[0006J In view of the importance of mutations of BRCA1 and BRCA2 in breast, ovarian cancers and other cancers, there is a need for methods for treatment of cancer subjects having BRCA2 mutations or in whom BRCA2 activity is otherwise reduced.

4. SUMMARY

[0007] In one aspect, the present invention refers to the use of (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid in the manufacture of a medicament for treating cancer in a subject having a BRCA2 mutation that impairs BRCA2 activity. In another aspect, the present invention refers to a method of identifying a cancer subject suitable for treatment with (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid comprising: (a) screening a biological sample obtained from a candidate having cancer for a BRCA2 mutation; and (b) if the candidate has a mutation that impairs activity of BRCA2, identifying the candidate as a cancer subject suitable for treatment with (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid.

In another aspect, the present invention refers to a method of identifying one or more cancer subjects suitable for treatment with (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid comprising: (a) screening the biological samples obtained from a plurality of candidates having cancer for BRCA2 mutations; and (b) identifying each candidate having a BRCA2 mutation as a cancer subject suitable for treatment with (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid.

In another aspect, the present invention refers to an *in vitro* method comprising contacting a cancer cell having a mutation that impairs BRCA2 activity with an amount of (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid that is effective to induce double-strand DNA breaks in the cell.

In another aspect, the present invention refers to the use of (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid in the manufacture of a medicament for treating cancer in a subject having reduced BRCA2 activity.

In another aspect, the present invention refers to the use of (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid in the manufacture of a medicament for treating cancer in a subject having a BRCA2 mutation that impairs BRCA2 activity, wherein the medicament comprises about 1-1000 mg of

(+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid.

In another aspect, the present invention refers to the use of (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid in the manufacture of a medicament for treating cancer in a subject having reduced BRCA2 activity, wherein the medicament comprises about 1-1000 mg of (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid. It has been observed that presence of a BRCA2 mutation increases responsiveness of cancer cells in a subject to treatment by SNS-595, which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methyiamino)-l -pyrrolidinyl]-4-oxo-1 -(2-thiazolyl)-1 ,8-naphthyridinc-3-carboxylic acid. Accordingly, ~~provided in one embodiment~~described herein is a method for treating a cancer subject, such as a cancer patient having a BRCA2 mutation that impairs activity of BRCA2 (or in whose cells BRCA2 activity is down-regulated or reduced relative to normal, e.g., reduced expression), comprising administering to the subject a therapeutically effective amount of SNS-595.

[00081 In certain ~~embodiments~~examples, the methods provided herein comprise diagnosing a BRCA2 mutation in a cancer subject and treating the subject with SNS-595. In certain ~~embodiments~~examples, the methods provided herein comprise diagnosing a BRCA2 activity down-regulation or reduction in a cancer subject and treating the subject with SNS-595.

[0009] In certain ~~embodiments~~examples, the methods provided herein comprise administering a dose of about 10-100 mg/m^2 of SNS-595 to the cancer subject having a BRCA2 mutation or in whom BRCA2 activity (or expression) is reduced.

[0010] In certain ~~embodiments~~examples, methods provided herein comprise contacting a cancer cell having a BRCA2 mutation with an amount of SNS-595 effective to induce double-strand DNA breaks.

[0011] The methods ~~provided~~described herein encompass treatment of breast, ovarian. prostate, pancreas and other cancers wherein a cancer cell exhibits a BRCA2 mutation.

[0012] In another ~~aspect~~example, provided herein is a method of identifying a subject for treatment with SNS-595, comprising diagnosing a BRCA2 mutation in the subject.

[0013] In certain ~~embodiments~~examples, SNS-595 is used alone, i.e., without other chemotherapeutic agents.

[0014] In other ~~embodiments~~examples, SNS-595 is administered in combination with one or more therapeutic agents, i.e., pharmaceutical agents with activity against cancer or its symptoms. Examples of therapies within the scope of the methods include, but arc not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy, immunotherapy, and combinations thereof. The combinations encompass simultaneous as well as sequential administration.

[0015] In some ~~embodiments~~examples, the additional therapeutic agent is selected from alkylating agents, antimetabolites, aurora kinase inhibitors, purine antagonists, pyrimidine antagonists, spindle poisons, mitotic inhibitors, topoisomerase II inhibitors and poisons, topoisomcrasc I inhibitors, anti-ncoplastic antibiotics, nitrosoureas, inorganic ion complexes, enzymes, hormones and hormone analogs, EGFR inhibitors, antibodies and antibody derivatives, IMIDs, HDAC inhibitors, Bcl-2 inhibitors, VEGF-stimulated tyrosine kinase inhibitors, VEGFR inhibitors, proteasome inhibitors, cyclin-dependent kinase inhibitors, PARP mhibitors, aromatase inhibitors, and dexamcthasone.

[0016] In a particular ~~embodiment~~example, the combination therapy comprises administering SNS-595 and at least one therapeutic agent selected from docetaxei, taxotcrc. vinoreibine, capecitabine, doxorubicin, goserelin. zoledronic acid, paclitaxel, pamidronate, anastrozole, exemestane, cyclophosphamide, epirubicin, fulvestrant, ietrozole, gemcitabinc. [euprolide, filgrastim, G-CSF or granulocyte colony stimulating factor, pegfilgrastim, toremifene, tamoxifen, bevacizumab, trasruzumab, 5-fluorouracil, methotrexate, trabectidin epoetin alfa, and darbepoetin alfa. In another ~~embodiment~~example, the combination therapy comprises administering SNS-595 and a support care agent.

[0017] Also ~~provided~~described are dosing regimens, dosing schedules and methods of using SNS-595 in cancer subjects having impaired BRCA2 activity.

[0018] In certain ~~embodiments~~examples, provided herein are pharmaceutical compositions comprising SNS-595 and a pharmaceutically acceptable carrier, adjuvant or diluent for treatment of the cancer subjects having reduced BRCA2 activity.

5. BRIEF DESCRIPTION OF DRAWINGS

[0019] FIG. 1 illustrates inhibition of growth in Chinese hamster cells that are mutant for BRCA2 (VC8) and complemented for functional BRCA2 (VC8-B2) in the presence of doxorubicin.

[0020] FIG. 2 illustrates inhibition of growth in VC8 and VC8-B2 cells in the presence of SNS-595.

[00211 FIG. 3 illustrates colony outgrowth in human sarcoma U-20S cells (wild-type cells and cells depleted for BRCA2 using siRNA) upon treatment with doxorubicin.

[0022] FIG. 4 illustrates colony outgrowth in human sarcoma U-20S cells (wild-type cells and cells depleted for BRCA2 using siRNA) upon treatment with SNS-595.

[0023] FIG. 5 provides Pulsed field gel electrophoresis (PFGE) for an 18-hour run for treatment with SNS-595, and doxorubicin, each alone and in co-treatment with aphidicolin, for 240 seconds switch time.