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(54) Titre : METHODES DE TRAITEMENT DU CANCER
(54) Title: METHODS FOR TREATING CANCER

(57) Abrégé/Abstract:
The present invention relates to methods of treating patients with advanced forms of cancer, such as unresectable or metastatic renal cell carcinoma or kidney cancer, in which X4P-001 or a pharmaceutically acceptable salt thereof is administered as monotherapy or in combination with an immune checkpoint inhibitor, such as nivolumab. The methods demonstrate surprising results, including regression of disease, with comparatively little toxicity.

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(54) Title: METHODS FOR TREATING CANCER

(57) Abstract: The present invention relates to methods of treating patients with advanced forms of cancer, such as unresectable or metastatic renal cell carcinoma or kidney cancer, in which X4P-001 or a pharmaceutically acceptable salt thereof is administered as monotherapy or in combination with an immune checkpoint inhibitor, such as nivolumab. The methods demonstrate surprising results, including regression of disease, with comparatively little toxicity.

METHODS FOR TREATING CANCER

FIELD OF THE INVENTION

[0001] The present invention relates to methods for treating cancer, for example, methods for treatment of patients with a cancer such as renal cell carcinoma.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims the benefit of priority to United States Provisional Patent Application serial number USSN 62/319,857, filed April 8, 2016, the entirety of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0003] Renal cell carcinoma is the seventh most common cancer in men and the ninth most common cancer in women in the United States, with an estimated 65,000 new cases and 13,500 deaths expected in 2015. While stage I, II and III are frequently treated by partial or radical nephrectomy, up to 30% of patients with localized tumors experience relapse. Cytoreductive nephrectomy, followed by systemic therapy is generally recommended in patients with stage IV renal cell carcinoma with a surgically resectable primary tumor. Systemic therapy is then recommended for patients with residual metastatic disease. Chittoria and Rini (2013) Renal Cell Carcinoma; www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/renal-cell-carcinoma/.

[0004] Adjuvant therapies with immunomodulating drugs, such as the anti-PD-1 antibody nivolumab (Opdivo®, Bristol-Myers Squibb, also known as ONO-4538, MDX1106 and BMS-936558), have shown potential to improve the overall survival in patients with RCC who had experienced disease progression during or after prior anti-angiogenic therapy.

[0005] The benefit of neoadjuvant chemo- and immunotherapy has been demonstrated in several operable cancers. Compared to adjuvant therapy, neoadjuvant

therapy in patients with locally and regionally advanced cancer has several potential benefits:

• Reducing the size of the primary and metastatic tumor increases the probability of achieving negative margin resection;

• Tumor exposure to potentially effective systemic therapy is increased while blood and lymphatic vessels remain intact; and

• Collection of pre- and intra-operative samples of tumor tissue following neoadjuvant therapy offers real-time, *in vivo* assessment of the effects of the therapy on the tumor cells, the tumor microenvironment (TME), and the immune system.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

[0006] CXCR4 (C-X-C chemokine receptor type 4) is a chemokine receptor expressed on a wide range of cell types, including normal stem cells, hematopoietic stem cells (HSC), mature lymphocytes, and fibroblasts. CXCL12 (previously referred to as SDF-1α) is the sole ligand for CXCR4. The primary physiologic functions of the CXCL12/CXCR4 axis include the migration of stem cells both during embryonic development (CXCR4-/- knock-out embryos die in utero) and subsequently in response to injury and inflammation. Increasing evidence indicates multiple potential roles for CXCR4/CXCL12 in malignancy. Direct expression of one or both factors has been observed in several tumor types. CXCL12 is expressed by cancer-associated fibroblasts (CAFs) and is often present at high levels in the TME. In clinical studies of a wide range of tumor types, including breast, ovarian, renal, lung, and melanoma, expression of CXCR4/CXCL12 has been associated with a poor prognosis and with an increased risk of metastasis to lymph nodes, lung, liver and brain, which are sites of CXCL12 expression. CXCR4 is frequently expressed on melanoma cells, particularly the CD133+ population that is considered to represent melanoma stem cells and *in vitro* experiments and murine models have demonstrated that CXCL12 is chemotactic for those cells.

[0007] Nivolumab (Opdivo®, Bristol-Myers Squibb, also known previously as ONO-

4538, MDX1106 and BMS-936558) is a human IgG4 anti-PD-1 monoclonal antibody. It belongs to the emerging class of immunotherapeutics referred to as checkpoint modulators (CPM). These agents have been developed based on observations that in multiple types of malignancies, the tumor suppresses the host anti-tumor immune response by exploiting counter-regulatory mechanism that normally act as "checkpoints" to prevent the overactivation of the immune system in infection and other situations. In the case of melanoma, PD-L1 is expressed by cells in the TME, engages PD-1, a membrane-associated receptor on CD8+ effector T cells, and triggers inhibitory signaling that reduces the killing capacity of cytotoxic T cells.

[0008] Nivolumab is currently FDA approved for the treatment of patients with advanced renal cell carcinoma (RCC), who have received prior anti-angiogenic therapy. The recommended dose of nivolumab is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. In a clinical trial, patients previously treated with nivolumab showed improved overall survival compared with patients being treated with a cancer chemotherapeutic, everolimus.

[0009] Multiple observations implicate the CXCL12/CXCR4 axis in contributing to the lack (or loss) of tumor responsiveness to angiogenesis inhibitors (also referred to as "angiogenic escape"). In animal cancer models, interference with CXCR4 function has been demonstrated to disrupt the tumor microenvironment (TME) and unmask the tumor to immune attack by multiple mechanisms, including eliminating tumor re-vascularization and increasing the ratio of CD8+ T cells to Treg cells. These effects result in significantly decreased tumor burden and increased overall survival in xenograft, syngeneic, as well as transgenic, cancer models. See Vanharanta et al. (2013) Nat Med 19: 50-56; Gale and McColl (1999) BioEssays 21: 17-28; Highfill et al. (2014) Sci Transl Med 6: ra67; Facciabene et al. (2011) Nature 475: 226-230.

[0010] X4P-001, formerly designated AMD11070, is a potent, orally bioavailable CXCR4 antagonist (see Montane et al. (2011) J Clin Invest 121: 3024-8), that has

demonstrated activity in solid and liquid tumor models (see Acharyya et al. (2012) Cell 150: 165-78, and unpublished data) and has previously (under the designations AMD070 and AMD11070) been in Phase 1 and 2a trials involving a total of 71 healthy volunteers (see Montane et al. (2011) J Clin Invest 121: 3024-8; Zhao et al. (2012) J Clin Invest 122: 4094-4104; Silva et al. (2008) Science 319: 617-20) and HIV-infected subjects (see Schlabach et al. (2008) Science 319: 620-24; Shen et al. (2013) Tumour Biol 34: 1839-45). These studies demonstrated that oral administration of up to 400 mg BID for 3.5 days (healthy volunteers) and 200 mg BID for 8-10 days (healthy volunteers and HIV patients) was well-tolerated with no pattern of adverse events or clinically significant laboratory changes. These studies also demonstrated pharmacodynamic activity, with dose- and concentration-related changes in circulating white blood cells (WBCs); and a high volume of distribution (VL), suggesting high tissue penetration.

[0011] Plerixafor (formerly designated AMD3100, now marketed as Mozobil) is the only CXCR4 antagonist currently FDA approved. Plerixafor is administered by subcutaneous injection and has a very short half life; the only FDA-approved indication is for courses of 3 to 5 days to release HSC from the bone marrow into the peripheral blood for harvesting. Both X4P-001 and plerixafor have been studied in murine models of melanoma, renal cell carcinoma, and ovarian cancer and have demonstrated significant anti-tumor activity, including decreased metastasis and increased overall survival. The treatment effect has been associated with decreased presence of myeloid-derived suppressor cells (MDSCs) in the TME and increased presence of tumor-specific CD-8+ effector cells. See D'Alterio, et al. (2012) Cancer Immunol Immunother 61:1713-1720; Feig, et al. (2013) PNAS 110:20212-20217; and Zhang et al. (2006) Cancer Biol Ther. 5:1034-1312.

[0012] Without wishing to be bound by any particular theory, it is believed that administration of X4P-001 will increase the density of CD8+ T cells among tumor cells and that this effect will be sustained or increased when X4P-001 is given in combination with nivolumab. Because X4P-001 is well-tolerated in the body, and may increase the ability of the body to mount a robust anti-tumor immune response, administering X4P-

001 in combination with checkpoint modulators may substantially increase the objective response rate in multiple tumor types, the frequency of durable long-term responses, and overall survival.

[0013] It is further believed that such results will be achieved with comparatively little toxicity because CXCR4-targeted drugs are not be expected to induce cell cycle arrest in bone marrow and other normal proliferating cell populations. Accordingly, the present invention provides significant advantages in treatment outcomes utilizing the low toxicity and effects of the CXCR4 inhibitor AMD11070 (X4P-001) on MDSC trafficking, differentiation and tumor cell gene expression in RCC.

[0014] It has now been found that CXCR4 antagonism by X4P-001 provides significant effects which in turn would provide significant treatment benefits in patients with advanced renal cell carcinoma and other cancers by multiple mechanisms. In certain embodiments, administration of X4P-001 increases the density of CD8+ T cells, thereby resulting in increased anti-tumor immune attack. In certain embodiments, administration of X4P-001 additionally decreases neoangiogenesis and tumor vascular supply. In other embodiments, administration of X4P-001 interferes with the autocrine effect of increased expression by tumors of both CXCR4 and its only ligand, CXCL12, thereby reducing cancer cell metastasis.

[0015] In one aspect of the present invention, patients with advanced forms of cancer, including kidney cancer, such as renal cell carcinoma, are treated with X4P-001, either as a single agent (monotherapy), or in combination with an immune checkpoint inhibitor, such as nivolumab. Nivolumab is an antibody to PD-1, which binds to the programmed cell death 1 receptor (PD-1) to prevent the receptor from binding to the inhibitory ligand PDL-1, thus overriding the ability of tumors to suppress the host anti-tumor immune response, dubbed an immune checkpoint inhibitor.

[0016] Without wishing to be bound by any particular theory, it is believed that by combining the two medicaments X4P-001, or a pharmaceutically acceptable salt thereof,

and an immune checkpoint inhibitor, a patient's treatment outcome can be further improved by increasing the body's ability to mount a robust anti-tumor immune response.

[0017] In some embodiments, X4P-001, or a pharmaceutically acceptable salt thereof, is administered to a patient in a fasted state.

[0018] In some embodiments, the present invention provides a method for treating patients with cancer that presents as a solid tumor, particularly renal cell carcinoma. In some embodiments, the patient has resectable RCC, meaning that the patient's tumor is deemed susceptible to being removed by surgery. In other embodiments, the patient has unresectable carcinoma, meaning that the patient's tumor has been deemed not susceptible to being removed by surgery.

[0019] In some embodiments, the present invention provides a method for treating advanced cancer, such as kidney cancer or renal cell carcinoma, in a patient in need thereof comprising administering X4P-001, or a pharmaceutically acceptable salt or pharmaceutical composition thereof. In certain embodiments, the patient was previously administered an immune checkpoint inhibitor. In some embodiments, the patient was previously administered an immune checkpoint inhibitor selected from the group consisting of nivolumab (Opdivo®, Bristol-Myers Squibb), pembrolizumab (Keytruda®, Merck) and ipilumumab (Yervoy®, Bristol-Myers Squibb). In some embodiments, the patient has previously received a tumor resection or anticancer chemotherapy or immunotherapy, such as previous treatment with anti-angiogenic therapy and/or an immune checkpoint inhibitor but not X4P-001 or a pharmaceutically acceptable salt thereof.

[0020] In certain embodiments, the present invention provides a method for treating cancer in a patient comprising administering to said patient X4P-001 or a pharmaceutically acceptable salt thereof in combination with an immunotherapeutic drug, such as an immune checkpoint inhibitor. In certain embodiments, the X4P-001 and the checkpoint inhibitor are administered simultaneously or sequentially. In certain embodiments, X4P-001 or a pharmaceutically acceptable salt thereof is administered

prior to the initial dosing with the immune checkpoint inhibitor. In certain embodiments, the immune checkpoint inhibitor is administered prior to the initial dosing with X4P-001 or a pharmaceutically acceptable salt thereof.

[0021] In certain embodiments, the immune checkpoint inhibitor is selected from a PD-1 antagonist, a PD-L1 antagonist, and a CTLA-4 antagonist. In some embodiments, X4P-001 or a pharmaceutically acceptable salt thereof is administered in combination with an immunotherapeutic drug selected from the group consisting of nivolumab (Opdivo®, Bristol-Myers Squibb), ipilimumab (Yervoy®, Bristol-Myers Squibb); and pembrolizumab (Keytruda®, Merck). In some embodiments, X4P-001 or a pharmaceutically acceptable salt thereof is administered in combination with nivolumab (Opdivo®, Bristol-Myers Squibb) previously known as BMS-93568, MDX1106 or ONO-4538.

[0022] Other immune checkpoint inhibitors in development are suitable for use in combination with X4P-001 or a pharmaceutically acceptable salt thereof. These include atezolizumab (Genentech/Roche), also known as MPDL3280A, a fully humanized engineered antibody of IgG1 isotype against PD-L1, in clinical trials for non-small cell lung cancer and advanced bladder cancer such as advanced urothelial carcinoma; and as adjuvant therapy to prevent cancer from returning after surgery; durvalumab (Astra-Zeneca), also known as MEDI4736, in clinical trials for metastatic breast cancer, multiple myeloma, esophageal cancer, myelodysplastic syndrome, small cell lung cancer, head and neck cancer, renal cancer, glioblastoma, lymphoma and solid malignancies; pidilizumab (CureTech), also known as CT-011, an antibody that binds to PD-1, in clinical trials for diffuse large B-cell lymphoma and multiple myeloma; avelumab (Pfizer/Merck KGaA), also known as MSB0010718C), a fully human IgG1 anti-PD-L1 antibody, in clinical trials for non-small cell lung cancer, Merkel cell carcinoma, mesothelioma, solid tumors, renal cancer, ovarian cancer, bladder cancer, head and neck cancer, and gastric cancer; and PDR001 (Novartis), an inhibitory antibody that binds to PD-1, in clinical trials for non-small cell lung cancer, melanoma, triple negative breast cancer and advanced or metastatic solid tumors.

[0023] Nivolumab (Opdivo®, BMS-93568/MDX1106; Bristol-Myers Squibb), is a fully human IgG4 monoclonal antibody that acts as an immunomodulator by binding to the programmed cell death 1 (PD-1) receptor and selectively blocking interaction with its ligands PD-L1 and PD-L2. The structure and other properties of nivolumab are specified at http://www.drugbank.ca/drugs/DB09035, accessed on March 14, 2016, the disclosure of which is hereby incorporated herein. Nivolumab is approved for use in treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy; as a single agent in certain types of unresectable or metastatic melanoma; in treating unresectable or metastatic melanoma or in combination with ipilimumab in treating unresectable or metastatic melanoma; and for treatment of metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Additionally, nivolumab has been tested or mentioned as a possible treatment in other oncologic indications, including solid tumors; skin melanoma; glioblastoma; glioma; gliosarcoma; astrocytoma; brain cancer; leukemia; acute myeloid leukemia; chronic myeloid leukemia; chronic lymphocytic leukemia; advanced liver cancer or hepatocellular carcinoma; uveal melanoma; prostate cancer; pancreatic neoplasm and pancreatic cancer; bladder cancer; colorectal cancer; myelodysplastic syndrome; Hodgkin Lymphoma; Non-Hodgkin Lymphoma; multiple myeloma; cervical cancer; endometrial cancer; uterine cancer; ovarian cancer and ovarian carcinoma; peritoneal carcinoma; head and neck squamous cell cancer; gastric cancer; esophageal cancer; Kaposi sarcoma; breast neoplasm, breast adenocarcinoma and breast cancer; bone sarcoma; soft tissue sarcoma; meningiomas; and mesothelioma.

[0024] In a phase 3 trial of over 800 patients with advanced clear-cell renal-cell carcinoma, for which they had received previous treatment with one or two regimens of antiangiogenic therapy were randomly assigned to receive 3 mg/kg body weight of nivolumab, intravenously every two weeks, or a 10 mg everolimus tablet orally daily. Patients treated with nivolumab exhibited longer median overall survival, decreased hazard ratio for death, and higher objective response rate than those patients treated with nivolumab (25%) compared to everolimus (5%) ($P<0.001$), with lower incidence of

Grade 3 or 4 treatment-related adverse events (Motzer et al. (2015), New England Journal of Medicine, 373:1803-1813).

[0025] In its current prescribed labeling for unresectable or metastatic renal cell carcinoma, the recommended course of administration for nivolumab is 3 mg/kg as an intravenous infusion over 60 minutes every two weeks, until disease progression or unacceptable toxicity. In the discretion of the clinician, depending upon individual tolerance, the prescribed dose of nivolumab may be increased, for example, increased in dosage and/or frequency. In the discretion of the clinician, together with the warnings provided with prescribing information, administration of nivolumab may be discontinued, or the dose reduced in the case of significant adverse effects.

[0026] In some embodiments, the present invention provides a method for treating renal cell carcinoma in a patient by administering X4P-001 or a pharmaceutically acceptable salt thereof in combination with an immune checkpoint inhibitor. In some embodiments, the carcinoma is resectable and metastatic. In other embodiments, the carcinoma is unresectable and metastatic. In some embodiments, the immune checkpoint inhibitor is nivolumab.

[0027] In some embodiments, the present invention provides a method for treating a refractory cancer in a patient, wherein said method comprises administering to said patient X4P-001 or a pharmaceutically acceptable salt thereof in combination with an immune checkpoint inhibitor. In some embodiments, the refractory cancer is metastatic renal cell carcinoma whose tumors express PD-L1, and who have disease progression after treatment with anti-angiogenic therepy or platinum-containing chemotherapy. In some embodiments, the refractory cancer is metastatic renal cell carcinoma and the immune checkpoint inhibitor is nivolumab.

[0028] In some embodiments of the disclosed methods, X4P-001, or a pharmaceutically acceptable salt thereof, is administered to a patient in need thereof in a

fasted state and the immune checkpoint inhibitor is administered to the patient in either a fasted or fed state.

[0029] In certain embodiments, the present invention provides a method for treating cancer in a patient, wherein said method comprises administering to said patient X4P-001 or a pharmaceutically acceptable salt thereof in combination with an immune checkpoint inhibitor, further comprising the step of obtaining a biological sample from the patient and measuring the amount of a disease-related biomarker. In some embodiments, the biological sample is a blood sample. In certain embodiments, the disease-related biomarker is circulating CD8+ cells, plasma levels of PD-1, and/or plasma levels of PDL-1.

[0030] In certain embodiments, the present invention provides a method for treating advanced cancer, such as metastatic renal cell carcinoma, in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 or a pharmaceutically acceptable salt thereof in combination with nivolumab, further comprising the step of obtaining a biological sample from the patient and measuring the amount of a disease-related biomarker. In some embodiments, the biological sample is a blood sample. In certain embodiments, the disease-related biomarker is circulating CD8+ cells, plasma levels of PD-1, and/or plasma levels of PDL-1.

[0031] In other embodiments of the invention, X4P-001 or a pharmaceutically acceptable salt thereof is administered in combination with an immune checkpoint inhibitor. The immune checkpoint inhibitor may be an antibody to PD-1, PDL-1, or CTLA-4. In certain embodiments, the immune checkpoint inhibitor is selected from the group consisting of nivolumab, pembrolizumab, and ipilimumab.

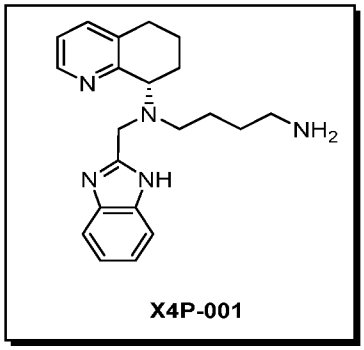
[0032] In some embodiments, the present invention provides a method of treating cancer in a patient, wherein said method comprises administering to said patient X4P-001 or a pharmaceutically acceptable salt thereof in combination with an immune checkpoint inhibitor, wherein the X4P-001 and the immune checkpoint inhibitor act synergistically.

One of ordinary skill in the art will appreciate that active agents (such as X4P-001 and an immune checkpoint inhibitor) act synergistically when the combination of active agents results in an effect that is greater than the additive effect of each agent taken separately. In some embodiments, the immune checkpoint inhibitor is nivolumab.

Dosage and Formulations

[0033] X4P-001 is a CXCR4 antagonist, with molecular formula $C_{21}H_{27}N_5$; molecular weight 349.48 amu; and appearance as a white to pale yellow solid. Solubility: X4P-001 is freely soluble in the pH range 3.0 to 8.0 (>100 mg/mL), sparingly soluble at pH 9.0 (10.7 mg/mL) and slightly soluble at pH 10.0 (2.0 mg/mL). X4P-001 is only slightly soluble in water. Melting point: 108.9 °C.

[0034] The chemical structure of X4P-001 is depicted below.



X4P-001

[0035] In certain embodiments, a pharmaceutical composition containing X4P-001 or a pharmaceutically acceptable salt thereof is administered orally in an amount from about 200 mg to about 1200 mg daily. In certain embodiments, the dosage composition may be provided twice a day in divided dosage, approximately 12 hours apart. In other embodiments, the dosage composition may be provided once daily. The terminal half-life of X4P-001 has been generally determined to be between about 12 to about 24 hours, or approximately 14.5 hrs. Dosage for oral administration may be from about 100 mg to about 1200 mg once or twice per day. In certain embodiments, the dosage of X4P-001 or a pharmaceutically acceptable salt thereof useful in the invention is from about 200 mg to about 600 mg daily. In other embodiments, the dosage of X4P-001 or a pharmaceutically acceptable salt thereof useful in the invention may range from about 400 mg to about 800 mg, from about 600 mg to about 1000 mg or from about 800 mg to about 1200 mg daily.

In certain embodiments, the invention comprises administration of an amount of X4P-001 or a pharmaceutically acceptable salt thereof of about 10 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, or about 1600 mg.

[0036] In some embodiments, a provided method comprises administering to the patient a pharmaceutically acceptable composition comprising X4P-001 or a pharmaceutically acceptable salt thereof wherein the composition is formulated for oral administration. In certain embodiments, the composition is formulated for oral administration in the form of a tablet or a capsule. In some embodiments, the composition comprising X4P-001 or a pharmaceutically acceptable salt thereof is formulated for oral administration in the form of a capsule.

[0037] In certain embodiments, a provided method comprises administering to the patient one or more capsules comprising 100-1200 mg X4P-001 or a pharmaceutically acceptable salt thereof as an active ingredient; and one or more pharmaceutically acceptable excipients. In some embodiments, each capsule or capsules administered may independently comprise about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 400 mg or about 800 mg X4P-001 or a pharmaceutically acceptable salt thereof as an active ingredient; and one or more pharmaceutically acceptable excipients.

[0038] In certain embodiments, the present invention provides a pharmaceutical composition comprising X4P-001 or a pharmaceutically acceptable salt thereof, one or more diluents, a disintegrant, a lubricant, a flow aid, and a wetting agent. In some embodiments, the present invention provides a composition comprising 10-1200 mg X4P-001 or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, dibasic calcium phosphate dihydrate, croscarmellose sodium, sodium stearyl fumarate, colloidal

silicon dioxide, and sodium lauryl sulfate. In some embodiments, the present invention provides a unit dosage form wherein said unit dosage form comprises a composition comprising 10-200 mg X4P-001, or a pharmaceutically acceptable salt thereof, microcrystalline cellulose, dibasic calcium phosphate dihydrate, croscarmellose sodium, sodium stearyl fumarate, colloidal silicon dioxide, and sodium lauryl sulfate. In certain embodiments, the present invention provides a unit dosage form comprising a composition comprising X4P-001 or a pharmaceutically acceptable salt thereof, present in an amount of about 10 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, or about 1600 mg. In some embodiments, a provided composition (or unit dosage form) is administered to the patient once per day, twice per day, three times per day, or four times per day. In some embodiments, a provided composition (or unit dosage form) is administered to the patient once per day or twice per day. In some embodiments, the unit dosage form comprises a capsule containing about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 400 mg, or about 800 mg of X4P-001, or a pharmaceutically acceptable salt thereof.

[0039] In some embodiments, the present invention provides a unit dosage form comprising a pharmaceutical composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof – about 30-40% by weight of the composition;

(b) microcrystalline cellulose – about 20-25% by weight of the composition;

(c) dibasic calcium phosphate dehydrate – about 30-35% by weight of the composition;

(d) croscarmellose sodium – about 5-10% by weight of the composition;

(e) sodium stearyl fumarate – about 0.5-2% by weight of the composition;

(f) colloidal silicon dioxide – about 0.1-1.0 % by weight of the composition; and

(g) sodium lauryl sulfate – about 0.1-1.0 % by weight of the composition.

[0040] In some embodiments, the present invention provides a unit dosage form comprising a composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof – about 37% by weight of the composition;

(b) microcrystalline cellulose – about 23% by weight of the composition;

(c) dibasic calcium phosphate dehydrate – about 32% by weight of the composition;

(d) croscarmellose sodium – about 6% by weight of the composition;

(e) sodium stearyl fumarate – about 1% by weight of the composition;

(f) colloidal silicon dioxide – about 0.3 % by weight of the composition; and

(g) sodium lauryl sulfate – about 0.5 % by weight of the composition.

[0041] In some embodiments, the present invention provides a unit dosage form comprising a composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof – about 55-65% by weight of the composition;

(b) microcrystalline cellulose – about 10-15% by weight of the composition;

(c) dibasic calcium phosphate dehydrate – about 15-20% by weight of the composition;

(d) croscarmellose sodium – about 5-10% by weight of the composition;

(e) sodium stearyl fumarate – about 0.5-2% by weight of the composition;

(f) colloidal silicon dioxide – about 0.1-1.0 % by weight of the composition; and

(g) sodium lauryl sulfate – about 0.1-1.0 % by weight of the composition.

[0042] Nivolumab has been approved by the FDA for treatment of unresectable or metastatic renal cell carcinoma and is generally administered at a dosage of 3 mg/kg as an intravenous infusion over 60 minutes once every 2 weeks. Generally, the amount of nivolumab or other immune checkpoint inhibitor useful in the present invention will be dependent upon the size, weight, age and condition of the patient being treated, the severity of the disorder or condition, and the discretion of the prescribing physician.

[0043] Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for co-administration of the compositions. Thus the kit of the invention includes two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

[0044] The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically includes directions for administration and may be provided with a memory aid.

[0045] The examples below explain the invention in more detail. The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. The present invention, however, is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only, and methods which are functionally equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

[0046] The contents of each document cited in the specification are herein incorporated by reference in their entireties.

EXEMPLIFICATION

EXAMPLE 1 – Measurement of CD8+ T Cells

[0047] Assessment of the effectiveness of the present invention can be made in part by measurement of the CD8+ T cell population. Expanding or increasing the density of CD8+ T cells, such as T-infiltrating lymphocytes (TIL), can help increase tumor recognition and ultimately tumor regression. Dudley et al., (2010) Clin. Cancer Research, 16:6122-6131. CD8+ T cells can be detected, isolated and quantified utilizing methods described in Herr et al., (1996), J. Immunol. Methods 191:131-142; Herr et al., (1997) J. Immunol. Methods 203:141-152; and Scheibenbogen et al., (2000) J Immunol. Methods 244:81-89. The full disclosure of each of these publications is hereby incorporated by reference herein.

EXAMPLE 2 – Renal Cell Carcinoma Xenograft Model

[0048] In order to assess the effects of the present invention on the presence of human CD8+ effector T cells, accumulation of Treg cells in the tumor microenvironment and, ultimately, the effects on renal cell carcinoma, a human RCC xenograft model can be used, as described in Pavia-Jimenez et al. (2014) Nature Protocols 9:1848-1859; Grisanzio et al. (2011) J Pathol 225:212-221. The full disclosure of each of these publications is hereby incorporated by reference herein.

EXAMPLE 3 – Criteria for Evaluating Response in Patients with Solid Tumors

[0049] The response of patients with solid tumors to treatment can be evaluated using the criteria set forth in RECIST 1.1, Eisenhauer et al., (2009) Eur. J. Cancer, 45:228-247, the full disclosure of which is hereby incorporated by reference herein.

EXAMPLE 4 – Cytokine and Chemokine Studies

[0050] The *in vivo* effects of treatment with X4P-001 and nivolumab on chemokine production by RCC cells are assessed as follows:

[0051] Tumors excised from the mice undergoing treatment with X4P-001 and nivolumab in Example 1 and 2 are analyzed by RT-PCR for drug-induced changes in the expression of M-CSF (CSF-1), CXCL1 (MGSA/gro-), CXCL2 (MIP-2/gro-), MIP-2/gro-, CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL8 (IL-8), GM-CSF, VEGF, TNF, CCL22, and CCL28. The various ELR-containing CXCL chemokines listed are known to activate CXCR2 (Gale and McColl (1999) BioEssays 21: 17-28), a chemokine receptor recently implicated in MDSC recruitment (Highfill et al. (2014) Sci Transl Med 6: ra67). The cytokines VEGF, GM-CSF, and TNF are also thought to mediate MDSC chemotaxis into tumor tissue. CCL22 and CCL28 have been likewise implicated in the recruitment of Treg cells (Facciabene et al. (2011), Nature 475: 226-230; Montane et al. (2011) J Clin Invest 2011; 121: 3024-8).

[0052] Numerous chemokines and other inflammatory mediators have been shown to regulate the trafficking of MDSC into tumor tissue (Highfill et al. (2014) Sci Transl Med 6: ra67; Acharyya et al. (2012) Cell 150:165-7813; Zhao et al. (2012) Clin Invest 122: 4094-4104). To determine which chemokines/cytokines are responsible for the influx of MDSC into RCC during treatment with VEGF-targeted therapies, CD11b+/Gr-1+ MDSC are isolated from the spleens of tumor-bearing mice undergoing treatment with nivolumab. The MDSC are then infected with a small pooled lentiviral shRNA library (DeCode GIPZ, Thermo Scientific) for a select group of G protein-coupled and other receptors known to regulate MDSC trafficking. The library will include shRNAs for TNFR-1 and -2, IL-4R, and whole array of CXCR and CCR chemokine receptors (CXCR1-5, CCR 1-9). Several of these (e.g. CXCR-1, -2, and -4) engage chemokines known to promote MDSC recruitment (Highfill et al. (2014) Sci Transl Med 6: ra67; Acharyya et al. (2012) Cell 150:165-7813; Zhao et al. (2012) Clin Invest 122: 4094-4104).

EXAMPLE 5 – Clinical Treatment Regimen

[0053] Treatment with X4P-001 as a monotherapy, or in combination with a checkpoint inhibitor, such as nivolumab, may be performed in cycles, such as on a 2 week, 4 week, 6 week or 8 week cycle. In certain embodiments, the cycle is 4 weeks

long. X4P-001 at a determined dose from 200 mg to 1200 mg daily is administered orally either once daily or twice daily in divided doses. Patients are instructed about both dosing schedule and requirements relating to food or drink near the time of dosing.

[0054] **Dosing Schedule.** The daily dose is taken first thing in the morning. Where the dose is divided, the first daily dose is taken in the morning and the second daily dose approximately 12 hours later using the following guidelines:

Dosing should be at the same time(s) each day ± 2 hr.

For twice daily dosing, the interval between successive doses should not be <9 hours nor >15 hours. If the interval would be >15 hrs, the dose should be omitted and the usual schedule resumed at the next dose.

Restrictions relating to food. Absorption is impacted by food and patients will be instructed as follows:

For the morning dose

– No food or drink (except water) after midnight until the time of dosing

– No food or drink (except water) for 2 hour after dosing.

For the second daily dose, if applicable

– No food or drink (except water) for 1 hour before dosing

– No food or drink (except water) for 2 hours after dosing.

[0055] Nivolumab is administered consistent with prescribed labeling information. Concomitant treatment with X4P-001 and nivolumab may be administered, beginning with daily administration of X4P-001 at day 1. Initial treatment with nivolumab is at 3 mg/kg administered by intravenous infusion over 60 minutes in clinic at the week 4 and 7 visits. Patients may, with the approval of their clinician, vary the dosing schedule or dosage of nivolumab,

[0056] Dosing of X4P-001 and/or nivolumab may be adjusted by the clinician as appropriate. The dose of X4P-001 and/or nivolumab may be lowered according to the judgment of the clinician. If a patient receiving X4P-001 in combination with nivolumab experiences an adverse event at Grade >2, the dose of X4P-001 and/or nivolumab may be

lowered according to the judgment of the clinician. If a patient successfully completes the first 4 weeks of treatment, that is, without experiencing any adverse events greater than Grade 2, the daily dose of X4P-001 and/or nivolumab may be increased, consistent with the judgment of the clinician.

[0057] **Evaluation of Response to Treatment and Disease Status.** Classification of tumor response may be performed according to codified tumor response evaluation, according to the Response Evaluation Criteria in Solid Tumors Group ("RECIST"), as described in Therasse et al. (2000), J. National Cancer Institute, 92:205-216. Radiologic assessment of ccRCC is accomplished by Computed Tomography (CT) with slice thickness ≤5 mm and contrast. CT is performed prior to treatment (baseline) and may be made at intervals during treatment to determine the response.

[0058] Key terminology:

Measurable non-nodal lesions – ≥10 mm in longest diameter.

Measurable nodal lesions – ≥15 mm in short axis

Nonmeasurable lesions – lesions that are smaller, including those that cannot be measured.

Measurable disease – presence of at least one measurable lesion.

Target Lesions

[0059] At baseline, four (4) measureable lesions, two (2) for each individual organ, are identified, documented, and the appropriate diameter of each is recorded. If measurable extra-renal lesions are present, a measurable extra-renal lesion is also identified, documented, and the appropriate diameter is recorded. Lesions are selected based on size, to be representative of disease, and suitable for reproducible repeat measurement. Target lesions may include measurable lymph nodes.

[0060] During treatment, each target lesion is assessed for Complete Response, Partial Response, Stable Disease, or Progressive Disease as follows:

Complete Response (CR)

(a) Disappearance of all non-nodal lesions, and

(b) Absence of pathologic lymph nodes[a].

Partial Response (PR)

(a) ≥30% decrease from baseline in the SOD of the target lesions

Stable Disease (SD)

(a) Persisting disease that does not meet criteria for either PR or PD

Progressive Disease (PD)

a) ≥20% increase in the SOD of the target lesions, compared to the smallest sum, which may be either at baseline or while on treatment; and

(b) an absolute increase of ≥5 mm in the SOD.

Non-target lesions

[0061] All other lesions present at baseline, including pathologic nodes (defined as nodes >10 mm in short axis) should be documented (quantitative measurements are not required) so that they can be classified on follow-up as present, absent, or unequivocal progression.

Complete Response (CR)

(a) Disappearance of all non-target lesions, and

(b) Absence of pathologic lymph nodes[a].

Non-CR/non-PD

Persistence of one or more non-target lesions

Progressive Disease (PD)

Unequivocal progression of existing non-target lesions.

[Note: a = All lymph nodes, whether or not designated target or non-target lesions, have short axis diameter ≤10 mm]

New lesions

[0062] A new lesion should be unequivocal (e.g., not attributable to variation in technique); includes lesions in a location not scanned at baseline.

Pharmacokinetic Assessments

[0063] If desired, pharmacokinetic assessment of blood samples for plasma levels of X4P-001 and nivolumab may be conducted. Blood samples are collected as scheduled. Samples are analyzed for X4P-001 concentration using reversed-phase high performance liquid chromatography (RP-HPLC) with MS/MS detection. The validated range of this bioanalytic method is 30 to 3,000 ng/mL in plasma.

[0064] Pharmacokinetic assessment of nivolumab may be accomplished using techniques, such as those described in Glassman and Balthasar (2014) Cancer Biol. Med.. 11:20-33; Wang et al. (2014), Cancer Immunology Research, 2:1-11; or the Assessment Report of the European Medicines Agency (EMA) for nivolumab EMEA, assessment report EMA/CHMP/76688/2015, April 23, 2015. The full disclosure of these documents are hereby specifically incorporated herein by reference.

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CLAIMS

We claim:

1. A method for treating cancer in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 or a pharmaceutically acceptable salt thereof in combination with an immune checkpoint inhibitor.

2. The method of claim 1, wherein the cancer is selected from the group consisting of metastatic renal cell carcinoma and metastatic renal cell cancer.

3. The method of claim 1 or 2, wherein the patient has previously been treated with an immune checkpoint inhibitor.

4. The method of any of claims 1-3, wherein the immune checkpoint inhibitor is nivolumab.

5. The method of any of claims 1-3, wherein the patient is treated with X4P-001 or a pharmaceutically acceptable salt thereof in an amount effective to increase CD8+ T cell density, and the patient is then treated with an immune checkpoint inhibitor.

6. The method of any of claims 1-5, further comprising the step of obtaining a biological sample from the patient and measuring the amount of a disease-related biomarker.

7. The method of claim 6, wherein the biological sample is a blood sample.

8. The method of claim 7, wherein the disease-related biomarker is circulating CD8+ T cells.

9. The method of any of claims 1-8, wherein the X4P-001 or a pharmaceutically acceptable salt thereof is administered orally twice per day.

10. A method for increasing responsiveness to treatment with an immune checkpoint inhibitor in a patient receiving said treatment, said method comprising administering to said patient X4P-001 or a pharmaceutically acceptable salt thereof in an amount effective to increase CD8+ T cell density.

11. A unit dosage form comprising a composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof – about 30-40% by weight of the composition;

(b) microcrystalline cellulose – about 20-25% by weight of the composition;

(c) dibasic calcium phosphate dehydrate – about 30-35% by weight of the composition;

(d) croscarmellose sodium – about 5-10% by weight of the composition;

(e) sodium stearyl fumarate – about 0.5-2% by weight of the composition;

(f) colloidal silicon dioxide – about 0.1-1.0 % by weight of the composition; and

(g) sodium lauryl sulfate – about 0.1-1.0 % by weight of the composition.

12. The unit dosage form of claim 11, in the form of a capsule.

13. The unit dosage form of claim 12, wherein the capsule comprises about 100 mg X4P-001, or a pharmaceutically acceptable salt thereof.

14. A method for treating renal cell carcinoma in a patient, comprising the step of administering to the patient the unit dosage form of claim 13 in combination with an immune checkpoint inhibitor.

15. The method of claim 14, wherein the immune checkpoint inhibitor is nivolumab, pembrolizumab, or ipilimumab.

16. The method of claim 14, wherein the immune checkpoint inhibitor is nivolumab.

17. The method of claim 16, wherein the renal cell carcinoma is resectable.

18. The method of claim 17, wherein the patient has undergone surgery for removal of some or all of the renal cell carcinoma.

19. The method of claim 16, wherein the renal cell carcinoma is unresectable.

20. The method of claim 1, 2, 10, or 14-19, wherein the patient has previously received anticancer chemotherapy or immunotherapy.

21. The method of claim 20, wherein the patient has previously received

treatment with anti-angiogenic therapy and/or an immune checkpoint inhibitor but not X4P-001 or a pharmaceutically acceptable salt thereof.