

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
13 October 2016 (13.10.2016)

(10) International Publication Number
WO 2016/164336 A1

(51) International Patent Classification:

A61K 31/44 (2006.01) *A61K 31/7072* (2006.01)
A61P 35/00 (2006.01)

(21) International Application Number:

PCT/US2016/025986

(22) International Filing Date:

5 April 2016 (05.04.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/143,702 6 April 2015 (06.04.2015) US
62/299,965 25 February 2016 (25.02.2016) US

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(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: HEPATOCELLULAR CARCINOMA TREATMENT USING A COMBINATION OF CC 122 AND SORAFENIB

(57) Abstract: Provided herein are methods for treating, preventing, and/or managing hepatocellular carcinoma using combination therapy.



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HEPATOCELLULAR CARCINOMA TREATMENT USING A COMBINATION OF CC 122 AND SORAFENIB

1. FIELD

[0001] Provided herein are methods for treating, preventing and/or managing hepatocellular carcinoma using combination therapy.

2. BACKGROUND

[0002] Hepatocellular carcinoma (HCC), also known as malignant hepatoma, is the most common primary malignancy of the liver and accounts for 80–90% of primary liver tumors. HCC is one of the most common and devastating malignant diseases worldwide, responsible for more than 1 million deaths annually in the world (Parkin *et al.*, *CA Cancer J. Clin.* **1999**, *49*, 33-64; Bruix *et al.*, *Cancer Cell* **2004**, *5*, 215-219).

[0003] The major risk factors for the development of HCC include hepatitis B or C viral infection, and alcoholic liver disease (Rustgi, *Gastroenterol. Clin. North Am.* **1987**, *16*, 545-551; Bosch *et al.*, *Semin. Liver Dis.* **1999**, *19*, 271-285; Bosch *et al.*, *Gastroenterology* **2004**, *127*, S5–S16; Moradpour *et al.*, *Eur. J. Gastro & Hepatol.* **2005**, *17*, 477–483; Koike *et al.*, *J. Gastroenterol. Hepatol.* **2008**, *23*, S87-S91; de Oliveria Andrade, *J. Glob. Infect. Dis.* **2009**, *1*, 33-37). HCC arises most commonly in cirrhotic livers following infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) (Liaw, *Semin. Liver Dis.* **2005**, *25*, 40-47; Koike *Clin. Gastroenterol. Hepatol.* **2005**, *3*, 132-135). HCC is associated with HBV infection in about 50% of cases (Liaw, *Semin. Liver Dis.* **2005**, *25*, 40-47). HCV infection is the cause of 70% of the cases of HCC in Japan (Hasan, *et al.*, *Hepatology*, 1990, 12:589-591; El-Serag *et al.*, *N. Engl. J. Med.* **1999**, *340*, 745-750). The HCC incidence has been increasing in Western countries in recent years due to the spread of hepatitis C virus (HCV) infection (El-Serag, *Hepatology* **2002**, *36*, S74-83; Trevisani *et al.*, *Carcinogenesis* **2008**, *29*, 1299-1305).

[0004] The prognosis for HCC remains poor despite advances in diagnostic technology and treatment. Five-year survival rates for advanced stage disease are only 3% to 5% worldwide. HCC that is diagnosed at an advanced stage or with progression after locoregional therapy has dismal prognosis, owing to the underlying liver disease

and the lack of effective treatment option. The risk of recurrence is approximately 70% at 5 years after resection and prognosis after recurrence is poor. Patients with HCC of Stage B and C have a median survival ranging from 10 to 14 months following appropriate treatments.

[0005] Although various chemotherapy regimens are available, traditionally, chemotherapy is not considered an effective treatment option for HCC. Systemic chemotherapy response rates of 10% can be seen, with response rates up to 20% using intra-arterial chemotherapy. Treatment options for subjects with unresectable HCC are severely limited and there remains a high unmet medical need for effective therapies in this disease.

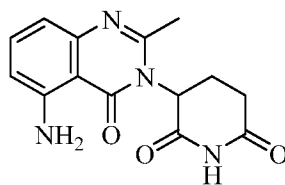
3. SUMMARY

[0006] Provided herein are methods of treating, preventing, and/or managing hepatocellular carcinoma (HCC) comprising administering to a patient in need thereof a therapeutically effective amount of Compound A described below, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, in combination with sorafenib, or a pharmaceutically acceptable salt or solvate thereof. Further provided herein is compound A described below, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, in combination with sorafenib, or a pharmaceutically acceptable salt or solvate thereof for use in the methods of treating, preventing, and/or managing hepatocellular carcinoma (HCC)

[0007] Also provided herein is a pharmaceutical compositions, dosage forms, dosing regimen in connection with the above-described methods.

4. DETAILED DESCRIPTION

[0008] Provided herein are methods of treating, preventing, or managing hepatocellular carcinoma (HCC) comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of Compound A of following formula, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



in combination with a therapeutically or prophylactically effective amount of sorafenib, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, HCC is unresectable HCC.

[0009] Also provided herein are pharmaceutical compositions, dosage forms, and kits that can be used in connection with methods provided herein.

4.1 Brief Description of Figures

[0010] **Figure 1** is a schematic illustration of overall design for clinical study of combination therapy for hepatocellular carcinoma.

[0011] **Figure 2** is a table summarizing the list of events during clinical study.

[0012] **Figure 3** shows the effects of Compound A concentration on colony formation of JHH4 cell line.

[0013] **Figure 4** shows the enhanced inhibition effects of combination of Compound A with sorafenib on colony formation of JHH4 cell line.

[0014] **Figure 5** shows the enhanced inhibition effects of combination of sorafenib with Compound A on colony formation of JHH4 cell line.

[0015] **Figure 6** shows the effects of combination of Compound A with sorafenib on IL-2 secretion in 72 hour anti-CD3-stimulated CD3⁺ T-cell assay.

[0016] **Figure 7A** shows the enhanced effects of combination of Compound A with sorafenib or Compound A with DC-101 on tumor volume.

[0017] **Figures 7B and 7C** show enhancement of tumor cell apoptosis and vascular normalization by the combination treatment, while tumor cell proliferation is significantly decreased.

[0018] **Figure 7D** shows enhanced effects of combination of Compound A with sorafenib on animal survival.

4.2 Definitions

[0019] As used herein, unless otherwise specified, the term “treat,” “treating,” or “treatment” refers to alleviating or abrogating a disease, *e.g.*, hepatocellular carcinoma, or one or more of the symptoms associated with the disease; or alleviating or eradicating the cause(s) of the disease itself.

[0020] As used herein, unless otherwise specified, the term “preventing” refers to the treatment with or administration of a compound provided herein, with or without other additional active compound, prior to the onset of symptoms, particularly to patients at risk of cancer and/or other disorders described herein. The term “prevention” includes the inhibition or reduction of a symptom of the particular disease. Patients with familial history of a disease in particular are candidates for preventive regimens in certain embodiments. In addition, patients who have a history of recurring symptoms are also potential candidates for the prevention. In this regard, the term “prevention” may be interchangeably used with the term “prophylactic treatment.”

[0021] As used herein, and unless otherwise specified, the terms “manage,” “managing” and “management” refer to preventing or slowing the progression, spread or worsening of a disease or disorder, or of one or more symptoms thereof. In certain cases, the beneficial effects that a subject derives from a prophylactic or therapeutic agent do not result in a cure of the disease or disorder.

[0022] As used herein, unless otherwise specified, the term “therapeutically effective amount” of a compound refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of a disease, *e.g.*, hepatocellular carcinoma, being treated. The term also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician. Furthermore, a therapeutically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment or management of a disease, *e.g.*,

hepatocellular carcinoma. The term encompasses an amount that improves overall therapy, reduces, or avoids symptoms or causes of a disease, *e.g.*, hepatocellular carcinoma, or enhances the therapeutic efficacy of another therapeutic agent.

[0023] As used herein, and unless otherwise specified, a “prophylactically effective amount” of a compound is an amount sufficient to inhibit or reduce a symptom of a disease or to prevent recurrence of a disease. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the inhibition or reduction of a symptom of a disease or recurrence of a disease. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0024] As used herein, and unless otherwise specified, the term “pharmaceutically acceptable salt” refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include inorganic and organic acids such as, but not limited to, acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, gluconic, glutamic, glucuronic, galacturonic, glycidic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, propionic, phosphoric, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, p-toluenesulfonic and the like. In one embodiment, suitable are hydrochloric, hydrobromic, phosphoric, and sulfuric acids.

[0025] As used herein, and unless otherwise specified, the term “solvate” means a compound that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

[0026] As used herein, and unless otherwise specified, the term “stereoisomer” encompasses all enantiomerically/stereomerically pure and enantiomerically/stereomerically enriched compounds provided herein.

[0027] As used herein and unless otherwise indicated, the term “stereomerically pure” means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a

stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound, greater than about 98% by weight of one stereoisomer of the compound and less than about 2% by weight of the other stereoisomers of the compound or greater than about 99% by weight of one stereoisomer of the compound and less than about 1% by weight of the other stereoisomers of the compound.

[0028] As used herein and unless otherwise indicated, the term “stereomerically enriched” means a composition that comprises greater than about 55% by weight of one stereoisomer of a compound, greater than about 60% by weight of one stereoisomer of a compound, greater than about 70% by weight, or greater than about 80% by weight of one stereoisomer of a compound.

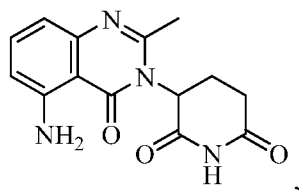
[0029] As used herein, and unless otherwise indicated, the term “enantiomerically pure” means a stereomerically pure composition of a compound having one chiral center. Similarly, the term “enantiomerically enriched” means a stereomerically enriched composition of a compound having one chiral center.

[0030] As used herein, unless otherwise specified, the term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term “about” or “approximately” means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

4.3 Compounds

4.3.1 Compound A

[0031] In some embodiments, the compound suitable for use in the methods provided herein is 3-(5-amino-2-methyl-4-oxo-4*H*-quinazolin-3-yl)-piperidine-2,6-dione (Compound A) having the structure of the following formula:



or an enantiomer or a mixture of enantiomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

[0032] Compound A can be prepared according to the methods described in the Examples provided herein or as described in U.S. Pat. No. 7,635,700, the disclosure of which is incorporated herein by reference in its entirety. The compound can be also synthesized according to other methods apparent to those of skill in the art based upon the teaching herein.

[0033] Compound A markedly inhibits TNF- α , IL-1 β , and other inflammatory cytokines in LPS-stimulated hPBMC and human whole blood. TNF- α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation. TNF- α is responsible for a diverse range of signaling events within cells. TNF- α may play a pathological role in cancer. Without being limited by theory, one of the biological effects exerted by Compound A is the reduction of synthesis of TNF- α . Compound A enhances the degradation of TNF- α mRNA. Compound A also potently inhibits IL-1 β , IL-2, upregulates interferon, and stimulates IL-10 under these conditions.

[0034] Further, without being limited by theory, Compound A is a potent co-stimulator of T cells and increase cell proliferation in a dose dependent manner under appropriate conditions.

[0035] In certain embodiments, without being limited by theory, the biological effects exerted by Compound A include, but not limited to, anti-angiogenic and immune modulating effects.

[0036] In certain embodiments, Compound A is a solid. In certain embodiments, Compound A is hydrated. In certain embodiments, Compound A is solvated. In certain embodiments, Compound A is anhydrous. In certain embodiments, Compound A is nonhygroscopic.

[0037] In certain embodiments, Compound A is amorphous. In certain embodiments, Compound A is crystalline. In certain embodiments, Compound A is in a crystalline form described in U.S. Publication No. 2012/0232100-A1, which is incorporated herein by reference in its entirety.

[0038] The solid forms of Compound A can be prepared according to the methods described in the disclosure of U.S. Publication No. 2012/0232100-A1. The solid forms can be also prepared according to other methods apparent to those of skill in the art.

[0039] In certain embodiments, Compound A is a hydrochloride salt of 3-(5-amino-2-methyl-4-oxo-4*H*-quinazolin-3-yl)-piperidine-2,6-dione, or an enantiomer or a mixture of enantiomers thereof; or a pharmaceutically acceptable solvate, hydrate, co-crystal, clathrate, or polymorph thereof. In certain embodiments, the hydrochloride salt is a solid. In certain embodiments, the hydrochloride salt is anhydrous. In certain embodiments, the hydrochloride salt is nonhygroscopic. In certain embodiments, the hydrochloride salt is amorphous. In certain embodiments, the hydrochloride salt is crystalline. In certain embodiments, the hydrochloride salt is in crystalline Form A.

[0040] The hydrochloride salt of Compound A and solid forms thereof can be prepared according to the methods described in the disclosure of U.S. Publication No. 2012/0232100-A1. The hydrochloride salt the solid forms thereof can be also prepared according to other methods apparent to those of skill in the art.

[0041] Compound A provided herein contains one chiral center, and can exist as a mixture of enantiomers, *e.g.*, a racemic mixture. This disclosure encompasses the use of stereomerically pure forms of such a compound, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers

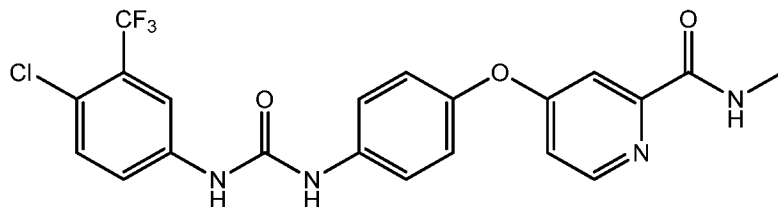
of Compound A provided herein may be used in methods and compositions disclosed herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.,* Jacques, J., *et al., Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al., Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0042] In some embodiment, Compound A can contain unnatural proportions of atomic isotopes at one or more of the atoms. For example, the compound may be radiolabeled with radioactive isotopes, such as for example tritium (3H), iodine-125 (125I), sulfur 35 (35S), or carbon-14 (14C), or may be isotopically enriched, such as with deuterium (2H), carbon-13 (13C), or nitrogen-15 (15N). As used herein, an “isotopologue” is an isotopically enriched compound. The term “isotopically enriched” refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. “Isotopically enriched” may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term “isotopic composition” refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically enriched compounds are useful as therapeutic agents, research reagents, *e.g.*, binding assay reagents, and diagnostic agents, *e.g.*, in vivo imaging agents. All isotopic variations of Compound A, whether radioactive or not, are intended to be encompassed within the scope of the embodiments provided herein. In some embodiments, provided herein are isotopologues of Compound A, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched Compound A.

[0043] It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of the structure.

4.3.2 Sorafenib

[0044] In some embodiments, a compound that can be used in connection with methods provided herein is sorafenib, or a pharmaceutically acceptable salt or solvate thereof. Sorafenib is chemically known as 4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)-N-methylpicolinamide, and has the following structure:



[0045] Sorafenib is commercially available under the trade name Nexavar®. The compound can also be synthesized using the synthetic methods substantially similar to those described in U.S. Patent No. 7,235,576, the entirety of which is incorporated herein by reference.

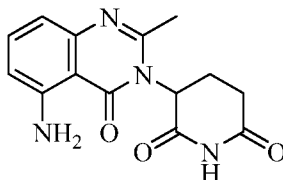
[0046] Without being limited by a particular theory, Sorafenib is a multikinase inhibitor that blocks tumor cell proliferation by targeting the Raf/mitogen-activated protein kinase/extracellular signal regulated kinase (Raf/MEK/ERK) signaling pathway and exerts an antiangiogenic effect by targeting the tyrosine kinases (TKs) VEGF receptor 2 (VEGFR-2), VEGFR-3, and platelet-derived growth factor receptor b (PDGFR-b) (Wilhelm, 2004). In preclinical models, evidence of dose-dependent activity against a wide range of tumor types, including HCC, was observed. Further without being limited by a particular theory, Sorafenib exhibited growth-inhibitory effects, induction of apoptosis, and down-regulation of the antiapoptotic protein Mcl-1 through a Raf/MEK/ERK-independent mechanism. Sorafenib also acts as an immunomodulator. It was reported sub-pharmacological concentrations of sorafenib activates T cells from HCC patients as measured by cytokine IL-2 production, increased proliferation and upregulation of CD25 cell surface expression while blocking Treg function. In addition, sorafenib triggers pro-inflammatory activity of tumor associated macrophages and subsequently induces antitumor natural killer (NK) cell responses in a cytokine-dependent manner.

[0047] In certain embodiments, the compound is a pharmaceutically acceptable salt of sorafenib. In some embodiment, the compound is a tosylate salt of sorafenib.

[0048] In some embodiments, provided herein are isotopologues of sorafenib, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched sorafenib.

4.4 Methods of treatment, prevention and/or management

[0049] Provided herein are methods of treating, preventing, or managing hepatocellular carcinoma (HCC) comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of Compound A of following formula, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



in combination with a therapeutically or prophylactically effective amount of sorafenib, or a pharmaceutically acceptable salt or solvate thereof.

[0050] In one embodiment, HCC is unresectable HCC.

[0051] In one embodiment, the patient has received one or more prior systemic therapies for HCC. In another embodiment, the patient has received no prior systemic therapy for HCC.

[0052] In certain embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form. In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is orally administered.

[0053] Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered at an amount of about 0.01 mg to about 100 mg per day, about 0.1 mg to about 75 mg per day, about 0.5 mg to about 50 mg per day, about 0.1 mg to about 25 mg per day, about 1 mg to about 25 mg per day, about 0.5 mg to about 10 mg

per day, about 1 mg to about 10 mg per day, about 0.5 mg to about 5 mg per day, about 1 mg to about 5 mg per day, about 1 mg to about 3 mg per day, or about 2 mg to about 5 mg per day.

[0054] In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered at an amount of about 1 mg to about 5 mg per day. In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered at an amount of about 1 mg per day. In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered at an amount of about 2 mg per day. In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered at an amount of about 3 mg per day. In one embodiment, Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 4 mg per day.

[0055] In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered once daily for 28 consecutive days in a 28 days cycle. In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered once daily for 5 consecutive days followed by 2 days of no administration in a 28 days cycle. In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered once daily for 21 consecutive days followed by 7 days of no administration in a 28 days cycle.

[0056] In certain embodiment, sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form. In one embodiment, sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is orally administered.

[0057] In one embodiment, sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 50 mg per day, about 100 mg per day, about 150 mg per day, about 200 mg per day, about 250 mg per day, about 300 mg

per day, about 350 mg per day, about 400 mg per day, about 450 mg per day, about 500 mg per day, about 550 mg per day, about 600 mg per day, about 650 mg per day, about 700 mg per day, about 750 mg per day, or about 800 mg per day.

[0058] In one embodiment, sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 400 mg per day.

[0059] In one embodiment, sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days in a 28 days cycle.

[0060] In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is orally administered at an amount of about 1 mg to about 5 mg per day, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is orally administered at an amount of about 400 mg per day.

[0061] In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered once daily for 28 consecutive days, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

[0062] In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered once daily for 5 consecutive days followed by 2 days of no administration in a 28 days cycle, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

[0063] In one embodiment, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered once daily for 21 consecutive days followed by 7 days of no administration in a 28 days cycle, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

[0064] Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, may be administered using the same route or via different routes. Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and sorafenib, or a

pharmaceutically acceptable salt or solvate thereof, may be administered simultaneously or sequentially. Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, may be administered in one pharmaceutical composition or in separate compositions.

[0065] In certain embodiments, compounds provided herein can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), three times daily (TID), and four times daily (QID). In addition, the administration can be continuous (*i.e.*, daily for consecutive days or every day), intermittent, *e.g.*, in cycles (*i.e.*, including days, weeks, or months of rest without drug).

[0066] In certain embodiments, Compound A, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, may be administered in combination with one or more additional active agents.

[0067] Examples of such additional agents include, but are not limited to: Abraxane®; ace-11; acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amrubicin; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib (COX-2 inhibitor); chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; herceptin; hydroxyurea; idarubicin

hydrochloride; ifosfamide; ilmofofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; lapatinib; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprime; romidepsin; safinol; safinol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; stem cell treatments such as PDA-001; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; tricycline phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulazole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

[0068] Other examples include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives;

beta-alethine; betaclamycin B; betulinic acid; b-FGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorlins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatan; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; episteride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imatinib (*e.g.*, GLEEVEC[®]), imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocil; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase;

metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; oblimersen (GENASENSE[®]); O⁶-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin

receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

4.5 Pharmaceutical compositions

[0069] In one embodiment, provided herein are pharmaceutical compositions and dosage forms, which comprise: (1) Compound A, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; (2) and sorafenib, or a pharmaceutically acceptable salt or solvate thereof; or (3) a mixture thereof. In another embodiment, pharmaceutical compositions and dosage forms further comprise one or more excipients.

[0070] In certain embodiments, pharmaceutical compositions and dosage forms provided herein also comprise one or more additional active ingredients. Examples of optional second, or additional, active ingredients are disclosed herein elsewhere.

[0071] Single unit dosage forms provided herein are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (*e.g.*, eye drops or other ophthalmic preparations), transdermal, or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

[0072] The composition, shape, and type of dosage forms provided herein may vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients than an oral dosage form used to treat the same disease. *See, e.g.,* Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

[0073] Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form provided herein depends on a variety of factors, including, but not limited to, the route of administration. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, encompassed herein are pharmaceutical compositions and dosage forms that contain little, if any, lactose. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

[0074] Lactose-free compositions provided herein can comprise excipients that are listed, for example, in the U.S. Pharmacopeia (USP) 25 NF20 (2002). In certain embodiments, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. In certain embodiments, lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

[0075] Further encompassed herein are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.,* Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some

compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[0076] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[0077] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, in certain embodiments, provided herein are anhydrous compositions packaged using materials to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[0078] Encompassed herein are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as “stabilizers,” include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[0079] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients.

[0080] In certain embodiments, the dosage forms provided herein comprise Compound A, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in an amount ranging from about 0.10 to about 1000 mg, from about 0.10 to about 500 mg, from about 0.10 to about 200 mg, from about 0.10 to about 150 mg, from about 0.10 to about 100 mg, from about 0.10 to about 50 mg, from about 0.5 to about 10 mg, or from about 1 to about 5 mg. In certain embodiments, the dosage forms provided herein comprise Compound A, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph

thereof, in an amount of about 0.1, about 1, about 2, about 3, about 4, about 5, about 7.5, about 10, about 12.5, about 15, about 17.5, about 20, about 25, about 50, about 100, about 150, or about 200 mg.

[0081] In certain embodiments, the dosage forms provided herein comprise sorafenib, or a pharmaceutically acceptable salt or solvate thereof, in an amount ranging from about 1 to about 1000 mg, from about 10 to about 800 mg, from about 50 to about 600 mg, from about 100 to about 700 mg, from about 100 to about 500 mg, from about 300 to about 500 mg, from about 200 to about 400 mg, or from about 350 to about 450 mg. In certain embodiments, the dosage forms provided herein comprise Compound A, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in an amount of about 50, about 100, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, or about 1000 mg.

4.5.1 Oral dosage forms

[0082] In certain embodiments, pharmaceutical compositions provided herein that are suitable for oral administration are formulated as discrete dosage forms, examples of which include, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients and may be prepared by some known methods of pharmacy. *See generally*, Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

[0083] In certain embodiments, the oral dosage forms provided herein are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0084] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms may be prepared by some known methods of pharmacy. In certain embodiments, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[0085] In certain embodiments, a tablet is prepared by compression or molding. In certain embodiments, compressed tablets are prepared by compressing in a suitable machine the active ingredients in a free-flowing form, *e.g.*, powder or granules, optionally mixed with an excipient. In certain embodiments, molded tablets are made by molding in a suitable machine a mixture of a powdered compound moistened with an inert liquid diluent.

[0086] Examples of excipients that can be used in oral dosage forms provided herein include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[0087] Suitable forms of microcrystalline cellulose include, but are not limited to, AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose (*e.g.*, AVICEL RC-581). Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

[0088] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms provided herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates,

kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. In certain embodiments, the binder or filler in pharmaceutical compositions provided herein is present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[0089] Disintegrants are used in the compositions provided herein to provide tablets the ability to disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms provided herein. The amount of disintegrant used varies based upon the type of formulation. In certain embodiments, the pharmaceutical compositions provided herein comprise from about 0.5 to about 15 weight percent or from about 1 to about 5 weight percent of disintegrant.

[0090] Disintegrants that are suitable for use in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums, and mixtures thereof.

[0091] Lubricants that are suitable for use in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, but are not limited to, a syloid silica gel (AEROSIL200, W.R. Grace Co., Baltimore, MD), a coagulated aerosol of synthetic silica (Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide, Cabot Co. of Boston, MA), and mixtures thereof. In certain embodiments, if used at all, lubricants are used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

4.5.2 Delayed release dosage form

[0092] In certain embodiments, the active ingredients provided herein are administered by controlled release means or by delivery devices. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference in its entirety. In certain embodiments, such dosage forms are be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Encompassed herein are single unit dosage forms suitable for oral administration, including, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[0093] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[0094] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

4.5.3 Parenteral dosage forms

[0095] Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[0096] Some suitable vehicles that can be used to provide parenteral dosage forms provided herein include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[0097] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms provided herein. For example, cyclodextrin and its derivatives can be used to increase the solubility of a compound provided herein. *See, e.g.*, U.S. Patent No. 5,134,127, the disclosure of which is incorporated herein by reference in its entirety.

4.5.4 Topical and mucosal dosage forms

[0098] Topical and mucosal dosage forms provided herein include, but are not limited to, sprays, aerosols, solutions, emulsions, suspensions, eye drops or other ophthalmic preparations, or other forms known to one of skill in the art. *See, e.g.*, Remington's Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels.

[0099] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed herein depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, in certain embodiments, the excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Additional examples of such ingredients can be found, *e.g.*, in Remington's Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

[00100] The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

4.5.5 Kits

[00101] In certain embodiments, compounds provided herein are not administered to a patient at the same time or by the same route of administration. Therefore, encompassed herein are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

[00102] In certain embodiments, a kit provided herein comprises a dosage form of a compound provided herein. In certain embodiments, the kit provided herein further comprises additional active ingredients. Examples of the additional active ingredients include, but are not limited to, those disclosed herein elsewhere.

[00103] In certain embodiments, the kit provided herein further comprises a device that is used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

[00104] In certain embodiments, the kit provided herein further comprises cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5. EXAMPLES

[00105] The examples below are carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. The examples are intended to be merely illustrative.

5.1 Clinical studies – general design

5.1.1 Study design

[00106] A Phase 1b dose escalation and expansion clinical study of Compound A in combination with sorafenib in subjects with unresectable HCC who have received no prior systemic therapy for HCC is conducted. The dose escalation part of the study initially explores 3 dose levels of Compound A in combination with a fixed dose of sorafenib using a rolling-six dose escalation design, followed by an expansion part.

[00107] Compound A is initially administered orally continuously once daily (QD) on Days 1 to 28 of each 28-day cycle. The investigated daily doses of Compound A 1.0 mg, 2.0 mg, and 3.0 mg QD. Once the maximum tolerated dose (MTD) for daily dosing

of Compound A in combination with sorafenib is defined, further dose escalation on an intermittent schedule of Compound A [either on 5 consequent days out of a week (5 days on/2 days off weekly) or on 21 consequent days out of a 28-day cycle (21 days on/7 days off every 28 days)] starting at a comparable cycle dose intensity, a 4.0 mg Compound A dose QD may be explored at the discretion of the Safety review Committee (SRC). The dose of sorafenib investigated in combination with the Compound A dose-levels is fixed at 400 mg BID on Days 1 to 28 of each 28-day cycle.

[00108] A rolling-six dose escalation design is used to identify the initial toxicity of each combination. Up to six subjects are concurrently enrolled onto a dose level. Decisions as to which dose level to enroll a new subject are based on the number of subjects enrolled and evaluable, the number of subjects experiencing dose-limiting toxicities (DLTs) and the number of subjects enrolled but who are not yet evaluable for toxicity in current cohort at the time of new subject entry. Non-evaluable subjects without experiencing a DLT are replaced according to rolling-six rules.

[00109] All subjects who receive at least one dose of any study drug will be evaluable for safety. In the dose escalation part of the study, a subject evaluable for DLT is defined as one who: (1) Received at least 75% of the planned doses of Compound A during Cycle 1 without experiencing a DLT, and (2) Received at least 50% of the planned dose of sorafenib during Cycle 1 without experiencing a DLT, or experienced a DLT after receiving at least one dose of either study drug.

[00110] A dose is considered the normalized total dose (NTD) when 2 or more out of up to 6 evaluable subjects in a cohort experience a DLT in Cycle 1. The MTD is defined as the last dose level(s) below the NTD with 0 or 1 out of 6 evaluable subjects experiencing a DLT during Cycle 1. If 2 or more DLTs out of up to 6 evaluable subjects are observed at any dose level of the combination given continuously, an intermittent dose of Compound A or intermittent schedule (*e.g.*, 5 days on/2 days off weekly or 21 days on /7 days off every 28 days) may be explored at the discretion of the SRC. An intermediate dose of study drugs (one between the NTD and the last dose level before the NTD) may be evaluated to more precisely determine the MTD of the combination.

[00111] During dose escalation, the decision to either evaluate a higher dose level, an intermittent dose schedule, or declare an NTD, MTD, or recommended for Phase II dose

(RP2D) is determined by the SRC, based on their review of all available clinical data, PK, PD and laboratory safety data for a given dose cohort.

[00112] If zero DLTs occur in at least 3 evaluable subjects in a given cohort, the dose may be escalated in the next cohort. If one DLT occurs in a given cohort, the cohort must be expanded to enroll a total of 6 evaluable subjects. Once expanded to 6, if 1 DLT occurs out of 6 evaluable subjects the dose may be escalated. If 2 or more subjects out of up to 6 evaluable subjects in a given cohort experience a DLT at any time during enrollment, the NTD will have been met and the last dose level(s) below the NTD with 0 or 1 out of up to 6 evaluable subjects experiencing a DLT during Cycle 1 will be declared the MTD. Once the MTD for daily dosing of Compound A is defined, further dose escalation on an intermittent schedule (either 5 days on/2 days off weekly or 21 days on/7 days off every 28 days), starting at a comparable cycle dose intensity, a 4mg Compound A dose QD, may be explored at the discretion of the SRC.

[00113] Non-evaluable subjects without experiencing a DLT will be replaced based on rolling-six rules. Additional subjects within any dose cohort may be enrolled at the discretion of the SRC.

[00114] Following completion of dose escalation, up to 30 additional subjects are enrolled per dose expansion cohort. Expansion may occur at the MTD established in the dose escalation part, and or at an alternative tolerable combination dose level (RP2D) and schedule, based on review of study data by the SRC. Thus, one or more regimens may be selected for cohort expansion. The SRC continues to review safety data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate. A schematic illustration of overall study design is shown in **Figure 1**.

5.1.2 Study Population

[00115] Adult subjects with confirmed pathologic diagnosis of unresectable HCC, according to the American Association for the Study of Liver Diseases (AASLD) Guidelines, who have received no prior systemic therapy for HCC are potentially eligible. Subjects at screening must have a Child-Pugh score less than 7 (*i.e.*, class A or better) and have an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1.

[00116] The total number of subjects to be enrolled during dose escalation is approximately 20 to 40 depending on number of cohorts and their sizes. Up to 30 additional subjects are evaluated for safety, PK, PD, and preliminary antitumor effects during the dose expansion cohort.

5.1.3 Length of Study

[00117] The screening period lasts approximately 28 days. Subjects may remain on treatment until clinically significant disease progression, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death. If treatment is discontinued for reason other than disease progression, subjects will continue to be followed until progression. Subjects continue to be followed for survival status until death or until the last subject enrolled completes 24 months of study therapy.

[00118] Enrollment is expected to take approximately 27 months to complete (18 months for dose escalation, and 6-9 months for expansion). Completion of active treatment and post-treatment follow-up is expected to take an additional 12 to 15 months. The entire study is expected to last approximately 4 years.

5.1.4 Study treatments

[00119] All cohorts will receive different dose-levels of Compound A, as shown in the Table below, and a standard dose of sorafenib 400 mg BID.

Dose Level	CC-122 Dose (mg)	CC-122 Schedule	Sorafenib Dose (mg)	Sorafenib Schedule
1	1.0	daily	400	twice daily
2	2.0	daily	400	twice daily
3	3.0	daily	400	twice daily
4	4.0	intermittent	400	twice daily
5	5.0	intermittent	400	twice daily

[00120] Dosing starts at Dose Level 1. Each dose level must be cleared by SRC based on all available clinical, safety, PK, PD and laboratory data before initiating the next higher dose level.

[00121] If 2 or more DLTs out of up to 6 evaluable subjects are observed at any dose level of the combination given continuously, an intermittent schedule of Compound A (5 days on/2 days off weekly or 21 days on /7 days off every 28 days) may be explored at the discretion of the SRC. An intermediate dose of Compound A (one between the NTD and the last dose level before the NTD, *e.g.*, 1.5 or 2.5 mg daily) as well as an intermittent dosing schedule may be evaluated to more precisely accurately determine the MTD of the combination.

[00122] During dose escalation, the decision to either evaluate a higher dose level, an intermittent dose schedule, or declare an NTD, MTD, or RP2D is determined by the SRC, based on their review of all available clinical PK, PD and laboratory safety data for a given dose cohort.

[00123] Intra-subject dose escalation of study drugs is not permitted during Cycle 1 but may be permitted in later cycles if approved by the SRC.

[00124] Dose reduction and temporary interruption of one or both drugs due to toxicity during Cycle 1 will not by default constitute a DLT

[00125] Study treatment may be discontinued if there is evidence of clinically significant disease progression, unacceptable toxicity or subject/physician decision to withdraw. Subjects may continue to receive study drugs beyond disease progression at the discretion of the Investigator.

[00126] The estimated total number of subjects to be enrolled during dose escalation is approximately 20 to 40, depending on cohort size. Approximately 30 additional subjects are evaluated for safety, PK, PD, and preliminary anti-tumor effects in the expansion cohort.

5.1.5 End of trial

[00127] The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan (SAP), whichever is the

later date. A table summarizing the events during the studies is provided herein as Figure 2.

5.2 Efficacy assessment

[00128] Tumor assessments are performed at screening (up to 28 days before the start of study drugs), every 2 cycles (8 weeks $\pm$ 7 days) through cycle 6, thereafter every 3 cycles (12 weeks $\pm$ 7 days). Tumor assessments are also performed at any time, if clinically indicated. Tumor assessments continue at the defined schedule until progression, beyond the end of treatment if necessary.

[00129] Response is assessed using RECIST 1.1 (investigator assessment) and irRC, as an exploratory assessment. Other exploratory efficacy variables, such as ECOG-PS and AFP reduction, are summarized as well. New anticancer therapies are also collected at the same schedule. New anticancer therapy includes (but is not limited to) any systemic or locoregional medication, surgery, radiation, or any other therapy intended to treat the subject's cancer.

5.2.1 Assessment based on RECIST 1.1

[00130] Response assessments include computed tomography (CT) scan or MRI. The regions to be imaged are the chest and abdomen/pelvis, as well as any other sites required for tumor imaging. The same mode of imaging for lesion evaluation at screening must be used consistently throughout the study.

[00131] The CT imaging includes contrast unless medically contraindicated. Conventional CT is performed with contiguous cuts of 5 mm or less in slice thickness. Spiral CT is performed by use of a 5 mm contiguous reconstruction algorithm.

[00132] Mesurable diseases include tumor lesions and malignant lymph nodes. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray.

[00133] To be considered pathologically enlarged and measurable, a malignant lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

[00134] All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

[00135] When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs are identified as target lesions and will be recorded and measured at baseline. Target lesions are selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition are those that lend themselves to reproducible repeated measurements. Pathological nodes must meet the measurable criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) are considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and are not recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

[00136] Target lesions are assessed as follows:

- (1) Complete Response (CR) - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm;
- (2) Partial Response (PR) - At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters;
- (3) Progressive Disease (PD) - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In

addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression);

- (4) Stable Disease (SD) - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

[00137] Non-target lesions will be assessed as follows:

- (1) Complete Response (CR) - Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis);
- (2) Non-CR/Non-PD - Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits;
- (3) Progressive Disease (PD) - Unequivocal progression of existing non-target lesions (the appearance of one or more new lesions is also considered progression).

[00138] After baseline, a value is provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

[00139] All subjects with evidence of objective tumor response (CR or PR) should have the response confirmed with repeat assessments at the next scheduled scan, but after no less than 4 weeks. Response assessments must have occurred ≥ 6 weeks from Cycle 1 Day 1 to be considered as stable disease (SD) for a best response.

5.2.2 Other assessments

[00140] Additional scans, including brain scans, MRI of the head, or nuclear medicine bone scan are performed if clinically indicated (*e.g.*, symptoms of brain metastasis) at the discretion of the investigator.

5.2.3 Assessment based on immune-related response criteria (irRC)

[00141] For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions ($\geq 5 \times 5$ mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

[00142] Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (*i.e.*, the SPD of all index lesions at screening). The irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same.

[00143] The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- (1) irCR: complete disappearance of all lesions (whether measurable or not, and no new lesions) - confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
- (2) irPR: decrease in tumor burden $\geq 50\%$ relative to baseline - confirmed by a consecutive assessment at least 4 weeks after first documentation
- (3) irSD: not meeting criteria for irCR or irPR, in absence of irPD

- (4) irPD: increase in tumor burden $\geq 25\%$ relative to nadir (minimum recorded tumor burden) - confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

5.3 Pharmacokinetics assessment

[00144] Plasma samples are collected to assay plasma concentrations of stereoisomers of Compound A and sorafenib (Compound A is indirectly measured from the concentrations of the stereoisomers).

5.3.1 Dose escalation phase

[00145] Intensive PK sampling is performed in a minimum of 3 subjects at the first dose level at the following time points:

(1) Cycle 1, Day 1

0 hour (within 60 minutes prior to dosing), 1.5, and 5 hours post-dose

(2) Cycle 1, Day 15

0 hour (within 60 minutes prior to dosing) and 0.5, 0.75, 1, 1.5, 3, 5, 8, 24 hours post-dose

[00146] Sparse PK sampling is performed in the remaining patients at all other dose levels:

(1) Cycle 1, Day 15

0 hour (within 60 minutes prior to dosing) and 1.5, and 5 hours post-dose

[00147] A PK sample is collected at or near the time of biopsy in all subjects. In the escalation part, the biopsy is collected on Cycle 2, Day 1 – 15 at 3 to 6 (± 1) hours post-dose.

5.3.2 Dose expansion phase

[00148] Intensive PK sampling is performed in a minimum of 3 subjects at the following time points:

(1) Cycle 1, Day 1

0 hour (within 60 minutes prior to dosing), 1.5, and 5 hours post-dose

(2) Cycle 1, Day 15

0 hour (within 60 minutes prior to dosing) and 0.5, 0.75, 1, 1.5, 3, 5, 8, 24

hours post-dose

- (3) If 5 days on/ 2 days off regimen, samples will be collected on Cycle 1, Day 10, 11, or 12 at the following time points:
0 hour (within 60 minutes prior to dosing) and 0.5, 0.75, 1, 1.5, 3, 5, 8, 24 hours post-dose

[00149] Sparse PK sampling is performed in the remaining subjects at the following time points:

- (1) Cycle 1, Day 1
0 hour (within 60 minutes prior to dosing), 1.5, and 5 hours post-dose
- (2) Cycle 1, Day 15
0 hour (within 60 minutes prior dosing) and 1.5, 3 and 5 hours post-dose
- (3) If 5 days on/ 2 days off regimen, samples will be collected on Cycle 1, Day 10, 11, or 12 at the following time points:
0 hour (within 60 minutes prior to dosing) and 1.5, 3, and 5 hours post-dose

[00150] Should dose administration of Compound A be interrupted for at least 72 hours before the Day 15 sampling, serial PK samples are not collected until ≥ 3 days of Compound A continuous treatment has been re-established.

5.4 12-Lead electrocardiograms

[00151] Triplicate 12-lead ECGs are recorded at the visits listed in **Figure 2** and assessed centrally. The 12-lead ECGs (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR-interval, QRS complex, QT interval, and QTc interval) are performed after the subject has been in the supine position for at least 5 minutes.

[00152] Triplicate ECGs (3 recordings within 2 ± 2 minute intervals) will be performed at the following time points:

Screening

Cycle 1, Day 1 - Predose (0 hr) (within 90 minutes prior to dosing)

Cycle 1, Day 15 – Predose (0 hr) (within 90 minutes prior to dosing), 1.5 (± 15 minutes) and 3 hours (± 15 minutes) postdose

End of trial.

[00153] Screening and predose ECGs collected on C1D1 and C1D15 are collected at or near the same time.

5.5 Biomarker assessment

5.5.1 Archival tumor tissue

[00154] Collection is mandatory during dose escalation and dose expansion. The sample is retrieved and sent after subject eligibility is confirmed (Screening), preferably before the end of Cycle 1. If archival tumor tissue is not available or is insufficient for submission, an on screening biopsy is required.

5.5.2 Fresh tumor tissue

[00155] Collection is optional in the dose escalation phase but mandatory for the dose expansion phase. Paired tumor biopsies (formalin fixed paraffin embedded and fresh frozen) are collected at the following time points:

Screening

During dose escalation: After at least 4 weeks of dosing. Sample may be collected on Day 1-15 of Cycle 2. The sample must be collected at 3 to 6 (± 1) hours post-dose.

During expansion: After at least 2 weeks of dosing in Cycle 1. Sample may be collected on Day 15-28 of Cycle 1. The sample must be collected at 3 to 6 (± 1) hours post-dose.

[00156] For subjects on intermittent schedule(s), the tumor biopsy must be collected on a day that Compound A is administered per the intermittent schedule (preferably after at least 3 continuous days of administration).

5.5.3 Blood collection for biomarker assessment

[00157] Samples are collected and analyzed for T cell activation assay and aiolos expression assay in lymphocytes at the following time points:

(1) Cycle 1 Day 1

0 hour (predose), 1.5 hours and 5 hours post-dose

(2) Cycle 1 Day 15

(i) 0 hour (predose), 1.5 hours and 5 hours post-dose

- (ii) For 5 days on/2 days off regimen, the sample should be obtained at
Cycle 1 Day 10, 11 or 12
- (3) Concurrent with the on treatment biopsy procedure
- (4) Subsequent Cycles on Day 1

5.5.4 Pharmacogenomic blood collection

[00158] Sample for pharmacogenomic analysis are collected during screening.

[00159] From the foregoing, it will be appreciated that, although specific embodiments have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of what is provided herein. Accordingly, the following examples are intended to illustrate but not limit the present invention. All of the references referred to above are incorporated herein by reference in their entireties.

5.6 Effects of Compound A on Colony Formation of JHH4 HCC Cell Line *in vitro*

[00160] Cells were originally plated at a dilution of 5×10^4 cells per well and allowed to grow in the presence of DMSO or Compound A at concentrations between 1-10 μM for 28 days. Quantitation of colony numbers and total colony area shows a statistically significant decrease of both measurements for the JHH4 cells treated with Compound A compared to DMSO (Fig. 3).

5.6.1 Effects of Combination

[00161] Cells were originally plated at a dilution of 7.5×10^3 cells per well and allowed to grow in the presence of either DMSO, 1 μM Compound A, sorafenib at concentrations between 0.2-5 μM or 1 μM Compound A in combination with sorafenib at concentrations between 0.2-5 μM for 16-19 days. Quantitation of colony numbers, total colony area, and total colony volume shows an improvement in growth inhibition for the combination of Compound A with sorafenib as compared to either agent alone (Fig. 4). 1 μM Compound A decreased colony number, total colony area, and total colony volume by 37%, 55%, and 56%, respectively. Titration of sorafenib alone inhibited colony number 15%, 27%, 38%, 67%, and 95% at 0.2, 0.5, 1, 2, and 5 μM

doses, respectively. The combination of 1 μ M Compound A with titrated sorafenib enhanced this inhibition (48%, 52%, 66%, 84%, and 95% at 0.2, 0.5, 1, 2, and 5 μ M). Titration of single agent sorafenib inhibited total colony area, 26%, 48%, 63%, 86%, and 98% at 0.2, 0.5, 1, 2, and 5 μ M. The combination of 1 μ M Compound A with titrated sorafenib enhanced this inhibition (66%, 71%, 85%, 95%, and 98% at 0.2, 0.5, 1, 2, and 5 μ M). Titration of sorafenib as a single agent inhibited total colony volume, 28%, 49%, 65%, 87%, and 98% at 0.2, 0.5, 1, 2, and 5 μ M. The combination of 1 μ M Compound A with titrated sorafenib enhanced this inhibition (67%, 72%, 85%, 95%, 98%).

[00162] Cells were also allowed to grow in the presence of either DMSO, Compound A at concentrations between 1-5 μ M, 1 μ M sorafenib or 1 μ M sorafenib in combination with Compound A at concentrations between 1-5 μ M. Quantitation of colony numbers, total colony area, and total colony volume shows an improvement in growth inhibition for the combination of sorafenib with Compound A as compared to either agent alone (Fig. 5). Compound A treatment significantly decreased colony formation by 62% and 72% at 1 and 5 μ M, respectively and 35% by single agent sorafenib (1 μ M). The combination resulted in decreases of 68% and 78% for 1 and 5 μ M Compound A with sorafenib, respectively. Treatments of 1 and 5 μ M Compound A significantly inhibited total colony area by 73% and 82% , while inhibition of 51% was observed for sorafenib (1 μ M) alone. 80% and 87% decreased colony area was observed for the combination of sorafenib (1 μ M) with 1 and 5 μ M Compound A, respectively. Compound A treatment significantly decreased total colony volume by 73% and 82% at 1 and 5 μ M, respectively and sorafenib (1 μ M) resulted in a 36% decrease compared to DMSO. 79% and 86% decreased colony volume was observed for the combination of sorafenib (1 μ M) with 1 and 5 μ M Compound A, respectively.

5.6.1 72 hour anti-CD3-Stimulated CD3+ T-cell Assay

[00163] Compound A treated purified CD3+ T-cells from healthy donors were stimulated with 3 μ g/ml of anti-CD3 followed by addition of sorafenib. After 72 hours of incubation, supernatants were collected and an ELISA for IL-2 (BD Biosciences) was utilized to examine secreted IL-2.

[00164] Combination of 10 nM Compound A with sorafenib titrated from 0.004 μM to 3.33 μM demonstrated an enhancement of IL-2 secretion. The combination was found to be significantly increased compared to sorafenib treatment alone for 0.3-3.33 μM (Fig. 6).

5.7 Enhancement of Anti-tumor Activity of Sorafenib with Compound A *In Vivo*, Through Immune Modulation

[00165] The orthotopic HCC liver cancer model was developed by injecting about 2×10^5 BNL-1MEA cells (from American Type Culture Collection, ATCC) into the sub-capsular area of the left liver lobe of male BALB/c or SCID mice at age of 6-7 weeks. Mice were randomized to different treatment groups on day 6 after tumor implantation. Sorafenib (Bayer Schering Pharma) was given by gavage or intra-peritoneal injection. In some examples, Compound A was administered in addition to sorafenib. In some examples, Compound A was administered in addition to anti-VEGFR (vascular endothelial growth factor receptor) antibody DC-101.

[00166] In some examples Compound A was combined with sorafenib. In other examples Compound A was combined with anti-VEGFR (vascular endothelial growth factor receptor) antibody DC-101. The results indicated a similar trend of anti-tumor synergy between Compound A/sorafenib combination and Compound A/DC-101 combination (Fig. 7A, 7B and 7C).

[00167] Tumor volumes were measured after 22 days of treatment by using the formula: $\text{volume (mm}^3\text{)} = [\text{width}]^2 \times \text{length} \times 0.5$. Tumor volumes were significantly reduced by a combination treatment, Compound A/sorafenib and Compound A/DC-101, compared with vehicle or single-agent treatment (Fig. 7A).

[00168] Formalin-fixed, paraffin-embedded tumor samples were collected at the end of drug treatment. Slides of 5- μm thick sections were prepared for analysis of tumor apoptosis (TUNEL assay, DeadEnd Fluorometric TUNEL System) and tumor angiogenesis (CD31 immunohistochemical staining). The vascular normalization index (VNI) was calculated using the formula: $\text{VNI} = \text{MVD} \times (\text{Density}_{\alpha\text{-SMA}} / \text{Density}_{\text{CollagenIV}})$. MVD (microvessel density) was determined by IHC staining with CD31 antibody. $\text{Density}_{\alpha\text{-SMA}}$ and $\text{Density}_{\text{CollagenIV}}$ were determined by IHC staining with respective

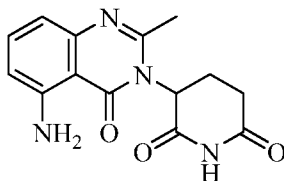
antibodies. Cell apoptosis (TUNEL assay) and vascular normalization were enhanced by the combination treatment, while tumor cell proliferation (Ki-67 staining) significantly decreased (Fig. 7B and 7C).

[00169] Animal survival was calculated by the Kaplan-Meier method and compared by log-rank test. Combination of Compound A and sorafenib, demonstrated significantly enhanced animal survival, compared with vehicle or single-agent treatment (Fig. 7D).

[00170] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference..

WHAT IS CLAIMED IS:

1. A method of treating, preventing, or managing hepatocellular carcinoma (HCC) comprising administering to a patient in need thereof Compound A of following formula, or a pharmaceutically acceptable salt or solvate thereof:



in combination with sorafenib, or a pharmaceutically acceptable salt or solvate thereof.

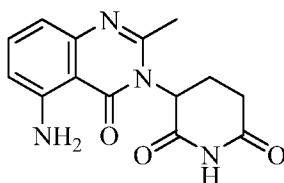
2. The method of claim 1, wherein the HCC is unresectable HCC.
3. The method of claim 1, wherein the patient has received no prior systemic therapy for HCC.
4. The method of claim 1, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is orally administered.
5. The method of claim 4, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 1 mg to about 5 mg per day.
6. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 1 mg per day.
7. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 2 mg per day.
8. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 3 mg per day.

9. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 4 mg per day.
10. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 28 consecutive days in a 28 days cycle.
11. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 5 consecutive days followed by 2 days of no administration in a 28 days cycle.
12. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 21 consecutive days followed by 7 days of no administration in a 28 days cycle.
13. The method of claim 1, wherein sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is orally administered.
14. The method of claim 13, wherein sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 400 mg per day.
15. The method of claim 14, wherein sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days in a 28 days cycle.
16. The method of claim 1, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is orally administered at an amount of about 1 mg to about 5 mg per day, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is orally administered at an amount of about 400 mg per day.
17. The method of claim 16, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 28 consecutive days, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

18. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 5 consecutive days followed by 2 days of no administration in a 28 days cycle, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

19. The method of claim 5, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 21 consecutive days followed by 7 days of no administration in a 28 days cycle, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

20. Compound A of following formula, or a pharmaceutically acceptable salt or solvate thereof:



for use in a method of treating, preventing, or managing hepatocellular carcinoma (HCC) in combination with sorafenib, or a pharmaceutically acceptable salt or solvate thereof.

21. The compound for use according to claim 20, wherein the HCC is unresectable HCC.

22. The compound for use according to claim 20 or 21, wherein the patient has received no prior systemic therapy for HCC.

23. The compound for use according to any of the claims 20-22, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is orally administered.

24. The compound for use according to claim 23, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 1 mg to about 5 mg per day.

25. The compound for use according to claim 24, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 1 mg per day.

26. The compound for use according to claim 24, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 2 mg per day.

27. The compound for use according to claim 24, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 3 mg per day.

28. The compound for use according to claim 24, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 4 mg per day.

29. The compound for use according to any of the claims 19-28, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 28 consecutive days in a 28 days cycle.

30. The compound for use according to any of the claims 19-28, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 5 consecutive days followed by 2 days of no administration in a 28 days cycle.

31. The compound for use according to any of the claims 19-28, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 21 consecutive days followed by 7 days of no administration in a 28 days cycle.

32. The compound for use according to any of the claims 19-31, wherein sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is orally administered.

33. The compound for use according to any of the claims 19-31, wherein sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered at an amount of about 400 mg per day.

34. The compound for use according to any of the claims 19-33, wherein sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days in a 28 days cycle.

35. The compound for use according to any of the claims 19-34, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is orally administered at an amount of about 1 mg to about 5 mg per day, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is orally administered at an amount of about 400 mg per day.

36. The compound for use according to any of the claims 19-35, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 28 consecutive days, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

37. The compound for use according to any of the claims 24-29, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 5 consecutive days followed by 2 days of no administration in a 28 days cycle, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

38. The compound for use according to any of the claims 24-29, wherein Compound A, or a pharmaceutically acceptable salt or solvate thereof, is administered once daily for 21 consecutive days followed by 7 days of no administration in a 28 days cycle, and sorafenib, or a pharmaceutically acceptable salt or solvate thereof, is administered twice daily for 28 consecutive days.

39. The compound for use according to any of the claims 20-38, wherein compound A is in a solid form.

40. The compound for use according to claim 39, wherein compound A is in a hydrated solid form.

41. The compound for use according to claim 39, wherein compound A is in a solvated solid form.

42. The compound for use according to claim 39, wherein compound A is in an anhydrous solid form.

43. The compound for use according to any of the claims 39-42 wherein compound A is in an amorphous solid form.

44. The compound for use according to any of the claims 39-42 wherein compound A is in a crystalline solid form.

45. The compound for use according to claim 44, wherein Compound A is a hydrochloride salt of 3-(5-amino-2-methyl-4-oxo-4*H*-quinazolin-3-yl)-piperidine-2,6-dione.

46. The compound for use according to claim 45, wherein the hydrochloride salt is in crystalline Form A.

47. The compound for use according to any of claims 39-46, wherein sorafenib is administered as a pharmaceutical acceptable salt.

48. The compound for use according to any of claims 39-47, wherein the pharmaceutical acceptable salt of sorafenib is a tosylate salt.

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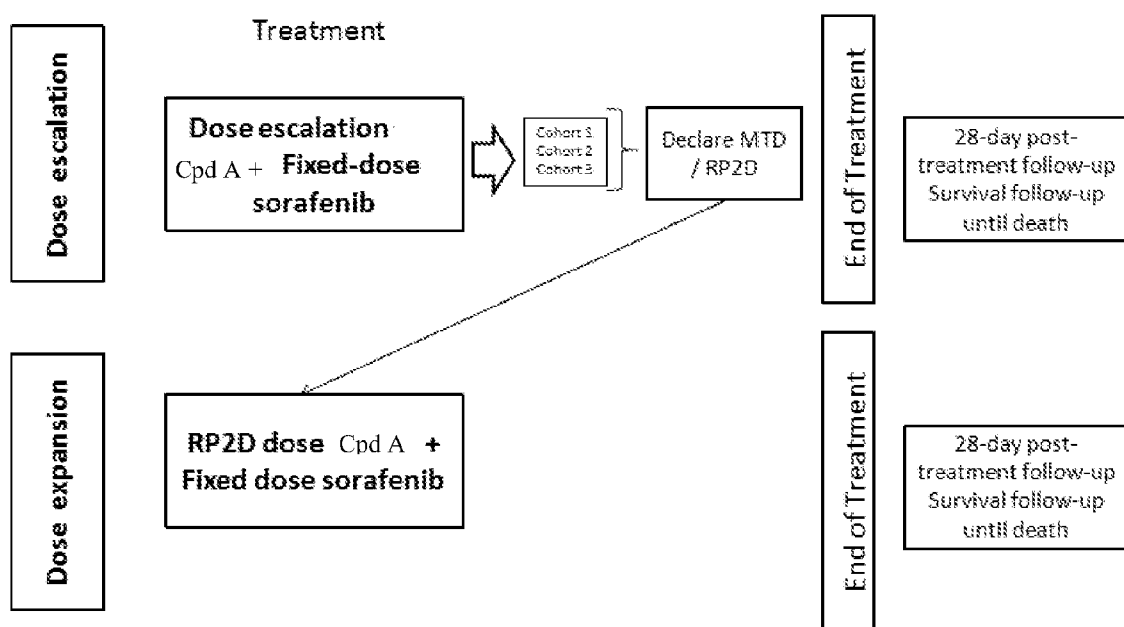


FIG. 1

	Screening Period	Treatment Period										Follow-up Period			
		Screening	Cycle 1					Cycle 2					EOT		Disease progression/ survival
			1	8	15	22	1	8	15	22	1	15			
Day ^{a)}	-28 to -1 ^{b)}														
STUDY ENTRY															
Informed consent and pregnancy prevention counseling	X														
Demographics	X														
Prior cancer history	X														
Prior cancer therapies ^{c)}	X														
Complete medical history	X														
Prior/ concomitant medication evaluation	X	Continuous, until 28 days after treatment discontinuation													
Prior/ concomitant procedures evaluation	X	Continuous, until 28 days after treatment discontinuation													
Inclusion/exclusion criteria	X														

FIG. 2

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	Screening Period	Treatment Period												Follow-up Period		
		Cycle 1						Cycle 2							Subsequent cycles	EOT
		1	8	15	22	1	8	15	22	1	15					
Day ^{a)}	-28 to -1 ^{b)}	1	8	15	22	1	8	15	22	1	15	EOT		Disease progression/ survival		
Enrollment	X															
SAFETY ASSESSMENTS																
Adverse event collection	Continuous starting after informed consent signature, until 28 days after last dose of IP															
Physical examination (source documented only)	X	X					X					X		X		
Weight	X	X					X					X		X		
Height	X															
Vital signs	X	X	X	X	X		X	X	X	X		X	X	X		
ECOG performance status	X	X					X					X		X		
Ophthalmologic exam	X	As clinically indicated														

FIG. 2 (continued)

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	Screening Period	Treatment Period											Follow-up Period
		Screening	Cycle 1				Cycle 2				Subsequent cycles		
			1	8	15	22	1	8	15	22	1	15	
Day ^{a)}	-28 to -1 ^{b)}												Disease progression/ survival
CBC with differential	X	X	X	X	X	X	X	X	X	X	Cycle s 3-6 only	X	
Coagulation: PT, INR, PTT	X	X				X				X			
Troponin-T and BNP	X	X				X				X			
Chemistry laboratory (routine)	X	X	X	X	X	X	X	X	X	X		X	
Amylase, lipase, cholesterol and triglycerides, CK, TSH, fT4, immuno-globulins and	X					X					X, Cycle s 3 and 4 only		
T-cell subsets (CD4+ and CD8+)													
Alpha fetoprotein	X	X				X				X		X	

FIG. 2 (continued)

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	Screening Period	Treatment Period										Follow-up Period
		Screening	Cycle 1			Cycle 2				Subsequent cycles		EOT
Day ^{a)}	-28 to -1 ^{b)}	1	8	15	22	1	8	15	22	1	15	
HBV and HCV serologies (HBsAg, HBcAg, HBsAb, HBcAb, HBcAb, HCVAb)	X											
HBV/HCV viral load ^{d)}	X	X				X				X		
Urinalysis	X (-7 to -1)					X				X		
12-lead electrocardiogram (central assessment)	X	X		X		X				X		
LVEF (MUGA or ECHO)	X					X				X, Every 3 rd cycle starti ng in Cycle 5		

FIG. 2 (continued)

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	Screening Period	Treatment Period											Follow-up Period
		Treatment Period											
		Cycle 1					Cycle 2					Subsequent cycles	
Day ^{a)}	-28 to -1 ^{b)}	1	8	15	22	1	8	15	22	1	15	Disease progression/ survival	
Serum β -hCG (in FCBP)	X	As clinically indicated											
Urine β -hCG (in FCBP)	X ^{e)} (as per PPRMP)						X				X		X
PK samples (Intensive or sparse, multiple timepoints)		X			X ^f								
Blood for biomarkers assessments		X			X ^f						X		
Pharmacogenomic blood sampling	X												
Archival tumor collection (mandatory)	X												

FIG. 2 (continued)

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	Screening Period	Treatment Period										Follow-up Period	
		Cycle 1					Cycle 2					Subsequent cycles	
Day ^{a)}	Screening	1	8	15	22	1	8	15	22	1	15		
Fresh tumor biopsy (Fresh frozen and FFPE)	X			X (Expansion only, Mandatory, anytime between Day 15 and 28)			X (Escalation only, Optional, anytime between Day 1 and 15)						
Additional blood samples for PK and biomarkers (matched with biopsy)				X (Expansion only, at the same time as the biopsy)			X (Escalation only, at the same time as the biopsy)						
EFFICACY ASSESSMENTS													
Tumor evaluation (CT/MRI, see Section)	X (-28 to -1)	RECIST 1.1 algorithm: Every 2 cycles through cycle 6, thereafter every 3 cycles until progression (e.g., end of C2, 4, 6, 9, 12, 15, 18, 21, 24 . . .).										The irRC will be evaluated as exploratory efficacy assessment	
INVESTIGATIONAL PRODUCT													
Administer Cpd A		Daily, continuously ^g											
Administer sorafenib		Twice daily, continuously											

FIG. 2 (continued)

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	Screening Period	Treatment Period										Follow-up Period	
		Cycle 1					Cycle 2						EOT
		Subsequent cycles											
	Screening	1	8	15	22	1	8	15	22	1	15	Disease progression/ survival	
Day ^{a)}	-28 to -1 ^{b)}												
Study drug accountability		X				X				X		X	
FOLLOW-UP													
Survival follow-up												Every 8 weeks for the first 12 months (± 7 days) and 12 weeks (±7 days) thereafter	
Anticancer therapy after treatment discontinuation												At every survival visit	

Abbreviations: β -hCG = beta human chorionic gonadotropin; BNP = Brain Natriuretic Peptide; CBC = complete blood count; CT = computed tomography; ECHO = echocardiogram; ECOG Eastern Cooperative Oncology Group; EOT = End of Treatment; FCBP = females of child bearing potential; FFPE = formalin-fixed, paraffin embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition scan; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time.

^a All visits have a $\pm$ 5 day window, except Cycle 1 Day 1 which has a $\pm$ 2 day window

^b Screening assessments must be performed prior to randomization, however, these events may occur on the same calendar day as long as the chronological order is followed.

FIG. 2 (continued)

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- ^c Prior cancer therapies include surgery, radiation, systemic or any other therapy (e.g., hormonal, locoregional) for the subject's cancer.
- ^d For HBsAg or HBV core Ab and/or HCVAb positive subjects only, respectively. HCV viral load should be checked if clinically indicated. HBV viral load must be monitored once every cycle.
- ^e As per PPRMP, FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drugs. The first pregnancy test must be performed within 10-14 days prior to the start of study drugs and the second pregnancy test must be performed within 24 hours prior to the start of study drugs. The subject may not receive study drugs until the study doctor has verified that the results of these pregnancy tests are negative.
- ^f An intermittent schedule of Cpd A administration (e.g., 1 mg 5 days on/2 days off weekly or 21 days on /7 days off every 28 days) may be explored at the discretion of the SRC.
- ^g For 5 days on/2 days off regimen, the PK and biomarker sample should be obtained at Cycle 1 Day 10, 11 or 12.

FIG. 2 (continued)

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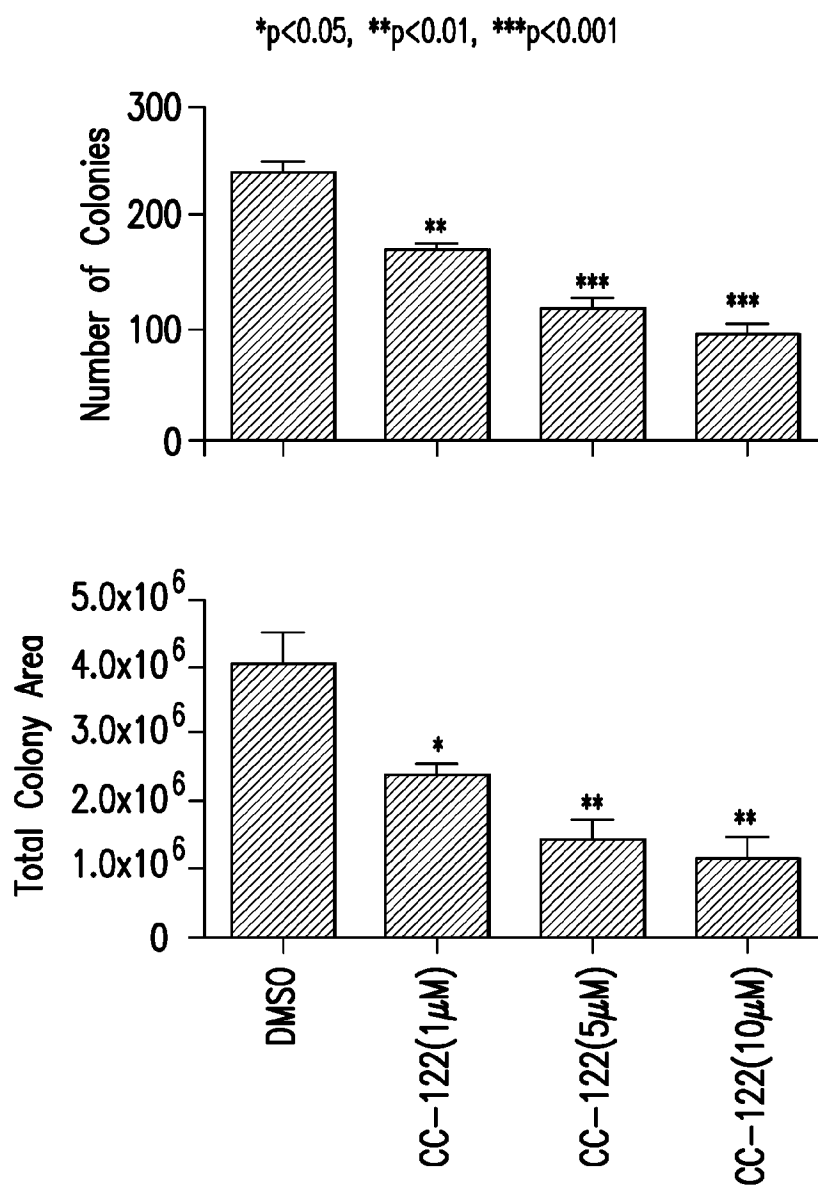


FIG. 3

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p<0.01, * p<0.001, **** p<0.0001

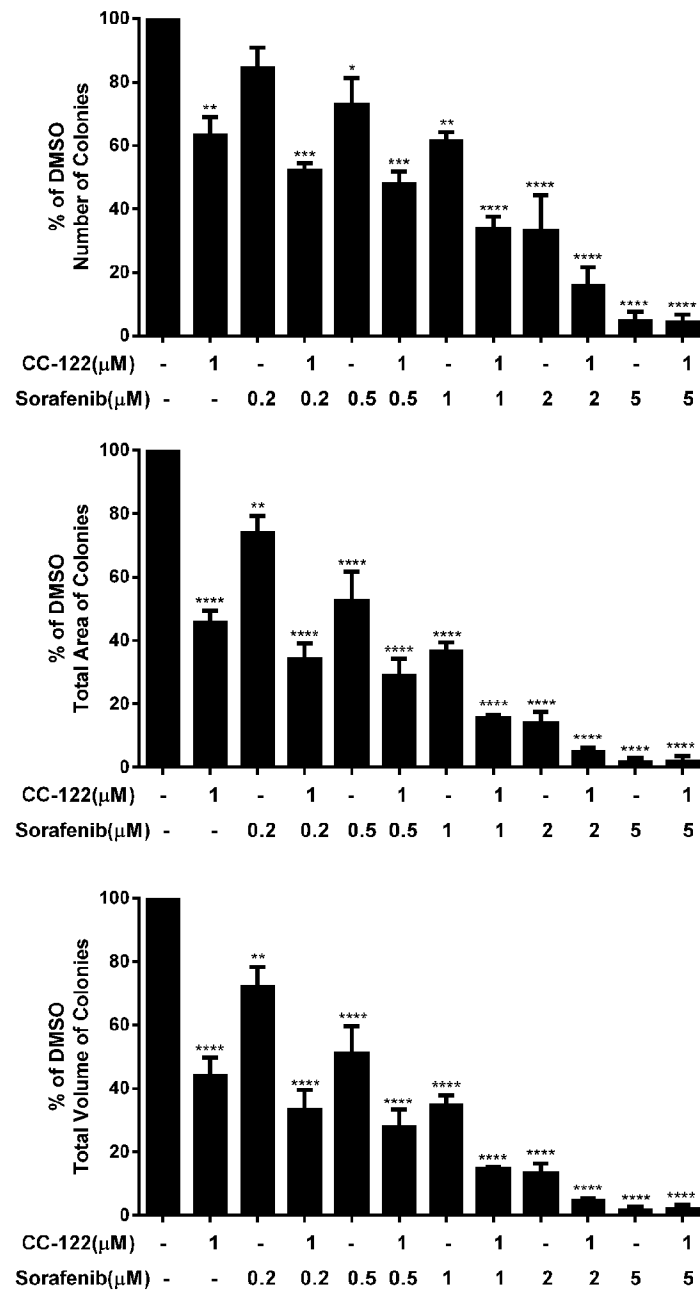


FIG. 4

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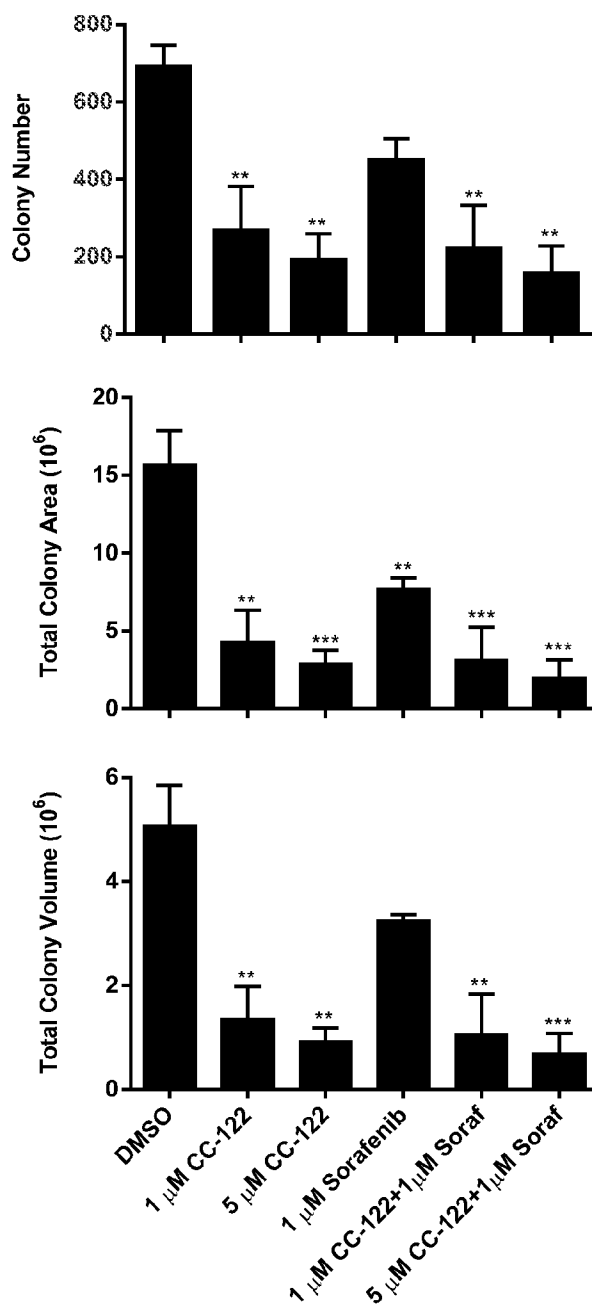
 $**p<0.01$, $***p<0.001$ 

FIG. 5

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*p<0.05, ** p<0.01

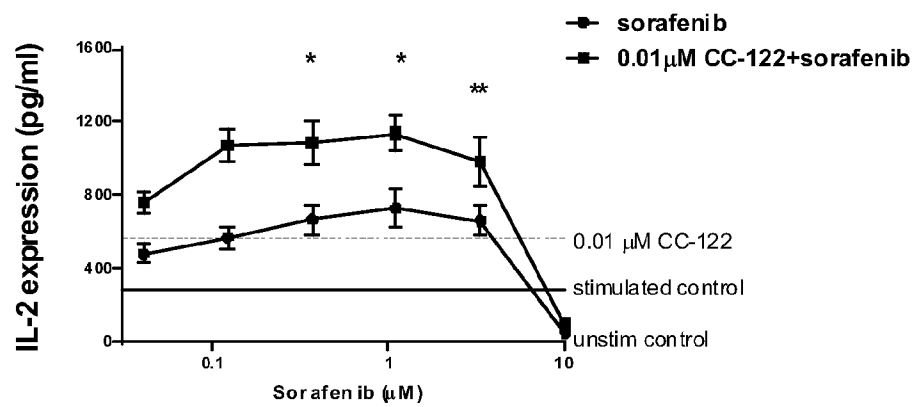


FIG. 6

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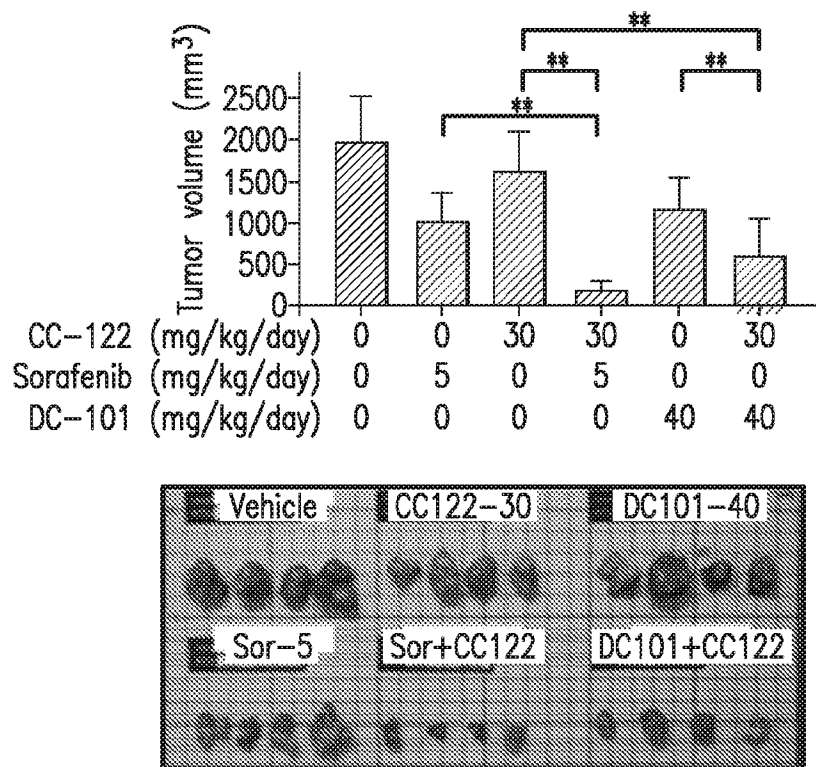


FIG. 7A

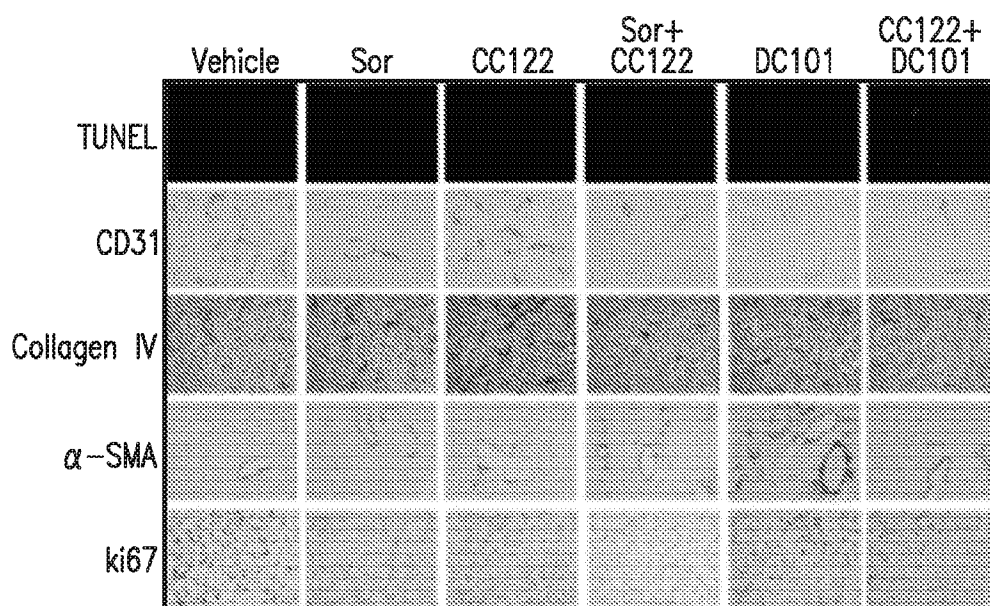


FIG. 7B

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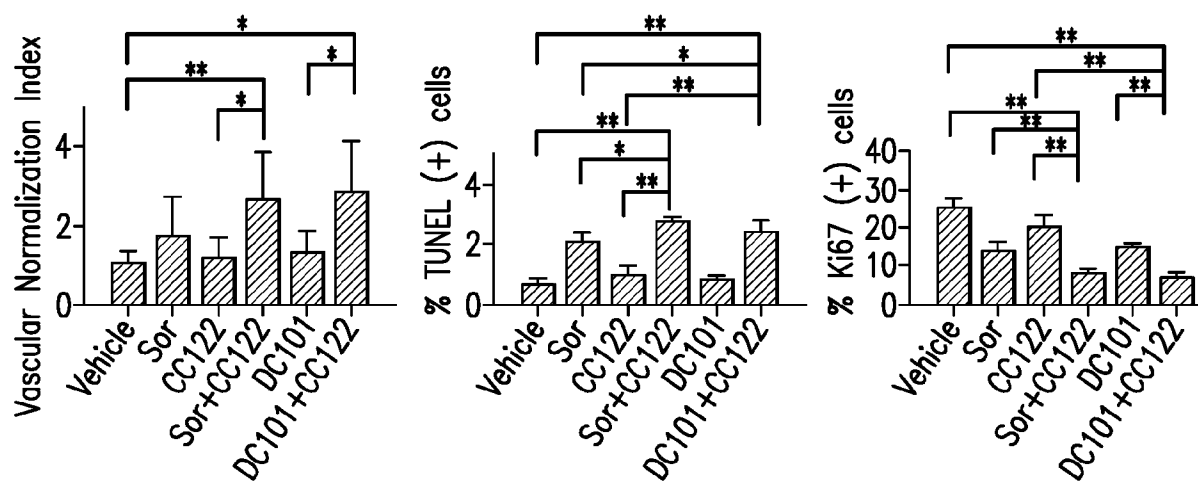


FIG. 7C

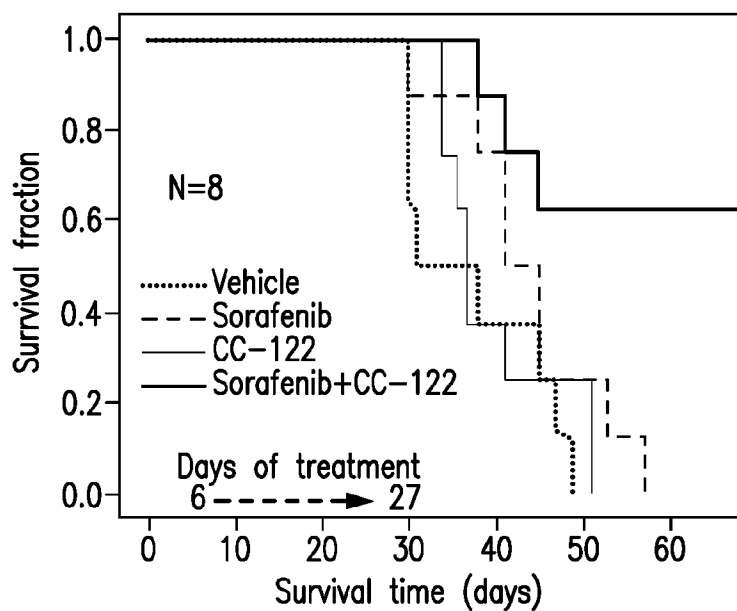


FIG. 7D

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/025986

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/44 A61P35/00 A61K31/7072
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

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

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/230983 A1 (MULLER GEORGE W [US] ET AL) 13 September 2012 (2012-09-13) claims 1,2,7	1-48
Y	----- FURUSE JUNJI: "Sorafenib for the treatment of unresectable hepatocellular carcinoma", BIOLOGICS: TARGETS & THERAPY, DOVE MEDICAL PRESS, NEW ZEALAND, vol. 2, no. 4, 1 December 2008 (2008-12-01), pages 779-788, XP002686599, ISSN: 1177-5475 [retrieved on 2008-12-01] abstract -----	1-48

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

1 June 2016

Date of mailing of the international search report

07/06/2016

Name and mailing address of the ISA/

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Strack, Eberhard

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/025986

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