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Description

FIELD OF THE INVENTION

[0001] The present invention relates to compositions for use in treating cancer, in particular, compositions for use in overcoming resistance to treatment with VEGF-R antagonists in cancers, such as renal cell carcinoma.

BACKGROUND OF THE INVENTION

[0002] In ~75% of patients with sporadic clear-cell renal cell carcinoma (ccRCC) there is functional loss of the VHL gene, typically by mutation, but also silencing by hypermethylation. VHL encodes the von Hippel-Lindau tumor suppression protein, which mediates proteolytic degradation of the hypoxia-inducible factor (HIF)-α [2]. Loss of this function results in increased levels of HIF-α, increased expression of VEGF, tumor angiogenesis, and, ultimately, the hypervascularity characteristic of these malignancies. Multiple agents that block the activation of the VEGF pathway have been shown to improve outcomes, including tyrosine kinase inhibitors (TKIs), such as sunitinib, axitinib, sorafenib or pazopanib, that block the VEGF signaling pathway and bevacizumab, a monoclonal antibody, that binds circulating VEGF and thus prevents the ligand from binding to the VEGF receptor.

[0003] Despite the demonstrated benefits of such angiogenesis inhibitors in ccRCC, the approach is not curative. Although many patients respond initially, most of them experience relapse and progression. There is a clear unmet need for agents that improve outcomes by preventing or delaying treatment resistance.

BRIEF DESCRIPTION OF THE FIGURES

[0004]

Figures 1A and **1B** illustrates the increase in tumor regression observed in two murine models of tumor xenografts that have been treated with a combination of X4P-001 and axitinib, as described in Example 1. **Figure 1A** shows the relative effects on tumor volume of treatment of murine 786-0 xenografts in mice treated with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib. **Figure 1B** shows the relative effects on tumor volume of treatment of murine A498 xenografts with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib. Treatment was initiated when tumor nodules reached ~7 mm mean diameter.

Figures 2A-2D illustrate the increase in tumor cell death observed in the murine 786-0 xenograft model described in Example 1 in mice treated with control **(Figure 2A),** axitinib **(Figure 2B)** or X4P-001 **(Figure 2C)** as single agents, or with a combination of X4P-001 and axitinib **(Figure 2D).**

Figure 3A-3D illustrate the increase in tumor cell death observed in the murine 498 xenograft model described in Example 1 in mice treated with control **(Figure 3A),** axitinib **(Figure 3B)** or X4P-001 **(Figure 3C)** as single agents, or with a combination of X4P-001 and axitinib **(Figure 3D).**

Figures 4A-4D illustrate the decreased presence of Ki-67+ and CD34+ cells observed in two murine models of tumor xenografts described in Example 1 that have been treated with a combination of X4P-001 and axitinib. **Figure 4A** shows the relative preponderance of expression of Ki-67 by tumor cells in the murine 786-0 xenograft model after treatment with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib. **Figure 4B** shows the relative preponderance of expression of CD34 by tumor cells in the murine 786-0 xenograft model after treatment with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib. **Figure 4C** shows the relative preponderance of expression of Ki-67 by tumor cells in the murine A498 xenograft model after treatment with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib. **Figure 4D** shows the relative preponderance of expression of CD34 by tumor cells in the murine A498 xenograft model after treatment with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib. In all instances, the reduction in expression of Ki-67 and CD34 was significantly reduced ($p<0.05$) in mice treated with the combination compared to mice treated with X4P-001.

Figures 5A-5D illustrate the significantly reduced MDSC infiltration observed in two murine models of tumor xenografts described in Example 1 in mice that have been treated with a combination of X4P-001 and axitinib. **Figure 5A** shows the relative reduction in area of MDSC infiltration in xenografts in the murine 786-0 xenograft model after treatment with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib. **Figure 5B** shows the relative reduction in area of MDSC infiltration in xenografts in the murine A498 xenograft model after treatment with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib. **Figure 5C** shows the relative number of MDSC (CDIIb+ GR-1+) cells infiltrating xenografts in the murine 786-0 xenograft model after treatment with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and

axitinib. **Figure 5D** shows the relative number of MDSC (CDllb+ GR-1+) cells infiltrating xenografts in the murine A498 xenograft model after treatment with control, axitinib or X4P-001 as single agents, and with a combination of X4P-001 and axitinib.

Figure 6 and **Figure 7** illustrate through immunofluorescence (IF) the MDSC (CDllb+ GR-1+) infiltrating 786-0 xenografts treated with axitinib alone under low power **(Figure 6)** and high power **(Figure 7),** respectively.

Figure 8 illustrates a process flow diagram for manufacturing 200 mg X4P-001 Capsules.

Figure 9 illustrates measurements of X4P-001 200 mg capsule fills vs. theoretical capsule fill.

Figure 10 illustrates the dissolution profile of the developed X4P-001 200 mg capsules vs. the dissolution profile of the X4P-001 100 mg capsules.

Figure 11 illustrates Western blots of 786 xenografts treated with X4P-001 showed reduction in the level of HIF-2α relative to that caused by axitinib treatment.

Figure 12 illustrates that axitinib suppressed the micro-RNAs mir-30a and mir-30c, and the addition of X4P-001 to axitinib resulted in increased mir-30a and mir-30c after 8 days of treatment (786-0 xenograft tumor). mir-30a and mir-30c microRNA and HIF-2α mRNA expression from tumors of xenografts treated with axitinib +/- X4P-001. Data is presented as mir-30a or mir-30c expression relative to the mean control value (left side) and relative HIF-2α RNA expression.

Figure 13 illustrates that axitinib and X4P-001 together act to reduce HIF-2α expression after 8 days of treatment in 786 xenograft tumors.

Figures 14A-C illustrate the effect of X4P-001 treatment on 786 hypoxic cells *in vitro* on mir-30a and mir-30c induction and HIF-2α reduction. **Figure 14A** shows a Western blot of 786 cells treated with X4P-001 for 24 hours in normoxic and hypoxic (1% O_2) conditions. **Figure 14B** illustrates mir-30a and mir-30c microRNA and **(Figure 14C)** total HIF-2α RNA expression from the same cells from **Figure 14A.**

Figure 15A illustrates Western blot results from lysates of A375 cells or A375 cells transfected with a constitutively active Stat3 construct. Cells were treated with X4P-001 for 24 h in normoxic or hypoxic conditions. **Figure 15B** shows mir-30c microRNA and **Figure 15C** shows total RNA expression from the same cells from **Figure 15A.** The suppression of HIF-2α and induction of mir-30a and 30c is thus dependent on Stat3 expression. Stat3 is known to be important in promoting CXCL12-mediated invasion of tumors.

Figure 16 illustrates particle size distribution of the X4P-001 batch used in developing the 10 mg, 25 mg, and 100 mg capsules.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

[0005] The present invention relates to compositions as defined in claims 1 to 4 with preferred embodiments being set out in the dependent claims.

[0006] CXCR4 (C-X-C chemokine receptor type 4) is the receptor for CXCL12 (C-X-C chemokine ligand type 12; also referred to as SDF-1α, stromal-derived-factor 1α). CXCL12 has potent chemotactic activity for lymphocytes and MDSCs (myeloid-derived suppressor cells), and is important in homing of hematopoietic stem cells to the bone marrow. CXCR4 is also expressed and active on multiple types of human cancers, including ccRCC, ovarian cancer, and melanoma, and increased expression of CXCR4 on tumor cells has been associated with significantly decreased overall patient survival [3,4,5,6].

[0007] 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 [7,8], and increasing the ratio of CD8+ T cells to Treg cells [7,9,10]. These effects result in significantly decreased tumor burden and increased overall survival in xenograft, syngeneic, as well as transgenic, cancer models [7,9,8].

[0008] X4P-001 is a potent, orally bioavailable CXCR4 antagonist [11], that has demonstrated activity in solid and liquid tumor models [12, 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 [11,13,14] and HIV-infected subjects [15,16]. 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 penetrance.

[0009] Earlier work by some of the inventors on the mechanisms of acquired resistance to VEGF-targeted therapies, demonstrated that treatment with sunitinib treatment resulted in a marked increase in the infiltration of renal cell carcinoma (RCC) xenografts with CD11b+/Gr-1+ myeloid-derived suppressor cells (MDSC)(1). These cells have been repeatedly implicated in the development of resistance to a diverse array of anticancer therapies, including VEGF-targeted agents

(2-5). The inventors further observed that the influx of MDSC, as well as the development of sunitinib resistance, could be prevented by the concurrent administration of the HDM2 antagonist MI-319 (Sanofi-Aventis), a drug whose biological effects are mediated primarily through the up regulation of p53. MDSC trafficking into tumor tissue is regulated by chemokines, many of which (e.g. SDF-1 and CXCL-12) are produced in response to hypoxia in a HIF-dependent manner. p53 is known to directly repress SDF-1 transcription (6) and the inventors have shown that MI-319 suppresses HIF-2 expression, suggesting that the drug may have both direct and indirect effects on SDF-1 expression. Based on these data, the inventors considered the possibility that MI-319 might mediate its effects on MDSC through the suppression of chemokine (e.g. SDF-1) production. Subsequent western blot analysis of tumor lysates confirmed this hypothesis.

[0010] These findings suggested that the ability of MI-319 to prevent sunitinib resistance might be due at least in part to the suppression of SDF-1 production and MDSC recruitment. To the extent that this is the case, the inventors conceived that agents that block SDF-1/CXCR4 signaling directly (e.g. AMD11070) could duplicate the effects of HDM2 blockade on MDSC trafficking and prevent sunitinib resistance.

[0011] Moreover, the inventors conceived that such a result might be achieved with comparatively little toxicity since, unlike HDM2 antagonists, CXCR4-targeted drugs would 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.

[0012] It has now been found that CXCR4 antagonism by X4P-001 provides significant effects which may provide significant treatment benefits in patients with advanced ccRCC and other cancers by multiple mechanisms. Administration of X4P-001 decreased recruitment of MDSC, resulting in increased anti-tumor immune attack. Administration of X4P-001 additionally sustained decreases in neoangiogenesis and tumor vascular supply; and interferes with the autocrine effect of increased expression by ccRCC of both CXCR4 and its only ligand, CXCL12, thereby potentially reducing cancer cell metastasis. Administering X4P-001, a CXCR4 antagonist, sequentially (e.g. administered at the same time as separate unit dosage forms or administered as separate unit dosage forms at different times separated by up to 12 h) or concurrently (e.g. taken together) with a TKI inhibitor such as axitinib, blocks communication between the tumor and the MDSC, suppresses HIF-2α expression, reduces MDSC tumor infiltration, and appreciably improves the anti-tumor treatment effect.

[0013] In the present disclosure, patients with advanced forms of cancer, such as clear cell renal cell carcinoma (ccRCC) are treated with X4P-001, either as a single agent (monotherapy), or in combination with axitinib, a small molecule tyrosine kinase inhibitor (TKI) that is approved for second-line treatment of patients with ccRCC.

[0014] Without wishing to be bound by any particular theory, it is believed that by combining the two medicaments, the patients' treatment outcome can be further improved by reducing the angiogenic escape that typically occurs with TKI therapy.

[0015] In some embodiments, X4P-001, or a pharmaceutically acceptable salt thereof, is administered to a patient in a fasted state.

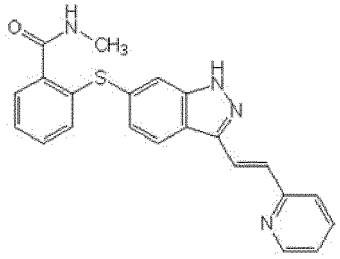
[0016] In some embodiments, the present invention provides compositions for use in treating patients with cancer that presents as a solid tumor. In some embodiments, the patient has kidney cancer, renal tumor, renal carcinoma (including clear cell and papillary renal carcinoma), ovarian cancer, or melanoma.

[0017] In some embodiments, the present invention provides compositions for use in treating refractory cancer in a patient in need thereof, the use comprising administering X4P-001, or a pharmaceutically acceptable salt and/or composition thereof. In certain embodiments, the patient was previously administered a protein kinase inhibitor. In some embodiments, the patient was previously administered a VEGF-R antagonist. In some embodiments, the patient was previously administered a VEGF-R antagonist selected from axitinib (Inlyta) (Pfizer Inc., NY, USA), sorafenib (Nexavar® Bayer AG and Onyx); sunitinib (Sutent, Pfizer, New York, US); pazopanib (Votrient, GlaxoSmithKline, Research Triangle Park, US); cabozanitib (Cometriq, Exelexis, US); regorafenib (Stivarga, Bayer); lenvatinib (Lenvima, Eisai); bevacizumab (Avastin, Genentech, Inc. of South San Francisco, Calif.,), an anti-VEGF monoclonal antibody; and aflibercept, also known as VEGF Trap (Zaltrap; Regeneron/Sanofi). Other kinase inhibitors/VEGF-R antagonists that are in development and may be used in the present disclosure include tivozanib (Aveo Pharmaceuticals, Cambridge, MA); vatalanib (Bayer, Novartis, Basel, Switzerland); lucitanib (Clovis Oncology); dovitinib (Novartis); CEP-11981 (Cephalon, US); linifanib (Abbott Laboratories, Abbott Park, US); PTC299 (PTC Therapeutics, South Plainfield, US); CP-547,632 (Pfizer); foretinib (Exelexis, GlaxoSmithKline); and motesanib (Amgen, Takeda).

[0018] In certain embodiments, the present disclosure provides a method for treating cancer in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 in combination with a tyrosine kinase inhibitor. In certain embodiments, the X4P-001 and the tyrosine kinase inhibitor are administered simultaneously or sequentially. In certain embodiments, the tyrosine kinase inhibitor is selected from axitinib, sunitinib, sorafenib, pazopanib, cabozanitib or regorafenib. In a some embodiments of the disclosure, X4P-001 is administered in combination with axitinib.

[0019] Axitinib (Inlyta® Pfizer laboratories) is a kinase inhibitor. Axitinib has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic

plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib *in vitro* and in mouse models. Axitinib was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models. Axitinib has the chemical name *N*-methyl-2-[3-((*E*)-2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylsulfanyl]-benzamide. The molecular formula is $C_{22}H_{18}N_4OS$ and the molecular weight is 386.47 Daltons. The chemical structure is depicted below.



[0020] Axitinib is a white to light-yellow powder with a pKa of 4.8. The solubility of axitinib in aqueous media over the range pH 1.1 to pH 7.8 is in excess of 0.2 μg/mL. The partition coefficient (n-octanol/water) is 3.5.

[0021] Axitinib has been approved by the FDA for treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy, i.e., as second line therapy. Axitinib has been tested or mentioned as a possible treatment in other oncologic indications. Accordingly, in some embodiments of the present invention, the cancer is selected from the group consisting of solid tumors (including solid fibrous tumors), neoplasms (including pancreatic, kidney, colorectal, lung, breast, thyroid and stomach neoplasms), glioblastoma, hepatocellular carcinoma or liver cancer, melanoma and intraocular melanoma, prostate cancer (including castrate-resistant prostate cancer), non-small cell lung cancer, renal tumor, renal carcinoma (including clear cell and papillary renal carcinoma) or kidney cancer, colorectal cancer, advanced gastric cancer, malignant mesothelioma, neurofibromatosis, including Schwannomatosis, soft tissue sarcoma, head and neck squamous cell carcinoma, nasopharyngeal carcinoma, adenocarcinoma, neuroendocrine carcinoma, acute myeloid leukemia, myelodysplastic syndrome, pheochromocytoma, paraganglioma, lymphoma, mantle-cell cancer, gastrointestinal-stromal tumors, or pancreatic ductal carcinoma.

[0022] In its current prescribed labeling for RCC, recommended starting oral dose of axitinib is 5 mg twice daily, approximately 12 hours apart. Depending upon individual tolerance, it is recommended that the prescribed dose of axitinib may be increased to 7 mg or 10 mg, twice daily; or reduced to 3 mg or 2 mg twice daily.

[0023] In some embodiments, the present disclosure provides a method for treating a refractory cancer in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 in combination with a tyrosine kinase inhibitor. In some embodiments, the refractory cancer is ccRCC. In some embodiments, the refractory cancer is ccRCC and the tyrosine kinase inhibitor is axitinib.

[0024] In some embodiments, a provided method of this disclosure comprises administering the X4P-001, or a pharmaceutically acceptable salt thereof, is administered to a patient in a fasted state and administering the tyrosine kinase inhibitor to a patient in either a fasted or fed state.

[0025] In certain embodiments, the present disclosure provides a method for treating cancer in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 in combination with a tyrosine kinase 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 CD34+ cells and/or plasma levels of soluble VEGF-R.

[0026] In certain embodiments, the present disclosure provides a method for treating a refractory cancer in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 in combination with a tyrosine kinase 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 CD34+ cells and/or plasma levels of soluble VEGF-R.

[0027] In certain embodiments, the present disclosure provides a method for treating a refractory cancer in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 in combination with axitinib, 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 CD34+ cells and/or plasma levels of soluble VEGF-R.

[0028] In certain embodiments, the present disclosure provides a method for treating ccRCC in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 in combination with axitinib, 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 CD34+ cells and/or plasma levels of soluble VEGF-R.

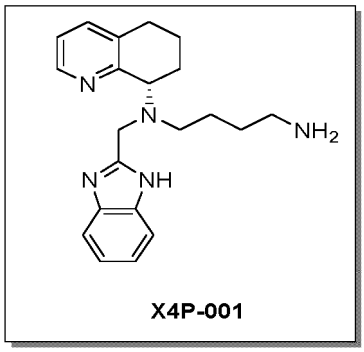
[0029] In other embodiments of the disclosure, X4P-001 is administered in combination with a VEGF antagonist. The VEGF antagonist may be an antibody to VEGF or a VEGF trap. In certain embodiments, the VEGF antagonist is selected from bevacizumab or aflibercept.

[0030] In some embodiments, the present disclosure provides a method of treating cancer in a patient in need thereof, wherein said method comprises administering to said patient X4P-001 in combination with a tyrosine kinase inhibitor wherein the X4P-001 and the tyrosine kinase inhibitor act synergistically. One of ordinary skill in the art will appreciate that active agents (such as X4P-001 and a tyrosine kinase inhibitor) act synergistically when the combination of active agents results in an effect that is greater than additive. In some embodiments, the tyrosine kinase inhibitor is axitinib.

Dosage and Formulations

[0031] X4P-001 is a CXCR4 antagonist, with molecular formula $C_{21}H_{27}N_5$; molecular weight 349.48 amu; appearance 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; and melting point of 108.9 °ΔC.

[0032] The chemical structure of X4P-001 is depicted below.



X4P-001

[0033] In certain embodiments, the composition containing X4P-001, or a pharmaceutically acceptable salt thereof, is administered orally, in an amount from 200 mg to 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 100 mg to 1200 mg once or twice per day. In certain embodiments, the dosage of X4P-0001, or a pharmaceutically acceptable salt thereof, useful in the invention is from 200 mg to 800 mg daily. In other embodiments, the dosage of X4P-001, or a pharmaceutically acceptable salt thereof, useful in the invention may range from 200 mg to 600 mg, from 400 mg to 800 mg, from 600 mg to 1000 mg or from 800 mg to 1200 mg daily.

[0034] In some embodiments, a provided use comprises administering to the patient a pharmaceutically acceptable composition comprising X4P-001 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 is formulated for oral administration in the form of a capsule.

[0035] In certain embodiments, a provided use comprises administering to the patient one or more capsules comprising 10-1200 mg X4P-001 active ingredient; and one or more pharmaceutically acceptable excipients.

[0036] In certain embodiments, the present invention provides a 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 10 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 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.

[0037] In some embodiments, the present invention provides a composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 30-40% by weight of the composition;
(b) microcrystalline cellulose - 20-25% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 30-35% by weight of the composition;
(d) croscarmellose sodium - 5-10% by weight of the composition;
(e) sodium stearyl fumarate - 0.5-2% by weight of the composition;
(f) colloidal silicon dioxide - 0.1-1.0% by weight of the composition; and
(g) sodium lauryl sulfate - 0.1-1.0% by weight of the composition.

[0038] In some embodiments, the present invention provides a composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 37% by weight of the composition;
(b) microcrystalline cellulose - 23% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 32% by weight of the composition;
(d) croscarmellose sodium - 6% by weight of the composition;
(e) sodium stearyl fumarate - 1% by weight of the composition;
(f) colloidal silicon dioxide - 0.3% by weight of the composition; and
(g) sodium lauryl sulfate - 0.5% by weight of the composition.

[0039] In some embodiments, the present invention provides a composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 8-25% by weight of the composition;
(b) microcrystalline cellulose - 65-85% by weight of the composition;
(c) croscarmellose sodium - 2-10% by weight of the composition;
(d) sodium stearyl fumarate - 0.1-3% by weight of the composition; and
(e) colloidal silicon dioxide - 0.05-0.7% by weight of the composition.

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

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 25-45% by weight of the composition;
(b) microcrystalline cellulose - 10-35% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 15-45% by weight of the composition;
(d) croscarmellose sodium - 2-10% by weight of the composition;
(e) sodium stearyl fumarate - 0.3-2.5% by weight of the composition;
(f) colloidal silicon dioxide - 0.05-1.2% by weight of the composition; and
(g) sodium lauryl sulfate - 0.2-1.2% by weight of the composition.

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

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 35-75% by weight of the composition;
(b) microcrystalline cellulose - 5-28% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 7-30% by weight of the composition;
(d) croscarmellose sodium - 2-10% by weight of the composition;
(e) sodium stearyl fumarate - 0.3-2.5% by weight of the composition;
(f) colloidal silicon dioxide - 0.05-1.2% by weight of the composition; and
(g) sodium lauryl sulfate - 0.2-1.2% by weight of the composition.

[0042] In some embodiments, the present invention provides a composition according to **Table 1** or **Table 2,** below.

Table 1: 25 mg Capsule Formulation

Component	Reference to Standard	Function	Quantity (mg/capsule)	% w/w
X4P-001	In-House	Active Ingredient	25.0	14.7
Microcrystalline Cellulose	NF	Diluent	132.7	78.1

(continued)

Component	Reference to Standard	Function	Quantity (mg/capsule)	% w/w
Croscarmellose Sodium	NF	Disintegrant	10.2	6.0
Sodium Stearyl Fumarate	NF	Lubricant	1.7	1.0
Colloidal Silicon Dioxide	USP	Flow Aid	0.4	0.2
Sum Total			170.0	100.0
Hard Gelatin Capsules, Size 1	USP	Packaging	NA	NA

Table 2: 100 mg and 200 mg Capsule Formulations

	200 mg			100 mg	
Ingredients	**Percent Per Capsule (%)**	**Theoretical Amount Per Capsule (mg)**		**Percent Per Capsule (%)**	**Theoretical Amount Per Capsule (mg)**
X4P-001 Drug Substance	61.5	200.0		37.6	100
Microcrystalline Cellulose, NF/EP (Avicel PH 101) or equivalent	12.9	41.93		22.9	60.9
Dibasic Calcium Phosphate Dihydrate, USP/NF	17.8	57.85		31.7	84.3
Croscarmellose Sodium, NF/EP (Ac-Di-Sol)	6.0	19.50		6.0	16.0
Sodium Lauryl Sulfate, NF / Ph. Eur.	0.5	1.625		0.5	1.3
Colloidal Silicone Dioxide, NF/ Ph. Eur. (Cab-O-Sil M-5P)	0.3	0.9750		0.3	0.8
Sodium Stearyl Fumarate, NF (Pruv)	1.0	3.250		1.0	2.7
Total Capsule Fill	**100**	**325.0**		**100**	**266.0**

[0043] In some embodiments, the present invention provides a unit dosage form comprising a composition described above. In some embodiments, the unit dosage form is a capsule.

[0044] 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 disclosure 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 coadministration of the compositions. Thus the kit of the disclosure 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.

[0045] The kit of the disclosure 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.

[0046] 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. 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.

EXEMPLIFICATION

EXAMPLE 1: Murine Models with Human Cell Lines

[0047] The effects were examined of treatment with X4P-001 and axitinib singly, and in combination on the trafficking of MDSC and other immunosuppressive cell populations and on chemokine production by RCC cells.

[0048] Mice were inoculated with 786-0 and A498 RCC xenografts, the tumors permitted to grow to ~300 mm^3, and then treatment initiated with the CXCR4 inhibitor X4P-001, axitinib, both agents in combination, or saline (control).

[0049] With each of the human cell lines, 1 x 107 tumor cells were implanted subcutaneously in the flanks of 36 nude/beige mice and tumors allowed to grow to roughly 7 mm in diameter. The mice were randomly divided into 4 treatment groups of 9 mice each and treated with X4P-001 (at the recommended dose), axitinib (30 mg/kg daily by gavage), both drugs, or vehicle (control). We have previously shown that MDSC tumor influx is maximal at 7 days (not shown). Therefore, on day 7, the mice were sacrificed and the tumors were measured and immediately excised and divided into three parts. One part of each tumor was paraffin-embedded for dual color immunofluorescence. Another part was mechanically disaggregated and treated with collagenase/DNAse to generate a single cell suspension for flow cytometry. The third part was frozen for future pharmacokinetic analysis. Microscope slides were made from the paraffin-embedded tumor tissue, which were stained with antibodies against CD11b, Gr-1, and FAP. The number of infiltrating CD11b+/Gr-1+ MDSC and FAP+ fibroblasts present in the tumor tissue was then determined by immunofluorescence (IF) as previously described (1).

[0050] The disaggregated tumor specimens were analyzed for CD11b+/Gr-1+ MDSC and FAP+ fibroblasts by flow cytometry. The fraction of both populations expressing CXCR4 were also determined. At the time the mice were sacrificed, the spleens were removed and cut in half. One part was disaggregated into single cell suspensions and analyzed by flow cytometry as above for MDSC. The second half was frozen for future analyses, such as PK analysis. Finally, a bone marrow (BM) sample was generated by extruding marrow from an excised femur with a syringe filled with saline and analyzed by flow cytometry for MDSC.

Results:

[0051] Whereas either drug alone either had no (axitinib) or modest (X4P-001) effects on tumor growth, the combination of X4P-001 and axitinib had additive and/or synergistic antitumor effects. Specifically, combination treatment resulted in massive tumor cell death, with the established implants actually regressing in size (See Figure 1A and 1B) - an effect not previously seen with VEGFR-targeted drugs given as single agents. IHC staining demonstrated, as previously, that mice treated with axitinib alone had an increase in Ki-67 positive tumor cells (See Figure 4A and 4C). This effect was not observed in mice that received both X4P-001 plus axitinib (See Figure 4A and 4C), suggesting an anti-proliferative effect of the combination. Finally, the tumors from mice receiving axitinib alone had extensive MDSC infiltration (see Figures 5A through 5D, whereas the tumors from mice receiving either X4P-001 alone or the axitinib/X4P-001 combination had significantly less MDSC infiltration (see Figures 5A through 5D).

Suppression of miRNAs mir-30a and mir-30c and Effect on HIF-2α in Xenografts:

[0052] As shown in Figure 11, Western blots of 786 xenografts treated with X4P-001 showed reduction in the level of HIF-2α relative to that caused by axitinib treatment. Furthermore, as shown in Figures 12 and 13, axitinib suppressed the micro-RNAs mir-30a and mir-30c, and the addition of X4P-001 to axitinib resulted in increased mir-30a and mir-30c after 8 days of treatment (786-0 xenograft tumor). mir-30a and mir-30c microRNA and HIF-2α mRNA expression from tumors of xenografts treated with axitinib +/- X4P-001. Data is presented as mir-30a or mir-30c expression relative to the mean control value (left side) and relative HIF-2α RNA expression. Figure 13 illustrates that axitinib and X4P-001 together act to reduce HIF-2α expression after 8 days of treatment in 786 xenograft tumors.

[0053] Figures 14A-C illustrate the effect of X4P-001 treatment on 786 hypoxic cells *in vitro* on mir-30a and mir-30c induction and HIF-2α reduction. Figure 14A shows a Western blot of 786 cells treated with X4P-001 for 24 hours in normoxic and hypoxic (1% O_2) conditions. Figure 14B illustrates mir-30a and mir-30c microRNA and (Figure 14C) total HIF-2α RNA expression from the same cells from Figure 14A.

[0054] Figure 15A illustrates Western blot results from lysates of A375 cells or A375 cells transfected with a constitutively active Stat3 construct. Cells were treated with X4P-001 for 24 h in normoxic or hypoxic conditions. Figure 15B shows mir-30c microRNA and Figure 15C shows total RNA expression from the same cells from Figure 15A. The suppression of HIF-2α and induction of mir-30a and 30c is thus dependent on Stat3 expression. Without wishing to be bound by theory, it is believed that Stat3 is important in promoting CXCL-12 mediated invasion of tumors.

[0055] What these results show is that axitinib suppressed the micro-RNAs mir-30a and mir-30c, which, without wishing to be bound by theory, are believed to inhibit HIF-2α translation. The addition of X4P-001 to axitinib *in vivo* and in hypoxic

cells *in vitro* results in increased mir-30a and mir-30c.

EXAMPLE 2: Further Xenograft Studies

[0056] Further studies are conducted in order to determine how treatment with X4P-001 and axitinib alone or in combination affects the distribution of MDSC and other immunosuppressive CXCR4+ cell populations (Tregs and CAF) and how CXCR4 expression by these cells affects their trafficking in tumor-bearing mice. Example 1 above is repeated with additional testing of syngeneic murine RCC Renca model and 786-M1A cells, the latter of which is a 786-0 variant known to express CXCR4 at extremely high levels (7). The studies with Renca cells are done as described above for the human cell lines except that tumors are also analyzed for CD4+/CD25bright/Foxp3+ Tregs, CD3+/CD8+ T cells in addition to MDSC and fibroblasts.

[0057] Following the procedures of Example 1, the effects of treatment with X4P-001 and axitinib on bone marrow, spleen, and tumor infiltration by CD11b+/Gr-1+ MDSC, CD4+/CD25bright/Foxp3+ Tregs, CD3+/CD8+ T cells, and FAP+ cancer-associated fibroblasts (CAF) are examined and the levels of CXCR4 expression on these cells are determined.

EXAMPLE 3: Cytokine and Chemokine Studies

[0058] The *in vivo* effects of treatment with X4P-001 and axitinib on chemokine production by RCC cells are assessed as follows:

Tumors excised from the mice undergoing treatment with X4P-001 and axitinib in Example 1 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 (8), a chemokine receptor recently implicated in MDSC recruitment (9). 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 Tregs (10,11).

[0059] Numerous chemokines and other inflammatory mediators have been shown to regulate the trafficking of MDSC into tumor tissue (9,12,13). 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 axitinib. 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 (9,12,13).

EXAMPLE 4: Pharmacokinetics Studies

[0060] In order to evaluate the pharmacokinetic properties of combined therapy with X4P-001 and axitinib, levels of X4P-001 and axitinib in blood, tumor tissue, and spleen are measured 4 hr after dosing. To measure drug levels in blood, spleen, and tumor tissue, blood is collected by ventricular puncture at the time the mice are sacrificed - 4 hrs after the day 7 drug dosing. The blood samples as well as the spleen and tumor tissue are then subjected to PK analysis.

EXAMPLE 5: Clinical Treatment Regimens

[0061] 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.

[0062] **Dosing Schedule.** 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 times each day $\pm$ 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 hours 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.

[0063] Axitinib is administered consistent with prescribed labeling information. Initial treatment with axitinib is at 5 mg orally BID in addition to X4P-001 at the determined dose level. Administration of axitinib. Axitinib may be taken at the same time as axitinib. Alternatively, since axitinib has been associated with gastrointestinal adverse events and its absorption is not altered by food (see current product label), patients may, with the approval of their clinician, take the axitinib separately, following the same BID dosing schedule guidelines noted.

[0064] Dosing of X4P-001 and/or axitinib may be adjusted by the clinician as appropriate. The dose of X4P-001 and/or axitinib may be lowered according to the judgment of the clinician. If a patient receiving X4P-001 in combination with axitinib experiences an adverse event at Grade >2, the dose of X4P-001 and/or axitinib 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 axitinib may be increased. consistent with the judgment of the clinician.

Evaluation of Response to Treatment and Disease Status

[0065] 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.

[0066] 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

[0067] 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.

[0068] 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

[0069] 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.

[0070] [Note: [a] = All lymph nodes, whether or not designated target or non-target lesions, have short axis diameter ≤10 mm.]

New Lesions

[0071] 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

[0072] If desired, pharmacokinetic assessment of blood samples for plasma levels of X4P-001 and axitinib 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.

[0073] Pharmacokinetic assessment of axitinib may be accomplished using techniques such as described in Tortorici et al., (2011) Invest. New Drugs 29:1370-1380.

EXAMPLE 6: Formulation Trial Results for X4P-001

[0074] This Example summarizes pilot trial results on chosen formulation for each of the 3 dose strengths for X4P-001. The powder blend containing AFT, fillers/diluents, a disintegrant, a glidant and a lubricant was prepared and filled into size 1 hard gelatin capsules on an automated capsule filling machine. The process developed for all 3 formulations showed adequate flowability, acceptable weight variation and content uniformity. All 3 formulations showed more than 90% release after 45 minutes dissolution test. Amber glass bottles, each containing 30 capsules, polyester coils and one desiccant pack, were individually sealed in aluminum foil bags and placed on stability testing under 2 storage conditions (2-8 °C and 25 °C/60% RH).

Introduction

[0075] A total of 9 formulations (3 for each of the 3 dose strengths for X4P-001) were prepared and manually filled into size 1 hard gelatin capsules. The best capsule formulation of X4P-001 for each dose level was selected from three (3) formulation candidates based on 1-month R&D stability data (Table 3). The chosen formulation for each dose level was scaled-up for blending and capsule filling using V-blender and automated capsule filler, respectively.

[0076] The objectives of the pilot trial were: 1) to confirm the stability of the chosen formulations for X4P-001 10 mg, 25 mg and 100 mg capsules using a new lot of X4P-001; and 2) to collect information on scale up and the new process used for making X4P-001 capsules.

Materials and Equipment

List of Materials

[0077] X4P-001, lot # 2893-A-3P

Microcrystalline Cellulose, NF, Avicel® PH-101, Lot # 1155
Dibasic Calcium Phosphate Dihydrate, USP, Emcompress®, Lot # B10E Croscarmellose Sodium, NF, Ac-Di-Sol®, Lot # T050N
Colloidal Silicon Dioxide, USP, Cab-O-Sil® M-5P, Lot # 1J021
Sodium Stearyl Fumarate, NF, PRUV™, Lot # 30001902
Sodium Lauryl Sulfate, NF, Lot # 12810
Empty Hard Gelatin Capsules, Size 1 White Opaque, Lot # 582410
60cc Amber Glass Bottles, with a green screw-on cap
Silica Gel Desiccant Pouches, 0.5 g
Rayon Coil 12-gram/y
2x3 3-Spot Humidity Indicator Card, Lot # 10018
Aluminum Foil Bags MIL-PRF-131J

List of Equipment

[0078]

2-Qt. V-Blender
Bonapace In-Cap Capsule Filling Machine
Pouch Sealer
Tap Density Tester
Particle Size Analyzer (Sonic Sifter)

Experimental and Results

Selection of Formulation for the Pilot Trial

[0079] One formulation (10-E, 25-E and 100-F) was chosen for the pilot X4P-001 trial at each of the 10 mg, 25 mg and 100 mg dose levels. The selection of the formulation was mainly based on the 1-month stability profile of the 3 formulations for each dose under 2 storage conditions (25 °C/60%RH and 2-8 °C) (Table 3). None of the formulations were stable under the 40°C/75%RH storage condition.

[0080] Only Avicel® serves as a diluent/filler in both 10 mg and 25 mg formulations. To facilitate the capsule filling process on an automated capsule filler, a glidant such as colloidal silicon dioxide (Cab-O-Sil®) was explored for addition to the formulation. The trial on 2 placebo batches confirmed that the Cab-O-Sil® helps to reduce the weight variation of capsules (Table 4). Cab-O-Sil® was also added to the 100 mg formula (100-F) that contains both Avicel® and Emcompress® to ensure adequate flow of the powder blend.

In-Process Testing

[0081] A total of 3 formulations (1 for each of the 3 dose strength for X4P-001) were prepared. The powder blend was filled into size 1 hard gelatin capsules on In-Cap Capsule Filling Machine. The weight of the filled capsules showed about 1% in weight variability (RSD) (Table 5).

Initial Testing on Final Products

[0082] The average capsule fill weight of all batches was well within 1% of the target. The composite assay test results for batches # 1191-10-PP, 1191-25-PP and 1191-100-PP were 98.8%, 99.0% and 99.9% respectively (Table 6).

[0083] The blend uniformity of all batches was evaluated using the USP Content Uniformity test. The content uniformity of the powder blend met the required 6% RSD (Table 6).

[0084] The dissolution test on 6 capsules from each batch was performed per USP dissolution method. All batches showed more than 99% drug release at 45 minutes (Table 6).

Stability Testing

[0085] Twenty (20) amber glass bottles each containing 30 capsules, appropriate amount of polyester coils and one desiccant pack were individually sealed in aluminum foil bags and placed on stability testing under 2 storage conditions (24°C and 25 °C/60%RH) per Pilot Stability Protocol (Table 8). One humidity indicating card was included in each aluminum foil bag for testing the seal of each sample.

Physical Properties of X4P-001 and the Powder Blend

[0086] Particle size distribution of X4P-001 is shown in Table 9 and Figure 16. The results of bulk density, tap density and Carr's Index are summarized in Table 7. The physical properties of the low strength blend for the 10 and 25 mg formulation were comparable to the R&D batches. However, the powder blend of the 100 mg batch showed lower bulk and tap density due to differences in two lots of X4P-001. The new lot is more bulky than the previous lot.

Conclusions

[0087] Three (3) pilot stability batches were successfully manufactured for the active pharmaceutical ingredient ("API"), X4P-001. The current process for all three dose levels is recommend for supporting the manufacturing of upcoming clinical batches. As used herein and in the following Tables, "API" refers to X4P-001. "API" is an abbreviation for "active pharmaceutical ingredient" that is commonly used in the art.

Table 3: Summary of 1-Month Stability Results on Chosen R&D Batches

		LOT NO.					
Batch Information →	**Parameters**	**1191-10-E**		**1191-25-E**		**1191-100-F**	
		2 - 8 °C	**25 °C/60% RH**	**2 - 8 °C**	**25 °C/60% RH**	**2 - 8 °C**	**25 °C/60% RH**
	API (mg)	10		25		100	
	Batch Size (g)	175		175		250	
Dissolution →	**% at 45 min.**	112	110	91	95	99	96
Assay @ 1- month →	**% LC**	105.5	110.5	99. 2	100.7	94. 1	91.5
Related Substances →	**Tot. % Area**	2.0	2.2	2.0	2.3	0.9	1.2
Assay @ time zero* →	**% LC**	99.4		100.9		94.0	
Related Substances * →	**Tot. % Area**	0.4		0.7		94.0	
*The time zero data were included as reference							

Table 4: Summary of Weight Variation Results on X4P-001 Capsules from Pilot Trials

Batch Information →		**PILOT BATCH LOT NO.**					
	Parameters	**Placebo-1**	**Placebo-2**	**1191-100-H**	**1191-10-P**	**1191-25-P**	**1191-100-P**
	API (mg)	0	0	100	10	25	100

(continued)

Batch Information →		PILOT BATCH LOT NO.					
	Parameters	**Placebo-1**	**Placebo-2**	**1191-100-H**	**1191-10-P**	**1191-25-P**	**1191-100-P**
	Batch Size (g)	200	200	200	650	650	1200
Formulation →	API %	0.0	0.0	37.6	6.0	14.7	37.6
	Avicel %	92.8	92.5	22.9	86.7	78.1	22.9
	Emcomp. %	0.0	0.0	31.7	0.0	0.0	31.7
	Ac-Di-Sol %	6.3	6.3	6.0	6.0	6.0	6.0
	Cab-O-Sil %	0.00	0.25	0.23	0.25	0.24	0.30
	PRUV %	1.0	1.0	1.0	1.0	1.0	1.0
	SLS %	0.0	0.0	0.5	0.0	0.0	0.5
	TOTAL %	100.1	100.1	99.9	100.0	100.0	100.0
Weight Statistics →	N	20	20	20	20	20	20
	MIN	225.7	219.9	296.0	234.1	236.9	334.1
	MAX	271.3	252.8	355.9	248.5	251.0	349.6
	MEAN	250.6	244.6	339.0	241.9	245.0	341.0
	SD	11.9	7.8	14.8	3.6	3.6	4.3
Weight Variation →	**RSD**	**4.8%**	**3.2%**	**4.4%**	**1.5%**	**1.5%**	**1.3%**
Wt. Var. w/o outliers →	N	19	19	18	N/A		
	MEAN	251.9	245.9	343.3			
	RSD	**4.2%**	**2.2%**	**2.0%**			

Table 5: Summary of In-Process Weight Check Results on X4P-001 Capsules

		LOT NO.		
Batch Information →	**Parameters**	**1191-10-P**	**1191-25-P**	**1191-100-P**
	API (mg)	10	25	100
	Batch Size (g)	650	650	1200
Weight Statistics →	N	11	10	11
	MIN	239.5	239.0	336.9
	MAX	245.0	249.0	344.8
	MEDIAN	242.1	245.5	341.7

(continued)

		LOT NO.		
Batch Information →	**Parameters**	**1191-10-P**	**1191-25-P**	**1191-100-P**
	MEAN	242.5	245.1	341.6
	SD	1.7	3.0	2.3
Weight Variation →	**RSD**	**0.7%**	**1.2%**	**0.7%**
Capsule Wt. →**	1	241.9	244.9	339.9
	2	244.6	245.7	341.7
	3	245.0	249.0	336.9
	4	241.5	245.9	344.8
	5	242.1	247.3	343.3
	6	242.1	239.0	342.9
	7	240.7	242.7	341.9
	8	244.6	245.3	344.3
	9	242.9	242.9	341.7
	10	242.1	248.7	338.9
	11	239.5		340.8
**Average weight of 10 capsule samples, taken every 10 minutes during encapsulation.				

Table 6: Summary of Time Zero Results on Pilot Stability Batches

		LOT NO.		
Batch Information →	**Parameters**	**1191-10-PP**	**1191-25-PP**	**1191-100-PP**
	API (mg)	10	25	100
	Batch Size (g)	650	650	1200
	Target Fill Wt. (mg)	167	170	266
Wt. Var. Capsules →	MEAN	241.9	245.0	341.0
	RSD	1.5%	1.5%	1.3%
Fill Wt. Capsules →	MEAN	168	171	267
Content Uniformity →	MEAN	96.9%	95.8%	99.9%
	RSD	2.2%	2.3%	5.2%
Dissolution →	% at 45 min.	99.6%	100.8%	99.7%
Assay →	%LC	98.8%	99.0%	99.9%
Related Substances →	Tot. % Area	1.4%	1.4%	1.5%

Table 7: Comparison of Physical Properties of Powder Blends of R&D Batches

Physical Parameters	Dev. Batches	Pilot Batches
10 mg Batches →	**1191-10-E**	**1191-10-P**

(continued)

Physical Parameters	Dev. Batches	Pilot Batches
Bulk Density (g/cc)	0.34	0.36
Tap Density (g/cc)	0.53	0.51
Carr's Index (%)	36%	28%
Mean PS (um)	n/a	50
25 mg Batches →	**1191-25-E**	**1191-25-P**
Bulk Density (g/cc)	0.36	0.36
Tap Density (g/cc)	0.55	0.52
Carr's Index (%)	34%	32%
Mean PS (um)	n/a	54
100 mg Batches →	**1191-100-F**	**1191-100-P**
Bulk Density (g/cc)	0.8	0.62
Tap Density (g/cc)	1.08	0.84
Carr's Index (%)	26%	26%
Mean PS (um)	n/a	85

Table 8: Pilot Stability Protocol

PACKAGING INFORMATION:			
		Amber 60cc glass bottle (sealed in aluminum foil bag)	
Cap/Closure Type		Green plastic screw-on top	
Number of Bottles Packaged		15 bottles from each batch	
Number of Capsules Per Bottle		30 capsules (with polyester coils and 1 desiccant pack)	
STORAGE CONDITIONS:			
	Storage Conditions	**Time Points**	**Total Number of Bottles**
A	**Ambient Temperature**	**Stability Time Zero**	**2+1****
B	**25°C + 2°C / 60% + 5% RH**	**1M, 3M**	**2+2****
C	**2 °C - 8 °C**	**1M, 3M**	**2+2****
	Totals		**11**
**Additional back-up bottles for all conditions.			
TESTING TO BE COMPLETED AT EACH TIME POINT:			
No.	**Test**	**Method**	**Performed By**	**Acceptance Criteria**
1.	Appearance	Visual	Analytical Lab	Record results
2.	Content Uniformity (initial time zero only)	HPLC	Analytical Lab	USP Requirements <905>
3.	Assay	HPLC	Analytical Lab	Record results

(continued)

TESTING TO BE COMPLETED AT EACH TIME POINT:				
No.	**Test**	**Method**	**Performed By**	**Acceptance Criteria**
4.	Dissolution	USP Apparatus 2	Analytical Lab	Record results
5.	Odor	Olfactory	Formulation	Record results

Table 9: Particle Size Distribution

Product:	**X4P-001 Free Base**	
Lot#:	**2893-A-3P**	
Date:	10-Jan-03	
Sample Wt.:	5 grams	
Testing Time:	5 minutes	
# Mesh Size	**Par. Size (μm)**	**% Retained**
40	425	1.3
60	250	2.5
80	180	5.8
100	150	37.8
170	90	36.1
270	53	13.8
Pan	<53	2.7
	Sum:	100.0

EXAMPLE 7: Development and Formulation of 200 mg Capsule

[0088] This Example describes the development of a 200 mg strength of X4P-001 Capsules and process development activities.

[0089] The formulation for X4P-001 Capsules, 100 mg was employed as a baseline for the proposed 200 mg formulation. The goal of the formulation development activities was to obtain a higher dosage form of API with a similar dissolution profile to the 100 mg strength and manufacture the product in a size 1 gelatin capsule.

[0090] A feasibility batch was manufactured using a prototype capsule formulation (developed by Metrics) based on the excipients used in the 100 mg CTM batch formulation as shown in Table 10 below. This feasibility batch met all previously established drug product specifications and displayed a drug release similar to the 100 mg strength CTM batch (15K227). The goal of the X4P-001 Capsules, 200 mg formulation development activities was to identify an acceptable capsule formulation to be deployed in Phase 1 clinical studies and advanced into subsequent clinical study phases as appropriate using a scalable formulation and manufacturing process using a size 1 gelatin capsule, consistent with the current strengths (25 mg and 100 mg) of the subject product line.

Table 10: Formulation of 200 mg and 100 mg Capsules

		200 mg Strength		**100 mg Strength**	
INGREDIENTS		**Percent Per Capsule (%)**	**Theoretical Amount Per Capsule (mg)**	**Percent Per Capsule (%)**	**Theoretical Amount Per Capsule (mg)**
X4P-001 Drug Substance		61.5	200.0	37.6	100.0

(continued)

		200 mg Strength		100 mg Strength	
INGREDIENTS		**Percent Per Capsule (%)**	**Theoretical Amount Per Capsule (mg)**	**Percent Per Capsule (%)**	**Theoretical Amount Per Capsule (mg)**
Microcrystalline Cellulose, NF/EP (Avicel PH 101) or equivalent		12.9	41.93	22.9	60.9
Dibasic Calcium Phosphate Dihydrate, USP/NF		17.8	57.85	31.7	84.30
Croscarmellose Sodium, NF/EP (Ac-Di-Sol)		6.0	19.50	6.0	16.00
Sodium Lauryl Sulfate, NF / Ph. Eur.		0.5	1.625	0.5	1.300
Colloidal Silicone Dioxide, NF/ Ph. Eur. (Cab-O-Sil M-5P)		0.3	0.9750	0.3	0.8000
Sodium Stearyl Fumarate, NF (Pruv)		1.0	3.250	1.0	2.700
Total Capsule Fill		100.0	325.0	100.0	266.0
Capsules, Empty, Hard Gelatin Size 1 White/White		**1 Capsule**		**1 Capsule**	

[0091] One feasibility batch was prepared using the formulation outlined in Table 10 above. Feasibility batch manufacturing equipment included: V-shell blender (4 quart), 30 mesh hand screen, and MF-30 Manual Capsule Filler. The manufacturing process for each batch is described below and depicted in Figure 8. The batch manufacture process utilized the same process train as the current 100 mg strength.

1. Add the X4P-001 active ingredient to the 4 quart V-Blender.
2. Sift Avicel PH-101 and Dibasic Calcium Phosphate through a 30 mesh hand screen and add to the 4 quart V-blender. Mix for 4 minutes (100 rotations).
3. Sift Croscarmellose Sodium and Sodium Lauryl Sulfate through a 30 mesh hand screen and add to the 4 quart V-Blender. Mix for 2 minutes (50 rotations).
4. Sift Colloidal Silicon Dioxide through a 30 mesh hand screen and add to the 4 quart V-Blender. Mix for 2 minutes (50 rotations).
5. Discharge blended materials from the 4 quart V-Blender and sift through a 30 mesh screen. Transfer screened material back to the 4 quart V-Blender and mix for 2 minutes (50 rotations).
6. Sift Sodium Stearyl Fumarate through a 30 mesh hand screen and add to the 4 quart V-Blender. Mix for 3 minutes (75 rotations).
7. Encapsulate the blended material using an MF-30 Manual Capsule Filler to a target weight of 325.0 mg/capsule.

[0092] The completed final blend was encapsulated using an MF-30 Manual Capsule Filler, filled capsule properties are presented in Table 11, below.

Table 11: X4P-001 Capsules, 200 mg Capsule Fill Weight

Capsule Parameter	Batch 15/858-034 (X4P-001 Capsules, 200 mg)
Tray 1 Average Weight	319.1 mg
Tray 2 Average Weight	320.1 mg
Tray 3 Average Weight	327.6 mg
Individual Max	350.6 mg
Individual Min	298.1 mg

(continued)

Capsule Parameter	Batch 15/858-034 (X4P-001 Capsules, 200 mg)
RSD (%)	3.5

[0093] Following completion of the encapsulation activities a single capsule was filled using the MF-30 manual encapsulation to determine the maximum fill weight that could be filled into a size 1 capsule using the remaining finished blend. A fill weight of 425.0 mg was obtained during execution of the activity.

[0094] The conclusion of the encapsulation process development effort showed that encapsulation is a viable operation for processing the product.

[0095] **Analytical Results of X4P-001 Capsules, 200 mg Feasibility Batch.** Feasibility batch 15/858-034 was tested for Assay/Related Substances, Moisture, Dissolution, and Content Uniformity. Results of this testing are shown in Figures 9 and 10. The result of the assay testing was 97.4% of label claim with total impurities of 0.75% and a moisture value of 3.9% w/w.

[0096] Comparison of the dissolution profile results of the 200 mg formulation composition compared to the 100 mg formulation CTM batch (15K227) is presented in Figure 10. The proposed 200 mg formulation compared favorable to the current 100 mg formulation with an f_2 similarity factor of 83.

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[0097]

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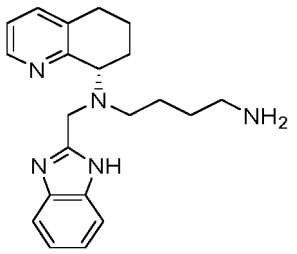
Claims

1. A composition comprising:

(a) X4P-001



X4P-001

,

or a pharmaceutically acceptable salt thereof - 30-40% by weight of the composition;
(b) microcrystalline cellulose -20-25% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 30-35% by weight of the composition;
(d) croscarmellose sodium - 5-10% by weight of the composition;
(e) sodium stearyl fumarate - 0.5-2% by weight of the composition;
(f) colloidal silicon dioxide - 0.1-1.0 % by weight of the composition; and
(g) sodium lauryl sulfate - 0.1-1.0 % by weight of the composition.

2. A composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 8-25% by weight of the composition;
(b) microcrystalline cellulose - 65-85% by weight of the composition;
(c) croscarmellose sodium - 2-10% by weight of the composition;

(d) sodium stearyl fumarate - 0.1-3% by weight of the composition; and
(e) colloidal silicon dioxide - 0.05-0.7% by weight of the composition.

3. A composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 25-45% by weight of the composition;
(b) microcrystalline cellulose - 10-35% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 15-45% by weight of the composition;
(d) croscarmellose sodium - 2-10% by weight of the composition;
(e) sodium stearyl fumarate - 0.3-2.5% by weight of the composition;
(f) colloidal silicon dioxide - 0.05-1.2% by weight of the composition; and
(g) sodium lauryl sulfate - 0.2-1.2% by weight of the composition.

4. A composition comprising:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 35-75% by weight of the composition;
(b) microcrystalline cellulose - 5-28% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 7-30% by weight of the composition;
(d) croscarmellose sodium - 2-10% by weight of the composition;
(e) sodium stearyl fumarate - 0.3-2.5% by weight of the composition;
(f) colloidal silicon dioxide - 0.05-1.2% by weight of the composition; and
(g) sodium lauryl sulfate - 0.2-1.2% by weight of the composition.

5. The composition according to any one of claims 1-4, wherein the X4P-001, or a pharmaceutically acceptable salt thereof, is present in an amount of 10 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, or 1200 mg.

6. The composition of claim 1, wherein the composition comprises 37 wt% of X4P-001, or a pharmaceutically acceptable salt thereof; or:
wherein the composition comprises 100 mg of X4P-001, or a pharmaceutically acceptable salt thereof; or:
wherein the composition comprises:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 37% by weight of the composition;
(b) microcrystalline cellulose - 23% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 32% by weight of the composition;
(d) croscarmellose sodium - 6% by weight of the composition;
(e) sodium stearyl fumarate - 1% by weight of the composition;
(f) colloidal silicon dioxide - 0.3% by weight of the composition; and
(g) sodium lauryl sulfate - 0.5% by weight of the composition.

7. The composition of claim 2, wherein the composition comprises 15 wt% of X4P-001, or a pharmaceutically acceptable salt thereof; or:
wherein the composition comprises 25 mg of X4P-001, or a pharmaceutically acceptable salt thereof; or:
wherein the composition comprises:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 14.7% by weight of the composition;
(b) microcrystalline cellulose - 78.1% by weight of the composition;
(c) croscarmellose sodium - 6.0% by weight of the composition;
(d) sodium stearyl fumarate - 1.0% by weight of the composition; and
(e) colloidal silicon dioxide - 0.2% by weight of the composition.

8. The composition of claim 3, wherein the composition comprises 38 wt% of X4P-001, or a pharmaceutically acceptable salt thereof; or:
wherein the composition comprises 100 mg of X4P-001, or a pharmaceutically acceptable salt thereof; or:
wherein the composition comprises:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 37.6% by weight of the composition;
(b) microcrystalline cellulose - 22.9% by weight of the composition;

(c) dibasic calcium phosphate dihydrate -31.7% by weight of the composition;
(d) croscarmellose sodium - 6.0% by weight of the composition;
(e) sodium stearyl fumarate - 1.0% by weight of the composition;
(f) colloidal silicon dioxide - 0.3% by weight of the composition; and
(g) sodium lauryl sulfate - 0.5% by weight of the composition.

9. The composition of claim 4, wherein the composition comprises 61 wt% of X4P-001, or a pharmaceutically acceptable salt thereof; or:
wherein the composition comprises 200 mg of X4P-001, or a pharmaceutically acceptable salt thereof; or:
wherein the composition comprises:

(a) X4P-001, or a pharmaceutically acceptable salt thereof - 61.5% by weight of the composition;
(b) microcrystalline cellulose - 12.9% by weight of the composition;
(c) dibasic calcium phosphate dihydrate - 17.8% by weight of the composition;
(d) croscarmellose sodium - 6.0% by weight of the composition;
(e) sodium stearyl fumarate - 1.0% by weight of the composition;
(f) colloidal silicon dioxide - 0.3% by weight of the composition; and
(g) sodium lauryl sulfate - 0.5% by weight of the composition.

10. A unit dosage form comprising the composition of any one of claims 1 to 9; optionally wherein the unit dosage form is in the form of a capsule.

11. A composition of any one of claims 1 to 9 for use in treating cancer in a patient.

12. The composition for use of claim 11, wherein the cancer is refractory; and/or:
wherein the patient has previously been treated with a tyrosine kinase inhibitor and wherein the patient has exhibited resistance to the tyrosine kinase inhibitor via angiogenic escape; and/or:
wherein the cancer is selected from renal cell carcinoma (RCC), a solid tumor, a pancreatic, kidney, colorectal, lung, breast, thyroid, or stomach neoplasm, glioblastoma, hepatocellular carcinoma or liver cancer, melanoma, intraocular melanoma, prostate cancer, non-small cell lung cancer, renal tumor, renal carcinoma (including clear cell and papillary renal carcinoma) or kidney cancer, colorectal cancer, advanced gastric cancer, malignant mesothelioma, neurofibromatosis, Schwannomatosis, soft tissue sarcoma, head and neck squamous cell carcinoma, nasopharyngeal carcinoma, adenocarcinoma, neuroendocrine carcinoma, acute myeloid leukemia, myelodysplastic syndrome, pheochromocytoma, paraganglioma, lymphoma, mantle-cell cancer, gastrointestinal-stromal tumors, or pancreatic ductal carcinoma; and/or:
wherein the cancer is advanced renal cell carcinoma (RCC), clear cell renal carcinoma (ccRCC), or papillary renal carcinoma; preferably wherein the cancer is ccRCC.

13. The composition for use of claim 11 or claim 12, wherein a dosage amount of X4P-001, or a pharmaceutically acceptable salt thereof, from 100 mg to 1200 mg per day is administered to the patient; or:
wherein a dosage amount of X4P-001, or a pharmaceutically acceptable salt thereof, from 200 mg to 600 mg per day is administered to the patient; or:
wherein a dosage amount of X4P-001, or a pharmaceutically acceptable salt thereof, from 100 mg to 400 mg per day is administered to the patient.

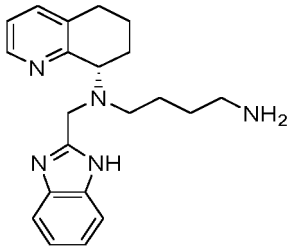
14. The composition for use of any one of claims 11 to 13, wherein a unit dosage form comprising 25 mg, 100 mg, or 200 mg of X4P-001, or a pharmaceutically acceptable salt thereof, is administered to the patient.

15. The composition for use of claim 14, wherein the unit dosage form is administered orally twice per day; wherein the unit dosage form is administered approximately 12 hours apart.

Patentansprüche

1. Zusammensetzung, umfassend:

(a) X4P-001



X4P-001

,

oder ein pharmazeutisch verträgliches Salz davon - 30-40 Gew.-% der Zusammensetzung;
(b) mikrokristalline Cellulose - 20-25 Gew.-% der Zusammensetzung;
(c) dibasisches Calciumphosphat Dihydrat - 30-35 Gew.-% der Zusammensetzung;
(d) Croscarmellose-Natrium - 5-10 Gew.-% der Zusammensetzung;
(e) Natriumstearylfumarat - 0,5-2 Gew.-% der Zusammensetzung;
(f) kolloidales Siliziumdioxid - 0,1-1,0 Gew.-% der Zusammensetzung; und
(g) Natriumlaurylsulfat - 0,1-1,0 Gew.-% der Zusammensetzung.

2. Zusammensetzung, umfassend:

(a) X4P-001 oder ein pharmazeutisch verträgliches Salz davon - 8-25 Gew.-% der Zusammensetzung;
(b) mikrokristalline Cellulose - 65-85 Gew.-% der Zusammensetzung;
(c) Croscarmellose-Natrium - 2-10 Gew.-% der Zusammensetzung;
(d) Natriumstearylfumarat - 0,1-3 Gew.-% der Zusammensetzung; und
(e) kolloidales Siliziumdioxid - 0,05-0,7 Gew.-% der Zusammensetzung.

3. Zusammensetzung, umfassend:

(a) X4P-001 oder ein pharmazeutisch verträgliches Salz davon - 25-45 Gew.-% der Zusammensetzung;
(b) mikrokristalline Cellulose - 10-35 Gew.-% der Zusammensetzung;
(c) dibasisches Calciumphosphat Dihydrat - 15-45 Gew.-% der Zusammensetzung;
(d) Croscarmellose-Natrium - 2-10 Gew.-% der Zusammensetzung;
(e) Natriumstearylfumarat - 0,3-2,5 Gew.-% der Zusammensetzung;
(f) kolloidales Siliziumdioxid - 0,05-1,2 Gew.-% der Zusammensetzung; und
(g) Natriumlaurylsulfat - 0,2-1,2 Gew.-% der Zusammensetzung.

4. Zusammensetzung, umfassend:

(a) X4P-001 oder ein pharmazeutisch verträgliches Salz davon - 35-75 Gew.-% der Zusammensetzung;
(b) mikrokristalline Cellulose - 5-28 Gew.-% der Zusammensetzung;
(c) dibasisches Calciumphosphat Dihydrat - 7-30 Gew.-% der Zusammensetzung;
(d) Croscarmellose-Natrium - 2-10 Gew.-% der Zusammensetzung;
(e) Natriumstearylfumarat - 0,3-2,5 Gew.-% der Zusammensetzung;
(f) kolloidales Siliziumdioxid - 0,05-1,2 Gew.-% der Zusammensetzung; und
(g) Natriumlaurylsulfat - 0,2-1,2 Gew.-% der Zusammensetzung.

5. Zusammensetzung nach einem der Ansprüche 1-4, wobei das X4P-001, oder ein pharmazeutisch verträgliches Salz davon, in einer Menge von 10 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1000 mg, 1100 mg oder 1200 mg vorhanden ist.

6. Zusammensetzung nach Anspruch 1, wobei die Zusammensetzung 37 Gew.-% X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst; oder:
wobei die Zusammensetzung 100 mg X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst; oder:
wobei die Zusammensetzung Folgendes umfasst:

(a) X4P-001 oder ein pharmazeutisch verträgliches Salz davon - 37 Gew.-% der Zusammensetzung;

(b) mikrokristalline Cellulose - 23 Gew.-% der Zusammensetzung;
(c) dibasisches Calciumphosphat Dihydrat - 32 Gew.-% der Zusammensetzung;
(d) Croscarmellose-Natrium - 6 Gew.-% der Zusammensetzung;
(e) Natriumstearylfumarat - 1 Gew.-% der Zusammensetzung;
(f) kolloidales Siliziumdioxid - 0,3 Gew.-% der Zusammensetzung; und
(g) Natriumlaurylsulfat - 0,5 Gew.-% der Zusammensetzung.

7. Zusammensetzung nach Anspruch 2, wobei die Zusammensetzung 15 Gew.-% X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst; oder:
wobei die Zusammensetzung 25 mg X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst; oder:
wobei die Zusammensetzung Folgendes umfasst:

(a) X4P-001 oder ein pharmazeutisch verträgliches Salz davon - 14,7 Gew.-% der Zusammensetzung;
(b) mikrokristalline Cellulose - 78,1 Gew.-% der Zusammensetzung;
(c) Croscarmellose-Natrium - 6,0 Gew.-% der Zusammensetzung;
(d) Natriumstearylfumarat - 1,0 Gew.-% der Zusammensetzung; und
(e) kolloidales Siliziumdioxid - 0,2 Gew.-% der Zusammensetzung.

8. Zusammensetzung nach Anspruch 3, wobei die Zusammensetzung 38 Gew.-% X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst; oder:
wobei die Zusammensetzung 100 mg X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst; oder:
wobei die Zusammensetzung Folgendes umfasst:

(a) X4P-001 oder ein pharmazeutisch verträgliches Salz davon - 37,6 Gew.-% der Zusammensetzung;
(b) mikrokristalline Cellulose - 22,9 Gew.-% der Zusammensetzung;
(c) dibasisches Calciumphosphat Dihydrat - 31,7 Gew.-% der Zusammensetzung;
(d) Croscarmellose-Natrium - 6,0 Gew.-% der Zusammensetzung;
(e) Natriumstearylfumarat - 1,0 Gew.-% der Zusammensetzung;
(f) kolloidales Siliziumdioxid - 0,3 Gew.-% der Zusammensetzung; und
(g) Natriumlaurylsulfat - 0,5 Gew.-% der Zusammensetzung.

9. Zusammensetzung nach Anspruch 4, wobei die Zusammensetzung 61 Gew.-% X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst; oder:
wobei die Zusammensetzung 200 mg X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst; oder:
wobei die Zusammensetzung Folgendes umfasst:

(a) X4P-001 oder ein pharmazeutisch verträgliches Salz davon - 61,5 Gew.-% der Zusammensetzung;
(b) mikrokristalline Cellulose - 12,9 Gew.-% der Zusammensetzung;
(c) dibasisches Calciumphosphat Dihydrat - 17,8 Gew.-% der Zusammensetzung;
(d) Croscarmellose-Natrium - 6,0 Gew.-% der Zusammensetzung;
(e) Natriumstearylfumarat - 1,0 Gew.-% der Zusammensetzung;
(f) kolloidales Siliziumdioxid - 0,3 Gew.-% der Zusammensetzung; und
(g) Natriumlaurylsulfat - 0,5 Gew.-% der Zusammensetzung.

10. Einheitsdosierungsform, umfassend die Zusammensetzung nach einem der Ansprüche 1 bis 9, wobei die Einheitsdosierungsform gegebenenfalls in Form einer Kapsel vorliegt.

11. Zusammensetzung nach einem der Ansprüche 1 bis 9 zur Verwendung bei der Behandlung von Krebs in einem Patienten.

12. Zusammensetzung zur Verwendung nach Anspruch 11, wobei der Krebs refraktär ist; und/oder:
wobei der Patient zuvor mit einem Tyrosinkinase-Inhibitor behandelt wurde und wobei der Patient eine Resistenz gegen den Tyrosinkinase-Inhibitor durch angiogenetisches Entweichen entwickelt hat; und/oder:
wobei der Krebs ausgewählt ist aus Nierenzellkarzinom (RCC), einem festen Tumor, einem Pankreas-, Nieren-, Kolorektal-, Lungen-, Brust-, Schilddrüsen- oder Magenneoplasma, Glioblastom, hepatozellulärem Karzinom oder Leberkrebs, Melanom, intraokularem Melanom, Prostatakrebs, nicht-kleinzelligem Lungenkrebs, Nierentumor, Nierenkarzinom (einschließlich klarzelligem und papillärem Nierenkarzinom) oder Nierenkrebs, Dickdarmkrebs, fortgeschrittenem Magenkrebs, malignem Mesotheliom, Neurofibromatose, Schwannomatose, Weichteilsarkom, Plat-

tenepithelkarzinom im Kopf-Hals-Bereich, nasopharyngealem Karzinom, Adenokarzinom, neuroendokrinem Karzinom, akuter myeloische Leukämie, myelodysplastischem Syndrom, Phäochromozytom, Paragangliom, Lymphom, Mantelzellkrebs, gastrointestinalen Stromatumoren oder duktalem Pankreaskarzinom; und/oder:
wobei der Krebs ein fortgeschrittenes Nierenzellkarzinom (RCC), ein klarzelliges Nierenkarzinom (ccRCC) oder ein papilläres Nierenkarzinom ist; wobei der Krebs vorzugsweise ccRCC ist.

13. Zusammensetzung zur Verwendung nach Anspruch 11 oder Anspruch 12, wobei dem Patienten eine Dosierungsmenge von X4P-001 oder einem pharmazeutisch verträglichen Salz davon von 100 mg bis 1200 mg pro Tag verabreicht wird; oder:
wobei dem Patienten eine Dosierungsmenge von X4P-001 oder einem pharmazeutisch verträglichen Salz davon von 200 mg bis 600 mg pro Tag verabreicht wird; oder:
wobei dem Patienten eine Dosierungsmenge von X4P-001 oder einem pharmazeutisch verträglichen Salz davon von 100 mg bis 400 mg pro Tag verabreicht wird.

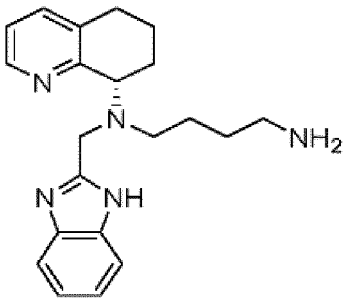
14. Zusammensetzung zur Verwendung nach einem der Ansprüche 11 bis 13, wobei dem Patienten eine Einheitsdosierungsform verabreicht wird, die 25 mg, 100 mg oder 200 mg X4P-001 oder ein pharmazeutisch verträgliches Salz davon umfasst.

15. Zusammensetzung zur Verwendung nach Anspruch 14, wobei die Einheitsdosierungsform zweimal täglich oral verabreicht wird; wobei die Einheitsdosierungsform im Abstand von etwa 12 Stunden verabreicht wird.

Revendications

1. Composition comprenant :

(a) du X4P-001



X4P-001

ou un sel pharmaceutiquement acceptable de celui-ci, à raison de 30 à 40 % en poids de la composition ;
(b) de la cellulose microcristalline à raison de 20 à 25 % en poids de la composition ;
(c) du phosphate de calcium dibasique dihydraté à raison de 30 à 35 % en poids de la composition ;
(d) de la croscarmellose sodique à raison de 5 à 10 % en poids de la composition ;
(e) du stéarylfumarate de sodium à raison de 0,5 à 2 % en poids de la composition ;
(f) du dioxyde de silicium colloïdal à raison de 0,1 à 1,0 % en poids de la composition ; et
(g) du laurylsulfate de sodium à raison de 0,1 à 1,0 % en poids de la composition.

2. Composition comprenant :

(a) du X4P-001, ou un sel pharmaceutiquement acceptable de celui-ci, à raison de 8 à 25 % en poids de la composition ;
(b) de la cellulose microcristalline à raison de 65 à 85 % en poids de la composition ;
(c) de la croscarmellose sodique à raison de 2 à 10 % en poids de la composition ;
(d) du stéarylfumarate de sodium à raison de 0,1 à 3 % en poids de la composition ; et
(e) du dioxyde de silicium colloïdal à raison de 0,05 à 0,7 % en poids de la composition.

3. Composition comprenant :

(a) du X4P-001, ou un sel pharmaceutiquement acceptable de celui-ci, à raison de 25 à 45 % en poids de la composition ;
(b) de la cellulose microcristalline à raison de 10 à 35 % en poids de la composition ;
(c) du phosphate de calcium dibasique dihydraté à raison de 15 à 45 % en poids de la composition ;
(d) de la croscarmellose sodique à raison de 2 à 10 % en poids de la composition ;
(e) du stéarylfumarate de sodium à raison de 0,3 à 2,5 % en poids de la composition ;
(f) du dioxyde de silicium colloïdal à raison de 0,05 à 1,2 % en poids de la composition ; et
(g) du laurylsulfate de sodium à raison de 0,2 à 1,2 % en poids de la composition.

4. Composition comprenant :

(a) du X4P-001, ou un sel pharmaceutiquement acceptable de celui-ci, à raison de 35 à 75 % en poids de la composition ;
(b) de la cellulose microcristalline à raison de 5 à 28 % en poids de la composition ;
(c) du phosphate de calcium dibasique dihydraté à raison de 7 à 30 % en poids de la composition ;
(d) de la croscarmellose sodique à raison de 2 à 10 % en poids de la composition ;
(e) du stéarylfumarate de sodium à raison de 0,3 à 2,5 % en poids de la composition ;
(f) du dioxyde de silicium colloïdal à raison de 0,05 à 1,2 % en poids de la composition ; et
(g) du laurylsulfate de sodium à raison de 0,2 à 1,2 % en poids de la composition.

5. Composition selon l'une quelconque des revendications 1 à 4, dans laquelle le X4P-001, ou un sel pharmaceutiquement acceptable de celui-ci, est présent en une quantité de 10 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, ou 1200 mg.

6. Composition selon la revendication 1, laquelle composition comprend 37 % en poids de X4P-001 ou d'un sel pharmaceutiquement acceptable de celui-ci ; ou :
laquelle composition comprend 100 mg de X4P-001 ou d'un sel pharmaceutiquement acceptable de celui-ci ; ou :
laquelle composition comprend :

(a) du X4P-001, ou un sel pharmaceutiquement acceptable de celui-ci, à raison de 37 % en poids de la composition ;
(b) de la cellulose microcristalline à raison de 23 % en poids de la composition ;
(c) du phosphate de calcium dibasique dihydraté à raison de 32 % en poids de la composition ;
(d) de la croscarmellose sodique à raison de 6 % en poids de la composition ;
(e) du stéarylfumarate de sodium à raison de 1 % en poids de la composition ;
(f) du dioxyde de silicium colloïdal à raison de 0,3 % en poids de la composition ; et
(g) du laurylsulfate de sodium à raison de 0,5% en poids de la composition.

7. Composition selon la revendication 2, laquelle composition comprend 15 % en poids de X4P-001 ou d'un sel pharmaceutiquement acceptable de celui-ci ; ou :
laquelle composition comprend 25 mg de X4P-001 ou d'un sel pharmaceutiquement acceptable de celui-ci ; ou :
laquelle composition comprend :

(a) du X4P-001, ou un sel pharmaceutiquement acceptable de celui-ci, à raison de 14,7 % en poids de la composition ;
(b) de la cellulose microcristalline à raison de 78,1 % en poids de la composition ;
(c) de la croscarmellose sodique à raison de 6,0 % en poids de la composition ;
(d) du stéarylfumarate de sodium à raison de 1,0 % en poids de la composition ; et
(e) du dioxyde de silicium colloïdal à raison de 0,2 % en poids de la composition.

8. Composition selon la revendication 3, laquelle composition comprend 38 % en poids de X4P-001 ou d'un sel pharmaceutiquement acceptable de celui-ci ; ou :
laquelle composition comprend 100 mg de X4P-001 ou d'un sel pharmaceutiquement acceptable de celui-ci ; ou :
laquelle composition comprend :

(a) du X4P-001, ou un sel pharmaceutiquement acceptable de celui-ci, à raison de 37,6 % en poids de la composition ;
(b) de la cellulose microcristalline à raison de 22,9 % en poids de la composition ;
(c) du phosphate de calcium dibasique dihydraté à raison de 31,7 % en poids de la composition ;
(d) de la croscarmellose sodique à raison de 6,0 % en poids de la composition ;
(e) du stéarylfumarate de sodium à raison de 1,0 % en poids de la composition ;
(f) du dioxyde de silicium colloïdal à raison de 0,3 % en poids de la composition ; et
(g) du laurylsulfate de sodium à raison de 0,5 % en poids de la composition.

9. Composition selon la revendication 4, laquelle composition comprend 61 % en poids de X4P-001 ou d'un sel pharmaceutiquement acceptable de celui-ci ; ou :
laquelle composition comprend 200 mg de X4P-001 ou d'un sel pharmaceutiquement acceptable de celui-ci ; ou :
laquelle composition comprend :

(a) du X4P-001, ou un sel pharmaceutiquement acceptable de celui-ci, à raison de 61,5 % en poids de la composition ;
(b) de la cellulose microcristalline à raison de 12,9 % en poids de la composition ;
(c) du phosphate de calcium dibasique dihydraté à raison de 17,8 % en poids de la composition ;
(d) de la croscarmellose sodique à raison de 6,0 % en poids de la composition ;
(e) du stéarylfumarate de sodium à raison de 1,0 % en poids de la composition ;
(f) du dioxyde de silicium colloïdal à raison de 0,3 % en poids de la composition ; et
(g) du laurylsulfate de sodium à raison de 0,5 % en poids de la composition.

10. Forme posologique unitaire comprenant la composition de l'une quelconque des revendications 1 à 9 ; éventuellement laquelle forme posologique unitaire est sous la forme d'une capsule.

11. Composition selon l'une quelconque des revendications 1 à 9, pour une utilisation dans le traitement d'un cancer chez un patient.

12. Composition pour une utilisation selon la revendication 11, dans laquelle le cancer est réfractaire ; et/ou

dans laquelle le patient a antérieurement été traité avec un inhibiteur de tyrosine kinase et dans laquelle le patient a présenté une résistance à l'inhibiteur de tyrosine kinase via une évasion angiogénique ; et/ou
dans laquelle le cancer est choisi parmi un carcinome à cellules rénales (RCC), une tumeur solide, un néoplasme pancréatique, rénal, colorectal, pulmonaire, mammaire, thyroïdien, ou stomacal, un glioblastome, un carcinome hépatocellulaire ou un cancer du foie, un mélanome, un mélanome intraoculaire, un cancer de la prostate, un cancer du poumon non à petites cellules, une tumeur rénale, un carcinome rénal (y compris un carcinome rénal à cellules claires ou papillaire) ou un cancer du rein, un cancer colorectal, un cancer gastrique avancé, un mésothéliome malin, une neurofibromatose, une schwannomatose, un sarcome d'un tissu mou, un carcinome à cellules squameuses de la tête et du cou, un carcinome rhinopharyngé, un adénocarcinome, un carcinome neuroendocrinien, une leucémie myéloïde aiguë, un syndrome myélodysplasique, un phéochromocytome, un paragangliome, un lymphome, un cancer à cellules de manteau, une tumeur gastrointestinale-stromale, ou un carcinome canalaire pancréatique ; et/ou :
dans laquelle le cancer est un carcinome à cellules rénales (RCC) avancé; un carcinome rénal à cellules claires (ccRCC), ou un carcinome rénale papillaire ; de préférence dans laquelle le cancer est un ccRCC.

13. Composition pour une utilisation selon la revendication 11 ou la revendication 12, dans laquelle une posologie du X4P-001, ou d'un sel pharmaceutiquement acceptable de celui-ci, de 100 mg à 1200 mg par jour est administrée au patient ; ou

dans laquelle une posologie du X4P-001, ou d'un sel pharmaceutiquement acceptable de celui-ci, de 200 mg à 600 mg par jour est administrée au patient ; ou
dans laquelle une posologie du X4P-001, ou d'un sel pharmaceutiquement acceptable de celui-ci, de 100 mg à 400 mg par jour est administrée au patient.

14. Composition pour une utilisation selon l'une quelconque des revendications 11 à 13, dans laquelle une forme posologique unitaire comprenant 25 mg, 100 mg ou 200 mg de X4P-001, ou d'un sel pharmaceutiquement acceptable de celui-ci, est administrée au patient.

15. Composition pour une utilisation selon la revendication 14, dans laquelle la forme posologique unitaire est administrée par voie orale deux fois par jour ; dans laquelle la forme posologique unitaire est administrée à intervalles d'environ 12 heures.

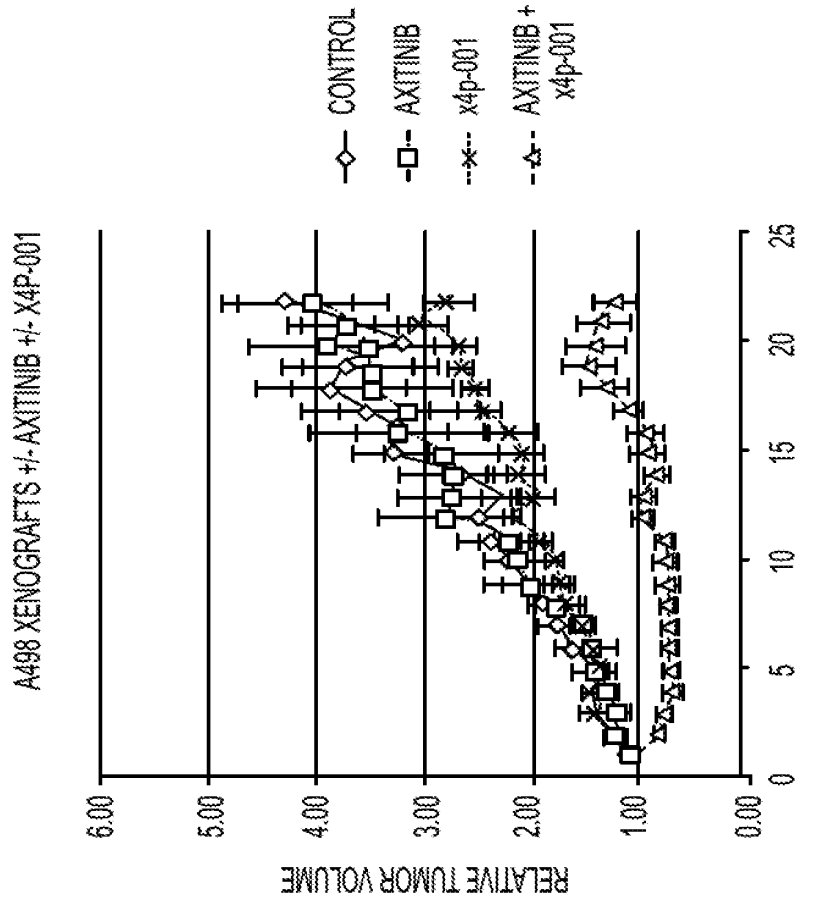


FIGURE 1B

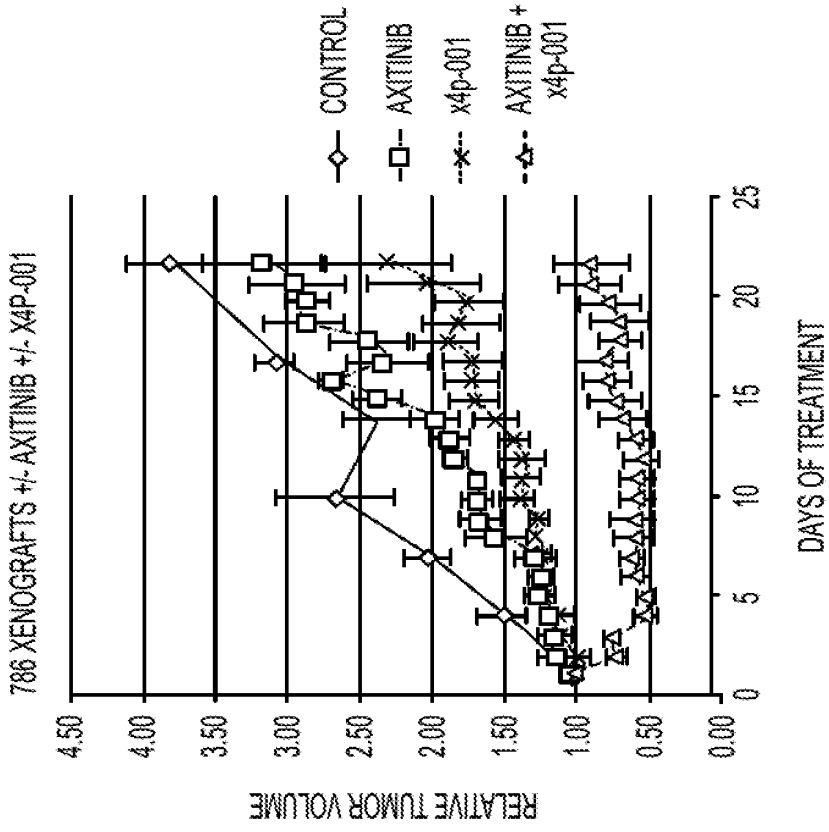


FIGURE 1A

CONTROL

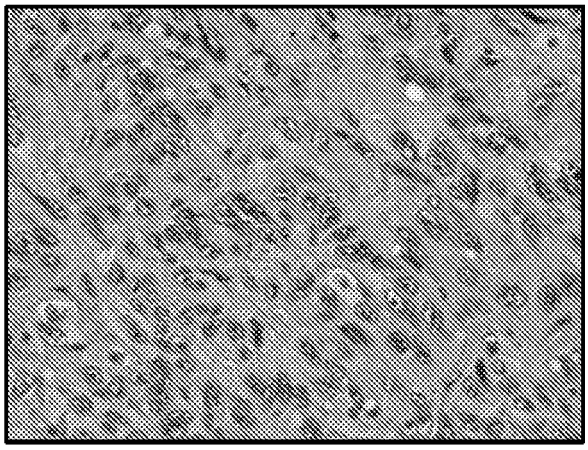


FIGURE 2A

AXITINIB

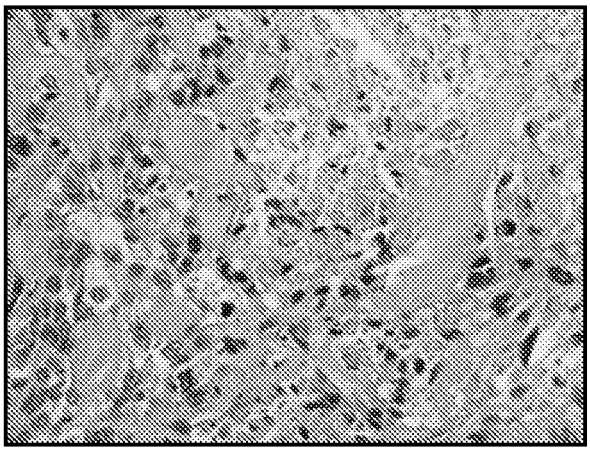


FIGURE 2B

X4P-001

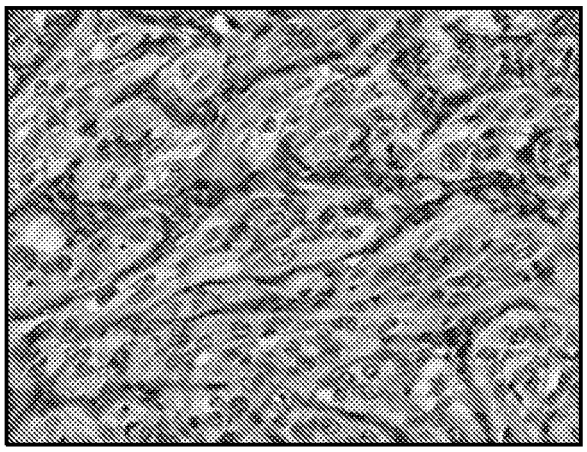


FIGURE 2C

X4P-001 + AXITINIB

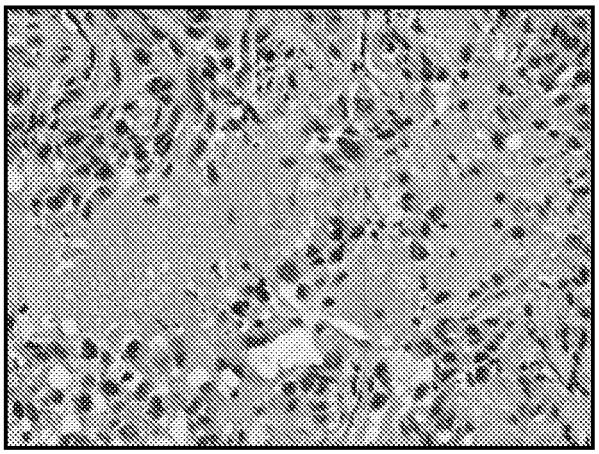


FIGURE 2D

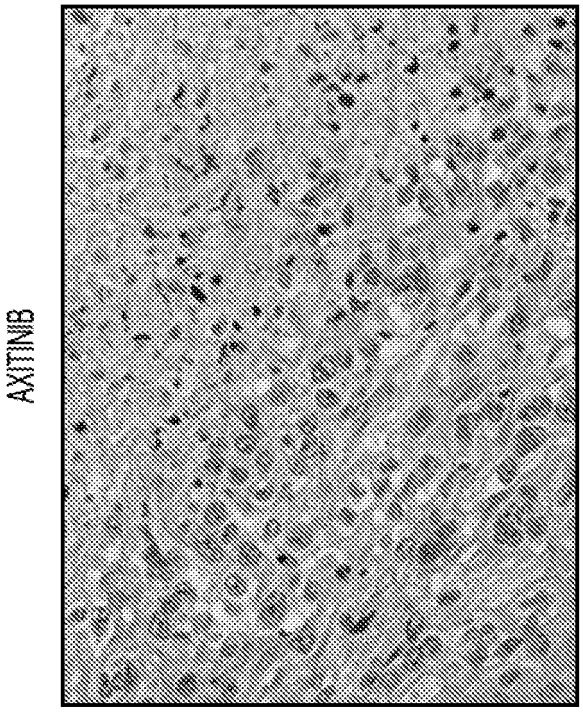


FIGURE 3B

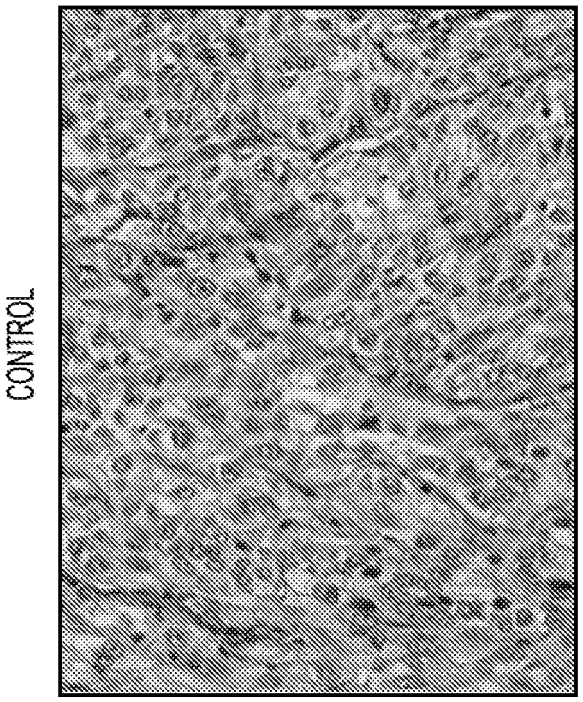


FIGURE 3A

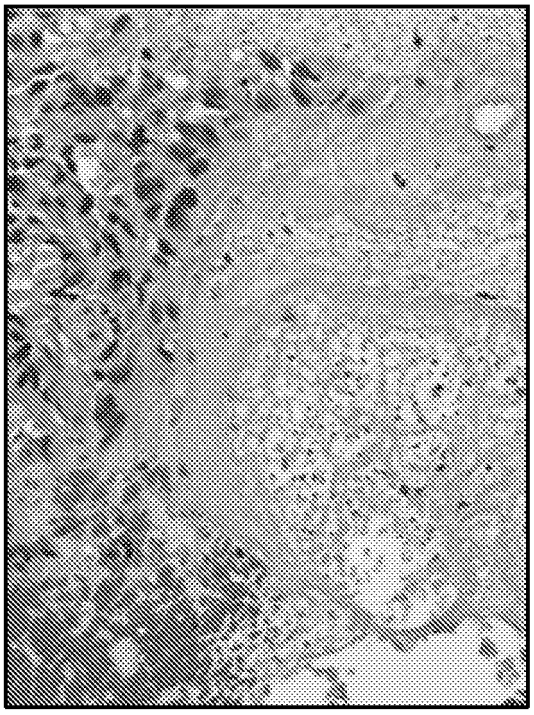


FIGURE 3D

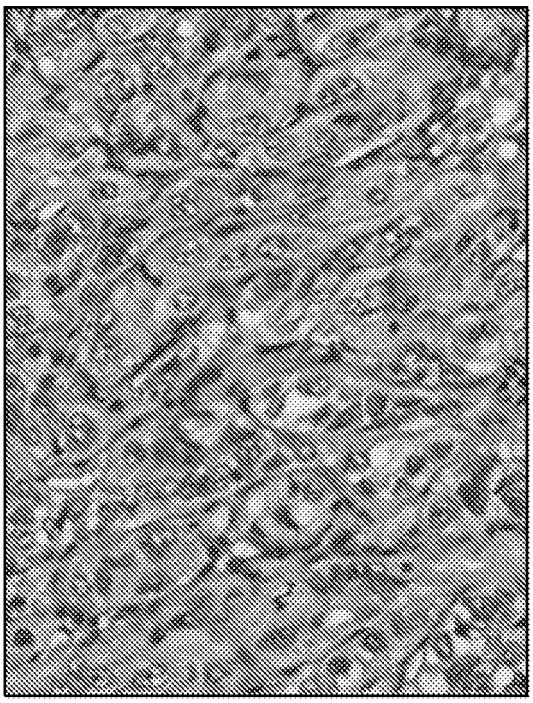


FIGURE 3C

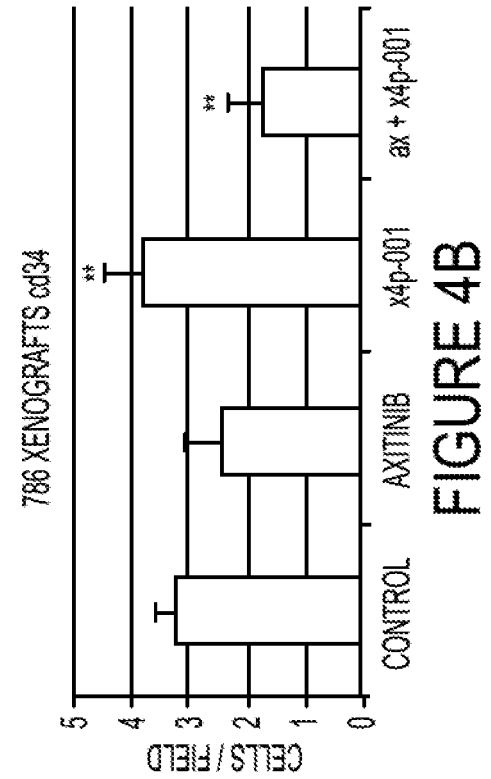


FIGURE 4B

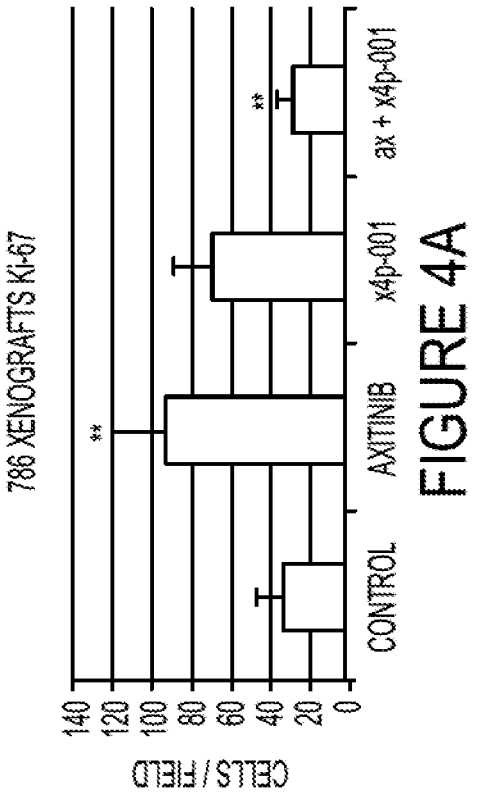


FIGURE 4A

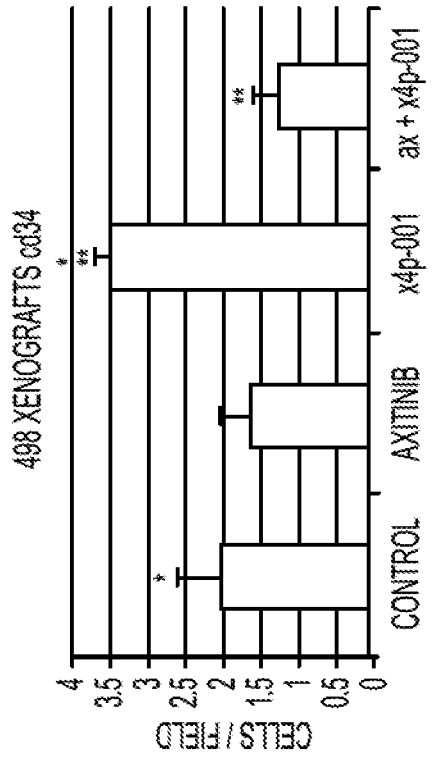
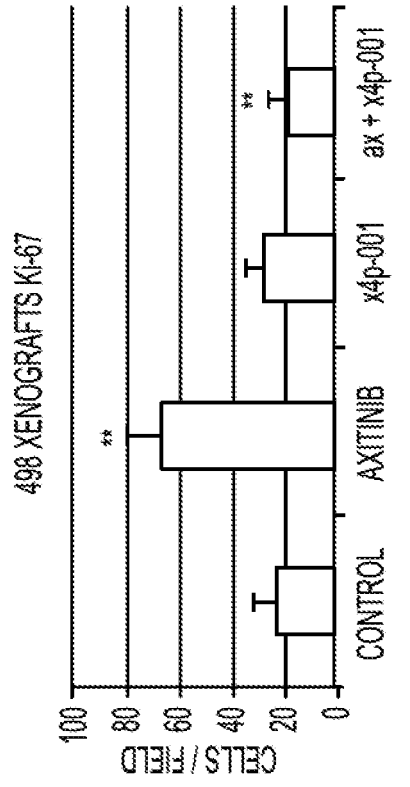


FIGURE 4D



* P<0.05 VS. CONTROL
** P<0.05 X4P-001 PLUS AXITINIB VS. X4P-001 ALONE

FIGURE 4C

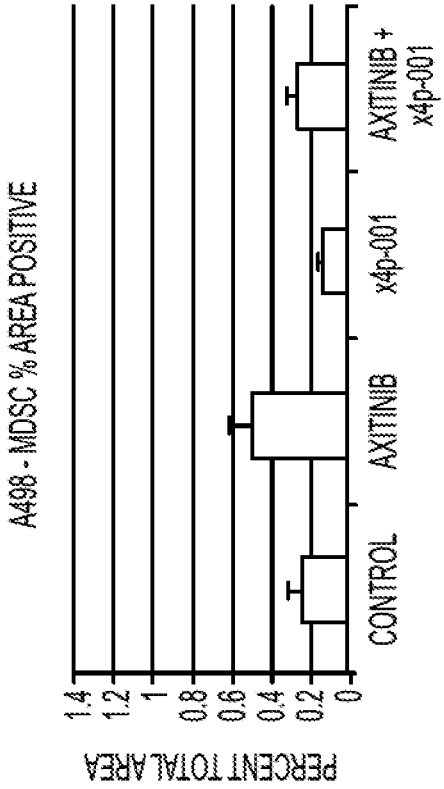


FIGURE 5A

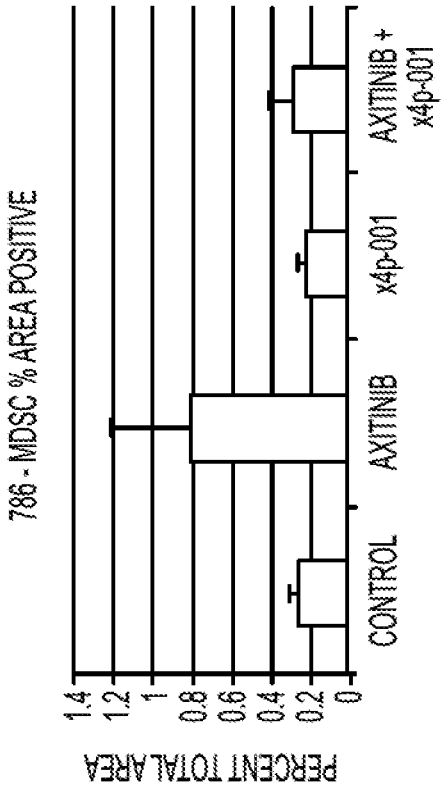


FIGURE 5B

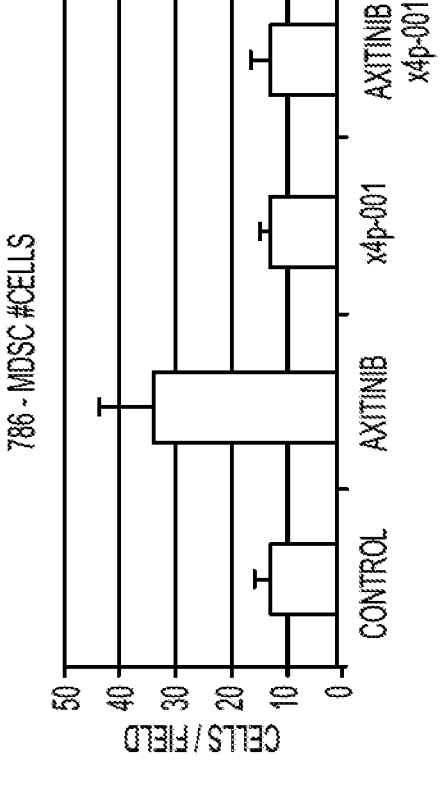
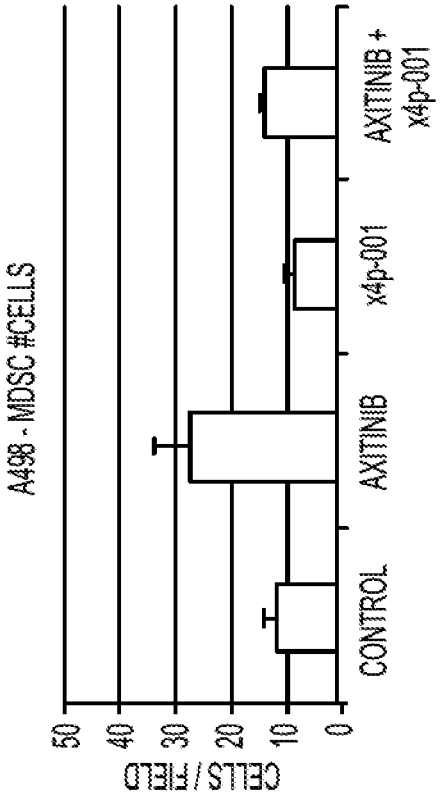


FIGURE 5C



MDSC CELLS = $CD11b^+$ $GR\text{-}1^+$

FIGURE 5D

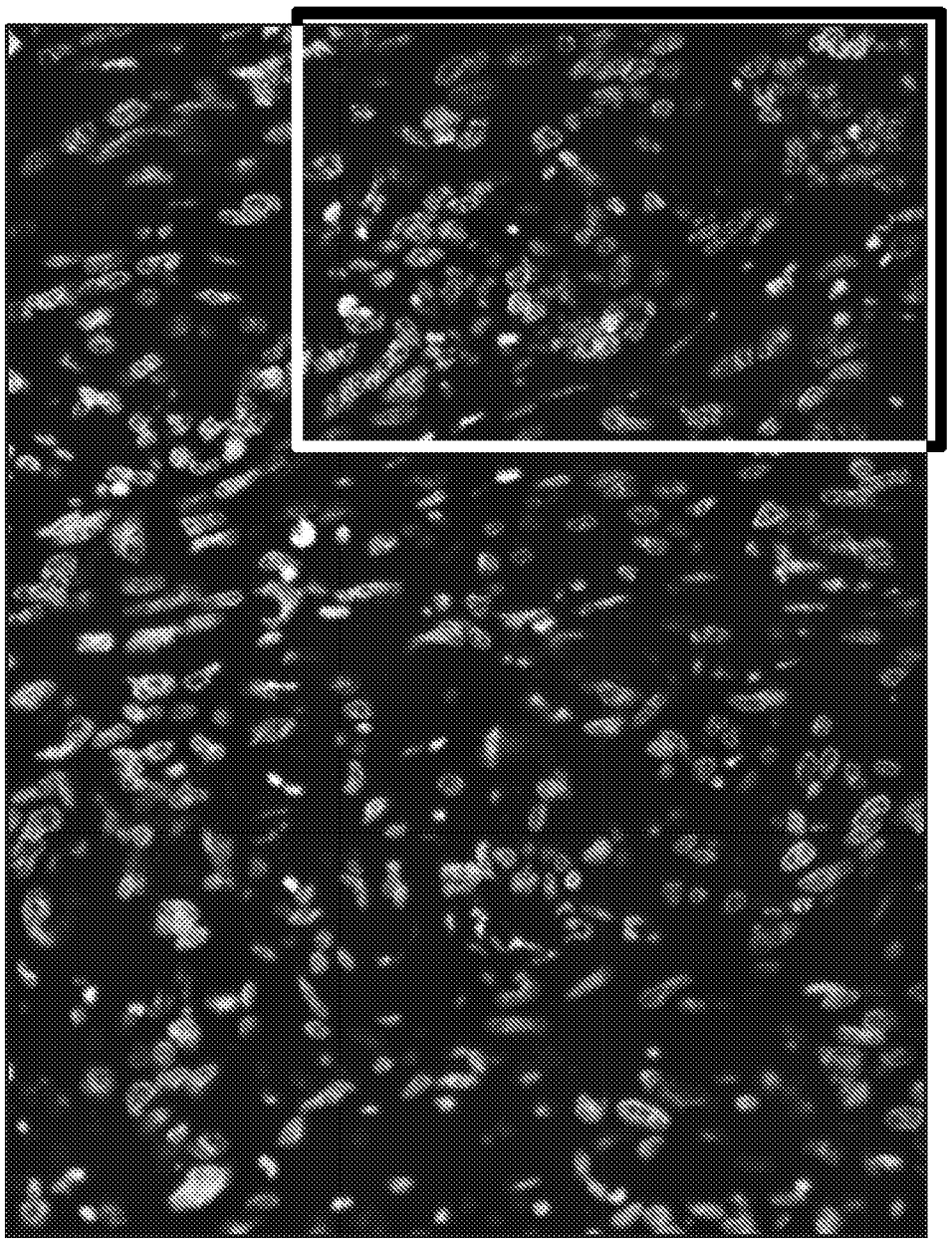
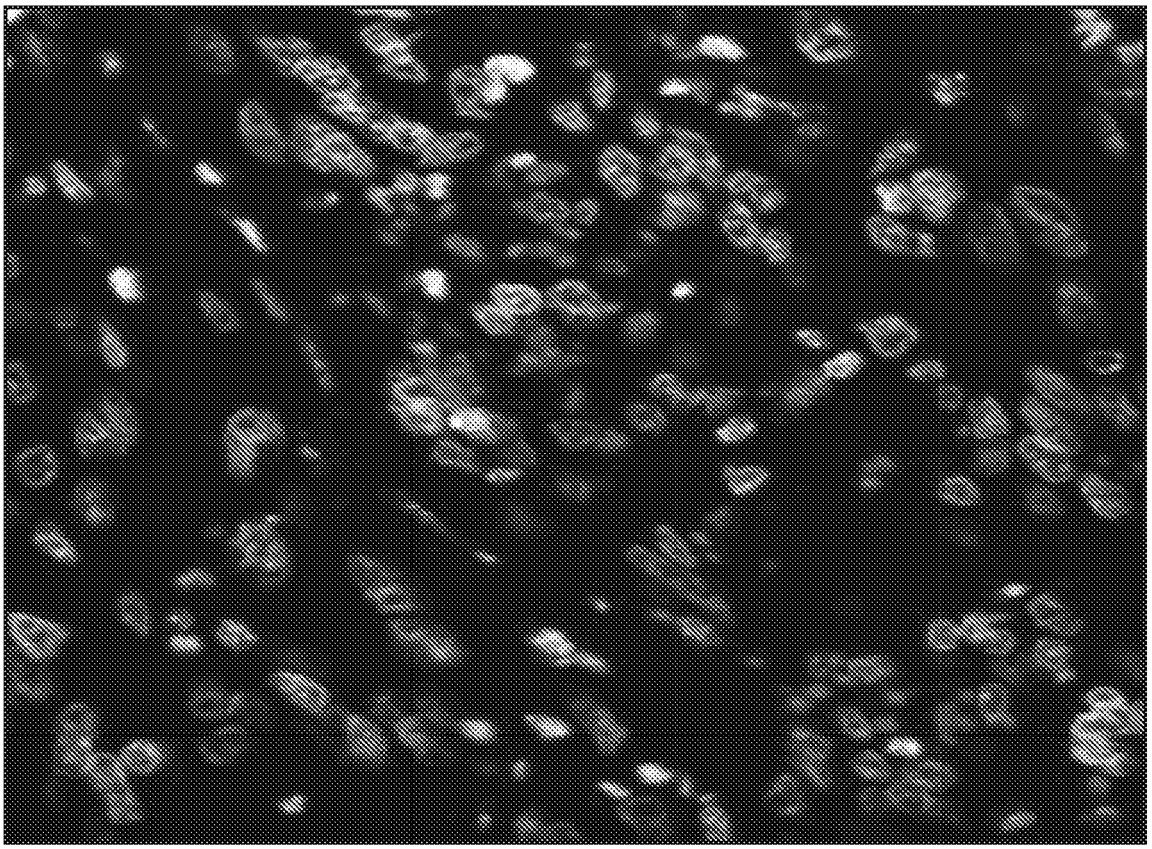

MDSC (CD11b+ GR-1+) INFILTRATING 786 XENOGRAFTS
TREATED WITH AXITINIB ALONE
(LOW POWER)

FIGURE 6

MDSC ($CD11b^+$ $GR\text{-}1^+$) INFILTRATING 786 XENOGRAFTS
TREATED WITH AXITINIB ALONE



(HIGH POWER)

FIGURE 7

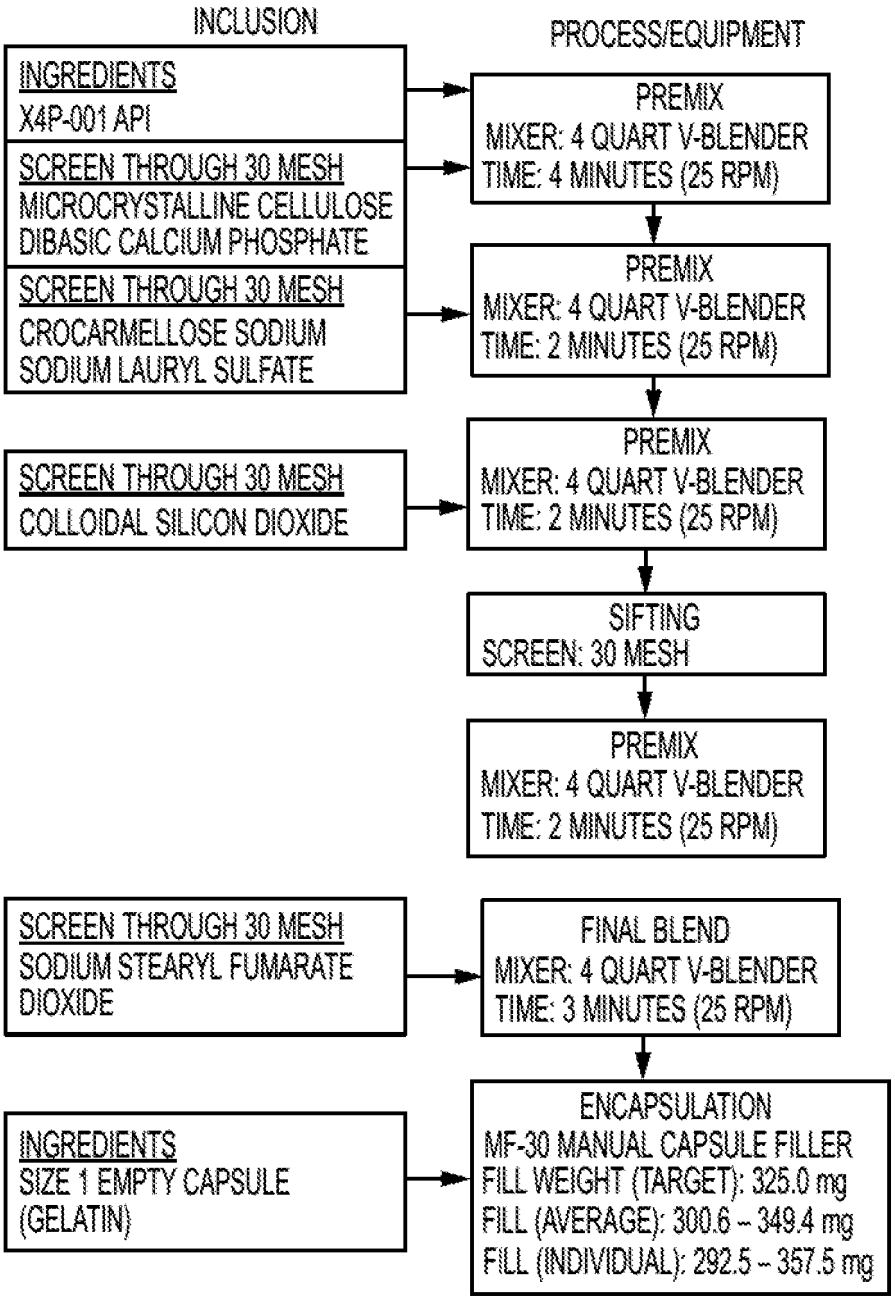

INCLUSION
PROCESS/EQUIPMENT
INGREDIENTS
X4P-001 API
SCREEN THROUGH 30 MESH
MICROCRYSTALLINE CELLULOSE
DIBASIC CALCIUM PHOSPHATE
SCREEN THROUGH 30 MESH
CROCARMELLOSE SODIUM
SODIUM LAURYL SULFATE
SCREEN THROUGH 30 MESH
COLLOIDAL SILICON DIOXIDE
SCREEN THROUGH 30 MESH
SODIUM STEARYL FUMARATE
DIOXIDE
INGREDIENTS
SIZE 1 EMPTY CAPSULE
(GELATIN)
PREMIX
MIXER: 4 QUART V-BLENDER
TIME: 4 MINUTES (25 RPM)
PREMIX
MIXER: 4 QUART V-BLENDER
TIME: 2 MINUTES (25 RPM)
PREMIX
MIXER: 4 QUART V-BLENDER
TIME: 2 MINUTES (25 RPM)
SIFTING
SCREEN: 30 MESH
PREMIX
MIXER: 4 QUART V-BLENDER
TIME: 2 MINUTES (25 RPM)
FINAL BLEND
MIXER: 4 QUART V-BLENDER
TIME: 3 MINUTES (25 RPM)
ENCAPSULATION
MF-30 MANUAL CAPSULE FILLER
FILL WEIGHT (TARGET): 325.0 mg
FILL (AVERAGE): 300.6 – 349.4 mg
FILL (INDIVIDUAL): 292.5 – 357.5 mg

FIGURE 8

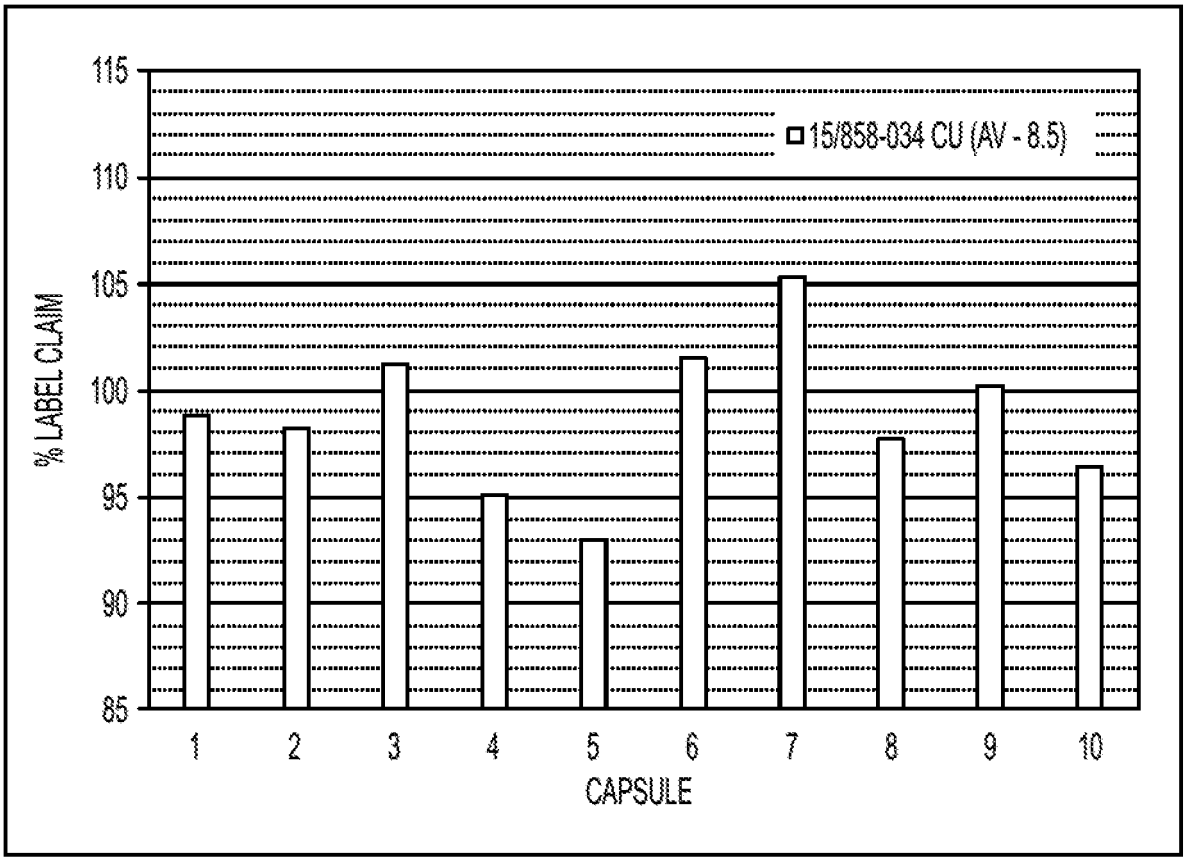

115
110
105
100
95
90
85
% LABEL CLAIM
15/858-034 CU (AV - 8.5)
1
2
3
4
5
6
7
8
9
10
CAPSULE

FIGURE 9

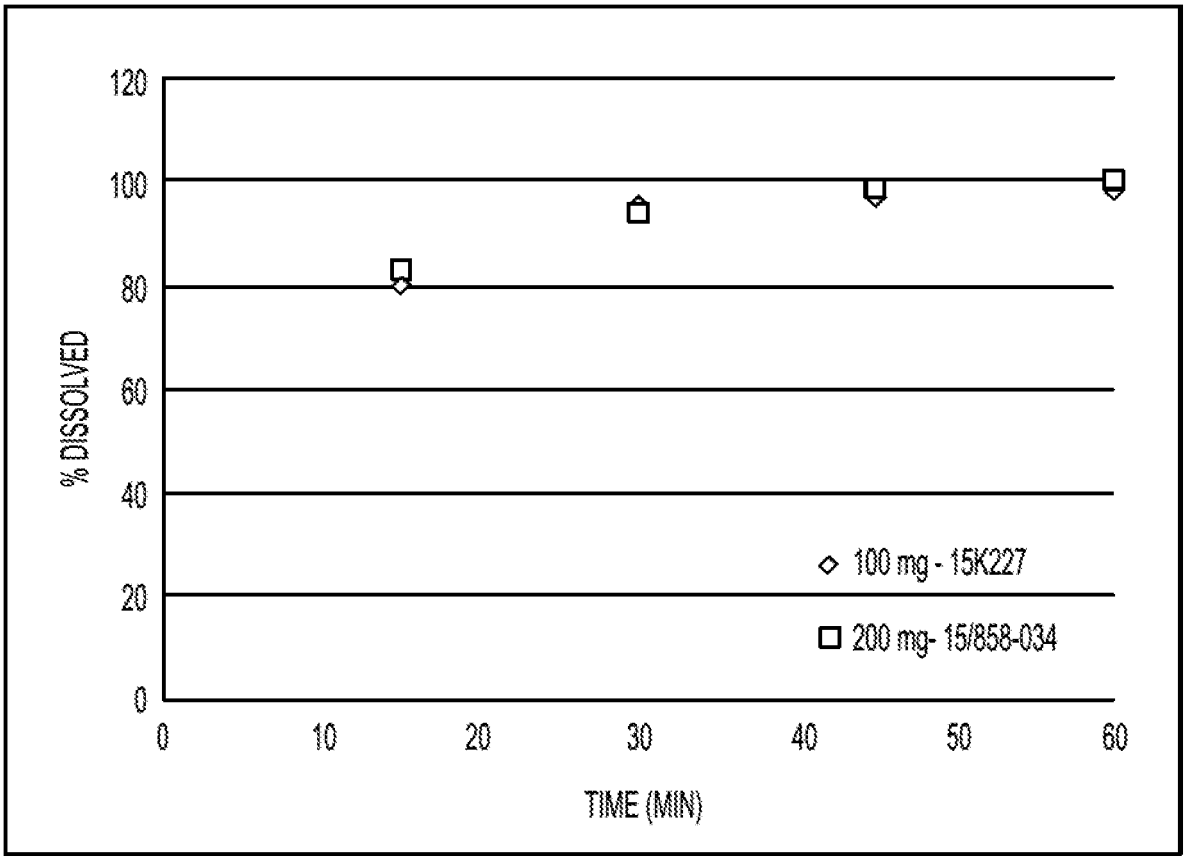

120
100
80
60
40
20
0
% DISSOLVED
0
10
20
30
40
50
60
TIME (MIN)
100 mg - 15K227
200 mg- 15/858-034

FIGURE 10

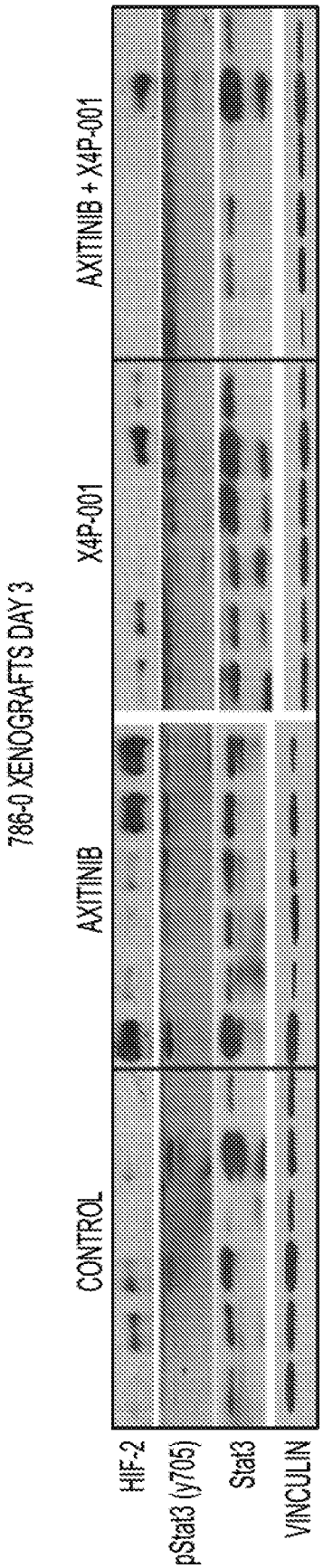

786-0 XENOGRAFTS DAY 3
CONTROL
AXITINIB
X4P-001
AXITINIB + X4P-001
HIF-2
pStat3 (y705)
Stat3
VINCULIN

FIGURE 11

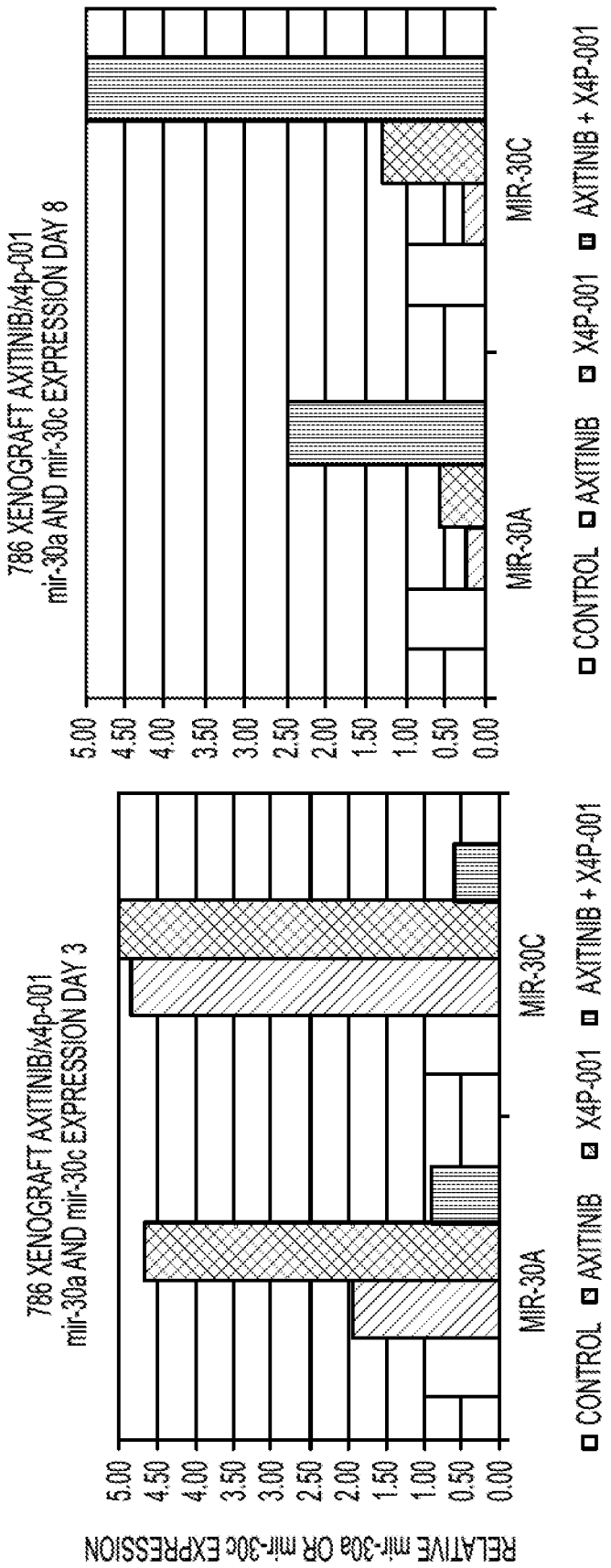

786 XENOGRAFT AXITINIB/x4p-001
mir-30a AND mir-30c EXPRESSION DAY 3
RELATIVE mir-30a OR mir-30c EXPRESSION
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
MIR-30A
MIR-30C
CONTROL
AXITINIB
X4P-001
AXITINIB + X4P-001
786 XENOGRAFT AXITINIB/x4p-001
mir-30a AND mir-30c EXPRESSION DAY 8
MIR-30A
MIR-30C
CONTROL
AXITINIB
X4P-001
AXITINIB + X4P-001

FIGURE 12

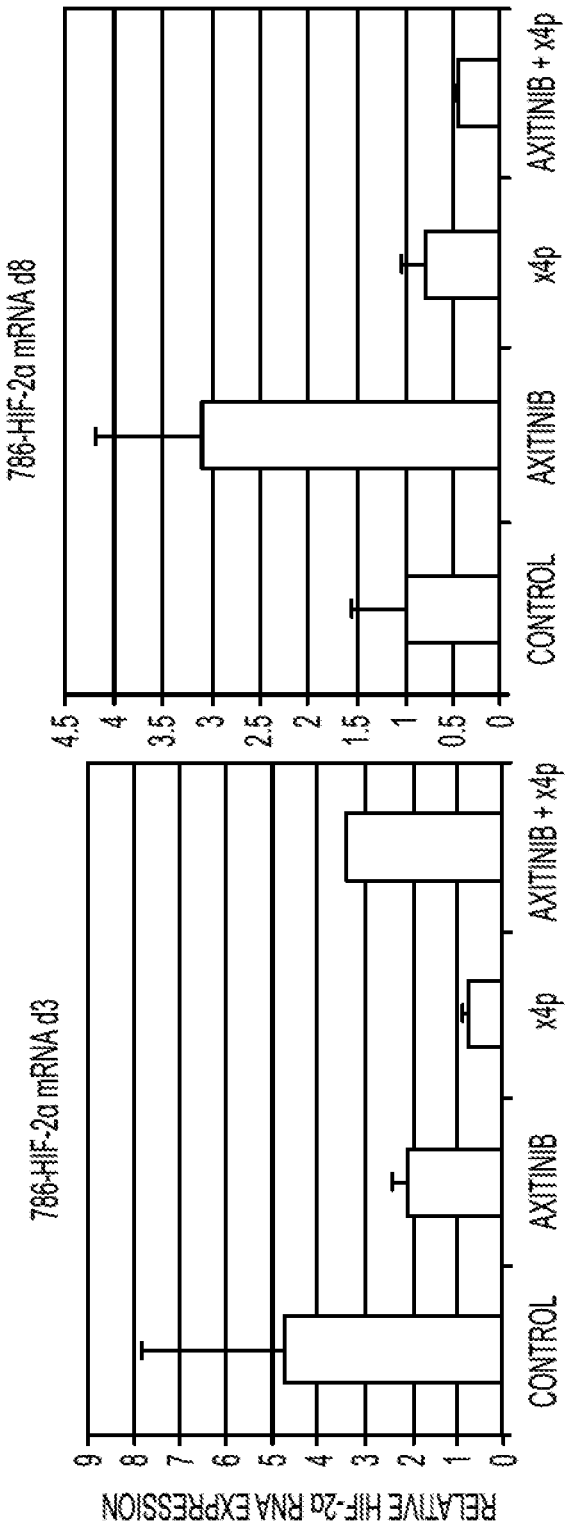

786-HIF-2α mRNA d3
786-HIF-2α mRNA d8
RELATIVE HIF-2α RNA EXPRESSION
0
1
2
3
4
5
6
7
8
9
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
CONTROL
AXITINIB
x4p
AXITINIB + x4p

FIGURE 13

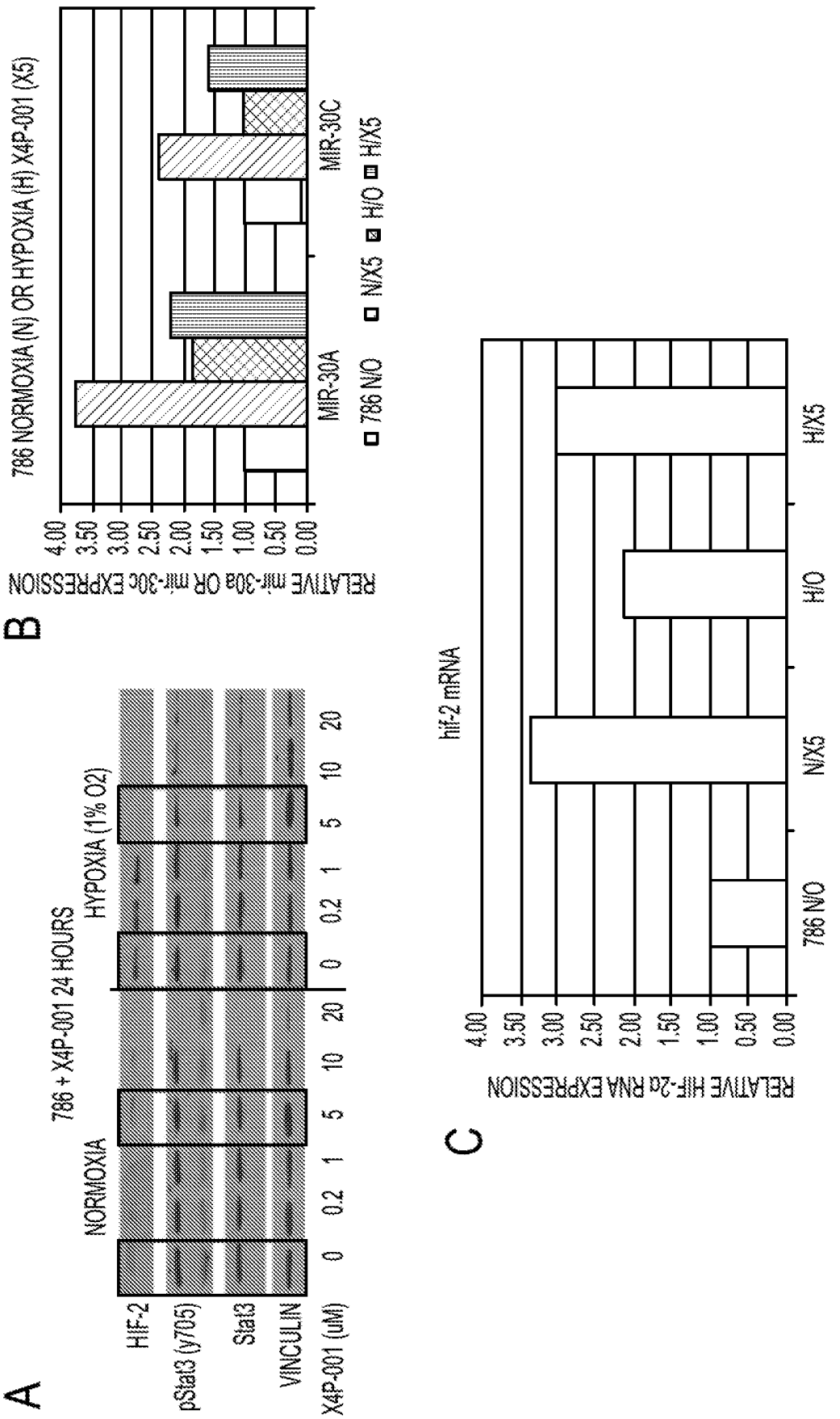

A
786 + X4P-001 24 HOURS
NORMOXIA
HYPOXIA (1% O2)
X4P-001 (uM) 0 0.2 1 5 10 20 0 0.2 1 5 10 20
HIF-2
pStat3 (y705)
Stat3
VINCULIN
B
786 NORMOXIA (N) OR HYPOXIA (H) X4P-001 (X5)
RELATIVE mir-30a OR mir-30c EXPRESSION
4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
MIR-30A
MIR-30C
786 N/O
N/X5
H/O
H/X5
C
hif-2 mRNA
RELATIVE HIF-2α RNA EXPRESSION
4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
786 N/O
N/X5
H/O
H/X5

FIGURE 14

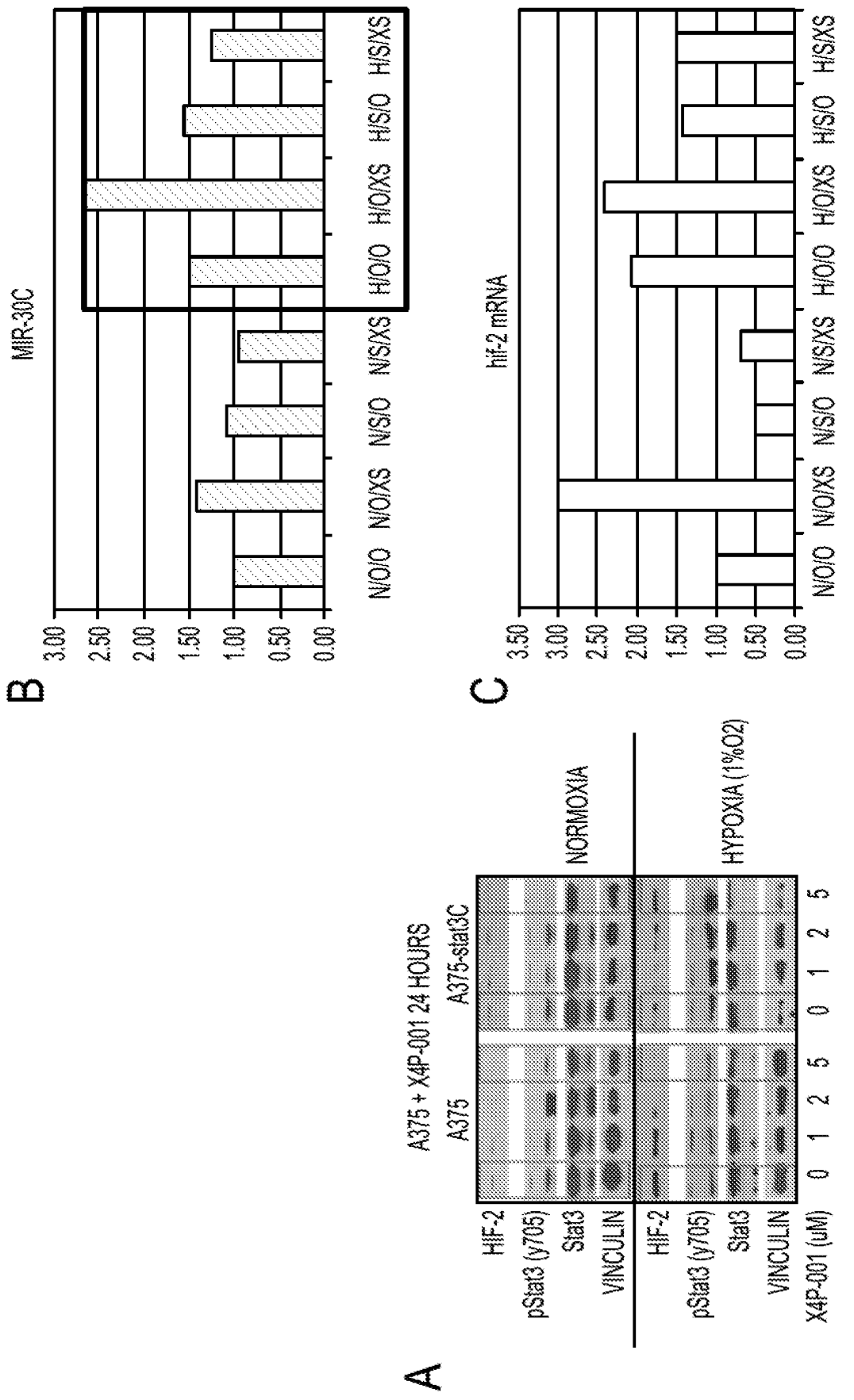

A
A375 + X4P-001 24 HOURS
A375
A375-stat3C
0 1 2 5 0 1 2 5
X4P-001 (uM)
HIF-2
pStat3 (y705)
Stat3
VINCULIN
NORMOXIA
HYPOXIA (1%O2)
B
MIR-30C
3.00
2.50
2.00
1.50
1.00
0.50
0.00
N/O/O
N/O/XS
N/S/O
N/S/XS
H/O/O
H/O/XS
H/S/O
H/S/XS
C
hif-2 mRNA
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

FIGURE 15

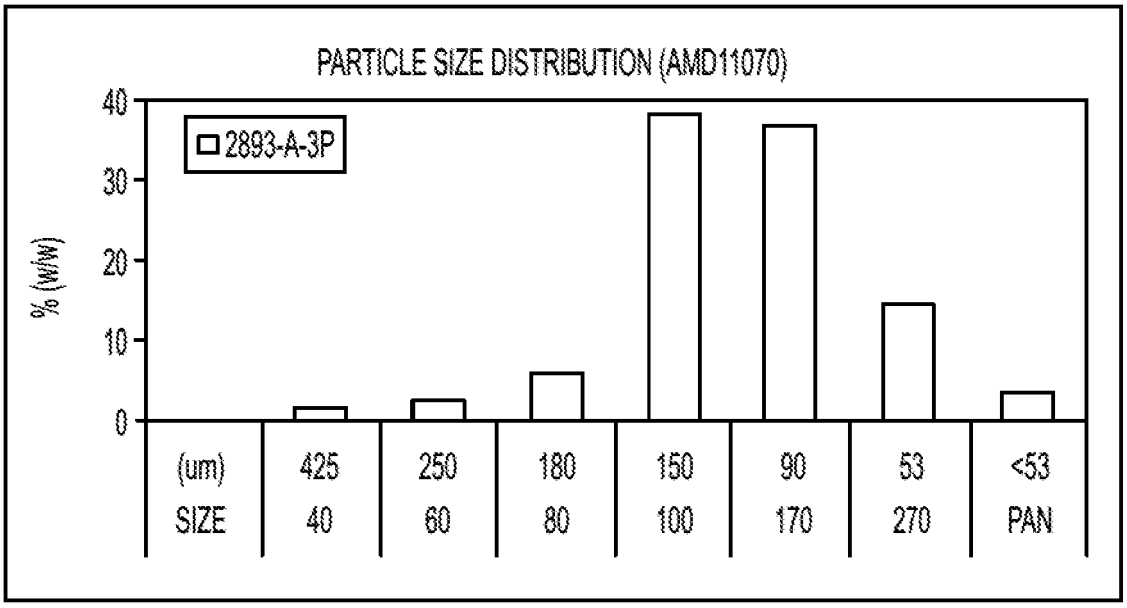

PARTICLE SIZE DISTRIBUTION (AMD11070)
2893-A-3P
% (w/w)
40
30
20
10
0
(um) 425 250 180 150 90 53 <53
SIZE 40 60 80 100 170 270 PAN

FIGURE 16

REFERENCES CITED IN THE DESCRIPTION

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