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(71) Applicant: **AUTOTELIC LLC** [US/US]; 17870 Castleton Street, Suite 250, City of Industry, California 91748 (US).

(72) Inventor: **TRIEU, Vuong**; 4003 Jim Bowie, Agoura Hills, California 91301 (US).

(74) Agent: **VAKHARIA-RAO, Hema** et al.; NIXON PEABODY LLP, 300 South Grand Avenue, Suite 4100, Los Angeles, California 90071-3151 (US).

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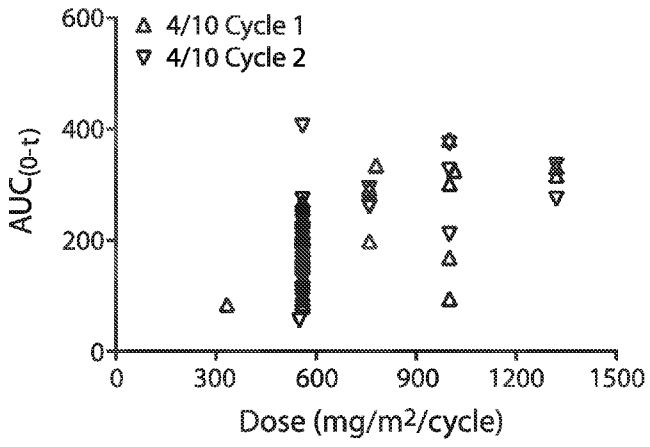
FIG. 3



(57) Abstract: Described herein are methods for trabedersen drug dosing by pharmacokinetic parameter determination. In one embodiment, the pharmacokinetic parameter is AUC. The methods are effective for sensitizing tumors to chemotherapeutic agents so as to treat cancer.

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METHODS FOR TRABEDERSEN DOSING BY AUC

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §119(e) to U.S. provisional patent application No. 62/360,101, filed on July 8, 2016, the content of which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The invention relates to methods for trabedersen dosing using pharmacokinetic parameters.

BACKGROUND

[0003] All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0004] Cancer therapeutic agents often result in high toxicity in the patient. There is a need in the art to improve the clinical effectiveness of administration of cancer therapeutic agents. The inventor has described the use of trabedersen to sensitize tumors to chemotherapeutic agents. The present invention describes dosing of trabedersen using pharmacokinetic parameter such as area-under-the curve (AUC).

SUMMARY

[0005] The following embodiments and aspects thereof are described and illustrated in conjunction with systems, compositions and methods which are meant to be exemplary and illustrative, not limiting in scope.

[0006] Provided herein are methods for trabedersen dosing by one or more pharmacokinetic parameters, comprising: administering trabedersen at a first dose to a subject in need thereof; obtaining a sample from the subject; determining the concentration of trabedersen in the sample at one or more time points after administration to provide a set of

trabedersen concentration/time data points; transforming the set of trabedersen concentration/time data points to provide one or more pharmacokinetic parameters; and administering trabedersen at subsequent doses to achieve a target optimal value for the one or more pharmacokinetic parameters.

[0007] In exemplary embodiments, the one or more pharmacokinetic parameters is selected from the group consisting of concentration time course, peak concentration (Cmax), and time after administration to peak concentration, terminal half-life, area-under-the-curve (AUC), bioavailability, absorption, distribution, metabolism, excretion, biotransformation, and combinations thereof. In one embodiment, the one or more pharmacokinetic parameters is area-under-the-curve (AUC).

[0008] In one embodiment, trabedersen is administered on a 4 days on and 10 days off cycle (4/10 cycle). In another embodiment, trabedersen is administered on a 7 days on and 7 days off cycle (7/7 cycle).

[0009] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 197 μg*hr/mL.

[0010] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 197 μg*hr/mL±5%.

[0011] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 197 μg*hr/mL±10 %.

[0012] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 197 μg*hr/mL±15%.

[0013] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 197 μg*hr/mL±20%.

[0014] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 197 μg*hr/mL±25%.

[0015] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 197 μg*hr/mL±30%.

[0016] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 200μg*h/mL.

[0017] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 200 μg*h/mL±5%.

[0018] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 200 μg*h/mL±10%.

[0019] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 200 μg*h/mL±15%.

[0020] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 200 μg*h/mL±20%.

[0021] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 200 μg*h/mL±25%.

[0022] In one embodiment, the administration cycle is a 4/10 cycle and the target AUC is about 200 μg*h/mL±30%.

[0023] In some embodiments, the pharmacokinetic parameters is area-under-the-curve (AUC), trabedersen is administered on a 4 days on and 10 days off cycle (4/10 cycle) and target AUC is the median AUC.

[0024] In one embodiment, the second dose is substantially the same as the first dose. In another embodiment, the second dose is lower than the first dose. In a further embodiment, the second dose is higher than the first dose.

[0025] In one embodiment, the subject has cancer. In some embodiments, trabedersen is administered prior to administration of a chemotherapeutic agent for at least one cycle so as to sensitize the tumor to the chemotherapeutic agent. In some embodiments, the sample is blood or plasma.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[0027] **Fig. 1A-Fig. 1B** depict in accordance with various embodiments of the invention, that trabedersen plasma exposure, i.e. area-under-the-curve (AUC), is dose proportional for the 7/7 cycle but not for the 4/10 cycle.

[0028] **Fig. 2** depicts in accordance with various embodiments of the invention, plot of $AUC_{(0\text{-}t)}$ vs. dose per cycle for trabedersen administered intravenously on 7-days-on/7-days-off treatment schedule. The indicated dose is mg/m^2/cycle (i.e. total trabedersen administered per cycle over the 7-days-on/7-days-off treatment schedule).

[0029] **Fig. 3** depicts in accordance with various embodiments of the invention, plot of $AUC_{(0\text{-}t)}$ vs. dose per cycle for trabedersen administered intravenously on 4-days-on/10-days-off treatment schedule. The indicated dose is mg/m^2/cycle (i.e. total trabedersen administered per cycle over the 4-days-on/10-days-off treatment schedule).

[0030] **Fig. 4** depicts in accordance with various embodiments of the invention, distribution of adverse events comparing gastrointestinal disorders and all others according to NCI-CTC (National Cancer Institute – Common Terminology Criteria for Adverse Events) intensity grade. 4-days-on/10-days-off therapy exhibits a highest proportion of grade 1 (mild) events for gastrointestinal disorders (56% of all events across 4-days-on/10-days-off therapy), while grade 2 (moderate) events comprised of the highest proportion of adverse events recorded for 7-days-on/7-days-off therapy (55% of all adverse events across 7-days-on/7-days-off therapy).

[0031] **Fig. 5** depicts in accordance with various embodiments of the invention, un-weighted GLM comparing gastrointestinal disorders with all others for proportion of grade 1 events. Significant effects were observed for cancer type (P = 0.0174), Log10 overall survival (P 0.0044), total dose administered (P = 0.0098) and a highly significant interaction of total dose administered and schedule (P = 0.0004). Prediction profiler demonstrated that at low total dose administered across all cycles per patient (4400), a higher proportion of grade 1 events was observed comparing 4-days-on/10-days-off therapy (0.61) to 7-days-on/7-days-off therapy (0.25) at the mid-point for Log10 overall survival.

[0032] **Fig. 6** depicts in accordance with various embodiments of the invention, un-weighted GLM including AUC comparing gastrointestinal disorders with all others for proportion of grade 1 events. Significant effects were observed for cancer type (P = 0.0166), Log10 overall survival (P

0.0039), total dose administered (P = 0.0286), a highly significant interaction of total dose administered and schedule (P = 0.0011) and AUC_{last} (P = 0.0144).

[0033] **Fig. 7** depicts in accordance with various embodiments of the invention, plot of dose vs. overall survival (OS) in pancreatic cancer patients treated with intravenous infusion of trabedersen using 4-days-on/10-days-off regimen. There is no clear correlation of dose with OS for both groups with or without subsequent chemotherapy.

DETAILED DESCRIPTION

[0034] All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Allen *et al.*, *Remington: The Science and Practice of Pharmacy 22nd ed.*, Pharmaceutical Press (September 15, 2012); Hornyak *et al.*, *Introduction to Nanoscience and Nanotechnology*, CRC Press (2008); Singleton and Sainsbury, *Dictionary of Microbiology and Molecular Biology 3rd ed., revised ed.*, J. Wiley & Sons (New York, NY 2006); Smith, *March's Advanced Organic Chemistry Reactions, Mechanisms and Structure 7th ed.*, J. Wiley & Sons (New York, NY 2013); Singleton, *Dictionary of DNA and Genome Technology 3rd ed.*, Wiley-Blackwell (November 28, 2012); and Green and Sambrook, *Molecular Cloning: A Laboratory Manual 4th ed.*, Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2012), provide one skilled in the art with a general guide to many of the terms used in the present application. For references on how to prepare antibodies, see Greenfield, *Antibodies A Laboratory Manual 2nd ed.*, Cold Spring Harbor Press (Cold Spring Harbor NY, 2013); Köhler and Milstein, *Derivation of specific antibody-producing tissue culture and tumor lines by cell fusion*, Eur. J. Immunol. 1976 Jul, 6(7):511-9; Queen and Selick, *Humanized immunoglobulins*, U. S. Patent No. 5,585,089 (1996 Dec); and Riechmann *et al.*, *Reshaping human antibodies for therapy*, Nature 1988 Mar 24, 332(6162):323-7.

[0035] One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, various features of embodiments of the invention. Indeed, the present invention is in no way limited to the methods and materials described. For

convenience, certain terms employed herein, in the specification, examples and appended claims are collected here.

[0036] Unless stated otherwise, or implicit from context, the following terms and phrases include the meanings provided below. Unless explicitly stated otherwise, or apparent from context, the terms and phrases below do not exclude the meaning that the term or phrase has acquired in the art to which it pertains. The definitions are provided to aid in describing particular embodiments, and are not intended to limit the claimed invention, because the scope of the invention is limited only by the claims. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0037] Unless stated otherwise, the terms "a" and "an" and "the" and similar references used in the context of describing a particular embodiment of the application (especially in the context of claims) can be construed to cover both the singular and the plural. The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (for example, "such as") provided with respect to certain embodiments herein is intended merely to better illuminate the application and does not pose a limitation on the scope of the application otherwise claimed. The abbreviation, "e.g." is derived from the Latin exempli gratia, and is used herein to indicate a non-limiting example. Thus, the abbreviation "e.g." is synonymous with the term "for example." No language in the specification should be construed as indicating any non-claimed element essential to the practice of the application.

[0038] As used herein the term "comprising" or "comprises" is used in reference to compositions, methods, and respective component(s) thereof, that are useful to an embodiment, yet open to the inclusion of unspecified elements, whether useful or not. It will be understood by those within the art that, in general, terms used herein are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). Although the open-

ended term "comprising," as a synonym of terms such as including, containing, or having, is used herein to describe and claim the invention, the present invention, or embodiments thereof, may alternatively be described using alternative terms such as "consisting of" or "consisting essentially of."

[0039] A "cancer" or "tumor" as used herein refers to an uncontrolled growth of cells which interferes with the normal functioning of the bodily organs and systems, and/or all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. A subject that has a cancer or a tumor is a subject having objectively measurable cancer cells present in the subject's body. Included in this definition are benign and malignant tumors, as well as dormant tumors or micrometastasis. Cancers which migrate from their original location and seed vital organs can eventually lead to the death of the subject through the functional deterioration of the affected organs. As used herein, the term "invasive" refers to the ability to infiltrate and destroy surrounding tissue. Melanoma is an invasive form of skin tumor. As used herein, the term "carcinoma" refers to a cancer arising from epithelial cells. Examples of cancer include, but are not limited to, nervous system tumor, brain tumor, nerve sheath tumor, breast cancer, colorectal cancer, colon cancer, rectal cancer, bowel cancer, carcinoma, lung cancer, hepatocellular cancer, gastric cancer, pancreatic cancer, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, thyroid cancer, renal cancer, renal cell carcinoma, carcinoma, melanoma, head and neck cancer, brain cancer, and prostate cancer, including but not limited to androgen-dependent prostate cancer and androgen-independent prostate cancer. Examples of brain tumor include, but are not limited to, benign brain tumor, malignant brain tumor, primary brain tumor, secondary brain tumor, metastatic brain tumor, glioma, glioblastoma, glioblastoma multiforme (GBM), medulloblastoma, ependymoma, astrocytoma, pilocytic astrocytoma, oligodendroglioma, brainstem glioma, optic nerve glioma, mixed glioma such as oligoastrocytoma, low-grade glioma, high-grade glioma, supratentorial glioma, infratentorial glioma, pontine glioma, meningioma, pituitary adenoma, and nerve sheath tumor. Nervous system tumor or nervous system neoplasm refers to any tumor affecting the nervous system. A nervous system tumor can be a tumor in the central nervous system (CNS), in the peripheral nervous system (PNS), or in both CNS and PNS. Examples of nervous system tumor include but are not limited to brain tumor, nerve sheath tumor, and optic nerve glioma.

[0040] As used herein, the term "administering," refers to the placement of an agent or a composition as disclosed herein into a subject by a method or route which results in at least partial localization of the agents or composition at a desired site. "Route of administration" may refer to any administration pathway known in the art, including but not limited to oral, topical, aerosol, nasal, via inhalation, anal, intra-anal, peri-anal, transmucosal, transdermal, parenteral, enteral, or local. "Parenteral" refers to a route of administration that is generally associated with injection, including intratumoral, intracranial, intraventricular, intrathecal, epidural, intradural, intraorbital, infusion, intracapsular, intracardiac, intradermal, intramuscular, intraperitoneal, intrapulmonary, intraspinal, intrasternal, intrathecal, intrauterine, intravascular, intravenous, intraarterial, subarachnoid, subcapsular, subcutaneous, transmucosal, or transtracheal. Via the parenteral route, the agent or composition may be in the form of solutions or suspensions for infusion or for injection, or as lyophilized powders. Via the enteral route, the agent or composition can be in the form of capsules, gel capsules, tablets, sugar-coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, microspheres or nanospheres or lipid vesicles or polymer vesicles allowing controlled release. Via the topical route, the agent or composition can be in the form of aerosol, lotion, cream, gel, ointment, suspensions, solutions or emulsions. In an embodiment, agent or composition may be provided in a powder form and mixed with a liquid, such as water, to form a beverage. In accordance with the present invention, "administering" can be self-administering. For example, it is considered as "administering" that a subject consumes a composition as disclosed herein.

[0041] As used herein, a "subject" means a human or animal. Usually the animal is a vertebrate such as a primate, rodent, domestic animal or game animal. Primates include chimpanzees, cynomologous monkeys, spider monkeys, and macaques, e.g., Rhesus. Rodents include mice, rats, woodchucks, ferrets, rabbits and hamsters. Domestic and game animals include cows, horses, pigs, deer, bison, buffalo, feline species, e.g., domestic cat, and canine species, e.g., dog, fox, wolf. The terms, "patient", "individual" and "subject" are used interchangeably herein. In an embodiment, the subject is mammal. The mammal can be a human, non-human primate, mouse, rat, dog, cat, horse, or cow, but are not limited to these examples. In addition, the methods described herein can be used to treat domesticated animals and/or pets.

[0042] "Mammal" as used herein refers to any member of the class Mammalia, including, without limitation, humans and nonhuman primates such as chimpanzees and other apes and

monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be included within the scope of this term.

[0043] A "subject" can be one who has been previously diagnosed with or identified as suffering from or having a condition in need of treatment (e.g., pancreatic cancer or melanoma or carcinoma) or one or more complications related to the condition, and optionally, have already undergone treatment for the condition or the one or more complications related to the condition. Alternatively, a subject can also be one who has not been previously diagnosed as having a condition or one or more complications related to the condition. For example, a subject can be one who exhibits one or more risk factors for a condition or one or more complications related to the condition or a subject who does not exhibit risk factors. For example, a subject can be one who exhibits one or more symptoms for a condition or one or more complications related to the condition or a subject who does not exhibit symptoms.

[0044] The term "cycle" as used herein refers to the number of days when the inhibitor of TGFβ is administered and number of days when the inhibitor of TGFβ is not administered. In an embodiment, one cycle is defined as administering the inhibitor for 7 days at a specific dosage per day and then not administering the inhibitor for 7 days. This is referred to as "7 days on and 7 days off" cycle. In another embodiment, one cycle is defined as administering the inhibitor for 4 days at a specific dosage per day and then not administering the inhibitor for 10 days. This is referred to as "4 days on and 10 days off cycle".

[0045] The term "sensitization" as used herein refers to making the tumors sensitive to treatment. In one embodiment, trabedersen or a variant, derivative or analog thereof sensitizes tumors to subsequent exogenously administered therapies such as chemotherapy, radiation therapy, hormonal therapy or combination thereof. In another embodiment, trabedersen or a variant, derivative or analog thereof sensitizes tumors to the patient's own endogenous immune system. In exemplary embodiments, when a tumor is sensitized with trabedersen or a variant, derivative or analog thereof prior to chemotherapy, administration of one or more chemotherapeutic agents following treatment with trabedersen or a variant, derivative or analog thereof results in at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%,

90% or 100% improved response to the chemotherapeutic agents compared to treatment with the chemotherapeutic agents without sensitization with trabedersen or a variant, derivative or analog thereof.

[0046] "Trabedersen" or "trabedersen" as used herein refers to a transforming growth factor (TGF)-beta2 (TGFβ2) specific phosphorothioate antisense oligodeoxynucleotide with the sequence 5'-CGGCATGTCTATTTTGTA-3', as shown in SEQ ID No: 1. In exemplary embodiments, inhibitors of TGFβ, including inhibitors of TGFβ2 (such as trabedersen) are described in WO94/25588, WO95/17507, WO95/02051, WO98/33904, WO99/63975, WO01/68146, WO01/68122, WO03/064457, WO2005/014812, WO2004/093945, WO2005/059133, WO2005/084712, WO2006/11740, WO2008/077956A2, WO2010/055148, WO2011/012713A1, WO2011/154542, EP application no. 20100191103, WO2014154835 A2, WO2015/140150A1, the contents of each of which are herein incorporated by reference. In one embodiment, trabedersen is LNA modified. A LNA is a modified RNA nucleotide, wherein the ribose moiety is modified with an extra bridge connecting the 2' oxygen and 4' carbon (2'- 4 'ribonucleoside). The bridge "locks" the ribose in the 3'-endo (North) conformation, which is often found in the A- form duplexes. LNA nucleosides and nucleotides, respectively, comprise for example the forms of thio-LNA, oxy-LNA, or amino-LNA, in alpha-D- or beta-L-configuration, and are mixable and combinable, respectively, with DNA or RNA residues in the oligonucleotide.

[0047] As used herein, "concentration/time data points" refers to the concentration of a drug in a series of blood samples obtained from the subject who has been administered the drug over a period of time. In one embodiment, trabedersen concentration/time data points refer to the concentration of trabedersen in the samples obtained from the subject over a period of time, wherein the samples are obtained at one or more points in time after administration of trabedersen.

[0048] Bioavailability of a drug is defined as the proportion of a drug or other substance that enters the circulation when introduced into the body and so is able to have an active effect. Measures of bioavailability well known in the art include the area under the plasma concentration-time curve (AUC), the concentration maximum (C_{max}), and the time to C_{max} (T_{max}). AUC is a measurement of the area under the plasma concentration-time curve, and is representative of the total drug exposure following administration of a single dose or multiple dose of a drug (Remington: The Science and Practice of Pharmacy, (Alfonso R. Gennaro ed.

2000), page 999). C_{max} is the maximum plasma concentration achieved after drug administration (Remington, page 999). T_{max} is the amount of time necessary to achieve the C_{max} after drug administration, and is related to the rate of absorption of a drug (Remington, page 999).

Trabedersen Dosing by AUC

[0049] When the mean AUC was taken into consideration, dose proportionality of trabedersen was demonstrated when trabedersen was administered for 7 days-on/7 days-off cycle. However, dose proportionality of trabedersen was not demonstrated when trabedersen was administered for 4 days-on/10 days-off cycle.

[0050] Provided herein are methods for dosing trabedersen for sensitizing tumors to chemotherapeutic agents using one or more pharmacokinetic parameters. The methods include administering trabedersen at a first dose to a subject in need thereof; determining the concentration of trabedersen in a sample obtained from the subject at one or more time points after administration of trabedersen to provide a set of trabedersen concentration/time data points; transforming the set of trabedersen concentration/time data points to provide one or more pharmacokinetic parameters; and administering trabedersen at subsequent doses to achieve a target optimal value for the one or more pharmacokinetic parameters. In some embodiments, the pharmacokinetic parameters is area-under-the-curve (AUC), trabedersen is administered on a 4 days on and 10 days off cycle (4/10 cycle) and target AUC is the median AUC.

[0051] In some embodiments, the sample is blood or plasma. In various embodiments, the sample is obtained before administration of trabedersen and at least once more after administration of trabedersen. In some embodiments, the sample is obtained at least 2, 3, 4, 5, 6 7, 8, 9 and/or 10 times after administration of trabedersen for each cycle at various time intervals. Time intervals post administration of trabedersen include but are not limited to any one or more of 0.1, 0.2, 0.3, 0.4, 0.5, 0.8, 1, 2, 3, 4, 5, 7, 9, 11, 15, 20, 24 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days and/or 10 days post administration of trabedersen.

[0052] In exemplary embodiments, the one or more pharmacokinetic parameters include but are not limited to concentration time course, peak concentration (C_{max}), and time after administration to peak concentration (T_{max}), terminal half-life, area-under-the-curve (AUC),

bioavailability, absorption, distribution, metabolism, excretion, biotransformation, or combinations thereof.

[0053] Provided herein are methods for dosing trabedersen for sensitizing tumors to chemotherapeutic agents using one or more pharmacokinetic parameters. The methods include administering trabedersen at a first dose to a subject in need thereof; determining the concentration of trabedersen in a sample obtained from the subject at one or more time points after administration of trabedersen to provide a set of trabedersen concentration/time data points; transforming the set of trabedersen concentration/time data points to provide area-under-the-curve (AUC); and administering trabedersen at subsequent doses to achieve a target AUC of about 200μg*hr/ml.

[0054] Provided herein are methods for dosing trabedersen for sensitizing tumors to chemotherapeutic agents using one or more pharmacokinetic parameters. The methods include administering trabedersen at a first dose to a subject in need thereof; determining the concentration of trabedersen in a sample obtained from the subject at one or more time points after administration of trabedersen to provide a set of trabedersen concentration/time data points; transforming the set of trabedersen concentration/time data points to provide area-under-the-curve (AUC); and administering trabedersen at subsequent doses to achieve a target AUC of about 197μg*hr/ml.

[0055] Provided herein are methods for dosing trabedersen for sensitizing tumors to chemotherapeutic agents using AUC as a pharmacokinetic parameter. The methods include administering trabedersen at a first dose (for example, under a first regimen, such as one cycle) to a subject in need of sensitizing a tumor to cancer therapy (such as cancer chemotherapy); determining the concentration of trabedersen in the subject's blood at one or more time points (for example, a series of time points, such as any one or more of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24 hours) after administration of trabedersen to provide a set of trabedersen concentration/time data points; transforming the set of trabedersen concentration/time data points to provide area-under-the-curve (AUC) (i.e. AUC resulting from the first dose); and administering trabedersen at subsequent doses to achieve a target AUC of about 200μg*hr/ml.

[0056] Provided herein are methods for dosing trabedersen for sensitizing tumors to chemotherapeutic agents using AUC as a pharmacokinetic parameter. The methods include

administering trabedersen at a first dose (for example, under a first regimen, such as one cycle) to a subject in need of sensitizing a tumor to cancer therapy (such as cancer chemotherapy); determining the concentration of trabedersen in the subject's blood at one or more time points (for example, a series of time points, such as any one or more of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24 hours) after administration of trabedersen to provide a set of trabedersen concentration/time data points; transforming the set of trabedersen concentration/time data points to provide area-under-the-curve (AUC) (i.e. AUC resulting from the first dose); and administering trabedersen at subsequent doses to achieve a target AUC of about 197μg*hr/ml.

[0057] In exemplary embodiments, trabedersen is used in cancer therapy, wherein trabedersen is administered prior to administration of a cancer therapeutic agent so as to sensitize the tumor to the cancer therapeutic agent.

[0058] In some embodiments, one treatment cycle of trabedersen comprises administering trabedersen to a subject on a 4/10 cycle wherein trabedersen is administered for four days and then not administered for ten days. In one embodiment, the pharmacokinetic parameter is AUC. In one embodiment, the target AUC is about 175μg*h/mL. In one embodiment, the target AUC is about 197μg*h/mL. In one embodiment, the target AUC is about 200μg*h/mL. In some embodiments, the target AUC is about 100-400μg*h/mL. In some embodiments, the target AUC is about 125-375μg*h/mL. In some embodiments, the target AUC is about 150-350μg*h/mL. In some embodiments, the target AUC is about 150-300μg*h/mL. In some embodiments, the target AUC is about 150-250μg*h/mL. In some embodiments, the target AUC is about 150-200μg*h/mL. In some embodiments, the target AUC is about 175-200μg*h/mL.

[0059] In some embodiments, the target AUC is about 197μg*h/mL±5%. In some embodiments, the target AUC is about 197μg*h/mL±10%. In further embodiments, the target AUC is about 197μg*h/mL±15%. In further embodiments, the target AUC is about 197μg*h/mL±20%. In some embodiments, the target AUC is about 197μg*h/mL±25%. In additional embodiments, the target AUC is about 197μg*h/mL±30%. In some embodiments, the target AUC is about 200μg*h/mL±5%. In some embodiments, the target AUC is about 200μg*h/mL±10%. In further embodiments, the target AUC is about 200μg*h/mL±15%. In further embodiments, the target AUC is about 200μg*h/mL±20%. In some embodiments, the

target AUC is about 200μg*h/mL±25%. In additional embodiments, the target AUC is about 200μg*h/mL±30%. The target AUC of about 197μg*h/mL was determined from statistical analysis of a population of subject receiving trabedersen. The target AUC is the median AUC value determination from a population of subject receiving trabedersen at a dose of 140mg/m^2/day using the 4/10 cycle. As described herein, dose-proportionality is not observed for the 4/10 treatment schedule. In one embodiment, the subjects have cancer.

[0060] Because of absence of drug accumulation, determination of the second dose is straight forward. When the determined AUC is the same as the target AUC (about 200μg*h/mL for the 4/10 cycle), the dose in the second cycle is the same or substantially the same as the dose in the first cycle. When the determined AUC is greater than the target AUC, the dose in the second cycle is less than the dose in the first cycle by the same proportions. When the determined AUC is less than the target AUC, the dose in the second cycle is greater than the dose in the first cycle by the same proportion.

[0061] The target AUC dosing can be varied to higher or lower target AUC when the patient is demonstrating resistance or sensitivity, respectively, to trabedersen. Regardless, once the targeted AUC for the patient has been defined, the target AUC may need to be maintained despite changes in physical conditions (weight) and physiological conditions (for example, organ function).

[0062] In certain embodiments, the method described herein comprises repeating the step set forth herein until the target AUC is achieved.

[0063] Area-under-the-curve (AUC) is a pharmacokinetic parameter that is used in the method of the invention to dose trabedersen. As used herein, the term "area under the curve (AUC)" is the area under the curve in a plot of concentration of drug in blood plasma as a function of time. Typically, the area is calculated starting at the time the drug is administered and ending when the concentration in plasma is negligible. AUC represents the total drug exposure over time. Assuming linear pharmacokinetics with elimination rate constant K, AUC is proportional to the total amount of drug absorbed by the body (i.e., the total amount of drug that reaches the blood circulation). The proportionality constant is 1/K.

[0064] As used herein, the phrase "transforming the concentration/time data points" refers to the application of mathematical operations, formulas, theories, and/or principles (i.e., a

formula for calculating AUC) to the concentrations/time data points of the individual subject to provide AUC.

[0065] In some embodiments, the concentration of trabedersen in the sample (such as blood or plasma) is measured using ELISA, capillary gel electrophoresis with subsequence UV detection at 260nm. In the methods of the invention, the nature of the device or method for determining the concentrations/time data points for calculating AUC is not critical. Methods and devices for determining trabedersen concentrations are known in the art and can be used. In certain embodiments, a point-of-care device can be used to determine the concentrations and create the concentration/time data, transmit the data to a central location, and/or transmitting instructions to the patient to alter the administration.

EXAMPLES

[0066] The following examples are not intended to limit the scope of the claims to the invention, but are rather intended to be exemplary of certain embodiments. Any variations in the exemplified methods which occur to the skilled artisan are intended to fall within the scope of the present invention.

Example 1

[0067] A total of 61 patients with pancreatic cancer (n=37), malignant melanoma (n=19), or colorectal carcinoma (n=5) were treated with Trabedersen with escalating doses in two treatment schedules. The first schedule was 7-days on and 7-days off (7/7 cycle) up to 10 cycles and the second schedule was 4-days on, 10-days off, also up to 10 cycles. The pharmacokinetic (PK) analysis was only performed on Cycle 1 and when applicable, Cycle 2. Blood samples were collected from patients at planned time points beginning at before start of infusion of trabedersen to 7 days (7/7 cycle) or 10 days (4/10 cycle) after stopping infusion of trabedersen. The plasma concentration of trabedersen was analyzed using capillary gel electrophoresis with subsequent UV detection (260 nm). The PK parameters were estimated using WinNonlin software using a non-compartmental approach.

[0068] For the 7/7 cycle, the escalating doses were 40mg/m^2/day, 80mg/m^2/day, 160mg/m^2/day or 240mg/m^2/day (**Table 1**). The maximum tolerated dose (MTD) for the 7/7 cycle was 160mg/m^2/day. As shown in **Fig. 1A**, in the 7/7 cycle, the AUC was proportional to the dose indicating that exposure to trabedersen in the subject is proportional to the dose of trabedersen administered over the 7-days dosing period and that AUC is an optimal

pharmacokinetic parameter to modulate trabedersen dosing when the 7/7 cycle is used. In the 7/7 cycle, the observed AUC for trabedersen dose of: 40mg/m^2/day is about 93μg*h/mL, 80mg/m^2/day is about 142μg*h/mL, 160mg/m^2/day is about 383μg*h/mL and 240mg/m^2/day is about 600μg*h/mL (**Fig. 1A**).

[0069] For the 4/10 cycle, the escalating doses were 140mg/m^2/day, 190mg/m^2/day, 250mg/m^2/day or 330mg/m^2/day (**Table 2**). The maximum tolerated dose (MTD) for the 4/10 cycle was not reached even at trabedersen dose of 330mg/m^2/day. As shown in **Fig. 1B**, in the 4/10 cycle, the AUC was not proportional to the dose..

[0070] The distribution half-life of trabedersen was estimated to be approximately between 1 and 2 hours. The PK profiles of trabedersen showed sustained plasma concentrations throughout the dosing period (4 or 7 days) with similar PK exposure parameters (C_{max} and AUC) between Cycle 1 and Cycle 2. There was no accumulation of peak (C_{max}) or total (AUC) plasma exposure measures following repeat administration.

[0071] **Table 1**.

7on/7off	Cycle 1					Cycle 2					DLT	MTD
Dose	**N**	**AUC(0-t) Mean**	**AUC SD**	**Cmax Mean**	**Cmax SD**	**N**	**AUC(0-t) Mean**	**AUC SD**	**Cmax Mean**	**Cmax SD**		
40	3	92.73	56.76	0.96	0.60	2	53.00	37.76	0.48	0.19	0	
80	3	141.50	76.03	1.46	1.02	3	127.33	24.09	1.35	0.55	0	
160	5	383.00	142.27	2.86	1.03	3	356.00	202.23	2.38	1.10	0	X
240	4	599.33	161.20	4.62	0.61	2	637.00		5.00	0.59	3	

[0072] **Table 2.**

4on/10off	Cycle 1					Cycle 2					DLT	MTD
Dose	**N**	**AUC(0-t) Mean**	**AUC SD**	**Cmax Mean**	**Cmax SD**	**N**	**AUC(0-t) Mean**	**AUC SD**	**Cmax Mean**	**Cmax SD**		
140	24	173.34	64.72	2.24	0.87	23	192.63	73.76	2.43	0.84	1	
190	3	277.33	72.46	3.24	0.70	3	271.33	18.77	3.31	0.25	0	

250	5	253.72	118.85	2.95	1.25	3	523.33	408.04	3.68	1.27	0	
330	2	323.50	10.61	3.91	0.16	2	304.50	43.13	3.50	0.68	0	

Example 2: **Trabedersen AUC-guided dosing**

[0073] *Clear dose-proportionality for 7-days-on/7-days-off, but not for 4-days-on/10-days-off treatment schedule*

[0074] For most drugs, increasing the dose of the drugs will increase exposure to the drug (AUC). When trabedersen is administered intravenously on 7-days-on/7-days-off schedule, $AUC_{(0\text{-}t)}$, a clear dose-proportional increase in trabedersen exposure was observed (**Fig. 2**). However, when trabedersen administered intravenously on 4-days-on/10-days-off schedule $AUC_{0\text{-}t}$, a dose-proportional increase in trabedersen exposure was not observed (**Fig. 3**).

[0075] *4-days-on/10-days-off is safer than the 7-days-on/7-days-off treatment regimen*

[0076] From the Phase I/II clinical study that was conducted with intravenously administered trabedersen in patients with advanced pancreatic cancer, malignant melanoma, or colorectal cancer, the 7-days-on/7-days-off treatment regimen reached the maximum tolerated dose (MTD) at 160 mg/m^2/day (1120 mg/m^2/cycle), while the 4-days-on/10-days-off treatment schedule did not reach MTD with dose up to 330 mg/m^2/day (1320 mg/m^2/cycle).

[0077] Generalized Linear Models (GLM) were fitted to binomial response model (proportion of NCI-CTC grade 1 relative to combined Grade 2,3,4 adverse events (AEs)) to investigate relationship of clinical parameters and treatment schedule to proportion of low severity grade 1 AEs in cancer patients. One model was used to test for the effect of schedule on the proportion of grade 1 AEs at different dosing levels in pancreatic cancers. Examination of the distribution of AEs comparing gastrointestinal disorders and all others according to NCI-CTC intensity grade (**Fig. 4**) revealed that 4-days-on/10-days-off therapy exhibits a highest proportion of grade 1 AEs for gastrointestinal disorders (56% of all events across 4-days-on/10-days-off therapy), while grade 2 AEs comprised of the highest proportion of AEs recorded for 7-days-on/7-days-off therapy (55% of all AEs across 7-days-on/7-days-off therapy). For all other primary organ disorders, grade 1 AEs constituted the highest proportion for both 4-day-on/10-days-off and 7-days-on/7-days-off therapies.

[0078] *Selection of 140 mg/m^2/day (4-days-on/10-days-off) as the safe and effective dose for the future study*

[0079] Higher dose with higher toxicity

[0080] The proportion of grade 1 AEs was dependent on the total dose exemplified by linear contrasts for the GLM model set at a low total dose value of 1000 mg predicted that 4 day on therapy results in a greater proportion of grade 1 AEs compared to 7 day on therapy for gastrointestinal disorders (P = 0.001), but not for any other disorders. Other organ class toxicities were either not significant or weakly borderline significant. Therefore, the most significant effect comparing intensity of AE for the 2 schedules was observed for the decrease in proportion of more severe grades 2, 3 and 4 events for the 4-days-on/10-days-off therapy delivered at low total dose for gastrointestinal disorders. The un-weighted GLM model was utilized to test the effect of different doses on the distribution of grade 1 events in gastrointestinal disorders (**Fig. 5**). Significant effects were observed for cancer type (P = 0.0174), Log_{10} overall survival (P 0.0044), total dose administered (P = 0.0098) and a highly significant interaction of total dose administered and schedule (P = 0.0004). With increase of dose, the proportion of grade 1 AE reduced, indicating higher toxicity with higher dose.

[0081] Higher exposure (AUC) with higher toxicity

[0082] With inclusion of drug exposure (AUC) into the un-weighted GLM model, AUC is also a significant factor for the proportion of grade 1 AE (p=0.0144). As shown in **Fig. 6**, with increase of AUC, the proportion of grade 1 AE reduced, indicating the higher toxicity with higher AUC.

[0083] Higher dose without better response

[0084] For pancreatic cancer patients treated with 4-days-on/10-days-off regimen, there is no clear correlation of dose with overall survival (OS) (**Fig. 7**). Patients treated with higher dose did not show a better OS but showed more toxicity, therefore the lowest safe and effective dose, 140/mg/m^2/day (4-days-on/10-days-off), will be used as the dosing regimen in the future clinical study.

[0085] *Median AUC at 140 mg/m^2/day as the target for AUC-guided dosing*

[0086] As shown from the Phase I/II study that 140 mg/m^2/day (4-days-on/10-days-off) is a safe and effective dose, the median AUC at 140 mg/m^2/day will used as the target for AUC-

guided dosing for intravenous administration of trabedersen. The median AUC at 140 mg/m^2/day is 176.23 μg*hr/mL (**Table 3**). The median AUC of patients across all the dose levels is 197.83 μg*hr/mL.

[0087] **Table 3**. Median AUC at each dose level with 4-days-on/10-days-off treatment regimen.

Dose per day (mg/m^2/day)	Dose per cycle (mg/m^2)	No. of patient cycles	Median AUC (ug*hr/mL)
140	560	47	176.23
190	760	6	276.77
250	1000	8	313.26
330	1320	4	323.66

[0088] Without being bound to a particular theory, the inventor shows that the drug exposure (AUC) of intravenously administered trabedersen is dose-proportional for 7-days-on/7-days-off treatment regimen, but not clear for 4-days-on/10-days-off regimen. The 7-days-on/7-days-off treatment regimen reached MTD at 160 mg/m^2/day (1120 mg/m^2/cycle), while the 4-days-on/10-days-off treatment schedule didn't reach MTD with dose up to 330 mg/m^2/day (1320 mg/m^2/cycle). Increase of dose and AUC of trabedersen associated with increased toxicity, but not overall survival of cancer patients, which justify using the lowest effective dose, 140 mg/m^2/day (4-days-on/10-days-off), for the future treatment, with AUC-guided dosing to minimize the toxicity associated with higher exposure.

[0089] The median AUC of all patients treated using the 4/10 schedule will be used as target AUC for patients treated with Trabedersen to minimize toxicity while maximizing efficacy.

[0090] The various methods and techniques described above provide a number of ways to carry out the application. Of course, it is to be understood that not necessarily all objectives or advantages described can be achieved in accordance with any particular embodiment described herein. Thus, for example, those skilled in the art will recognize that the methods can be performed in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other objectives or advantages as taught or suggested herein. A variety of alternatives are mentioned herein. It is to be understood that some preferred embodiments specifically include one, another, or several

features, while others specifically exclude one, another, or several features, while still others mitigate a particular feature by inclusion of one, another, or several advantageous features.

[0091] Furthermore, the skilled artisan will recognize the applicability of various features from different embodiments. Similarly, the various elements, features and steps discussed above, as well as other known equivalents for each such element, feature or step, can be employed in various combinations by one of ordinary skill in this art to perform methods in accordance with the principles described herein. Among the various elements, features, and steps some will be specifically included and others specifically excluded in diverse embodiments.

[0092] Although the application has been disclosed in the context of certain embodiments and examples, it will be understood by those skilled in the art that the embodiments of the application extend beyond the specifically disclosed embodiments to other alternative embodiments and/or uses and modifications and equivalents thereof.

[0093] Preferred embodiments of this application are described herein, including the best mode known to the inventors for carrying out the application. Variations on those preferred embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. It is contemplated that skilled artisans can employ such variations as appropriate, and the application can be practiced otherwise than specifically described herein. Accordingly, many embodiments of this application include all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the application unless otherwise indicated herein or otherwise clearly contradicted by context.

[0094] All patents, patent applications, publications of patent applications, and other material, such as articles, books, specifications, publications, documents, things, and/or the like, referenced herein are hereby incorporated herein by this reference in their entirety for all purposes, excepting any prosecution file history associated with same, any of same that is inconsistent with or in conflict with the present document, or any of same that may have a limiting affect as to the broadest scope of the claims now or later associated with the present document. By way of example, should there be any inconsistency or conflict between the description, definition, and/or the use of a term associated with any of the incorporated

material and that associated with the present document, the description, definition, and/or the use of the term in the present document shall prevail.

[0095] It is to be understood that the embodiments of the application disclosed herein are illustrative of the principles of the embodiments of the application. Other modifications that can be employed can be within the scope of the application. Thus, by way of example, but not of limitation, alternative configurations of the embodiments of the application can be utilized in accordance with the teachings herein. Accordingly, embodiments of the present application are not limited to that precisely as shown and described.

[0096] Various embodiments of the invention are described above in the Detailed Description. While these descriptions directly describe the above embodiments, it is understood that those skilled in the art may conceive modifications and/or variations to the specific embodiments shown and described herein. Any such modifications or variations that fall within the purview of this description are intended to be included therein as well. Unless specifically noted, it is the intention of the inventors that the words and phrases in the specification and claims be given the ordinary and accustomed meanings to those of ordinary skill in the applicable art(s).

[0097] The foregoing description of various embodiments of the invention known to the applicant at this time of filing the application has been presented and is intended for the purposes of illustration and description. The present description is not intended to be exhaustive nor limit the invention to the precise form disclosed and many modifications and variations are possible in the light of the above teachings. The embodiments described serve to explain the principles of the invention and its practical application and to enable others skilled in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. Therefore, it is intended that the invention not be limited to the particular embodiments disclosed for carrying out the invention.

[0098] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that, based upon the teachings herein, changes and modifications may be made without departing from this invention and its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as are within the true spirit and scope of this invention.

CLAIMS

1. A method for trabedersen dosing by one or more pharmacokinetic parameters, comprising:
   Administering trabedersen at a first dose to a subject in need thereof;
   Obtaining a sample from the subject;
   Determining the concentration of trabedersen in the sample at one or more time points after administration to provide a set of trabedersen concentration/time data points
   Transforming the set of trabedersen concentration/time data points to provide one or more pharmacokinetic parameters; and
   Administering trabedersen at subsequent doses to achieve a target optimal value for the one or more pharmacokinetic parameters.

2. The method of claim 1, wherein the one or more pharmacokinetic parameters is selected from the group consisting of concentration time course, peak concentration (Cmax), and time after administration to peak concentration, terminal half-life, area-under-the-curve (AUC), bioavailability, absorption, distribution, metabolism, excretion, biotransformation, and combinations thereof.

3. The method of claim 1, wherein the one or more pharmacokinetic parameters is area-under-the-curve (AUC).

4. The method of claim 3, wherein trabedersen is administered on a 4 days on and 10 days off cycle (4/10 cycle).

5. The method of claim 4, wherein the target AUC is about 197±15%μg*h/mL.

6. The method of claim 4, wherein the target AUC is about 197±20%μg*h/mL .

7. The method of claim 4, wherein the target AUC is about 197±25%μg*h/mL.

8. The method of claim 4, wherein the target AUC is about 197±30%μg*h/mL.

9. The method of claim 1, wherein the second dose is substantially the same as the first dose.

10. The method of claim 1, wherein the second dose is lower than the first dose.

11. The method of claim 1, wherein the second dose is higher than the first dose.

12. The method of claim 1, wherein the subject has cancer.

13. The method of claim 12, wherein the cancer is prostate cancer, melanoma or carcinoma.

14. The method of claim 1, wherein trabedersen is administered prior to administration of a chemotherapeutic agent.

15. The method of claim 1, wherein the sample is blood or plasma.

16. The method of claim 1, wherein the time points are any one or more of 10 minutes, 20 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 24 hours, 2 days, 3 days or 4 days.

17. The method of claim 1, wherein the pharmacokinetic parameters is area-under-the-curve (AUC), trabedersen is administered on a 4 days on and 10 days off cycle (4/10 cycle) and target AUC is the median AUC.

FIG. 1A

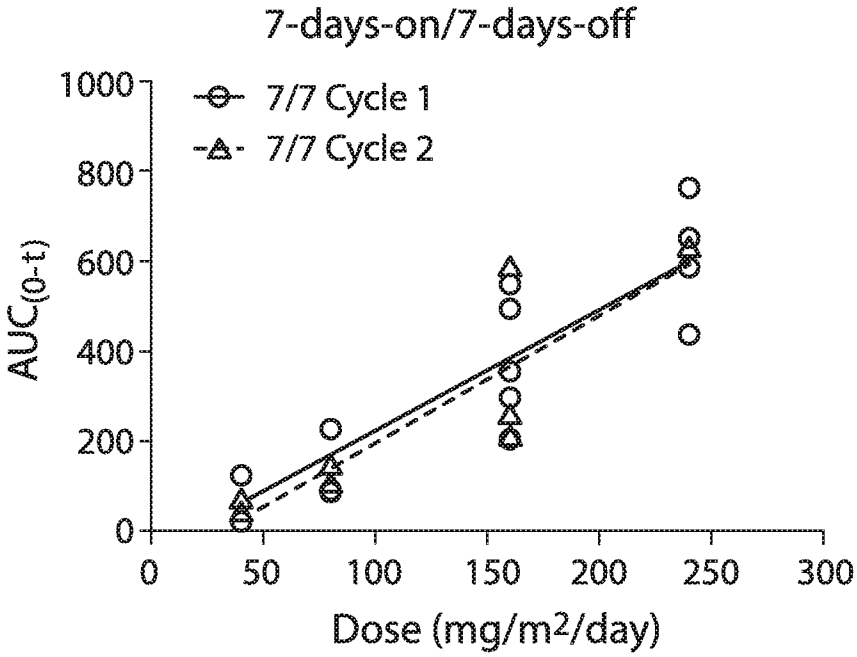

7-days-on/7-days-off
7/7 Cycle 1
7/7 Cycle 2
AUC(0-t)
1000
800
600
400
200
0
0
50
100
150
200
250
300
Dose (mg/m2/day)

FIG. 1B

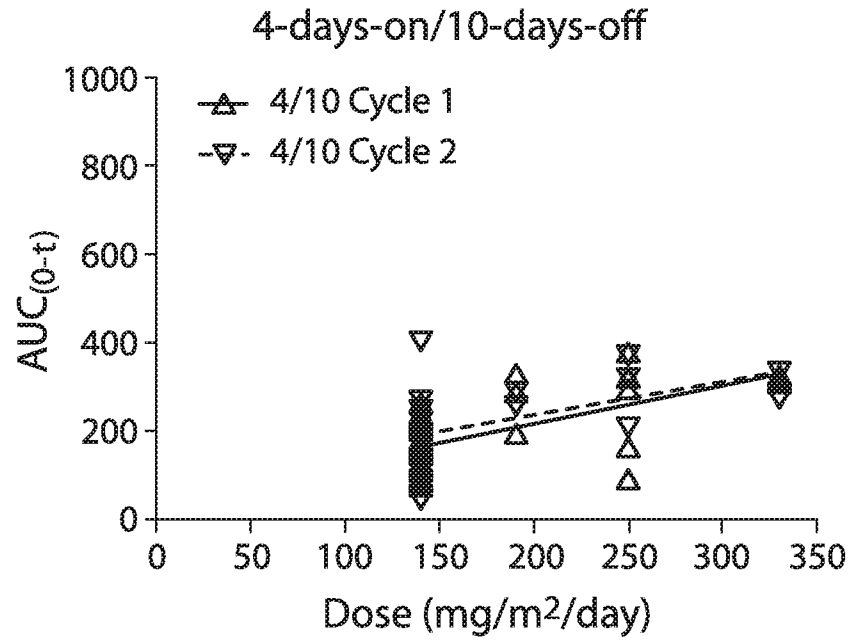

4-days-on/10-days-off
4/10 Cycle 1
4/10 Cycle 2
AUC(0-t)
1000
800
600
400
200
0
0
50
100
150
200
250
300
350
Dose (mg/m2/day)

FIG. 2

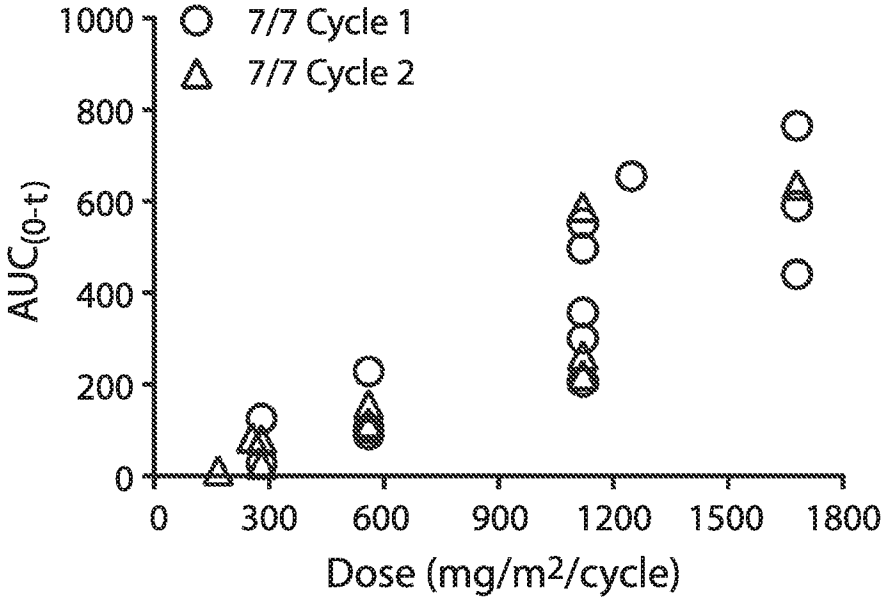

7/7 Cycle 1
7/7 Cycle 2
AUC(0-t)
1000
800
600
400
200
0
0
300
600
900
1200
1500
1800
Dose (mg/m2/cycle)

FIG. 3

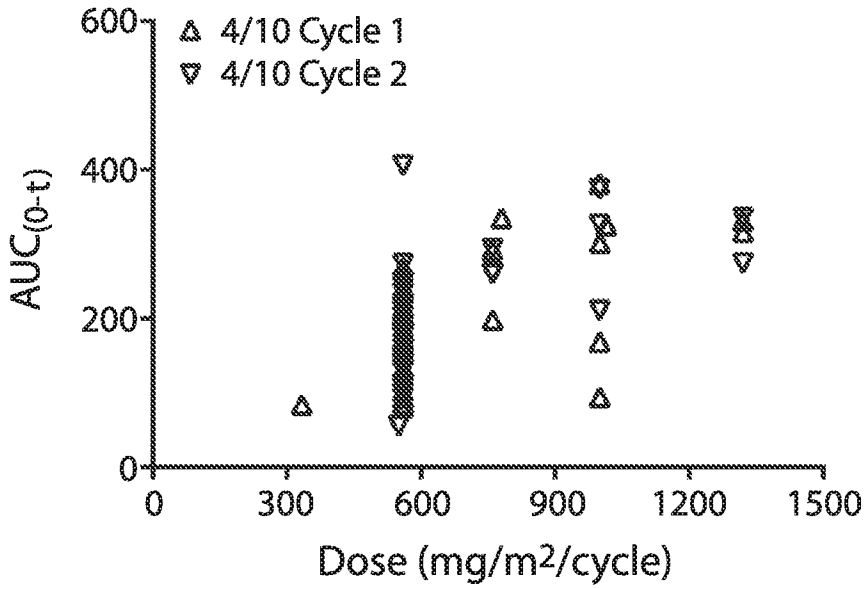
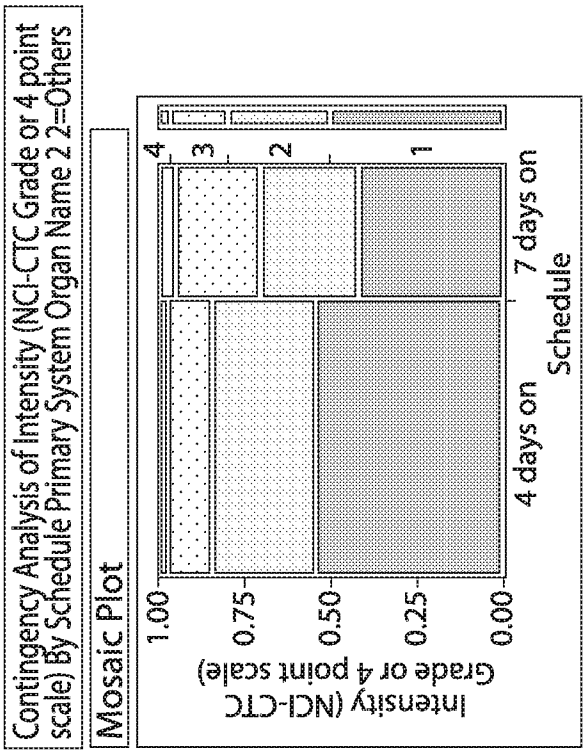

4/10 Cycle 1
4/10 Cycle 2
AUC(0-t)
600
400
200
0
0
300
600
900
1200
1500
Dose (mg/m2/cycle)

FIG. 4



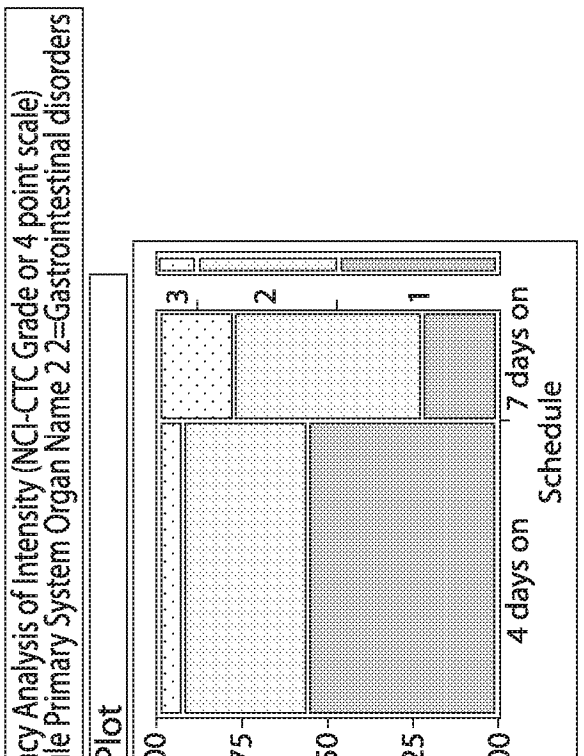
Contingency Table

Schedule	Intensity (NCI-CTC Grade or 4 point scale)				
Count / Row %	1	2	3	4	
4 days on	190 54.76	104 29.97	45 12.97	8 2.31	347
7 days on	71 42.51	47 28.14	41 24.55	8 4.79	167
	261	151	86	16	514

Tests

N	DF	-LogLike	RSquare (U)
514	3	7.0834916	0.0124

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	14.167	0.0027*
Pearson	14.731	0.0021*



Contingency Table

Schedule	Intensity (NCI-CTC Grade or 4 point...			
Count / Row %	1	2	3	
4 days on	75 55.97	49 36.57	10 7.46	134
7 days on	11 22.45	27 55.10	11 22.45	49
	86	76	21	183

Tests

N	DF	-LogLike	RSquare (U)
183	2	9.4596111	0.0534

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	18.919	<.0001*
Pearson	18.569	<.0001*

FIG. 5

Generalized Linear Model Fit

Overdispersion parameter estimated by Pearson Chisq/DF
Response: Intensity (NCI-CTC Grade or 4 point scale) 2
Modeling P(Intensity (NCI-CTC Grade or 4 point scale) 2=1)
Distribution: Binomial
Link: Logit
Estimation Method: Firth Adjusted Maximum Likelihood
Observations (or Sum Wgts) = 644

Whole Model Test

Model	-LogLikelihood	L-R ChiSquare	DF	Prob>ChiSq
Difference	31.8671146	63.7342	9	<.0001*
Full	414.469979			
Reduced	446.337094			

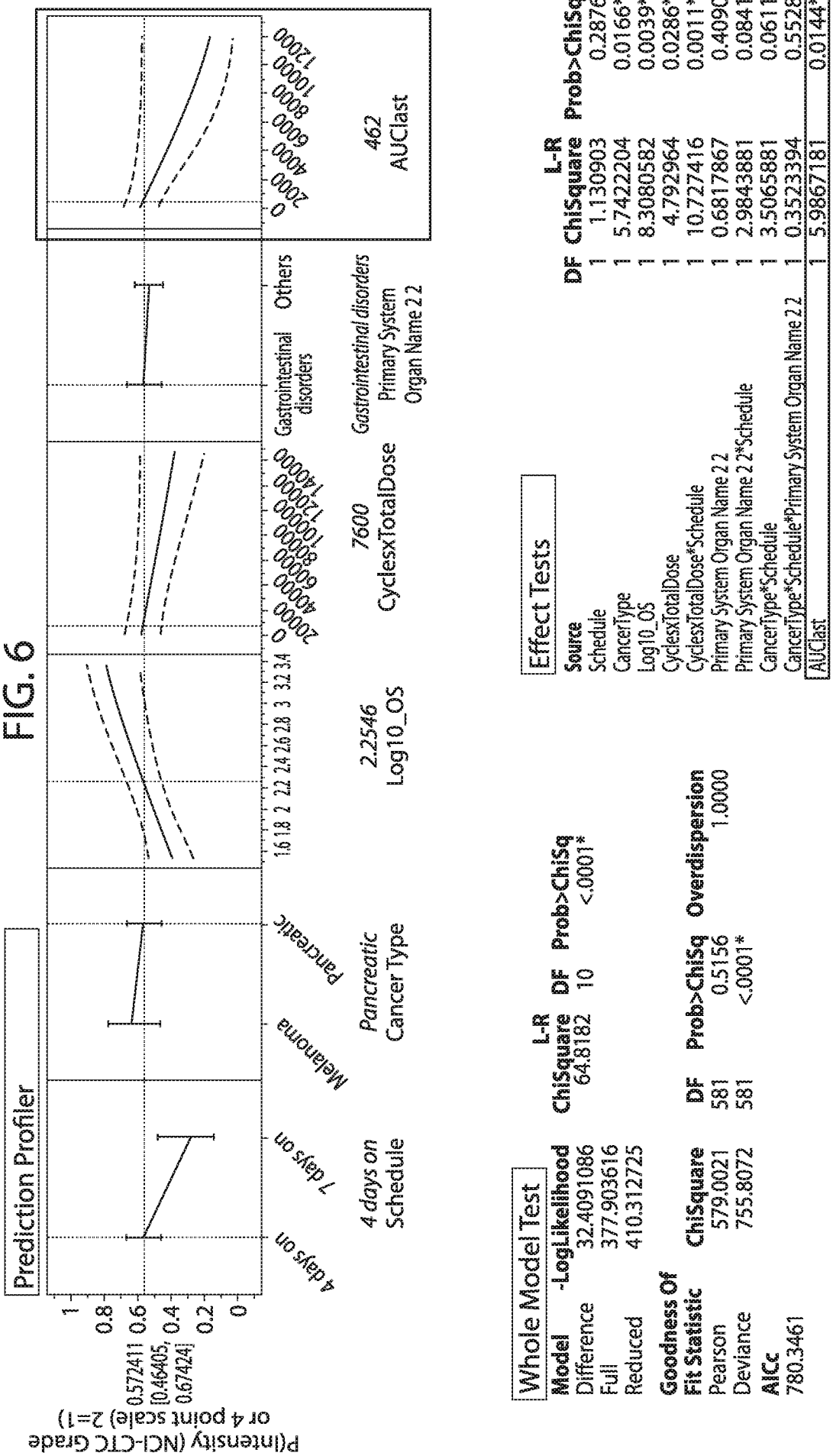
Goodness Of Fit Statistic	ChiSquare	DF	Prob>ChiSq	Overdispersion
Pearson	631.8504	634	0.5166	1.0000
Deviance	828.9400	634	<.0001*	

AICc
851.3577

Effect Tests

Source	DF	L-R ChiSquare	Prob>ChiSq
Schedule	1	0.985066	0.3210
CancerType	1	5.6567438	0.0174*
Log10_OS	1	8.1023261	0.0044*
CyclesxTotalDose	1	6.6643615	0.0098*
CyclesxTotalDose*Schedule	1	12.746281	0.0004*
Primary System Organ Name 2 2	1	1.9203576	0.1658
Primary System Organ Name 2 2*Schedule	1	4.1772225	0.0410*
CancerType*Schedule	1	4.2818429	0.0385*
CancerType*Schedule*Primary System Organ Name 2 2	1	0.1011377	0.7505

FIG. 6



Whole Model Test

Model	-Log Likelihood	L-R ChiSquare	DF	Prob>ChiSq
Difference	32.4091086	64.8182	10	<.0001*
Full	377.903616			
Reduced	410.312725			

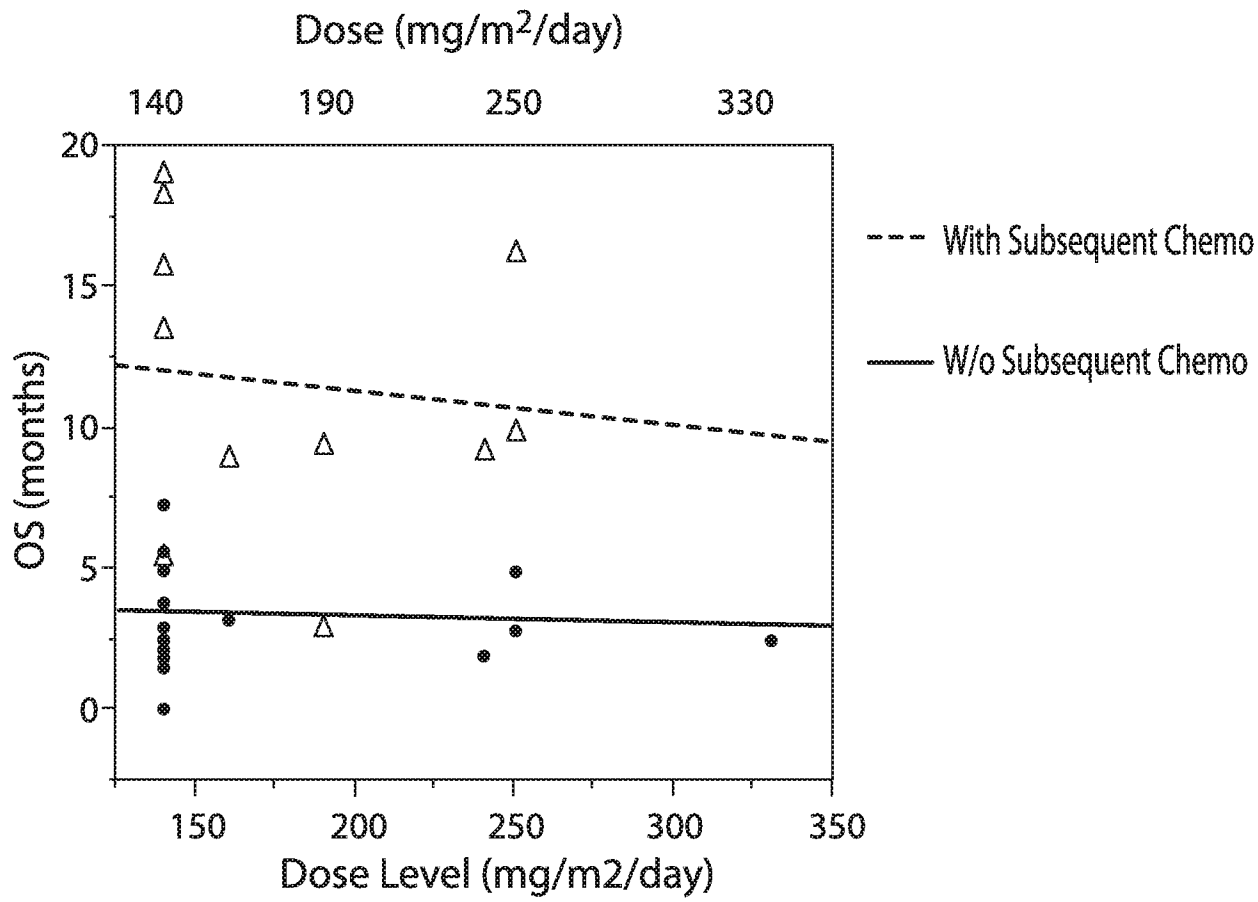
Goodness Of Fit Statistic	ChiSquare	DF	Prob>ChiSq	Overdispersion
Pearson	579.0021	581	0.5156	1.0000
Deviance	755.8072	581	<.0001*	

AICc
780.3461

Effect Tests

Source	DF	L-R ChiSquare	Prob>ChiSq
Schedule	1	1.130903	0.2876
CancerType	1	5.7422204	0.0166*
Log10_OS	1	8.3080582	0.0039*
CyclesxTotalDose	1	4.792964	0.0286*
CyclesxTotalDose*Schedule	1	10.727416	0.0011*
Primary System Organ Name 2 2	1	0.6817867	0.4090
Primary System Organ Name 2 2*Schedule	1	2.9843881	0.0841
CancerType*Schedule	1	3.5065881	0.0611
CancerType*Schedule*Primary System Organ Name 2 2	1	0.3523394	0.5528
AUClast	1	5.9867181	0.0144*

FIG. 7


Dose (mg/m2/day)
140
190
250
330
20
15
10
5
0
OS (months)
With Subsequent Chemo
W/o Subsequent Chemo
150
200
250
300
350
Dose Level (mg/m2/day)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/041242

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 9/00; A61K 31/505; A61K 31/5377; A61K 31/7088; A61K 31/7105; A61K 31/7125 (2017.01)
CPC - A61K 9/0019; A61K 31/7115; A61K 31/7125; A61K 31/713; A61K 45/06; C12N 15/113 (2017.08)

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/9.1; 435/375; 514/44A; 536/24.5; 702/19 (keyword delimited)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/055148 A2 (ANTISENSE PHARMA GMBH et al) 20 May 2010 (20.05.2010) entire document	1-17
A	SCHLINGENSIEPEN et al. "Transforming growth factor-beta 2 gene silencing with trabedersen (AP 12009) in pancreatic cancer," Cancer Science, 31 March 2011 (31.03.2011), Vol. 102, Pgs. 1193-1200. entire document	1-17
A	US 2016/0040167 A1 (ISARNA THERAPEUTICS GMBH) 11 February 2016 (11.02.2016) entire document	1-17
A	BOGDAHN et al. "Targeted therapy for high-grade glioma with the TGF-b2 inhibitor trabedersen: results of a randomized and controlled phase IIb study," Nuero-Oncology, 27 October 2010 (27.10.2010), Vol. 13, Iss. 1, Pgs. 132-142. entire document	1-17
A	US 2012/0114640 A1 (KULKARNI et al) 10 May 2012 (10.05.2012) entire document	1-17
A	US 2015/0141426 A1 (HIRAWAT et al) 21 May 2015 (21.05.2015) entire document	1-17

☐ 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	Date of mailing of the international search report
31 August 2017	29 SEP 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774