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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 September 2016 (15.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/144636 A1

(51) International Patent Classification:
A61K 31/496 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2016/020396

(22) International Filing Date:
2 March 2016 (02.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/129,623 6 March 2015 (06.03.2015) US
62/249,807 2 November 2015 (02.11.2015) US

(71) Applicant: **BEYONDSPRING PHARMACEUTICALS, INC.** [US/US]; 28 Liberty Street 39th Floor, New York, NY 10005 (US).

(72) Inventor: **HUANG, Lan**; 28 Liberty Street 39th Floor, New York, NY 10005 (US).

(74) Agent: **HART, Daniel**; Knobbe, Martens, Olson & Bear, LLP, 2040 Main Street, 14th Floor, Irvine, CA 92614 (US).

(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).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

WO 2016/144636 A1

(54) Title: METHOD OF TREATING A BRAIN TUMOR

(57) Abstract: Disclosed herein are methods of treating a brain tumor by administering Plinabulin. Some embodiments relate to treatment of glioblastoma multiforme by administering Plinabulin.

METHOD OF TREATING A BRAIN TUMOR

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/129623, filed March 6, 2015, and U.S. Provisional Application No. 62/249807, filed November 2, 2015, the disclosure of which are incorporated herein by reference in their entireties.

BACKGROUND

Field

[0002] The present invention relates to the field of chemistry and medicine. More particularly, the present invention relates to method of treating a brain tumor using Plinabulin.

Description of the Related Art

[0003] Cancers of the brain and nervous system are among the most difficult to treat. Prognosis for patients with these cancers depends on the type and location of the tumor as well as its stage of development. For many types of brain cancer, average life expectancy after symptom onset may be months or a year or two. Treatment consists primarily of surgical removal and radiation therapy. Chemotherapy is also used, but the range of suitable chemotherapeutic agents is limited, perhaps because most therapeutic agents do not penetrate the blood-brain barrier adequately to treat brain tumors. Using known chemotherapeutics along with surgery and radiation rarely extends survival much beyond that produced by surgery and radiation alone. Thus improved therapeutic options are needed for brain tumors, and this condition has a dire unmet medical need.

[0004] Glioblastoma multiforme (GBM) is the most common adult primary brain tumor and is notorious for its lethality and lack of responsiveness to current treatment approaches. There have been no substantial improvements in treatment options in recent years, and minimal improvements in the survival prospects for patients with GBM. For GBM, average life expectancy after symptom onset is around 6-12 month. In addition, there are no approved drugs for treating metastatic brain tumor, which has an average life expectancy after symptom onset at 4-6 months. Thus there remains an urgent need for improved treatments for cancers of the brain.

SUMMARY

[0005] Some embodiments relate to a method of treating a brain tumor comprising administering an effective amount of Plinabulin to a subject in need thereof.

[0006] Some embodiments relate to a method of inhibiting proliferation of brain tumor cell, comprising contacting the brain tumor cell with Plinabulin.

[0007] Some embodiments relate to a method of inducing apoptosis in brain tumor cell, comprising contacting the brain tumor cell with Plinabulin.

[0008] Some embodiments relate to a method of inhibiting progression of brain tumor, comprising administering an effective amount of Plinabulin to a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIGS 1a-1d show the proneural genetically engineered murine model (GEMM) of glioblastoma (GBM) that mimics human pathology. FIG. 1a shows T2 MRI images of a human GBM that display peritumoral edema; and FIG. 1b shows T2 MRI images of mouse GBM that display peritumoral edema; FIG 1c shows human micrograph images of H&E stains of a GBM showing hallmark pseudopalisading necrosis and microvascular proliferation; FIG. 1d shows mouse micrograph images of H&E stains of a GBM showing hallmark pseudopalisading necrosis and microvascular proliferation.

[0010] FIG 2A and 2B show the T2 weighted MRI images. FIG. 2A shows tumor size in mice with PDGF-induced gliomas treated with vehicle, temozolomide or fractionated radiation; and FIG. 2B shows survival of mice with PDGF-induced gliomas treated with vehicle, temozolomide or fractionated radiation.

[0011] FIG. 3 shows the survival rate of mice with glioblastoma tumor that were treated with control and Plinabulin.

[0012] FIG. 4 shows the survival rate of mice with PDGF-induced gliomas characterized by expression of KRAS mutation that were treated with the combination of plinabulin, temozolomide, and radiation and the combination of temozolomide and radiation.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0013] Plinabulin, (3Z,6Z)-3-Benzylidene-6-{[5-(2-methyl-2-propanyl)-1H-imidazol-4-yl]methylene}-2,5-piperazinedione, is a synthetic analog of the natural

compound phenylahistin. Plinabulin can be readily prepared according to methods and procedures detailed in U.S. Patents 7,064,201 and 7,919,497, which are incorporated herein by reference in their entireties. Some embodiments relate to using Plinabulin to treat brain cancer, including but are not limited to metastatic brain tumor, anaplastic astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymomas, and mixed glioma. Some embodiments relate to using Plinabulin to inhibit proliferation of brain tumor cells using Plinabulin. Some embodiments relate to using Plinabulin to induce apoptosis in brain tumor cells using Plinabulin. Some embodiments relate to using Plinabulin to inhibit progression of brain tumors. Some embodiments relate to using Plinabulin in combination with an additional therapeutic agent or radiation to inhibit progression of brain tumors.

Definitions

[0014] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications, and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0015] "Subject" as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate.

[0016] The term "mammal" is used in its usual biological sense. Thus, it specifically includes, but is not limited to, primates, including simians (chimpanzees, apes, monkeys) and humans, cattle, horses, sheep, goats, swine, rabbits, dogs, cats, rodents, rats, mice guinea pigs, or the like.

[0017] An "effective amount" or a "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent that is effective to relieve, to some extent, or to reduce the likelihood of onset of, one or more of the symptoms of a disease or condition, and includes curing a disease or condition.

[0018] "Treat," "treatment," or "treating," as used herein refers to administering a compound or pharmaceutical composition to a subject for prophylactic and/or therapeutic purposes. The term "prophylactic treatment" refers to treating a

subject who does not yet exhibit symptoms of a disease or condition, but who is susceptible to, or otherwise at risk of, a particular disease or condition, whereby the treatment reduces the likelihood that the patient will develop the disease or condition. The term "therapeutic treatment" refers to administering treatment to a subject already suffering from a disease or condition.

[0019] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of a compound and, which are not biologically or otherwise undesirable for use in a pharmaceutical. In many cases, the compounds disclosed herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable salts can also be formed using inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, bases that contain sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. In some embodiments, treatment of the compounds disclosed herein with an inorganic base results in loss of a labile hydrogen from the compound to afford the salt form including an inorganic cation such as Li^+, Na^+, K^+, Mg^{2+} and Ca^{2+} and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

[0020] In some embodiments, the composition can further include one or more pharmaceutically acceptable diluents. In some embodiments, the pharmaceutically

acceptable diluent can include Kolliphor® (Polyethylene glycol (15)-hydroxystearate). In some embodiments, the pharmaceutically acceptable diluent can include propylene glycol. In some embodiments, the pharmaceutically acceptable diluents can include kolliphor and propylene glycol. In some embodiments, the pharmaceutically acceptable diluents can include kolliphor and propylene glycol, wherein the kolliphor is about 40% by weight and propylene glycol is about 60% by weight based on the total weight of the diluents. In some embodiments, the composition can further include one or more other pharmaceutically acceptable excipients.

[0021] Standard pharmaceutical formulation techniques can be used to make the pharmaceutical compositions described herein, such as those disclosed in Remington's The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005), incorporated herein by reference in its entirety. Accordingly, some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of Plinabulin or pharmaceutically acceptable salts thereof; and (b) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0022] Other embodiments include co-administering Plinabulin and an additional therapeutic agent in separate compositions or the same composition. Thus, some embodiments include a first pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of Plinabulin or pharmaceutically acceptable salts thereof and (b) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof; and a second pharmaceutical composition comprising: (a) a safe and therapeutically effective amount of an additional therapeutic agent and (b) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof. Some embodiments include a pharmaceutical composition comprising: (a) a safe and therapeutically effective amount of Plinabulin or pharmaceutically acceptable salts thereof; (b) a safe and therapeutically effective amount of an additional therapeutic agent; and (c) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0023] Administration of the pharmaceutical compositions described herein can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, sublingually, buccally, subcutaneously, intravenously, intranasally, topically, transdermally, intradermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, or intraocularly. Oral and

parenteral administrations are customary in treating the indications that are the subject of the preferred embodiments.

[0024] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, which is incorporated herein by reference in its entirety.

[0025] Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[0026] The compositions described herein are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound or composition that is suitable for administration to an animal, preferably a mammalian subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during

a course of therapy, although a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.

[0027] The compositions useful as described above may be in any of a variety of suitable forms for a variety of routes for administration, for example, for oral, sublingual, buccal, nasal, rectal, topical (including transdermal and intradermal), ocular, intracerebral, intracranial, intrathecal, intra-arterial, intravenous, intramuscular, or other parental routes of administration. The skilled artisan will appreciate that oral and nasal compositions include compositions that are administered by inhalation, and made using available methodologies. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. Pharmaceutically-acceptable carriers include, for example, solid or liquid fillers, diluents, hydrotropies, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the activity of the compound or composition. The amount of carrier employed in conjunction with the compound or composition is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods described herein are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, 4th Ed., Chapters 9 and 10 (Banker & Rhodes, editors, 2002); Lieberman *et al.*, Pharmaceutical Dosage Forms: Tablets (1989); and Ansel, Introduction to Pharmaceutical Dosage Forms 8th Edition (2004).

[0028] Various oral dosage forms can be used, including such solid forms as tablets, capsules (*e.g.*, liquid gel capsule and solid gel capsule), granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

[0029] The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for peroral administration is well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, sucrose, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical, and can be readily made by a person skilled in the art.

[0030] Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0031] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject composition is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0032] Compositions described herein may optionally include other drug actives.

[0033] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0034] A liquid composition, which is formulated for topical ophthalmic use, is formulated such that it can be administered topically to the eye. The comfort may be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid may be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid may either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0035] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions may preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0036] Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0037] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0038] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. For many compositions, the pH will be between 4 and 9. Accordingly, buffers include acetate buffers, citrate buffers,

phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0039] Ophthalmically acceptable antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0040] Other excipient components, which may be included in the ophthalmic preparations, are chelating agents. A useful chelating agent is edetate disodium (EDTA), although other chelating agents may also be used in place or in conjunction with it.

[0041] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the composition disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, co-solvent, emulsifier, penetration enhancer, preservative system, and emollient.

[0042] For intravenous administration, the compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., Compendium of Excipients for Parenteral Formulations, *PDA J Pharm Sci and Tech* **1998**, *52* 238-311 and Nema et al., Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions, *PDA J Pharm Sci and Tech* **2011**, *65* 287-332, both of which are incorporated herein by reference in their entirety. Antimicrobial agents may also be included to achieve a bacteriostatic or fungistatic solution, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol.

[0043] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer parenterally.

In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound described herein and another agent, the combination may be provided to caregivers as a mixture, or the caregivers may mix the two agents prior to administration, or the two agents may be administered separately.

[0044] The actual dose of the active compounds described herein depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan. In some embodiments, a single dose of Plinabulin or other therapeutic agent may be from about 5 mg/m^2 to about 150 mg/m^2 of body surface area, from about 5 mg/m^2 to about 100 mg/m^2 of body surface area, from about 10 mg/m^2 to about 100 mg/m^2 of body surface area, from about 10 mg/m^2 to about 80 mg/m^2 of body surface area, from about 10 mg/m^2 to about 50 mg/m^2 of body surface area, from about 10 mg/m^2 to about 40 mg/m^2 of body surface area, from about 10 mg/m^2 to about 30 mg/m^2 of body surface area, from about 13.5 mg/m^2 to about 100 mg/m^2 of body surface area, from about 13.5 mg/m^2 to about 80 mg/m^2 of body surface area, from about 13.5 mg/m^2 to about 50 mg/m^2 of body surface area, from about 13.5 mg/m^2 to about 40 mg/m^2 of body surface area, from about 13.5 mg/m^2 to about 30 mg/m^2 of body surface area, from about 15 mg/m^2 to about 80 mg/m^2 of body surface area, from about 15 mg/m^2 to about 50 mg/m^2 of body surface area, or from about 15 mg/m^2 to about 30 mg/m^2 of body surface area. In some embodiments, a single dose of Plinabulin or other therapeutic agent may be from about 13.5 mg/m^2 to about 30 mg/m^2 of body surface area. In some embodiments, a single dose of Plinabulin or other therapeutic agent may be about 5 mg/m^2, about 10 mg/m^2, about 12.5 mg/m^2, about 13.5 mg/m^2, about 15 mg/m^2, about 17.5 mg/m^2, about 20 mg/m^2, about 22.5 mg/m^2, about 25 mg/m^2, about 27.5 mg/m^2, about 30 mg/m^2, about 40 mg/m^2, about 50 mg/m^2, about 60 mg/m^2, about 70 mg/m^2, about 80 mg/m^2, about 90 mg/m^2, or about 100 mg/m^2, of body surface area.

[0045] In some embodiments, a single dose of Plinabulin or other therapeutic agent may be from about 5 mg to about 300 mg, from about 5 mg to about 200 mg, from about 7.5 mg to about 200 mg, from about 10 mg to about 100 mg, from about 15 mg to about 100 mg, from about 20 mg to about 100 mg, from about 30 mg to about 100 mg, from about 40 mg to about 100 mg, from about 10 mg to about 80 mg, from about 15 mg to about 80 mg, from about 20 mg to about 80 mg, from about 30 mg to about 80 mg,

from about 40 mg to about 80 mg, from about 10 mg to about 60 mg, from about 15 mg to about 60 mg, from about 20 mg to about 60 mg, from about 30 mg to about 60 mg, or from about 40 mg to about 60 mg, In some embodiments, a single dose of Plinabulin or other therapeutic agent may be from about 20 mg to about 60 mg, from about 27 mg to about 60 mg, from about 20 mg to about 45 mg, or from about 27 mg to about 45 mg. In some embodiments, a single dose of Plinabulin or other therapeutic agent may be about 5 mg, about 10 mg, about 12.5 mg, about 13.5 mg, about 15 mg, about 17.5 mg, about 20 mg, about 22.5 mg, about 25 mg, about 27 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150mg, or about 200 mg.

[0046] The administration period can be a multi-week treatment cycle as long as the tumor remains under control and the regimen is clinically tolerated. In some embodiments, a single dosage of Plinabulin or other therapeutic agent can be administered once a week, and preferably once on each of day 1 and day 8 of a three-week (21 day) treatment cycle. In some embodiments, a single dosage of Plinabulin or other therapeutic agent can be administered once a week, twice a week, three times per week, four times per week, five times per week, six times per week, or daily during a one-week, two-week, three-week, four-week, or five-week treatment cycle. The administration can be on the same or different day of each week in the treatment cycle.

[0047] The treatment cycle can be repeated as long as the regimen is clinically tolerated. In some embodiments, the treatment cycle is repeated for n times, wherein n is an integer in the range of 2 to 30. In some embodiments, n is 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, a new treatment cycle can occur immediately after the completion of the previous treatment cycle. In some embodiments, a new treatment cycle can occur a period of time after the completion of the previous treatment cycle.

[0048] In some embodiments, the compositions described herein can be used in combination with other therapeutic agents. In some embodiments, the compositions described herein can be administered or used in combination with treatments such as chemotherapy, radiation, and biologic therapies.

Methods of Treatment

[0049] Some embodiments relate to a method of treating a brain tumor, the method comprising administering an effective amount of Plinabulin to a subject in need thereof.

[0050] In some embodiments, the brain tumor can be selected from metastatic brain tumor, anaplastic astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymomas, meningioma, mixed glioma, and a combination thereof. In some embodiments, the brain tumor is a glioblastoma multiforme. In some embodiments, the brain tumor is a metastatic brain tumor.

[0051] In some embodiments, the brain tumor can be selected from Anaplastic astrocytoma, Central neurocytoma, Choroid plexus carcinoma, Choroid plexus papilloma, Choroid plexus tumor, Dysembryoplastic neuroepithelial tumor, Ependymal tumor, Fibrillary astrocytoma, Giant-cell glioblastoma, Glioblastoma multiforme, Gliomatosis cerebri, Gliosarcoma, Hemangiopericytoma, Medulloblastoma, Medulloepithelioma, Meningeal carcinomatosis, Neuroblastoma, Neurocytoma, Oligoastrocytoma, Oligodendroglioma, Optic nerve sheath meningioma, Pediatric ependymoma, Pilocytic astrocytoma, Pinealoblastoma, Pineocytoma, Pleomorphic anaplastic neuroblastoma, Pleomorphic xanthoastrocytoma, Primary central nervous system lymphoma, Sphenoid wing meningioma, Subependymal giant cell astrocytoma, Subependymoma, central nervous system myeloma, and Trilateral retinoblastoma.

[0052] In some embodiments, the method described herein can include administering an additional therapeutic agent. In some embodiments, the additional therapeutic agent can be temozolomide, bevicizumab, everolimus, carmustine, lomustine, procarbazine, vincristine, irinotecan, cisplatin, carboplatin, methatrexate, etoposide, vinblasatine, bleomycin, actinomycin, cyclophosphamide, or ifosfamide. In some embodiments, the additional therapeutic agent can be temozolomide. In some embodiments, the additional therapeutic agent can be lomustine.

[0053] In some embodiments, the method described herein can further include subjecting the subject to a radiation therapy. In some embodiments, the radiation therapy can be a whole-brain irradiation, fractionated radiotherapy, and radiosurgery.

[0054] In some embodiments, the brain tumor is characterized by expression of a mutant form of KRAS. In some embodiments, the brain tumor is characterized by expression of a mutant gene that is not KRAS.

[0055] In some embodiments, the method described herein can further include identifying a patient having a cancer characterized by expression of a mutant type of KRAS. In some embodiments, the method described herein can further include identifying a patient having a cancer characterized by expression of a wild type of KRAS. In some embodiments, identifying a patient can include determining whether the patient has a KRAS mutation. Some embodiments relate to a method for treating cancer in a patient identified as having a KRAS mutation, the method comprising administering to the patient a pharmaceutically effective amount of Plinabulin, wherein the patient has been identified by (i) collecting a sample from the patient; (ii) isolating DNA from the sample; (iii) amplifying a KRAS gene or fragment thereof in the isolated DNA; and (iv) detecting whether there is a mutation in the amplified KRAS gene, thereby determining whether the patient has a cancer characterized by a KRAS mutation.

[0056] Some embodiments relate to a method of inhibiting proliferation of a brain tumor cell, the method including contacting the brain tumor cell with Plinabulin. In some embodiments, the contacting comprises administering an effective amount of Plinabulin to a subject having the brain tumor cell. In some embodiments, the brain tumor is a glioblastoma multiforme.

[0057] Some embodiments relate to a method of inducing apoptosis in a brain tumor cell, the method including contacting the brain tumor cell with Plinabulin. In some embodiments, the contacting comprises administering an effective amount of Plinabulin to a subject having the brain tumor cell. In some embodiments, the brain tumor is a glioblastoma multiforme.

[0058] Some embodiments relate to a method of inhibiting progression of brain tumor, the method including administering an effective amount of Plinabulin to a subject in need thereof.

[0059] To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled

artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

EXAMPLES

Example 1

[0060] The mouse model of glioma used was a PDGF-driven GEMM of glioma that mimics the proneural molecular subgroup of glioblastoma (GBM). This model was based on somatic cell-specific gene transfer; the replication-competent ALV-splice acceptor (RCAS) retroviral system allowed the instillation of particular genetic alterations within tightly regulated windows of differentiation in a cell type-specific manner. The RCAS/*tv-a* system employed the RCAS retroviral vector to infect mice genetically engineered to express the RCAS receptor (*tv-a)* in specific cell populations. Here, gliomas were generated by RCAS-mediated transfer of PDGF to nestin-expressing cells in the brain. Nestin was expressed in a stem/progenitor cell population in the brain, and has been demonstrated to be a marker for cancer stem cells located in perivascular regions (PVN) in both human and mouse brain tumors. PDGF-driven gliomas arose with complete penetrance when combined with *Ink4a-arf-/-* deletion by 4-5 weeks post-infection. These tumors closely mimicked the "proneural" subtype of GBM, in which *CDKN2A* (encoding for both *p16INK4A* and *p14ARF*) deletion was observed in 56% of "proneural" human gliomas. The tumor cell structures that define human gliomas, such as Scherer structures, microvascular proliferation and pseudopalisading necrosis were recreated in this GEMM as shown in FIGS. 1a-1d. Specifically, FIG. 1a shows T2 MRI images of a human GBM display peritumoral edema; FIG. 1b shows T2 MRI images of mouse GBM display peritumoral edema; FIG 1c shows human micrograph images of H&E stains of a GBM having hallmark pseudopalisading necrosis and microvascular proliferation; and FIG. 1d showed mouse micrograph images of H&E stains of a GBM having hallmark pseudopalisading necrosis and microvascular proliferation.

[0061] Glioma cells migrated along white matter tracks, surrounded neurons and blood vessels and accumulated at the edge of the brain in the sub-pial space. In this regard, PDGF-driven GEMMs of glioma closely resembles PVN-GBM, and represents an excellent experimental system to define the interactions between tumor cells and non-neoplastic cells in the tumor microenvironment.

[0062] The PDGF-induced model of glioma was used to determine response to radiation and temozolomide as shown in FIGS. 2A and 2B. FIG. 2A shows tumor size of mice with PDGF-induced gliomas treated with vehicle, temozolomide or fractionated radiation; and FIG. 2B shows the survival rate of mice with PDGF-induced gliomas treated with vehicle, temozolomide or fractionated radiation.

[0063] Glioma-bearing mice were identified by symptoms and verified by T2 weighted MRI. These mice were either treated with vehicle, temozolomide at 25 mg/kg daily for 12 days, or fractionated radiation at a dose of 2Gy per day 5 days per week for 2 weeks (20Gy total). The two top images in FIG 2A showed the growth of tumors that were untreated (vehicle), and in contrast, both the temozolomide treated and irradiated tumors shrank in volume over that same period of time. These tumors recurred after treatment and all animals died of recurrent tumor as can be seen in the survival curves for these corresponding cohorts of mice. The data illustrated that: 1) trials were performed in this mouse model, 2) the effect of these treatments on mouse survival mirrored the human condition, 3) all the mice died of disease, and 4) the relatively homogenous outcomes of these murine cohorts supported the use of this experimental paradigm to detect survival differences in the present study.

[0064] Mice with PDGF-induced gliomas using RCAS/tv-a were generated. The mice were transgenic for expression of the RCAS receptor (tv-a) from the nestin promoter and having a background of ink4a/arf-/- and lox-stop-lox luciferase, were infected with RCAS-PDGF, or the combination of RCAS-PDGF and RCAS-KRAS that expressed G12D mutant KRAS. The resultant tumors occurred within the first 4-5 weeks in this background for PDGF alone, and about a week shorter for the tumors arising from the combination of PDGF and RCAS. The tumors had the histological characteristics of GBM and were identified by symptoms of lethargy and poor grooming, MRI scans using a T2 weighted sequence, or bioluminescence imaging with an IVIS system. For radiation therapy, mice were treated with 10Gy per day cranially for a single dose. This treatment extended the median survival of cohorts of GBM bearing mice approximately 3 weeks as shown in FIG. 2B. These treated mice began to gain weight and show improved symptoms within a few days, and their MRI imaging characteristics showed stabilization or shrinking of tumor size, and then recurrence and death.

[0065] Plinabulin was tested on mice with PDGF-induced gliomas that expressed G12D mutant KRAS. 4-6 week old *nestin-tv-a/ink4a-arf-/-* mice were

anesthetized with Isoflurane and injected with Df-1 cells transfected RCAS-PDGF-B-HA, RCAS-KRAS. Mice were injected with one microliter of a 1:1 mixture of $2X10^5$ RCAS-PDGF-B-HA/RCAS-KRAS using a stereotactic frame via a 26-gauge needle attached to a Hamilton syringe. Cells were injected into the right frontal cortex, coordinates bregma 1.75 mm, Lat -0.5mm, and a depth of 2mm. Mice were monitored carefully for weight loss and put on the study when they lost > 0.3 grams total over 2 consecutive days or displayed outward signs of a tumor. In the KRAS group, mice were injected with Plinabulin 7.5 mg/kg i.p. twice per week for 10 weeks. In the control group, mice that were injected with Plinabulin diluent only (40% wt Kolliphor and 60% wt propylene glycol). The mice were monitored for lethargy, hunched posture, appetite loss, outward signs of tumor growth, agitation, weight-loss and overall failure to thrive. The mice were sacrificed when they lost more than 20% of their body weight, mobility, inability to feed or weighed less than 14 grams for a male/ 12 grams for a female. The mice were sacrificed using CO_2; brains were harvested and stored overnight in 10% Neutral buffered formalin and then replaced with Flex 80 and stored at 4 degrees.

[0066] FIG. 3 shows the survival rate of mice with Glioblastoma with the G12D Kras mutation. . As shown in FIG 3, mice having the PDGF-induced model of Glioblastoma generally had a significantly better survival rate in the Plinabulin treated group as compared to the control group (p=0.001).

Example 2.

[0067] Mice with PDGF-induced gliomas that expressed G12D mutant KRAS were prepared using the procedures according to Example 1 and used in this experiment. 4-6 week old *nestin-tv-a/ink4a-arf-/-* mice were anesthetized with Isoflurane and injected with Df-1 cells transfected RCAS-PDGF-B-HA, RCAS-KRAS. Mice were injected with one microliter of a 1:1 mixture of $2X10^5$ RCAS-PDGF-B-HA/RCAS-KRAS using a stereotactic frame via a 26-gauge needle attached to a Hamilton syringe. Cells were injected into the right frontal cortex, coordinates bregma 1.75 mm, Lat -0.5mm, and a depth of 2mm. Mice were monitored carefully for weight loss and put on the study when they lost > 0.3 grams total over 2 consecutive days or displayed outward signs of a tumor.

[0068] The mice were entered into two study groups. One group was treated with the combination of temozolomide (TMZ), Radiation and Plinabulin: radiation was given at 10gy x1, TMZ and Plinabulin 7.5 mg/kg in Plinabulin diluent was administered

intraperitoneally twice a week on Monday and Thursday for 10 weeks. The other group, the control group, was treated with the combination of TMZ and radiation: radiation was given at 10gy x1, TMZ was administered intraperitoneally twice a week on Monday and Thursday for 10 weeks. the mice were monitored for lethargy, hunched posture, appetite loss, outward signs of tumor growth, agitation, weight-loss and overall failure to thrive. The mice were sacrificed when they lost more than 20% of their body weight, mobility, inability to feed or weighed less than 14 grams for a male/ 12 grams for a female. The mice were sacrificed using CO_2; brains were harvested and stored O/N in 10% Neutral buffered formalin and then replaced with Flex 80 and stored at 4 degrees. As shown in FIG. 4, the mice having the PDGF-induced model of Glioblastoma generally had significantly better survival rate in the Plinabulin plus TMZ plus radiation treated group as compared to the control group that received TMZ plus radiation (p=0.0149).

WHAT IS CLAIMED IS:

1. A method of treating a brain tumor comprising administering an effective amount of Plinabulin to a subject in need thereof.

2. The method of any of claims 1, wherein the brain tumor is metastatic brain tumor, anaplastic astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymomas, or a combination thereof.

3. The method of claim 2, wherein the brain tumor is a glioblastoma multiforme.

4. The method of claim 2, wherein the brain tumor is a metastatic brain tumor.

5. The method of any one of claims 1 to 4, further comprising administering an additional therapeutic agent.

6. The method of claim 5, wherein the additional therapeutic agent is temozolomide.

7. The method of any one of claims 1 to 6, further comprising subjecting the subject to radiation therapy.

8. The method of any one of claims 1 to 7, wherein the brain tumor is characterized by expression of a mutant form of KRAS.

9. A method of inhibiting proliferation of brain tumor cell, comprising contacting the brain tumor cell with Plinabulin.

10. The method of Claim 9, wherein contacting comprises administering an effective amount of Plinabulin to a subject having the brain tumor cell.

11. A method of inducing apoptosis in brain tumor cell, comprising contacting the brain tumor cell with Plinabulin.

12. The method of Claim 11, wherein contacting comprises administering an effective amount of Plinabulin to a subject having the brain tumor cell.

13. A method of inhibiting progression of brain tumor, comprising administering an effective amount of Plinabulin to a subject in need thereof.

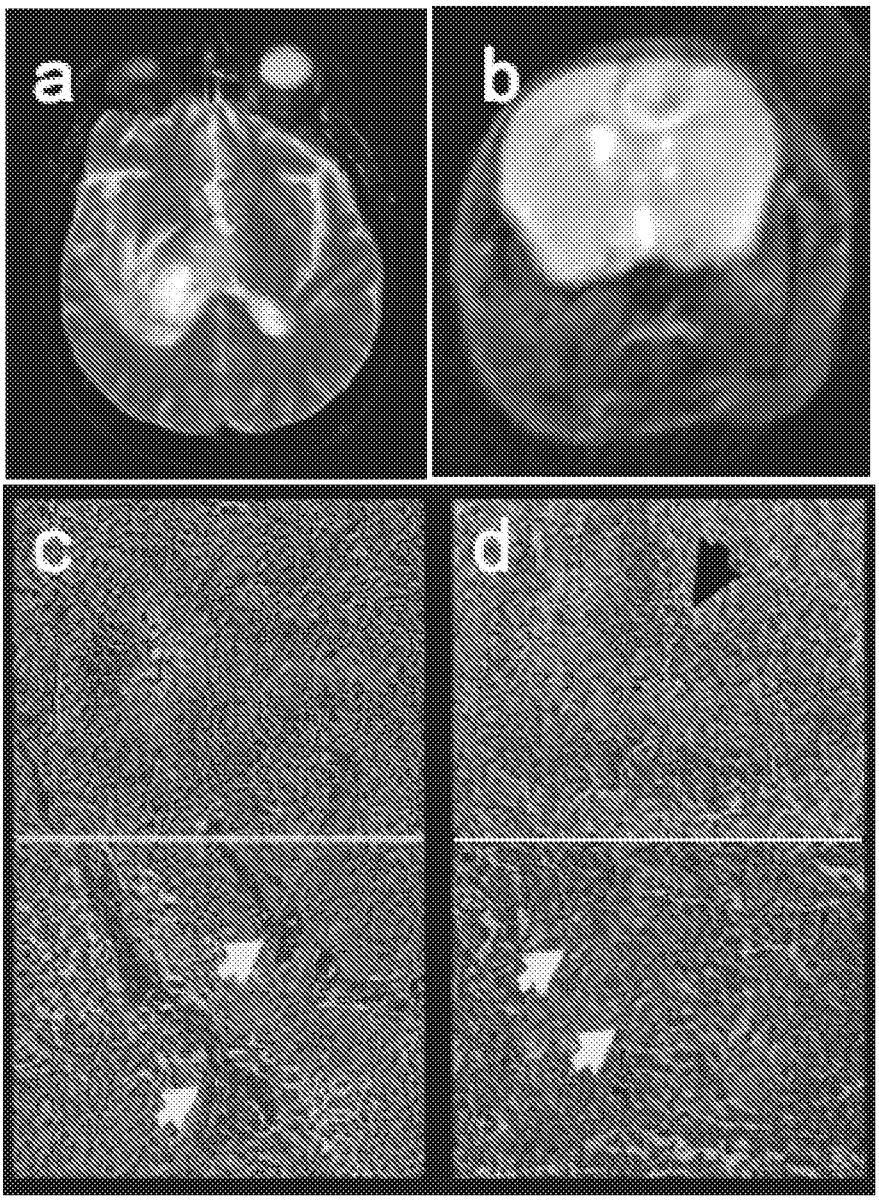

FIG. 1

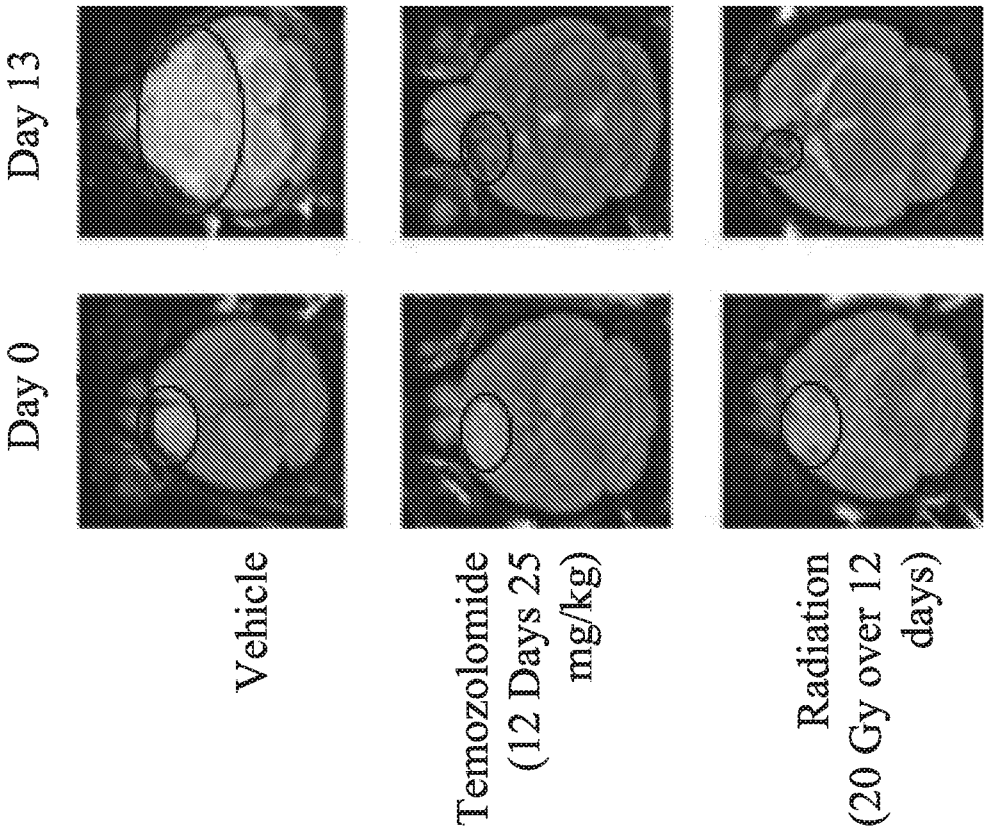
Day 0
Day 13
Vehicle
Temozolomide (12 Days 25 mg/kg)
Radiation (20 Gy over 12 days)

FIG. 2A

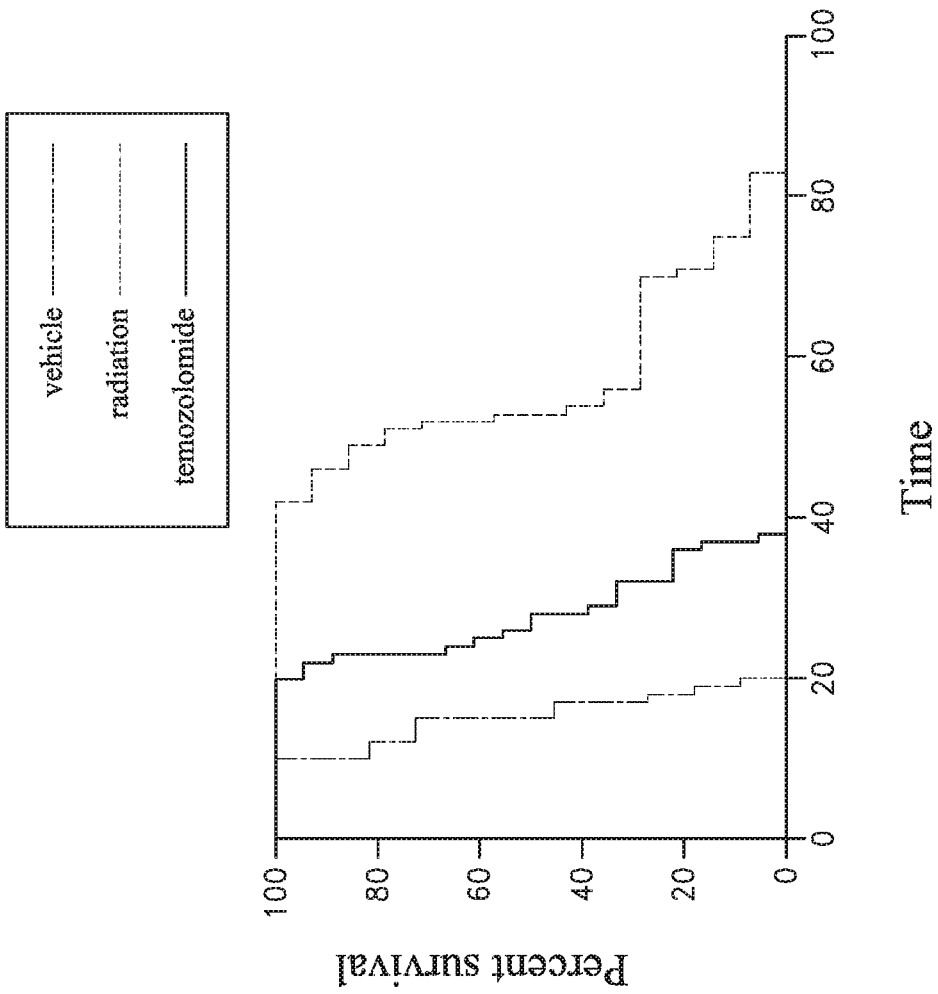
vehicle
radiation
temozolomide
Percent survival
Time
0
20
40
60
80
100

FIG. 2B

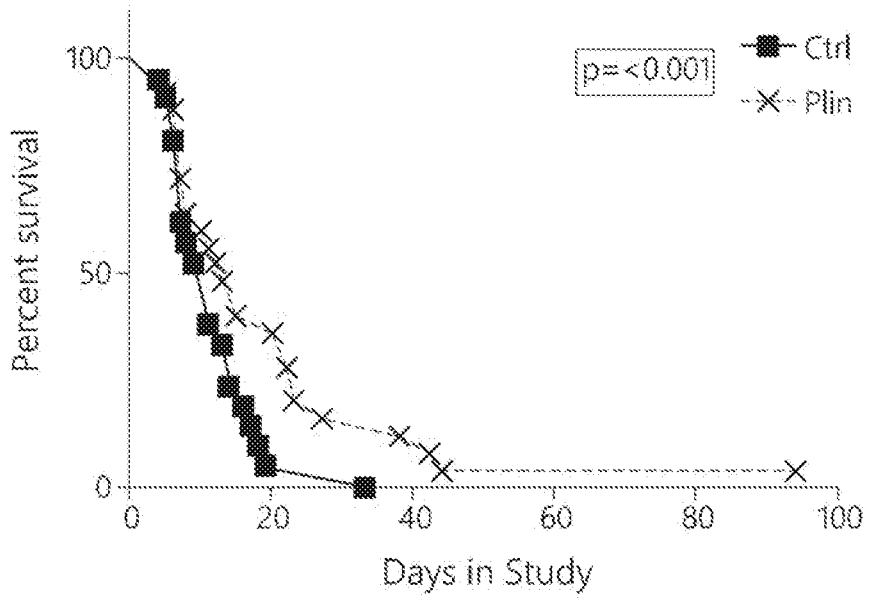
p=<0.001
Ctrl
Plin
Percent survival
100
50
0
0
20
40
60
80
100
Days in Study

FIG. 3

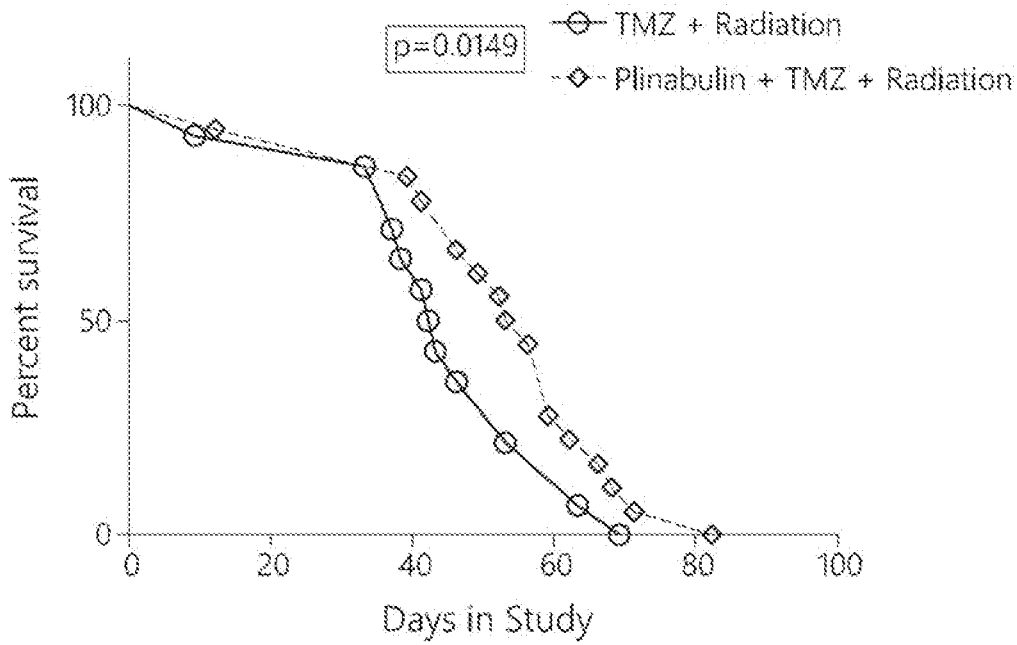
p=0.0149
TMZ + Radiation
Plinabulin + TMZ + Radiation
Percent survival
100
50
0
0
20
40
60
80
100
Days in Study

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/020396

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/496 (2006.01) A61P 35/00 (2006.01)

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)

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)

Databases: WPIAP, EPODOC, MEDLINE, CAPLUS, EMBASE, BIOSIS, Esp@cenet, PubMed and Internal databases provided by IP Australia

Keywords: Plinabulin, NPI-2358, UNII-986FY7F8XR, 714272-27-2, phenylahistin, brain, central nervous system, cancer, tumour, neoplasm, malignant, metastases, carcinoma, papilloma , sarcoma, myeloma, glioblastoma, astrocytoma, oligodendroglioma, ependymomas, glioma, neurocytoma, Gliomatosis cerebri, Gliosarcoma, Hemangiopericytoma, Medulloblastoma, Medulloepithelioma, Meningeal carcinomatosis, Neuroblastoma, Neurocytoma, Oligoastrocytoma, Oligodendroglioma, meningioma, Pinealoblastoma, Pineocytoma, xanthoastrocytoma, Subependymoma, retinoblastoma, proliferation, apoptosis, and similar terms, as well as the Applicants/Inventors names.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] 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	Date of mailing of the international search report
19 May 2016	19 May 2016
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Christina van Broekhoven AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262833196

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2016/020396**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	Mita, M. et al. 2010 "Phase 1 First-in-Human Trial of the Vascular Disrupting Agent Plinabulin (NPI-2358) in Patients with Solid Tumors or Lymphomas". Clin. Cancer. Res. Vol. 16, no. 23, pp. 5892-5899 see Table 1 and pp. 5893 and 5896-8 see Table 1 and pp. 5893 and 5896-8	1, 5-7 and 9-13 7
Y	Bertelsen, L. et al 2011 "Vascular effects of plinabulin (NPI-2358) and the influence on tumour response when given alone or combined with radiation", Int. J. Radiat. Biol. Vol. 87, no.11, pp. 1126-1134. see whole document	7
A	WO 2005/077940 A1 (NEREUS PHARMACEUTICALS, INC.) 25 August 2005 see whole document	1-13
P,A	WO 2015/051543 A1 (BEYONDSPRING PHARMACEUTICALS, INC.) 16 April 2015 see whole document	1-13

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2016/020396**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2005/077940 A1	25 August 2005	WO 2005077940 A1	25 Aug 2005
		AU 2003302721 A1	09 Jul 2004
		AU 2003302721 B2	08 Oct 2009
		AU 2005212399 A1	25 Aug 2005
		AU 2005212399 B2	22 Sep 2011
		BR 0313363 A	09 Aug 2005
		BR PI0506655 A	08 May 2007
		CA 2494049 A1	01 Jul 2004
		CA 2553630 A1	25 Aug 2005
		CN 1684955 A	19 Oct 2005
		CN 1934101 A	21 Mar 2007
		CN 1934101 B	12 Oct 2011
		CN 101633655 A	27 Jan 2010
		CN 101633655 B	30 Apr 2014
		CO 5721010 A2	31 Jan 2007
		EP 1529044 A2	11 May 2005
		EP 1529044 B1	03 Oct 2007
		EP 1711487 A1	18 Oct 2006
		EP 1926724 A1	04 Jun 2008
		HK 1078080 A1	01 Feb 2008
		HK 1084388 A1	24 Dec 2009
		IL 166628 A	30 Aug 2012
		JP 2006511534 A	06 Apr 2006
		JP 4616649 B2	19 Jan 2011
		JP 2007520565 A	26 Jul 2007
		KR 20050083610 A	26 Aug 2005
		KR 101049100 B1	15 Jul 2011
		KR 20110039500 A	18 Apr 2011
		KR 101184374 B1	20 Sep 2012
		KR 20060124743 A	05 Dec 2006
		KR 101228104 B1	01 Feb 2013
		MX PA05001217 A	16 May 2005

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2016/020396**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		NZ 538433 A	29 Feb 2008
		NZ 548659 A	28 Jan 2011
		US 2005090667 A1	28 Apr 2005
		US 7064201 B2	20 Jun 2006
		US 2006217553 A1	28 Sep 2006
		US 7674903 B2	09 Mar 2010
		US 2007078138 A1	05 Apr 2007
		US 7919497 B2	05 Apr 2011
		US 2005197344 A1	08 Sep 2005
		US 7935704 B2	03 May 2011
		US 2006223823 A1	05 Oct 2006
		US 7956058 B2	07 Jun 2011
		US 2011245260 A1	06 Oct 2011
		US 8247552 B2	21 Aug 2012
		US 2012277251 A1	01 Nov 2012
		US 8618292 B2	31 Dec 2013
		US 2006223822 A1	05 Oct 2006
		WO 2004054498 A2	01 Jul 2004
		WO 2007035841 A1	29 Mar 2007
		ZA 200501616 A	05 Sep 2005
		ZA 200607151 A	30 Apr 2008
WO 2015/051543 A1	16 April 2015	WO 2015051543 A1	16 Apr 2015
		CA 2926771 A1	16 Apr 2015

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

摘要

本文公開了通過施用普林布林治療腦腫瘤的方法。一些實施方案涉及通過施用普林布林來治療多形性膠質母細胞瘤。