLA4 antibody (e.g., ipilimumab) or an anti-PD-1 antibody (e.g., nivolumab) or an antigen-binding portion thereof; and (c) instructions for using the anti-PD-1 antibody and the anti-CTLA4 antibody in a method of the present invention. In certain specific embodiments, the dosage of the CK2 inhibitor of the kit is 1 to 25 mg/kg body weight and the dosage of the anti-PD-1 antibody is 1 or 3 mg/kg body weight. In certain specific embodiments, In certain specific embodiments, the dosage of the CK2 inhibitor of the kit is 1 to 25 mg/kg body weight and the dosage of the anti-CTLA4 antibody of the kit is 3 or 8 mg.

VI. EXAMPLES

EXAMPLE 1

Method of Assessing the Effect of the Combination of a CK2 Protein Kinase Inhibitor with a Co-stimulatory Pathway Modulator on Tumor Growth in Two Murine Tumor Models

The effect of the protein kinase CK2 on immune cell differentiation and function has been recently reported. It was demonstrated that inhibition of CK2 using pharmacologic agents or by depletion using RNA interference can alter the differentiation of myeloid progenitor cells causing reduced percentages of myeloid derived suppressor cells (MDSCs) together with increased percentages of Dendritic cells (DCs) (Cheng P et al. Effects of notch signaling on regulation of myeloid cell differentiation in cancer. Cancer Res. 2014 Jan 1;74(1):141-52). Other reports demonstrated that inhibition or depletion of CK2 kinase activity can diminish the immune suppressive function of regulatory T-cells (Tregs) (Ulges A, et al. Protein kinase CK2 enables regulatory T cells to suppress excessive TH2 responses in vivo. Nat Immunol. 2015 Mar;16(3):267-75). These results, along with others, led us to the hypothesis that pharmacologic inhibition of CK2 would alter the immune microenvironment in cancers rendering them more sensitive to treatment immunotherapeutic anti-cancer agents such as anti-PD-1 and anti-CTLA-4 monoclonal antibodies. Thus, there was an interest in determining whether a potentiation of an

antitumor immune response could be achieved by the combination of a CK2 inhibitor and either a CTLA-4 or PD-1 blocking mAb.

Efficacy studies were conducted in two mouse tumor models: MC38 colon carcinoma and 4T1 breast carcinoma. For these studies, female mice (strains: C57BL6 for MC38 and BalbC for 4T1) between the ages of 6 and 8 weeks were injected subcutaneously with 1.0×10^6 cells in 0.2 mL Hanks Balanced Salt Solution. Seven days post implant; mice were sorted into 6 groups of 8 mice with a mean tumor volume of $\sim 110 \text{ mm}^3$. Treatments are administered with antibodies and/or CK2 inhibitor at the doses and schedules described in Tables 1 and 2. CTLA-4 and PD-1 antibodies were formulated in Phosphate Buffered Saline (PBS) solution and were administered by intraperitoneal injection. The CK2 inhibitor was formulated in 80% PEG-300, 10% TPGS and 10% Ethanol and was administered by oral gavage. The mice were monitored twice weekly for tumor growth for approximately 6 weeks. Using an electronic caliper, the tumors were measured three dimensionally (height x width x length) and tumor volume was calculated. Mice were euthanized when the tumors reached 1500 mm^3 or when mice showed greater than 15% body weight loss. Measures of antitumor activity included; average % Tumor Growth Inhibition (%TGI), time of tumor progression to target size (T-C), Partial Response (PR) and complete response (CR). Average % TGI is calculated using the formula: $\text{TGI} = \{1 - [(T_t - T_0)/(C_t - C_0)]\} \times 100$ where C_t = the median tumor volume (mm^3) of vehicle control (C) treated mice at time, t , T_t = median tumor volume (mm^3) of treated mice at time t , C_0 = median tumor volume (mm^3) of vehicle control treated mice at time 0 and T_0 = median tumor volume (mm^3) of treated mice at time 0. Time of tumor progression to target size (T-C), refers to the time (days) for the median tumor size of control (C) mice to reach target size (1000 mm^3) subtracted from the time for median tumor size of treated (T) mice to reach target size (1000 mm^3). Partial regression (PR) indicates greater than 50% (but less than 100%) reduction in tumor size since the initiation of treatment. Complete regression indicates 100% reduction in tumor size for at least two measurements.

The results of the anti-tumor efficacy studies are shown in Tables 1 and 2. MC38 colon tumors are marginally sensitive to the CK2 inhibitor, Compound 1, as well as the PD-1 and CTLA-4 mAbs (%TGI equal 55, 57 and 72 respectively). As shown in Table 1, concurrent treatment with CTLA-4 mAb + the CK2 inhibitor Compound 1 resulted in synergistic effects. 75% of animals treated with the CTLA-4 mAb combined with the CK2

inhibitor demonstrated wither complete or partial regressions compared to 25% in animals treated with CTLA-4 mAb alone and 0% treated with the CK2 inhibitor alone. Synergy between anti-PD-1 mAb and the CK2 inhibitor Compound 1 was also observed in this model. While treatment with either the CK2 inhibitor or the PD-1 mAb produced few or
 5 no regressions (0% and 12.5% respectively), combination of the CK2 inhibitor and the PD1 mAb resulted in either partial or complete regression in 62.5% of the tumors.

In the 4T1 breast carcinoma model, Compound 1, anti-PD-1 and anti-CTLA4 have minimal effects on tumor growth as single agents (no partial or complete regressions were observed). However, the combination of the CTLA4 blocking monoclonal antibody with
 10 the CK2 inhibitor showed synergy in anti-tumor effects with 37.5% of treated animals achieving either complete or partial response, Table 2.

TABLE 1

15 Antitumor Activity of CTLA-4 mAb in Combination with Compound 1 in the MC38 Colon Carcinoma Subcutaneous Tumor Model

Treatment	Dose	Schedule (Study Days)	% TGI (Average)	T-C (1000 mm ³)	PR %	CR %	Outcome
CTLA-4 mAb	20 µg	7, 14, 21, 28	72	9.0	0	25.0	
PD-1 mAb	200 µg	7, 14, 21, 28	57	9.8	0	12.5	
Compound 1	15mg/kg bid	7-14	55	5.2	0	0	
Compound 1 + CTLA-4 mAb	15mg/kg bid 20 µg	7-14 7, 14, 21, 28	99	12.5	25.0	50.0	Synergy

Treatment	Dose	Schedule (Study Days)	% TGI (Average)	T-C (1000 mm ³)	PR %	CR %	Outcome
Compound 1 + PD-1 mAb	15mg/kg bid 200 µg	7-14 7, 14, 21, 28	89	12.5	25.0	37.5	Synergy

TVDT = 6.6 days

TABLE 2

Antitumor Activity of CTLA-4 mAb in Combination with Compound 1 in the 4T1 Breast
Carcinoma Subcutaneous Tumor Model

Treatment	Dose	Schedule (Study Days)	% TGI (Average)	T-C (1000 mm ³)	PR %	CR %	Outcome
CTLA-4 mAb	20 µg	7, 14, 21	23	1.6	0	0	
Compound 1	15mg/kg bid	7-21	24	2.4	0	0	
Compound 1 + CTLA-4 mAb	15mg/kg bid 20	7-21 7, 14, 21	74	8.3	12.5	25.0	Synergy

TVDT = 2.8 days

In summary, addition of a CK2 inhibitor to costimulatory pathway modulators such as PD-1 or CTLA-4 mAb resulted in synergistic activity supporting the use of CK2 inhibitor combinations with immunotherapeutic agents in clinical trials. All the combination regimens were well tolerated.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended Claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, GENBANK® Accession numbers, SWISS-PROT® Accession numbers, or other disclosures) in the Background of the Invention, Detailed Description, Brief Description of the Figures, and Examples is hereby
5 incorporated herein by reference in their entirety. Further, the hard copy of the Sequence Listing submitted herewith, in addition to its corresponding Computer Readable Form, are incorporated herein by reference in their entirety.

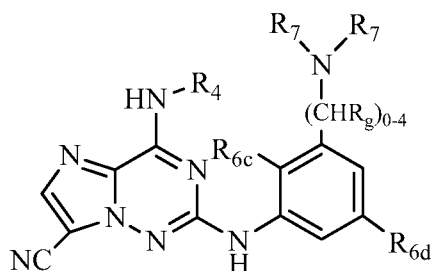
What Is Claimed Is:

1. A method of treating cancer in a subject comprising administering to the subject a synergistically-effective combination of (1) a CK2 inhibitor and (2) an immune
5 checkpoint inhibitor (ICM).
2. The method of claim 1 wherein the ICMt is selected from an antagonist of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1,
10 and TIM-4.
3. The method of claim 2, wherein the ICM is a CTLA-4 antagonist.
4. The method of claim 3, wherein the CTLA-4 antagonist is an antagonistic CTLA-
15 4 antibody.
5. The method of claim 4, wherein the antagonistic CTLA-4 antibody is selected from ipilimumab and tremelimumab.
- 20 6. The method of claim 2, wherein the ICM is a PD-1 antagonist.
7. The method of claim 6, wherein the PD-1 antagonist is an antagonistic PD-1 antibody.
- 25 8. The method of claim 7, wherein the antagonistic PD-1 antibody is selected from nivolumab, pembrolizumab, MEDI-0680, and pidilizumab.
9. The method of claim 4 or 7, wherein the antibody is a chimeric antibody.
- 30 10. The method of claim 4 or 7, wherein the antibody is a humanized antibody.
11. The method of claim 4 or 7, wherein the antibody is a fully human antibody.

12 The method of claim 4 or 7, wherein the antibody is a monoclonal antibody.

13. The method of claim 1 wherein the CK2 inhibitor is selected from a compound

5 having formula (I)



(I)

wherein

R₄ is selected from the group consisting of C₁₋₄alkyl substituted with 1-3 R_e, C₃₋

10 ₆cycloalkyl and heterocyclyl substituted with 1-3 R_e;

R₇ and R₇ together with the nitrogen atom to which they are both attached form a 4- to 7-membered monocyclic or 7- to 12-membered bicyclic heterocycle containing carbon atoms and additional 1-3 heteroatoms selected from the group consisting of NR_{8a}, O, and S(O)₂ and substituted with 1-4 R₈;

15 R₈, at each occurrence, is independently selected from the group consisting of H, F, Cl, Br, C₁₋₄alkyl substituted with 1-4 R_e, =O, C₂₋₄ alkenyl substituted with 1-5 R_e, - (CHR_g)_rOR_b, - (CHR_g)_rS(O)_pR_c, - (CHR_g)_rC(=O)(CHR_g)_rR_d, - (CHR_g)_rNR_aR_a, - (CHR_g)_rC(=O)NR_aR_a, - (CHR_g)_rC(=O)NR_aS(O)_pR_c, - (CHR_g)_rNR_a(CR_gR_g)_rC(=O)R_d, - (CHR_g)_rNR_aC(=O)OR_b, -

20 (CHR_g)_rOC(=O)(CHR_g)_rR_d, - (CHR_g)_rOC(=O)(CHR_g)_rC(=O)OR_d, - (CHR_g)_rOC(=O)(CHR_g)_rC(=O)NR_aR_a, - (CHR_g)_rOC(=O)(CHR_g)_rNR_aC(=O) R_b, - (CHR_g)_rOC(=O)(CHR_g)_rNR_aR_a, - (CHR_g)_rNR_aC(=O)NR_aR_a, - (CHR_g)_rC(=O)(CH₂)_rOR_b, - (CHR_g)_rC(=O)(CHR_g)_rOC(=O)R_b, - (CHR_g)_rS(O)₂NR_aR_a, - (CHR_g)_rNR_aS(O)_pNR_aR_a, - (CHR_g)_rNR_aS(O)_pR_c, - OPO₃H, -

25 (CHR_g)_r-C₃₋₆ cycloalkyl substituted with 1-5 R_e, - (CHR_g)_r-aryl substituted with 1-4 R_e and - (CHR_g)_r-heterocyclyl substituted with 1-4 R_e;

R_{8a} is selected from the group consisting of H, C₁₋₄alkyl substituted with 1-5 R_e, C₂₋₄ alkenyl substituted with 1-5 R_e, - (CHR_g)_rOR_b, - (CHR_g)_rS(O)_pR_c, -

- $(\text{CHR}_g)_r\text{C}(=\text{O})(\text{CHR}_g)_r\text{R}_d$, $-(\text{CHR}_g)_r\text{NR}_a\text{R}_a$, $-(\text{CHR}_g)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, -
 $(\text{CHR}_g)_r\text{C}(=\text{O})\text{NR}_a\text{S}(\text{O})_p\text{R}_c$, $-(\text{CHR}_g)_r\text{NR}_a(\text{CR}_g\text{R}_g)_r\text{C}(=\text{O})\text{R}_d$, -
 $(\text{CHR}_g)_r\text{NHC}(=\text{O})\text{OR}_b$, $-(\text{CHR}_g)_r\text{OC}(=\text{O})(\text{CHR}_g)_r\text{R}_d$, -
 $(\text{CHR}_g)_r\text{OC}(=\text{O})(\text{CHR}_g)_r\text{C}(=\text{O})\text{OR}_d$, $-(\text{CHR}_g)_r\text{OC}(=\text{O})(\text{CHR}_g)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, -
5 $(\text{CHR}_g)_r\text{OC}(=\text{O})(\text{CHR}_g)_r\text{NR}_a\text{C}(=\text{O})\text{R}_b$, $-(\text{CHR}_g)_r\text{OC}(=\text{O})(\text{CHR}_g)_r\text{NR}_a\text{R}_a$, -
 $(\text{CHR}_g)_r\text{NR}_a(\text{CHR}_g)_r\text{C}(=\text{O})\text{NR}_a\text{R}_a$, $-(\text{CHR}_g)_r\text{C}(=\text{O})\text{OR}_b$, -
 $(\text{CHR}_g)_r\text{C}(=\text{O})(\text{CHR}_g)_r\text{OC}(=\text{O})\text{R}_b$, $-(\text{CHR}_g)_r\text{S}(\text{O})_2\text{NR}_a\text{R}_a$, -
 $(\text{CHR}_g)_r\text{NR}_a\text{S}(\text{O})_p\text{NR}_a\text{R}_a$, $-(\text{CHR}_g)_r\text{NR}_a\text{S}(\text{O})_p\text{R}_c$, $-\text{OPO}_3\text{H}$, $-(\text{CHR}_g)_r\text{-C}_{3-6}$
cycloalkyl substituted with 1-5 R_e , $-(\text{CHR}_g)_r\text{-aryl}$ substituted with 1-4 R_e and -
10 $(\text{CHR}_g)_r\text{-heterocyclyl}$ substituted with 1-4 R_e ;
 R_a , at each occurrence, is independently selected from the group consisting of H, CN, C_{1-6}
alkyl substituted with 1-5 R_e , C_{2-6} alkenyl substituted with 1-5 R_e , C_{2-6} alkynyl
substituted with 1-5 R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}\text{carbocyclyl}$ substituted with 1-5 R_e , and -
 $(\text{CH}_2)_r\text{-heterocyclyl}$ substituted with 1-5 R_e ; or R_a and R_a together with the
15 nitrogen atom to which they are both attached form a heterocyclic ring substituted
with 1-5 R_e ;
 R_b , at each occurrence, is independently selected from the group consisting of H, C_{1-6}
alkyl substituted with 1-5 R_e , C_{2-6} alkenyl substituted with 1-5 R_e , C_{2-6} alkynyl
substituted with 1-5 R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}\text{carbocyclyl}$ substituted with 1-5 R_e , and -
20 $(\text{CH}_2)_r\text{-heterocyclyl}$ substituted with 1-5 R_e ;
 R_c , at each occurrence, is independently selected from the group consisting of C_{1-6} alkyl
substituted with 1-5 R_e , C_{2-6} alkenyl substituted with 1-5 R_e , C_{2-6} alkynyl
substituted with 1-5 R_e , C_{3-6} carbocyclyl, and heterocyclyl;
 R_d , at each occurrence, is independently selected from the group consisting of H, OH, C_{1-6}
25 alkyl substituted with 1-5 R_e , C_{2-6} alkenyl substituted with 1-5 R_e , C_{2-6} alkynyl
substituted with 1-5 R_e , $-(\text{CH}_2)_r\text{-C}_{3-10}\text{carbocyclyl}$ substituted with 1-5 R_e , and -
 $(\text{CH}_2)_r\text{-heterocyclyl}$ substituted with 1-5 R_e ;
 R_e , at each occurrence, is independently selected from the group consisting of H, N_3 , C_{1-6}
alkyl substituted with 1-5 R_f , C_{2-6} alkenyl, C_{2-6} alkynyl, $-(\text{CH}_2)_r\text{-C}_{3-6}$ cycloalkyl, -
30 $(\text{CH}_2)_r\text{-heterocyclyl}$, F, Cl, Br, $-(\text{CH}_2)_r\text{CN}$, NO_2 , $=\text{O}$, $-\text{OPO}_3\text{H}$, $-\text{OSi}(\text{C}_{1-4}\text{alkyl})_3$, -
 $(\text{CH}_2)_r\text{OC}_{1-5}$ alkyl, $-(\text{CH}_2)_r\text{O}(\text{CH}_2)_r\text{OC}_{1-5}$ alkyl, $-(\text{CH}_2)_r\text{OH}$, $-(\text{CH}_2)_r\text{S}(\text{O})_2\text{C}_{1-5}$
alkyl, $-(\text{CH}_2)_r\text{S}(\text{O})_2\text{R}_f$, $-(\text{CH}_2)_r\text{NHS}(\text{O})_2\text{C}_{1-5}\text{alkyl}$, $-\text{S}(\text{O})_2\text{NH}_2$, SH, $-(\text{CH}_2)_r\text{NR}_f\text{R}_f$, -

$(\text{CH}_2)_r\text{NHC}(=\text{O})\text{OR}_f$, $-(\text{CH}_2)_r\text{NHC}(=\text{O})\text{R}_f$, $-(\text{CH}_2)_r\text{NHC}(=\text{NH})\text{NR}_f\text{R}_f$, $-(\text{CH}_2)_r\text{C}(=\text{O})(\text{CH}_2)_r\text{R}_f$, and $-(\text{CH}_2)_r\text{C}(=\text{O})\text{OR}_f$;

R_f , at each occurrence, is independently selected from the group consisting of H, -

- 5 $(\text{CH}_2)_r\text{OH}$, $-(\text{CH}_2)_r\text{OC}_{1-5}\text{alkyl}$, $\text{C}_{1-5}\text{alkyl}$ (optionally substituted with F, Cl, OH, NH_2), C_{3-6} cycloalkyl optionally substituted with NH_2 , $-(\text{CH}_2)_r\text{S}(\text{O})_p\text{C}_{1-4}\text{alkyl}$, $-\text{NHC}(=\text{O})\text{C}_{1-4}\text{alkyl}$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{OC}_{1-4}\text{alkyl}$, $-\text{C}(=\text{O})\text{C}_{1-4}\text{alkyl}$, $-(\text{CH}_2)_r\text{phenyl}$, $-(\text{CH}_2)_r\text{heterocyclyl}$ optionally substituted with alkyl and CN, or R_f and R_f together with the nitrogen atom to which they are both attached form a heterocyclic ring optionally substituted with $\text{C}_{1-4}\text{alkyl}$;

- 10 R_g , at each occurrence, is independently selected from the group consisting of H, F, OH, and $\text{C}_{1-5}\text{alkyl}$;

p , at each occurrence, is independently selected from the group consisting of zero, 1, and 2; and

- 15 r , at each occurrence, is independently selected from the group consisting of zero, 1, 2, 3, 4, and 5.

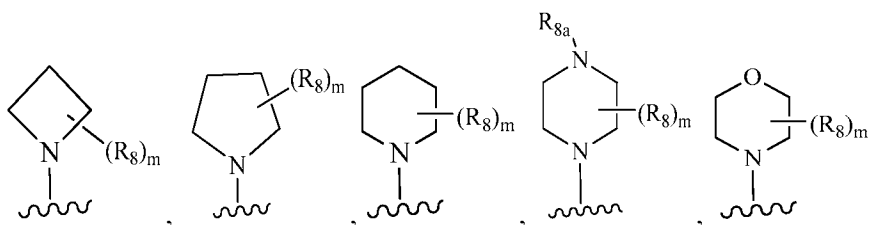
14. The method of claim 13 wherein the CK2 inhibitor is selected from a compound having formula (I) wherein

- 20 R_4 is selected from the group consisting of $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{3-6}\text{cycloalkyl}$, and heterocyclyl, each substituted with 1-3 R_e ;

R_{6c} is selected from the group consisting of F and Cl; and

R_{6d} is selected from the group consisting of CN, $-\text{NHC}(=\text{O})\text{O}(\text{C}_{1-4}\text{alkyl})$, and CHF_2 ;

NR_7R_7 is selected from the group consisting of



- 25 R_8 is selected from the group consisting of F, $\text{C}_{1-4}\text{alkyl}$ substituted with 1-4 R_e , $-\text{OH}$, $-\text{O}(\text{C}_{1-4}\text{alkyl})$, $-\text{NR}_a\text{R}_a$, $-\text{NR}_a\text{C}(=\text{O})\text{R}_b$, $-\text{NR}_a\text{C}(=\text{O})\text{OR}_b$, $-\text{OC}(=\text{O})(\text{CH}_2)_r\text{NH}_2$, $-\text{NHC}(=\text{O})\text{NR}_a\text{R}_a$, and $-\text{NHS}(\text{O})_2(\text{C}_{1-4}\text{alkyl})$; and

R_{8a} is selected from the group consisting of H, $\text{C}_{1-4}\text{alkyl}$, $\text{S}(\text{O})_2\text{C}_{1-4}\text{alkyl}$, and 5- to 6-membered heterocyclyl substituted with 1-4 R_e .

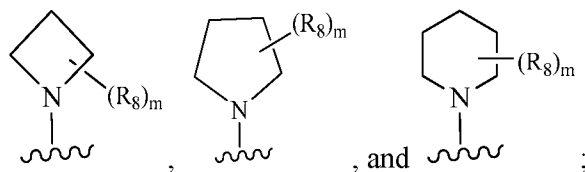
15. The method of claim 14 wherein the CK2 inhibitor is selected from a compound having formula (I) wherein

R₄ is selected from the group consisting of methyl, ethyl, propyl, and cyclopropyl;

5 R_{6c} is Cl;

R_{6d} is selected from the group consisting of CN, OCHF₂, and CHF₂;

NR₇R₇ is selected from the group consisting of



R₈ is selected from the group consisting of F, C₁₋₄alkyl substituted with 1-4 R_e, -OH, -

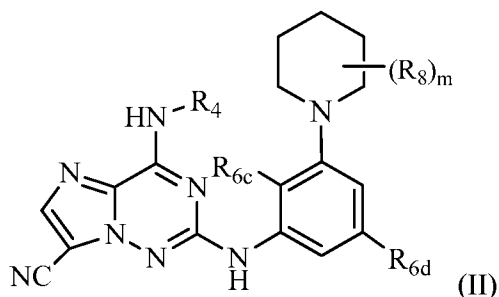
10 O(C₁₋₄alkyl), -NHC(=O)C₁₋₄alkyl, -NHC(=O)OC₁₋₄alkyl, and -NHS(O)₂(C₁₋₄alkyl); and

m, at each occurrence, is independently selected from the group consisting of zero, 1, and 2.

15 16. The method of claim 1, wherein the cancer is selected from the list consisting of bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers.

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17. A method of treating cancer in a subject comprising administering to the subject a synergistically-effective combination of (1) an anti-PD-1 antibody or a CTLA-4 antibody, and (2) a CK2 inhibitor of formula (II):



wherein

R₄ is selected from the group consisting of methyl, ethyl, propyl, and cyclopropyl;

R_{6c} is Cl;

R_{6d} is selected from the group consisting of CN, OCHF₂, and CHF₂; and m, at each

10 occurrence, is independently selected from the group consisting of zero, 1, and 2.

R₈ is selected from the group consisting of F, C₁₋₄alkyl substituted with 1-4 R_e, -OH, -

O(C₁₋₄alkyl), -NR_aR_a, -NR_aC(=O)R_b, -NR_aC(=O)OR_b, -OC(=O)(CH₂)_rNH₂, -

NHC(=O)NR_aR_a, and -NHS(O)₂(C₁₋₄alkyl); and

m, at each occurrence, is independently selected from the group consisting of zero, 1, and

15 2.

18. The method of claim 17, wherein the anti-PD-1 antibody is administered at a subtherapeutic dose.

20 19. The method of claim 17, wherein the anti-CTLA-4 antibody is administered at a subtherapeutic dose.

20. The method of claim 17, wherein the anti-PD-1 antibody or the anti-CTLA-4 antibody and the compound of Formula (II) are administered sequentially.

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21. The method of claim 17, wherein the anti-PD-1 antibody or the anti-CTLA-4 antibody is administered before the compound of Formula (II).

22. The method of claim 17, wherein the compound of Formula (II) is administered before the anti-PD-1 antibody or the anti-CTLA-4 antibody.

5 23. The method of claim 17, wherein the anti-PD-1 antibody or the anti-CTLA-4 antibody and the compound of Formula (II) are administered concurrently.

24 The method of claim 17 wherein the anti-PD-1 antibody or the anti-CTLA-4 antibody and the compound of Formula (II) are admixed as a single composition and
10 administered concurrently.

25. The method of claim 17 comprising administering to a subject (a) a composition comprising the anti-PD-1 antibody or the anti-CTLA-4 antibody and a pharmaceutically acceptable carrier and (b) a composition comprising the compound of Formula (II) and a
15 pharmaceutically acceptable carrier.

26. The method of claim 25 wherein the subject is a human.

27. The method of claim 25 wherein the anti-PD-1 antibody or the anti-CTLA-4
20 antibody is a human sequence antibody.

28. The method of claim 25 wherein the anti-PD-1 human sequence antibody or the anti-CTLA-4 human sequence antibody is a monoclonal antibody.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/057584

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K38/00 A61K45/06 A61K31/53 A61P35/00
ADD.

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)

A61K A61P

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

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

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2012/170827 A2 (CYLENE PHARMACEUTICALS INC [US]; HADDACH MUSTAPHA [US]; TRAN JOE A [US] 13 December 2012 (2012-12-13) page 206, line 7 - page 207, line 24 claims 56, 57 -----	1-5
Y	US 2014/018319 A1 (PURANDARE ASHOK VINAYAK [US] ET AL) 16 January 2014 (2014-01-16)	1-16
A	page 1, paragraph 0007 page 6, paragraph 0120 page 17, paragraph 0287 - paragraph 0294 page 149; example 327 ----- -/-	17-28



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search

11 January 2017

Date of mailing of the international search report

18/01/2017

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Authorized officer

Collins, Sally

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/057584

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	----- WO 2015/061752 A1 (PHARMACYCLICS INC [US]; UNIV LELAND STANFORD JUNIOR [US]) 30 April 2015 (2015-04-30) page 1, paragraph 0004 claims 137, 138 -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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