Description

Title of Invention: METHODS OF TREATING LSD1-RELATED DISEASES and Disorders WITH LSD1 INHIBITORS

Technical Field

[0001] The present invention relates to methods of treating a patient with an LSD1-related disease or disorder with an LSD1 inhibitor according to one or more specific dosing regimens. Aspects of the invention also include LSD1 inhibitors, as well as methods of making such LSD1 inhibitors and compositions, including pharmaceutical compositions, comprising such LSD1 inhibitors, and their various uses.

Background Art

[0002] Histone methylation modification is one of the epigenetic mechanisms that regulates gene expression. Histone methylation modification regulates various processes including, but not limited to, cellular maintenance, growth, and differentiation.

[0003] LSD1 (KDM1A), one of the enzymes that regulates histone methylation modification, is an FAD (flavin adenine dinucleotide)-dependent histone demethylase, and mainly demethylates the lysine residue at position 4 (K4) and the lysine residue at position 9 (K9) on histone H3 (Non-patent Literature (NPL) 1). With such functions, LSD1 is believed to positively or negatively regulate various aspects of gene transcription, and regulate stem cell self-renewal and cell differentiation in normal tissue types.

[0004] In general, abnormalities in cell self-renewal capacity or differentiation are believed to lead to malignant transformations in cells. Thus, aberrant control of LSD1, which plays a key role in these processes, can possibly cause malignant transformations in cells. In fact, in terms of various solid and blood cancers, many reports have been made regarding the correlation of overexpression of LSD1 and their prognosis (NPL 2). Further, in cell lines from carcinomas or in non-clinical models, LSD1 inhibition has been reported to have resulted in induction of cellular differentiation, growth inhibition, and an in vivo antitumor effect (NPL 3 and NPL 4), which strongly suggests that LSD1 serves as one of the important target molecules in cancer therapy. These carcinomas in which LSD1 is involved, such as small-cell lung cancer (SCLC) and acute myeloid leukemia (AML), have an extremely poor prognoses, and existing therapeutic methods have failed to achieve a satisfactory therapeutic benefit to patients.

[0005] Accordingly, LSD1 inhibitory drugs are expected to provide effective therapeutic means based on novel mechanisms to treat intractable cancers, for which no therapeutic methods currently exist.

[0006] Further, according to some reports, LSD1, which is involved in neuron programs and functions, can also possibly serve as a target in the treatment of diseases other than cancers, such as Alzheimer's disease, Huntington's disease, Rett syndrome, and other cranial nerve diseases (NPL 2); Herpesvirus infections, in which LSD1 function has been implicated (NPL 5); and sickle cell diseases (NPL 6).

[0007] There are some reports that LSD1 inhibitors were administered in clinical trials. LSD1 inhibitors are categorized into two groups: LSD1 inhibitors that covalently bind to FAD, and LSD1 inhibitors that compete with the substrate histone H3. For the former covalent-type, the most typical administration schedule was continuous daily administration. For example, the covalent-type LSD1 inhibitor GSK-2879552 (GlaxoSmithKline PLC) was administered continuously daily for their Phase 1 study of acute myeloid leukemia and Phase 1/2 study of myelodysplastic syndromes (NPL7). Another covalent-type LSD1 inhibitor INCB-59872 (Incyte Corp) was administered continuously daily in a 21-day cycle for their Phase 1/2 study of solid tumors, non-small cell lung cancer (NSCLC) and colon cancer, and administered continuously daily for a Phase 1 study of sickle cell disease (NPL8). The other typical administration schedules involved intermittent administration at 1 day or 2 day intervals. For example, another covalent-type LSD1 inhibitor ORY-1001/ RO7051790 (Oryzon Genomics) was administered for a Phase 1/2a study of acute myeloid leukemia in a 4-week administration schedule consisting of 4 cycles of 5 days continuous administration, followed by a two day interval period (NPL9). For the above-mentioned INCB-59872 study, the administration schedule of every other day (Quaque otra Die: QOD) was also applied for a Phase 1 study of sickle cell disease (NPL10). On the other hand, CC-90011, a unique LSD1 inhibitor which competes with the substrate histone H3 and has a long half-life in pharmacokinetics (~71 hrs, i.e., about 3 days) has been used with an administration schedule of once a week administration in 28 day (4 week) cycles (NPL 11).

[0008] The disclosures of all citations in the specification are expressly incorporated herein by reference in their entireties.

Citation List

Patent Literature

[0009] PTL 1: WO2017/090756

Non-patent Literature

[0010] NPL 1: Biochim. Biophys. Acta, 1829 (10), pp. 981-986 (2013)

NPL 2: Epigenomics, 7 (4), pp. 609-626 (2015)

NPL 3: Cancer Cell, 21 (4), pp. 473-487 (2012)

NPL 4: Cancer Cell, 28 (1), pp. 57-69 (2015)

NPL 5: Sci. Transl. Med., 6 (265), 265ra169 (2014)

NPL 6: Nat. Med., 19 (3), pp. 291-294 (2013)
NPL 7: NCT02177812
NPL 8: NCT02959437
NPL 9: ASH 2016 (4060)
NPL 10: NCT03132324
NPL 11: Annals of Oncology, Volume 30, Issue Supplement_5, October 2019, mdz256.003, https://doi.org/10.1093/annonc/mdz256.003

Summary of Invention

Technical Problem

[0011] The compound 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile (referred to herein as Compound A) has been known as a potent LSD1 inhibitor (PL 1). This compound is an LSD1 inhibitor that competes with the substrate histone H3. No administration schedules or dosage regimens for Compound A have been described in the art.

Solution to Problem

[0012] Aspects of the invention include methods of treating an LSD1-related disease or disorder in a patient in need by administering an effective amount of Compound A utilizing a specific administration schedule.

[0013] The present inventors have discovered that continuous administration of Compound A shows anti-tumor effects, but can at the same time result in one or more unfavorable events or side-effects, such as myelosuppression and/or body weight loss. The inventors conducted extensive studies, and consequently discovered that continuous administration of Compound A for a specific period of time, followed by a resting period having a specific length of time without administering Compound A, achieved an anti-tumor effect with fewer unfavorable events and side-effects. The present invention is based on this unexpected and surprising discovery.

[0014] In an embodiment, a method of treating a patient with an LSD1-related disease or disorder includes administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an administration schedule of continuous, daily dosing for one week followed by a resting period of one week.

[0015] In another embodiment, a method of treating a patient with an LSD1-related disease or disorder includes administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an admin-

istration schedule of continuous, daily dosing for two weeks followed by a resting period of one week.

Brief Description of Drawings

[0016] [fig.1A]FIG. 1A is a graph illustrating the number of platelets in a sample of Group I subject to a 1-week ON+1-week OFF dosing regimen. The left blank bar shows values from Test Compound A 0 mg/kg (vehicle as control) treated animals, and the right filled bar shows values from Test Compound A 16mg/kg treated animals. The "Week" columns "1", "2", "3" and "4" show the values from the samples obtained on Day 8, Day 15, Day 22 and Day 29, respectively. Error bars: standard deviations from averages, NE: not examined

[fig.1B]FIG. 1B is a graph illustrating the number of neutrophils in a sample of Group I subject to a 1-week ON+1-week OFF dosing regimen. The left blank bar shows values from Test Compound A 0mg/kg (vehicle as control) treated animals, and the right filled bar shows values from Test Compound A 16mg/kg treated animals. The "Week" columns "1", "2", "3" and "4" shows the values from the samples obtained on Day 8, Day 15, Day 22 and Day 29, respectively. Error bars: standard deviations from averages, NE: not examined

[fig.2A]FIG. 2A is a graph illustrating the number of platelets in a sample of Group II subject to a 2-week ON+1-week OFF dosing regimen. The left blank bar shows values from Test Compound A 0mg/kg (vehicle as control) treated animals, and the right filled bar shows values from Test Compound A 16mg/kg treated animals. The "Week" columns "2" and "3" shows the values from the samples obtained on Day 15 and Day 22, respectively. Error bars: standard deviations from averages.

[fig.2B]FIG. 2B is a graph illustrating the number of neutrophils in a sample of Group II subject to a 2-week ON+1-week OFF dosing regimen. The left blank bar shows values from Test Compound A 0mg/kg (vehicle as control) treated animals, and the right filled bar shows values from Test Compound A 16mg/kg treated animals. The "Week" columns "2" and "3" shows the values from the samples obtained on Day 15 and Day 22, respectively. Error bars: standard deviations from averages.

[fig.3]FIG. 3 is a photograph of abnormal neutrophil-lineage myelocytes (indicated by the arrow).

[fig.4A]FIG. 4A is a photograph of abnormal megakaryocytes.

[fig.4B]FIG. 4B is a photograph of abnormal megakaryocytes.

[fig.5]FIG. 5 is a graph showing tumor volume of the control group, the Continuous group, the Group I group and the Group II group. ***: $p<0.001$, Dunnett t-test, N.S.: Not Significant, Aspin-Welch t-test, Error bar: SE: Standard Error

[fig.6]FIG. 6 is a graph showing body weight change of the control group, the

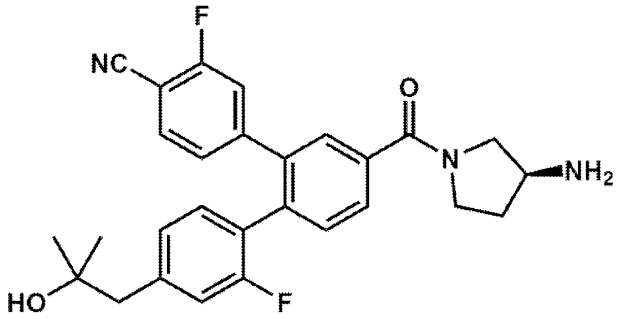
Continuous group, the Group I group and the Group II group. Error bar: SE: Standard Error

Description of Embodiments

[0017] Aspects of the invention include methods of treating a disease or disorder characterized by expression of LSD1 by administering an antitumor agent on an administration schedule including a period of continuous, daily dosing followed by a specific resting period with no dosing. In an embodiment, a method of treating a disease or disorder characterized by the expression of LSD1 includes administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile ("Compound A") or a salt thereof to a patient in need. In some embodiments, the methods involve administering Compound A or a salt thereof on an administration schedule comprising continuous, daily dosing for one week, followed by a resting period of one week. In some embodiments, the methods involve administering Compound A or a salt thereof on an administration schedule comprising continuous, daily dosing for a period of two weeks, followed by a resting period of one week.

[0018] 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl)phenyl]phenyl]-2-fluoro-benzonitrile is depicted in the following structure:

[Chem.1]



[0019] In the present application, the above compound is described as "Compound A." Compound A is described as Example compound 37 of PCT Publication No. WO2017/090756, the disclosure of which is incorporated by reference herein in its entirety. Compound A can be produced by any known methods in the art, including, but not limited to, those methods described in PCT Publication No. WO2017/090756, the disclosure of which is incorporated by reference herein in its entirety.

[0020] The novel methods of treatment described herein exhibit an effect of reducing one or more unfavorable observations, such as side effects, adverse reactions or adverse events, for example, weight loss and/or myelosuppression, while achieving an antitumor effect. In example embodiments, the antitumor agent is administered for a

one or two week period of continuous administration, followed by a resting period having a duration of one week. This surprising and unexpected discovery enabled longer term administration of Compound A with reduced side effects, etc., which ultimately contributes to a longer survival time and/or a longer period of progression-free survival.

[0021] The administration schedule described herein comprising a one week period of continuous administration followed by a resting period of one week demonstrated advantages in terms of reduction in one or more unfavorable events or side-effects.

[0022] Alternatively, the administration schedule described herein comprising a two week period of continuous administration followed by a resting period of one week demonstrated advantages in terms of drug safety, including reduced toxicity.

[0023] In the present invention, the administration schedule is not particularly limited, as long as it includes a one or two week period of continuous administration, followed by a resting period of one week. When a two week (14 day) administration schedule, consisting of one week (7 days) of continuous administration followed by a one week (7 day) resting period is defined as one (1) cycle, the cycle can be performed once or repeated twice or more to treat the disease or disorder. That is, the administration can be carried out in one cycle, or more than one cycle, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 cycles or more of a specific administration schedule. In some embodiments, the administration can be carried out in long-periods comprising several cycles. For example, the administration can be carried out for a period of 6-months with approximately 13 to 15 cycles of treatment or administration; a 1-year period with approximately 25 or 26 cycles of treatment; a 3-year period with approximately 75 to 100 cycles of treatment or more. When a three week (21 day) administration schedule, consisting of two weeks (14 days) of administration followed by a one week (7 day) resting period, is defined as one (1) cycle, the cycle can be performed once or repeated two or more times. That is, the administration can be carried out in one cycle, or more than one cycle, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 cycles, or more of the administration schedule. In some cases, the administration can be carried out in more cycles. For example, the administration can be carried out for a period of 6 months with approximately 10 cycles; a 1-year period with approximately 20 cycles; a 3-year period with approximately 50 to 60 cycles or longer periods of administration with more cycles.

[0024] Moreover, in the administration schedule of the present invention, as long as the administration is continued on the schedule of a one or two week period of continuous administration, followed by a resting period of one week, the administration may be stopped thereafter, and the administration may be restarted after a certain period of drug holiday (no administration). Similarly, the administration schedule of the present invention may include a schedule having a plurality of periods of drug holiday. In one

embodiment of an administration schedule having a drug holiday, it is sufficient that the conditions "one or two week continuous administration followed by a resting period of one week" are satisfied in the dosing period before the drug holiday and in the dosing period after the drug holiday. In another embodiment of an administration schedule having two periods of drug holiday, it is sufficient that the conditions "one or two week continuous administration followed by a resting period of one week " are satisfied in the dosing period before the first period of drug holiday, in the dosing period between the two periods of drug holiday, and in the dosing period after the second period of drug holiday. In another embodiment of an administration schedule having two or more periods of drug holiday, it is sufficient that the conditions "one or two week continuous administration followed by a resting period of one week " are satisfied in the dosing period before the first period of drug holiday, in the dosing period between the two adjacent periods of drug holiday, and in the dosing period after the last period of drug holiday. The period of drug holiday is not particularly limited, and can be suitably set according to the patient's state, and the like. For example, the period of drug holiday can be within the range of 1 to 35 days. Alternatively, the period of drug holiday can be within the range of 1 to 12 months.

[0025] In some embodiments, Compound A or a salt thereof is administered once or more than once each day. In a preferred embodiment, Compound A or a salt thereof is administered once per day.

[0026] A typical daily dose of Compound A or salt thereof can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 25 milligrams per kilogram of bodyweight. More typically, a daily dose of Compound A or salt thereof can be in the range from 100 nanograms to 20 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. For example, the daily dose may be 1 micrograms to 20 milligrams of bodyweight, more typically 10 micrograms to 20 milligrams per kilogram of bodyweight, and more typically 100 micrograms to 20 milligrams per kilogram of bodyweight.

[0027] Dosages may also be expressed as the amount of drug administered relative to the body surface area of the patient (mg/m^2). A typical daily dose of Compound A or salt thereof can be in the range from 3700 pg/m^2 to 3700 mg/m^2, although higher or lower doses may be administered where required. For example, the daily dose may be 370 ng/m^2 to 925 mg/m^2, more typically 3700 ng/m^2 to 740 mg/m^2, although higher or lower doses may be administered where required. For example, 37 micrograms/m^2 to 740 mg/m^2, and more typically 370 micrograms/m^2 to 740 mg/m^2, or 3700 micrograms/m^2 to 740 mg/m^2.

[0028] Compound A or salt thereof of the invention may be administered orally in a range

of single doses, for example 0.05 to 3000 mg. Typically, the range may be 10 to 1000 mg. Typical examples of doses include 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900 and 1000 mg. The doses may be increased or decreased in a stepwise manner from any dose in the above range (of 0.05 to 3000 mg) in increments/decrements of, for example, 1 mg, 5 mg, 10 mg, 20 mg, or 50 mg.

[0029] Pharmaceutical compositions containing Compound A or salts thereof used in the present invention can be formulated in accordance with known techniques. See for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA. The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, intrabronchial, sublingual, ophthalmic, otic, rectal, intravaginal, or transdermal administration. Of these, the embodiment in oral administration is preferred. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery. The delivery can be by bolus injection, short- term infusion or longer term infusion and can be via passive delivery or through the utilization of a suitable infusion pump or syringe driver.

[0030] Compound A or a salt thereof used in the present invention may be in the form of crystals. Single crystals and polymorphic crystal mixtures are included within the scope of Compound A or a salt thereof. Such crystals can be produced by crystallization according to a crystallization method known in the art. Compound A or a salt thereof may be a solvate (e.g., a hydrate) or a non-solvate. Any of such forms are included within the scope of the compound of the present invention or a salt thereof.

[0031] Compounds A labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, and ^{125}I) are also included within the scope of Compound A or a salt thereof used in the present invention.

[0032] The salts of Compound A used in the present invention refer to common salts used in the field of organic chemistry. Examples of such salts include base addition salts, and acid addition salts. The salts of Compound A are preferably pharmaceutically acceptable salts.

[0033] Examples of base addition salts include alkali metal salts, such as sodium salts and potassium salts; alkaline earth metal salts, such as calcium salts and magnesium salts; ammonium salts; and organic amine salts, such as trimethylamine salts, triethylamine salts, dicyclohexylamine salts, ethanolamine salts, diethanolamine salts, triethanolamine salts, procaine salts, and N,N'-dibenzylethylenediamine salts.

[0034] Examples of acid addition salts include inorganic acid salts, such as hydrochloride, sulfate, nitrate, phosphate, and perchlorate; organic acid salts, such as acetate, formate, maleate, fumarate, tartrate, citrate, ascorbate, benzoate and trifluoroacetate; and

sulfonates such as methanesulfonate, isethionate, benzenesulfonate, and p-toluenesulfonate.

[0035] One example of a salt of Compound A is benzoic acid salt or benzoate salt. Another example of a salt of Compound A is mesylate, esylate, malate, fumarate or tosylate salt.

[0036] Due to their excellent LSD1 inhibitory activity, Compound A or salts thereof used in the present invention are useful as a pharmaceutical preparation for preventing and treating LSD1-related diseases. The administration schedule of the present invention is useful for treating LSD1 related diseases.

[0037] Examples of "LSD1-related diseases or disorders" or diseases and disorders "characterized by expression and/or activity of LSD1", which terms are used inter-changeably herein, include diseases, the incidence of which can be reduced, and symptoms of which can be remitted, relieved, and/or completely cured by eliminating, suppressing, and/or inhibiting LSD1 function. Examples of such diseases include, but are not limited to, malignant tumors, etc. The type of malignant tumor to be treated by the Compound A or a salt thereof is not particularly limited. Examples of such malignant tumors include head and neck cancers, esophagus cancer, gastric cancer, colon cancer, rectum cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, biliary tract cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, renal cancer, bladder cancer, prostate cancer, testicular tumor, osteosarcoma, soft-tissue sarcoma, leukemia, myelodysplastic syndrome, chronic myeloproliferative disease, malignant lymphoma, multiple myeloma, skin cancer, brain tumor, mesothelioma, and the like. Preferable examples include lung cancers (e.g., non-small cell lung cancer and small cell lung cancer), leukemia, and myelodysplastic syndromes. More preferably, examples include lung cancers (non-small-cell lung cancer, small-cell lung cancer, etc.) and leukemia. More preferably, examples include small-cell lung cancer (SCLC) and acute myeloid leukemia (AML).

[0038] When Compound A or a salt thereof used in aspects of the present invention is used as a pharmaceutical preparation, a pharmaceutical carrier can be added, if required, thereby forming a suitable dosage form according to prevention and treatment purposes. Examples of the dosage form include oral preparations, injections, suppositories, ointments, patches, and the like. Of these, oral preparations are preferable. Such dosage forms can be formed by methods conventionally known to persons skilled in the art.

[0039] As the pharmaceutical carrier, various conventional organic or inorganic carrier materials used as preparation materials may be used. For example, such materials can be blended as an excipient, binder, disintegrant, lubricant, or coating agent in solid

preparations; or as a solvent, solubilizing agent, suspending agent, isotonizing agent, pH adjuster, buffer, or soothing agent in liquid preparations. Moreover, pharmaceutical preparation additives, such as antiseptics, antioxidants, colorants, taste-masking or flavoring agents, and stabilizers, can also be used, if required.

[0040] Oral solid preparations are prepared as follows. After an excipient is added optionally with a binder, disintegrant, lubricant, colorant, taste-masking or flavoring agent, etc., to Compound A of the present invention, the resulting mixture is formulated into tablets, coated tablets, granules, powders, capsules, or the like by methods known in the art.

[0041] Examples of excipients include lactose, sucrose, D-mannitol, glucose, starch, calcium carbonate, kaolin, microcrystalline cellulose, and silicic acid anhydride. Examples of binders include water, ethanol, 1-propanol, 2-propanol, simple syrup, liquid glucose, liquid α-starch, liquid gelatin, D-mannitol, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl starch, methyl cellulose, ethyl cellulose, shellac, calcium phosphate, polyvinylpyrrolidone, and the like. Examples of disintegrators include dry starch, sodium alginate, powdered agar, sodium hydrogen carbonate, calcium carbonate, sodium lauryl sulfate, stearic acid monoglyceride, lactose, and the like. Examples of lubricants include purified talc, sodium stearate, magnesium stearate, borax, polyethylene glycol, and the like. Examples of colorants include titanium oxide, iron oxide, and the like. Examples of taste-masking or flavoring agents include sucrose, bitter orange peel, citric acid, tartaric acid, and the like.

[0042] When a liquid preparation for oral administration is prepared, a taste-masking agent, a buffer, a stabilizer, a flavoring agent, and the like may be added to Compound A; and the resulting mixture may be formulated into an oral liquid preparation, syrup, elixir, etc., according to methods known in the art.

[0043] Examples of taste-masking or flavoring agents may be the same as those mentioned above. Examples of buffers include sodium citrate and the like. Examples of the stabilizer include tragacanth, gum arabic, gelatin, and the like. As necessary, these preparations for oral administration may be coated according to methods known in the art with an enteric coating or other coating for the purpose of, for example, persistence of effects. Examples of such coating agents include hydroxypropyl methylcellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, polyoxyethylene glycol, and Tween 80 (registered trademark).

[0044] When an injection is prepared, a pH adjuster, a buffer, a stabilizer, an isotonizing agent, a topical anesthetic, and the like may be added to Compound A; and the resulting mixture may be formulated into subcutaneous, intramuscular, and intravenous injections according to an ordinary method.

[0045] Examples of usable pH adjusters and buffers include sodium citrate, sodium acetate, sodium phosphate, and the like. Examples of usable stabilizers include sodium pyrosulfite, EDTA, thioglycolic acid, thiolactic acid, and the like. Examples of usable topical anesthetics include procaine hydrochloride, lidocaine hydrochloride, and the like. Examples of usable isotonizing agents include sodium chloride, glucose, D-mannitol, glycerin, and the like.

[0046] The amount of Compound A to be incorporated in each of such dosage unit forms used in the present invention depends on the condition of the patient to whom Compound A is administered, the dosage form, etc. In general, in the case of an oral agent, an injection, and a suppository, the amount of Compound A is preferably 0.05 to 1000 mg, 0.01 to 500 mg, and 1 to 1000 mg, respectively, per dosage unit form.

[0047] The daily dose of the medicine in such a dosage form depends on the condition, body weight, age, gender, etc., of the patient, and cannot be generalized. For example, the daily dose of Compound A for an adult (body weight: 50 kg) may be usually 0.05 to 5000 mg, and preferably 0.1 to 1000 mg; and is preferably administered in one dose, or in two to three divided doses, per day.

[0048] The administration schedule of the present invention can be applied for a single administration of Compound A or salts thereof. The administration schedule of the present invention can be applied for an administration of Compound A or salts in combination with other drug(s). When Compound A or salts is administered in combination with other drugs, Compound A or salts can be administered on the same day or at the same timing for those of such other drug(s), or, Compound A can be administered on a different day or at a different timing for those of such other drug(s). Such other drug(s) can be administered continuously, sporadically or intermittently during the administration schedule of Compound A or salts thereof of the present invention.

[0049] Using Compound A or a salt thereof in combination with one or more other antitumor agents enhances the antitumor effect. The present invention encompasses an administration schedule using Compound A or a salt in such a combinatory manner. The form of a combination of Compound A or a salt thereof and one or more other antitumor agents may be a single preparation (i.e., a combination drug) or two or more separate preparations to be administered in combination.

[0050] In the present invention, the antitumor effect can be evaluated as, for example, reduced tumor volume, tumor growth stasis, or prolonged survival time.

[0051] In an embodiment, an administration schedule includes administering an antitumor formulation comprising a combination of Compound A or a salt thereof and one or more other antitumor agents. In another embodiment, an administration schedule includes administering an antitumor effect potentiator for an antitumor agent, the po-

tentiator comprising Compound A or a salt thereof as an active ingredient.

[0052] The other antitumor agents are not particularly limited. Examples include antimetabolites, antitumor antibiotics, molecular target drugs, platinum-based drugs, and plant alkaloid-based drugs.

[0053] Examples of antimetabolites include 5-fluorouracil (5-FU), 5-fluoro-2'-deoxyuridine (FdUrd), tegafur, combination drugs of tegafur and uracil (e.g., UFT), combination drugs of tegafur, gimeracil, and oteracil (e.g., TS-1), pemetrexed, trifluridine, combination drugs of trifluridine and tipiracil hydrochloride (e.g., Lonsurf), gemcitabine, capecitabine, nelarabine, clofarabine, cytarabine, DNA methylation inhibitors (such as azacitidine, decitabine, cedazuridine and guadecitabine), and the like, with cytarabine or DNA methylation inhibitors, such as azacitidine, decitabine, cedazuridine and guadecitabine, being preferable, and cytarabine, azacitidine, decitabine, cedazuridine or guadecitabine being more preferable. Examples of antimetabolites are also described in U.S. Patent No. 8,268,800 incorporated by reference herein in its entirety.

[0054] Examples of antitumor antibiotics include daunorubicin, doxorubicin, amrubicin, idarubicin, epirubicin, and like anthracycline-based antitumor antibiotics, mitomycin C, bleomycin, and the like, with anthracycline-based antitumor antibiotics being preferable, and daunorubicin being more preferable.

[0055] Examples of molecular target drugs include all-trans retinoic acid (ATRA) or derivatives thereof, human MDM2 (mouse double minute 2)(HDM2; human double minute 2) inhibitors, and HDAC inhibitors.

[0056] The all-trans retinoic acid (ATRA) or a derivative thereof is preferably tretinoin (ATRA) or tamibarotene, and more preferably tretinoin (ATRA). In one embodiment, ATRA is administered every day of the 21-day cycle or 28-day cycle with no resting period. In one embodiment, ATRA is administered twice daily.

[0057] The human MDM2 (HDM2) inhibitor is preferably RG7388 (RO5503781), AMG-232, DS-3032b, RG7112 (RO5045337), SAR405838, MK-8242, or a 1-methoxyisoindoline such as (2S,3S)-3-(4-chlorophenyl)-3-[1 -(4-chlorophenyl)-7-fluoro-5-[(1 S)-1-hydroxy-1-(oxan-4-yl)propyl]-1-methoxy-3-oxo-2,3-dihydro-1 H-isoindol-2-yl]-2-methylpropanoic or (2S,3S)-3-(4-chlorophenyl)-3-[1 -(4-chlorophenyl)-7-fluoro-5-[(1 S)-1 -hydroxy-1 -(oxan-4-yl)propyl]-1-methoxy-3-oxo-2,3-dihydro-1 H-isoindol-2-yl]-2-methylpropanoic acid as described in PCT Publication No. WO2018/178691 and U.S. Application Publication No. 2019/0055215 both incorporated herein by reference in their entireties, and more preferably RG7388.

[0058] Examples of HDAC inhibitors include vorinostat, panobinostat, romidepsin, be-

linostat, and the like.

[0059] The molecular target drug is preferably all-trans retinoic acid (ATRA) or a derivative thereof, a human MDM2 (HDM2) inhibitor, or an HDAC inhibitor, and more preferably tretinoin (ATRA) or RG7388.

[0060] Examples of platinum-based drugs include oxaliplatin, carboplatin, cisplatin, nedaplatin, and the like, with carboplatin or cisplatin being preferable.

[0061] Examples of plant alkaloid-based drugs include microtubule inhibitors, such as paclitaxel, docetaxel, vinblastine, vincristine, vindesine, vinorelbine, and eribulin, and topoisomerase inhibitors, such as irinotecan (SN-38), nogitecan, and etoposide, with taxane microtubule inhibitors such as paclitaxel and docetaxel or topoisomerase inhibitors such as irinotecan (SN-38), nogitecan, and etoposide being preferable, and paclitaxel, irinotecan (SN-38), or etoposide being more preferable.

[0062] The one or more other antitumor agents are preferably an antimetabolite, an antitumor antibiotic, a molecular target drug, a platinum-based drug, or a plant alkaloid-based drug, more preferably an antimetabolite, an antitumor antibiotic, all-trans retinoic acid (ATRA) or a derivative thereof, a human MDM2 (HDM2) inhibitor, an HDAC inhibitor, a platinum-based drug, or a plant alkaloid-based drug, more preferably an antimetabolite, an antitumor antibiotic, all-trans retinoic acid (ATRA) or a derivative thereof, a human MDM2 (HDM2) inhibitor, a platinum-based drug, or a plant alkaloid-based drug, more preferably an antimetabolite, an antitumor antibiotic, all-trans retinoic acid (ATRA) or a derivative thereof, a human MDM2 (HDM2) inhibitor, a platinum-based drug, a topoisomerase inhibitor, or a taxane microtubule inhibitor, more preferably cytarabine, a DNA methylation inhibitor, an anthracycline-based antitumor antibiotic, all-trans retinoic acid (ATRA) or a derivative thereof, a platinum-based drug, a topoisomerase inhibitor, or a taxane microtubule inhibitor, and more preferably cytarabine, azacitidine, decitabine, guadecitabine, daunorubicin, tretinoin (ATRA), RG7388, carboplatin, cisplatin, paclitaxel, irinotecan (SN-38), or etoposide.

[0063] The preparations of the one or more other antitumor agents also include drug delivery system (DDS) preparations for them. For example, “paclitaxel” includes albumin-bound paclitaxel (e.g., Abraxane), paclitaxel micelles (e.g., NK105), and the like; and “cisplatin” includes cisplatin micelles (e.g., NC-6004) and the like.

[0064] The administration schedule of the present invention is also applicable for preventing diseases or disorders characterized by the expression of LSD1. It is also applicable for administration in pre-surgical operation or post-surgical operation, or as an adjuvant therapy or post-adjuvant therapy.

[0065] Notwithstanding the appended claims, aspects of the present invention and exemplary embodiments are described by the following clauses:

[0066] Clause [1] In an embodiment, a method of preventing and/or treating a disease or disorder characterized by the expression of LSD1 in a patient in need includes administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile, or a salt thereof, to the patient on an administration schedule comprising daily dosing for one week continuously, followed by a resting period of one week.

[0067] Clause [2] In another embodiment, the method described in clause [1] can include an administration schedule based on a 2-week cycle comprising continuous, daily dosing for one week, followed by a resting period of one week, and the cycle is performed once or repeated two or more times.

[0068] Clause [3] In another embodiment, the methods described in clauses [1] or [2] can include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof once per day for one week.

[0069] Clause [4] In another embodiment, the methods described in clauses [1], [2] or [3] can include orally administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof.

[0070] Clause [5] In another embodiment, the methods described in clauses [1], [2], [3] or [4] can be used to treat a disease or disorder characterized by a presence of a tumor.

[0071] Clause [6] In another embodiment, the methods described in clauses [1], [2], [3], [4] or [5] can be used to treat a disease or characterized by a presence of a malignant tumor.

[0072] Clause [7] In another embodiment, the methods described in clauses [1], [2], [3], [4] or [5] can include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or salt thereof at a daily dose in the range from 10 nanograms to 20 milligrams per kilogram of bodyweight.

[0073] Clause [8] In another embodiment, a method of treating a patient with a disease or disorder characterized by the expression of LSD1 can include administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an administration schedule comprising continuous, daily dosing for a period of two weeks, followed by a resting period of one week.

[0074] Clause [9] In another embodiment, the method described in clause [8] can include an administration schedule based on a 3-week cycle, with the cycle performed once or

repeated two or more times.

[0075] Clause [10] In another embodiment, the methods described in clauses [8] or [9] can include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof once per day for two weeks.

[0076] Clause [11] In another embodiment, the methods described in clauses [8], [9] or [10] can include orally administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof.

[0077] Clause [12] In another embodiment, the methods described in clauses [8], [9], [10] or [11] can be used to treat a disease or disorder characterized by a presence of a tumor.

[0078] Clause [13] In another embodiment, the methods described in clauses [8], [9], [10], [11] or [12] can be used to treat a disease or disorder characterized by a presence of a a malignant tumor.

[0079] Clause [14] In another embodiment, the methods described in clauses [8], [9], [10], [11], [12] or [13] can include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or salt thereof at a daily dose in the range from 10 nanograms to 20 milligrams per kilogram of bodyweight.

[0080] Clause [15] In another embodiment, a method of treating acute myeloid leukemia (AML) in a patient in need can include comprising administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient as a single agent administered once daily on specific days during a 28-day cycle.

[0081] Clause [16] In another embodiment, the method described in clause [15] can include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof daily for one week, followed by a resting period of one week.

[0082] Clause [17] In another embodiment, a method of treating acute myeloid leukemia (AML) in a patient in need can include comprising administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient as a single agent administered once daily on specific days during a 21-day cycle.

[0083] Clause [18] In another embodiment, the method described in clause [17] can

include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof for two weeks, followed by a resting period of one week.

[0084] Clause [19] In another embodiment, a method of treating acute myeloid leukemia (AML) in a patient in need can administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on specific days during a 28-day cycle, in combination with all-trans retinoic acid (ATRA) twice daily.

[0085] Clause [20] In another embodiment, the method described in clause [19] can include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof daily for one week, followed by a resting period of one week.

[0086] Clause [21] In another embodiment, a method of treating acute myeloid leukemia (AML) in a patient in need can administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on specific days during a 21-day cycle, in combination with all-trans retinoic acid (ATRA) twice daily.

[0087] Clause [22] In another embodiment, the method described in clause [21] can include administering a method of treating acute myeloid leukemia (AML) in a patient in need can include administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof for two weeks, followed by a resting period of one week.

[0088] Clause [23] In another embodiment, a method of reducing the risk of recurrence of acute myeloid leukemia (AML) or death for a patient diagnosed with AML can include comprising administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an administration schedule comprising daily dosing for one week, followed by a resting period of one week.

[0089] Clause [24] In another embodiment, a method of reducing the risk of recurrence of acute myeloid leukemia (AML) or death for a patient diagnosed with AML can include administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an administration schedule comprising daily dosing for two weeks, followed by a resting period

of one week.

[0090] Clause [25] In another embodiment, a method of reducing the risk of recurrence of acute myeloid leukemia (AML) or death for a patient diagnosed with AML can include administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an administration schedule comprising daily dosing for one week, followed by a resting period of one week, in combination with all-trans retinoic acid (ATRA) twice daily.

[0091] Clause [26] In another embodiment, a method of reducing the risk of recurrence of acute myeloid leukemia (AML) or death for a patient diagnosed with AML can include administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an administration schedule comprising daily dosing for two weeks, followed by a resting period of one week, in combination with all-trans retinoic acid (ATRA) twice daily.

[0092] Clause [27] In another embodiment, the method described in any one of one of claims 15-18 can reduce the risk of recurrence of AML or death by at least about 5%, at least about 10%, at least about 15%, at least about 20%, or at least about 25%.

[0093] Clause [28] In another embodiment, use of a compound comprising 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof can be for the manufacture of a medicament for treating acute myeloid leukemia (AML), wherein the medicament is prepared to be administered on an administration schedule comprising daily dosing for one week, followed by a resting period of one week.

[0094] Clause [29] In another embodiment, use of a compound comprising 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof can be for the manufacture of a medicament for treating acute myeloid leukemia (AML), wherein the medicament is prepared to be administered on an administration schedule comprising daily dosing for two weeks, followed by a resting period of one week.

[0095] Clause [30] In another embodiment, use of a compound comprising 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof can be for the manufacture of a medicament for treating acute myeloid leukemia (AML), wherein the medicament is prepared to be administered on an administration schedule comprising daily dosing for one week, followed by a resting period of one week, in combination with all-trans retinoic acid (ATRA) twice daily.

[0096] Clause [31] In another embodiment, use of a compound comprising

4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof can be for the manufacture of a medicament for treating acute myeloid leukemia (AML), wherein the medicament is prepared to be administered on an administration schedule comprising daily dosing for two weeks, followed by a resting period of one week, in combination with all-trans retinoic acid (ATRA) twice daily.

[0097] Clause [32] Aspects of the invention include a pharmaceutical composition for preventing and/or treating a disease or disorder characterized by the expression of LSD1 in a patient in need, wherein the pharmaceutical composition comprises 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof, and is administered to the patient on an administration schedule comprising continuous, daily dosing for one week, followed by a resting period of one week.

[0098] Clause [33] In another embodiment, the pharmaceutical composition described in clause [32] can include a pharmaceutical carrier.

[0099] Clause [34] In another embodiment, the pharmaceutical compositions described in clauses [32] or [33] can be administered on an administration schedule based on a 2-week cycle, with the cycle performed once or repeated two or more times.

[0100] Clause [35] In another embodiment, the pharmaceutical compositions described in clauses [32], [33] or [34] can be administered once per day for one week.

[0101] Clause [36] In another embodiment, the pharmaceutical compositions described in clauses [32], [33], [34] or [35] can be oral compositions.

[0102] Clause [37] In another embodiment, the pharmaceutical compositions described in clauses [32], [33], [34], [35] or [36] can be used to treat a disease or disorder characterized by a presence of a tumor.

[0103] Clause [38] In another embodiment, the pharmaceutical compositions described in clauses [32], [33], [34], [35], [36] or [37] can be used to treat a disease or disorder characterized by a presence of a malignant tumor.

[0104] Clause [39] In another embodiment, the pharmaceutical compositions described in clauses [32], [33], [34], [35], [36], [37] or [38] can be administered at a daily dose in the range from 10 nanograms to 20 milligrams per kilogram of bodyweight.

[0105] Clause [40] Aspects of the invention include a pharmaceutical composition for treating a disease or disorder characterized by the expression of LSD1 in a patient in need, wherein the pharmaceutical composition comprises 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof, and the pharmaceutical composition can be administered to the patient on an administration schedule comprising continuous, daily dosing for two weeks, followed by a resting period of one week.

[0106] Clause [41] In another embodiment, the pharmaceutical composition described in clause [40] can further include a pharmaceutical carrier.

[0107] Clause [42] In another embodiment, the pharmaceutical compositions described in clauses [40] or [41] can be administered on an administration schedule based on a 3-week cycle, with the cycle performed once or repeated two or more times.

[0108] Clause [43] In another embodiment, the pharmaceutical compositions described in clauses [40], [41] or [42] can be administered once per day for one week.

[0109] Clause [44] In another embodiment, the pharmaceutical compositions described in clauses [40], [41], [42] or [43] can be oral compositions.

[0110] Clause [45] In another embodiment, the pharmaceutical compositions described in clauses [40], [41], [42], [43] or [44] can be used to treat a disease or disorder characterized by a presence of a tumor.

[0111] Clause [46] In another embodiment, the pharmaceutical compositions described in clauses [40], [41], [42], [43], [44] or [45] can be used to treat a disease or disorder characterized by a presence of a malignant tumor.

[0112] Clause [47] In another embodiment, the pharmaceutical compositions described in clauses [40], [41], [42], [43], [44], [45] or [46] can be administered at a daily dose in the range from 10 nanograms to 20 milligrams per kilogram of bodyweight.

[0113] Clause [48] In another embodiment, a process for preparing a medicament for the prevention or treatment of a disease or disorder characterized by the expression of LSD1 includes preparing a composition comprising 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof, wherein the medicament is administered to the patient on an administration schedule comprising continuous, daily dosing for one week, followed by a resting period of one week.

[0114] Clause [49] In another embodiment, a process for preparing a medicament can include preparing a composition described in clause [48] that can be administered on an administration schedule based on a 2-week cycle, with the cycle performed once or repeated two or more times.

[0115] Clause [50] In another embodiment, a process for preparing a medicament includes preparing a composition described in clauses [48] or [49] that can include 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof for administration once per day for one week.

[0116] Clause [51] In another embodiment, a process for preparing a medicament includes preparing a composition described in clauses [48], [49] or [50] that can include 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof for oral administration.

[0117] Clause [52] In another embodiment, a process for preparing a medicament includes preparing a composition described in clauses [48], [49], [50] or [51] for use in treating a disease or disorder characterized by a presence of a tumor.

[0118] Clause [53] In another embodiment, a process for preparing a medicament includes preparing a composition described in clauses [48], [49], [50], [51] or [52] for use in treating a disease or disorder characterized by a presence of a malignant tumor.

[0119] Clause [54] In another embodiment, a process for preparing a medicament includes preparing a composition described in clauses [48], [49], [50], [51] or [52] that can include 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof for administration at a daily dose in the range from 10 nanograms to 20 milligrams per kilogram of bodyweight.

[0120] Clause [55] In an embodiment, a method of treating a disease or disorder characterized by the expression of LSD1 includes administering to a patient in need an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an administration schedule comprising continuous, daily dosing for two weeks, followed by a resting period of one week.

[0121] Clause [56] In another embodiment, a method of treating a disease or disorder characterized by the expression of LSD1 described in clause [55] can include administering an effective amount of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof to the patient on an administration schedule based on a 3-week cycle, with the cycle performed once or repeated two or more times.

[0122] Clause [57] In another embodiment, a method of treating a disease or disorder characterized by the expression of LSD1 described in clauses [55] or [56] can include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof once per day for two weeks.

[0123] Clause [58] In another embodiment, a method of treating a disease or disorder characterized by the expression of LSD1 described in clauses [55], [56] or [57] can include orally administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof.

[0124] Clause [59] In another embodiment, a method of treating a disease or disorder characterized by the expression of LSD1 described in clauses [55], [56], [57] or [58] can

include treating a disease or disorder characterized by a presence of a tumor.

[0125] Clause [60] In another embodiment, a method of treating a disease or disorder characterized by the expression of LSD1 described in clauses [55], [56], [57], [58] or [59] can include treating a disease or disorder characterized by a presence of a malignant tumor.

[0126] Clause [61] In another embodiment, a method of treating a disease or disorder characterized by the expression of LSD1 described in clauses [55], [56], [57], [58], [59] or [60] can include administering 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile or a salt thereof at a daily dose in the range from 10 nanograms to 20 milligrams per kilogram of bodyweight.

EXAMPLES

[0127] The present invention is described below in more detail with reference to Examples. However, the scope of the present invention is not limited to these Examples. The present invention is fully described below by way of Examples; however, it is understood that various changes and modifications by a skilled artisan are possible. Therefore, such changes and modifications are included in the present invention as long as they do not depart from the scope of the invention.

Reference Example 1. Intermittent dosing is more effectual treatment method for Test Compound A because Compound A doesn't affect hematopoietic stem cells.

[0128] The continuous dosing of hydrochloride of Compound A (in the Reference Example 1, hydrochloride of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile) was used, and this compound is referred to as "Test Compound A" for convenience) induced severe thrombocytopenia and neutropenia in rats, dogs and monkeys (data not shown). However, those toxicities were recovered after cessation of dosing. Therefore, the intermittent dose toxicity and its reversibility of Test Compound A was evaluated in 6-week old male Crl:CD(SD) rats (Charles River Laboratories Japan, Inc.) administered Test Compound A orally. In the case of pre-test group (1-week ON+1-week OFF dosing regimen), one cycle of administration of Test Compound A was performed. In the case of Group I (1-week ON+1-week OFF dosing regimen), two cycles of administration of Test Compound A were performed, with each cycle consisting of a dosing period of 7 consecutive days (1 week) once daily and a resting period of 7 days (1 week). In the case of Group II (2-week ON+ 1-week OFF dosing regimen), Test Compound A was administered continuously once daily for 14 days (2 weeks) and a resting period for 7 days (1 week). The resting period is a no-dosing period for recovery. Test Compound A was suspended in 5 mg/mL hypromellose solution. In the case of control, the vehicle

without Test Compound A was administered to the animals.

[0129] Test Compound A was administered at doses of 0 mg/kg (vehicle as control), 4 mg/kg (only for the pre-test group) and 16 mg/kg (for Group I and Group II) each at a dose volume of 5 mL/kg. For all rats, hematological evaluation and bone marrow smear examination were conducted. For the pre-test group, samples were collected on Days 8 and 15. For Group I, samples were collected on Days 8, 15, 22 and 29 for Test Compound A-treated animals, and on Days 8 and 29 for vehicle-treated animals. For Group II, samples were collected on Days 15 and 22 for both Test Compound A-treated animals and vehicle-treated animals.

[0130] In hematological examination, each rat was laparotomized under isoflurane anesthesia and blood was collected via the posterior vena cava using a disposable syringe with a needle. The collected blood was dispensed as a volume of approximately 1 mL into a container containing EDTA-2K for conducting the hematological tests using ADVIA2120i Multi-Species hematology system. After the blood collection, necropsy was conducted and bone marrow was collected from rats. Bone marrow liquid was collected and mixed with rat plasma, and used for making smear slide with Wedge-method. Bone marrow smear samples were stained with May-Grunwald Giemsa staining and were subjected to light microscopy. Approximately 200 cells (differential count) of all cells were counted in each of different microscopic fields to maintain representative ratios of cell types.

[0131] All animal experiment protocol of these studies were judged by the Institutional Animal Care and Use Committee and approved by the Director of Institution based on "Guidelines for Animal Experiment of Taiho Pharmaceutical Co., Ltd.". The handling of animals was performed appropriately in accordance with those guidelines.

[0132] In rats treated with 4 mg/kg of Test Compound A, platelet depletion (thrombocytopenia) and neutrophil depletion (neutropenia) were not induced by treatment of Test Compound A (data not shown). Therefore, 4 mg/kg was insufficient for evaluation of intermittent dose toxicity.

[0133] FIGS. 1A, 1B, 2A and 2B illustrate results of hematology analysis of peripheral blood samples. In hematology, rats of Group I treated with 16 mg/kg of Test Compound A showed decreases in platelets and neutrophils after 1-week (FIG. 1A (platelets) and FIG. 1B (neutrophils), "1 week" column, right filled bar) . Rats of Group II treated with 16 mg/kg of Test Compound A also showed decreases in platelets and neutrophils after 2-week (FIG. 2A (platelets) and FIG. 2B (neutrophils), "2 week" column, right filled bar). On the other hand, the number of platelets and neutrophils were dramatically recovered (rebounded elevation) after 1-week cessation or resting of Test Compound A dosing in rats of both Group I and Group II (FIG. 1A (platelets) and FIG. 1B (neutrophils), "2 week" column, right filled bar). ; FIG. 2A

(platelets) and FIG. 2B (neutrophils), "3 week" column, right filled bar).

[0134] FIGS. 3, 4A and 4B illustrate results of smear analysis of bone marrow. In this examination, myeloblasts, other progenitor cells and stem cells were not affected by treatment with Test Compound A. Neutrophil-lineage cells, such as myelocytes, metamyelocytes and mature neutrophils, were decreased at end of the dosing period (1-week or 2-week) (data not shown). Additionally, abnormal shaped neutrophil-lineage myelocytes appeared (FIG. 3). In contrast, promyelocytes in neutrophil-lineage were increased at the same period. However, there were no findings in other myelocyte-lineages, such as eosinophil- and basophil-lineages. Those findings indicated that Test Compound A affected bone marrow differentiation step from promyelocytes to myelocytes in the neutrophil-lineage. Additionally, in platelet-lineage, normal megakaryocytes were severely decreased and vulnerable or morphological abnormal megakaryocytes (FIGS. 4A and 4B) were markedly increased at the end of dosing period (data not shown). After 1-week cessation of dosing, neutrophil-lineage cells, especially mature neutrophils, were markedly increased and abnormal megakaryocytes disappeared.

[0135] These results suggested that Test Compound A induced myelosuppression in rats and affected bone marrow differentiation steps of neutrophil- and platelet-lineages. However, Test Compound A did not affect hematopoietic stem cells, progenitors and myeloblasts. Therefore, those myelosuppression effects disappeared after cessation of dosing for 1-week. Finally, intermittent dosing regimen with a cessation period (at least 1-week) is important for Test Compound A to manage and control myelosuppression which is induced by continuous dosing of Test Compound A.

Reference Example 2. Antitumor Effect and body weight change of Intermittent Administration Schedule in Mice (1-week ON + 1-week OFF regimen and 2-week ON + 1-week OFF is a very useful method that exhibits antitumor effects while avoiding toxicity resulting from Test Compound A administration)

[0136] (In the Reference Example 2, benzoate of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile) was used, and this compound is referred to as "Test Compound A" for convenience.) Human small cell lung cancer (NCI-H1417, American Type Culture Collection) cells were implanted in the right thorax of male SCID mice (Charles River Laboratories Japan, Inc.). After implantation of the tumor, the major axis (mm) and minor axis (mm) of the tumor were measured, and tumor volume (TV) was calculated. Then, the mice were assigned to groups so that the average TV of each group was equivalent. The day in which the grouping (n=5) was conducted was taken as Day 0. Test Compound A was prepared as follows: 0 mg/kg/day (vehicle without the compound), 100 mg/kg/day and 150mg/kg/day. The

compound was orally administered once daily for 3 weeks at 0 mg/kg/day (Control), consecutively once daily for 3 weeks at 100 mg/kg/day (Continuous group: 3-week ON regimen), once daily for 7 consecutive days (1 week) at 150 mg/kg/day followed by a resting period of 7 days (1 week) followed by 7 consecutive days (1 week) at 150 mg/kg/day (Group I: 1-week ON + 1-week OFF regimen), and once daily for 2 weeks at 100 mg/kg/day followed by a resting period of 7 days (1 week) (Group II: 2-week ON + 1-week OFF regimen), from Day 1. The dosages of Compound A are maximum tolerated doses (MTD) of each dosing schedule. The evaluation period was set to 21 days, and the last evaluation day was set to Day 22.

[0137] TV (mm^3) = (major axis x minor $axis^2$) / 2

[0138] As the index of antitumor effects during the dosing period, TV was sequentially measured in each group (FIG. 5).

[0139] As the index of toxicity during the dosing period, the body weight (BW) was sequentially measured, and the average body weight change [BWC (%)] relative to the body weight on Day 0 was calculated until the last evaluation day by the following formula (n: day of body weight measurement performed twice a week; the last measurement day corresponds to Day 22, which is the last evaluation day). FIG. 6 shows the results.

[0140] BWC (%) = [(BW on Day n) - (BW on Day 0)] / (BW on Day 0) x 100

[0141] FIG. 5 shows the antitumor effects. Compared with Day 0, regression of mean TV value was observed at Day 22 in Continuous group, Group I group, and Group II group, while mean TV was increased more than 4 fold during the dosing period in Control group. The mean TV values of all the groups except for the Control group were comparable during the dosing period. The evaluation assessment of effects was as follows: when the mean TV values of the administration group was statistically significantly (Dunnett's t-test, $p<0.001$) less than the mean TV value of the Control group (The Symbol *** indicates that a statistically significant difference from the Control group was observed.) On the other hand, when the antitumor effects were compared between each of the intermittent administration groups (Group I group and Group II group) and Control group, no statistically significant difference was observed between the groups (Aspin-Welch t-test). Therefore it was determined that there were antitumor effects and the effects were the same among all the compound administered groups.

[0142] FIG. 6 shows the body weight changes. As for the influence of compound administration on body weight, body weight loss was observed in Continuous group. On the other hand, intermittent dosing groups, such as Group I group and Group II group, did not show any body weight reduction at Day 22. Therefore, intermittent dosing schedules, such as 1-week ON + 1-week OFF regimen and 2-week ON + 1-week OFF, improved the body weight reduction over the continuous daily dosing regimen (3-week

ON).

[0143] Since the antitumor effects were same among the intermittent dosing groups and the continuous daily dosing group, these above results revealed that the intermittent regimens were less toxic dosing schedules.

[0144] The method for administering Test Compound A with intermittent dosing schedules, such as 1-week ON + 1-week OFF regimen and 2-week ON + 1-week OFF regimen, is sufficiently expected to become a very useful method that exhibits antitumor effects while avoiding toxicity resulting from administration of the compound in clinical treatment.

Reference Example 3. A Study of Test Compound A With All-Trans Retinoic Acid in Subjects With Relapsed or Refractory Acute Myeloid Leukemia

[0145] (In the Reference Example 3, 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl) phenyl]phenyl]-2-fluoro-benzonitrile) or a pharmaceutically acceptable salt thereof is used, and this compound is referred to as "Test Compound A" for convenience.)

[0146] This is a multicenter, 2-part, Phase 1 study to assess the safety, pharmacokinetics, pharmacodynamics, and preliminary clinical activity of Test Compound A administered as a single agent and in combination with all-trans retinoic acid (ATRA) in participants with acute myeloid leukemia (AML) who have relapsed or are refractory (r/r) to prior treatment. The study duration is expected to be approximately 30 months.

[0147] [Table 1]

TABLE 1

Condition or disease	Intervention/treatment	Phase
Acute Myeloid Leukemia	Drug: Test Compound A Drug: Test Compound A + ATRA	Phase 1

Study Design

[0148] Study Type: Interventional

[0149] Estimated Enrollment: 50 participants

[0150] Allocation: Non-Randomized

[0151] Intervention Model: Sequential Assignment

[0152] Masking: None (Open Label)

[0153] Primary Purpose: Treatment

[0154] Official Title: A Phase 1 Study of Safety, Pharmacokinetics, and Preliminary Activity of Test Compound A, as a Single Agent and in Combination With All-Trans Retinoic Acid (ATRA) in Subjects With Relapsed or Refractory (r/r) Acute Myeloid

Leukemia (AML).

[0155] [Table 2]

TABLE 2 Arms and Interventions

Arm	Intervention/treatment
Experimental: Test Compound A Test Compound A as a single agent administered once daily (QD) on specific days during each 28-day cycle in Part 1.	Drug: Test Compound A Form: Capsule Route of Administration: Oral
Experimental: Test Compound A + ATRA Test Compound A administered QD on specific days during each 28-day cycle in combination with ATRA twice daily (BID) in Part 2.	Drug: Test Compound A Form: Capsule Route of Administration: Oral Drug: Test Compound A + ATRA Form: Capsule Route of Administration: Oral Other Names: Tretinoin Vesanoid

Outcome Measures

[0156] Primary Outcome Measure:

[0157] 1. Safety: Number of participants with treatment-emergent adverse events (TEAEs) [Time Frame: Approximately 30 months]

[0158] 2. Safety: Number of participants with adverse events (AEs) [Time Frame: Approximately 30 months]

[0159] Secondary Outcome Measures:

[0160] 1. Response rate: Number of participants with complete remission (CR), complete remission with incomplete blood count recovery (CRi), partial remission (PR) and complete remission with partial hematological recovery (CRh) in Part 2 [Time Frame: Approximately 30 months]

[0161] 2. Overall survival: Time from the date of the first dose until death due to any cause [Time Frame: Approximately 30 months]

[0162] 3. Pharmacokinetic parameter: Area under the curve (AUC) [Time Frame: Up to Day 8 of Cycle 1 and Cycle 2 (28 days per cycle)]

[0163] 4. Pharmacokinetic parameter: Maximum plasma concentration (Cmax) [Time Frame: Up to Day 8 of Cycle 1 and Cycle 2 (28 days per cycle)]

[0164] 5. Pharmacokinetic parameter: Minimum plasma concentration (Cmin) [Time Frame: Up to Day 8 of Cycle 1 and Cycle 2 (28 days per cycle)]

[0165] 6. Pharmacokinetic parameter: Time to reach maximum plasma concentration (Tmax) [Time Frame: Up to Day 8 of Cycle 1 and Cycle 2 (28 days per cycle)]

[0166] 7. Pharmacokinetic parameter: Half-life (t1/2) [Time Frame: Up to Day 8 of Cycle 1 and Cycle 2 (28 days per cycle)]

Eligibility Criteria

[0167] Ages Eligible for Study: 18 Years and older

[0168] Sexes Eligible for Study: All

[0169] Gender Based: No

[0170] Accepts Healthy Volunteers: No

Inclusion/Exclusion Criteria

[0171] Inclusion Criteria:

[0172] 1. Have a projected life expectancy of at least 12 weeks and be in stable condition to complete 1 full cycle (4 weeks) of treatment.

[0173] 2. Have histological confirmation of AML by World Health Organization (WHO) 2016 criteria and who have failed all other available conventional therapies.

[0174] 3. Have a peripheral blood or bone marrow blast count >5% at the time of enrollment.

[0175] 4. Have disease that:

[0176] a. is refractory to standard induction chemotherapy, including but not limited to anthracycline and cytarabine combination therapy, or

[0177] b. has relapsed after anthracycline and cytarabine therapy or stem cell transplant (SCT), or

[0178] c. is refractory to or has relapsed after a front-line regimen containing a hypomethylating agent, alone or in combination.

[0179] 5. Have an Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 1.

[0180] 6. Have adequate renal function as demonstrated by a serum creatinine$\leqq$1.5 × upper limit of normal (ULN) or calculated creatinine clearance (by the standard Cockcroft-Gault formula) of$\geqq$60 mL/min.

[0181] 7. Have adequate liver function as demonstrated by the following:

[0182] a. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <3 × upper limit of normal (ULN)

[0183] b. AST and ALT <5 × ULN (if considered due to leukemic organ involvement).

[0184] 8. Women of child-bearing potential (according to recommendations of the Clinical Trial Facilitation Group [CTFG]) must not be pregnant or breastfeeding and must have a negative pregnancy test at screening.

[0185] Exclusion Criteria:

[0186] 1. Known clinically active central nervous system (CNS) leukemia.

[0187] 2. BCR-ABL-positive leukemia.

[0188] 3. Diagnosis of acute promyelocytic leukemia (M3 AML or APML or APL).

[0189] 4. Second malignancy currently requiring active therapy, except breast or prostate cancer stable on or responding to endocrine therapy.

[0190] 5. Grade 3 or higher graft versus host disease (GVHD), or GVHD requiring treatment with either:

[0191] a. a calcineurin inhibitor, or

[0192] b. prednisone more than 5 mg/day (Note: Prednisone at any dose for other indications is allowed).

[0193] 6. Total serum bilirubin ≧1.5 × ULN (except for subjects with Gilbert's Syndrome for whom direct bilirubin is >2.5 × ULN), or liver cirrhosis, or chronic liver disease Child-Pugh Class B or C.

[0194] 7. Known active human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection. Inactive hepatitis carrier status or low viral hepatitis titer being treated with antivirals is allowed. For subjects considered at risk of viral exposure, serologies should be used to establish negativity.

[0195] 8. Known significant mental illness or other condition such as active alcohol or other substance abuse or addiction that, in the opinion of the investigator, predisposes the subject to high risk of non-compliance with the protocol.

[0196] 9. Myocardial impairment of any cause (eg, cardiomyopathy, ischemic heart disease, significant valvular dysfunction, hypertensive heart disease, or congestive heart failure) resulting in heart failure by New York Heart Association (NYHA) Criteria (Class III or IV staging).

[0197] 10. Screening 12-lead echocardiogram with measurable QTc interval (according to either Fridericia's or Bazett's correction) of >480 milliseconds.

[0198] 11. Active, uncontrolled infection. Participants with an infection receiving treatment (antibiotic, antifungal, or antiviral treatment) must be afebrile and hemodynamically stable for ≧72 hours before enrollment.

[0199] 12. Non-AML-associated pulmonary disease requiring >2 liters per minute (LPM) oxygen.

[0200] 13. Proliferative AML with total white blood cells >20,000/μL OR high disease burden of blast % of >50% (in bone marrow or peripheral blood).

[0201] 14. Any other condition that puts the participant at an imminent risk of death.

[0202] 15. Treated with any investigational therapy within 2 weeks of the first dose of study treatment.

[0203] 16. Inability to swallow oral medication.

[0204] 17. Known hypersensitivity to ATRA, any of its components, or other retinoids.

[0205] 18. Known sensitivity to parabens.